Process flexibility in vaccine manufacturing under high demand uncertainty

by

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Declaration

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Abstract

The Covid-19 disease was first diagnosed in December 2019 in Wuhan, China. The transmission of the disease occurred at a rapid pace causing disruption to the world's health systems and the global economy. This created an incentive to quickly develop an effective vaccine against Covid-19. To manufacture the vaccine products and meet the global demand, requires large scale manufacturing capacity. Several vaccine platforms, based on different antigen production systems, have been employed in the search for effective vaccine products. Due to the rapid pace at which the development of vaccine products are occurring, great uncertainty is associated with which platforms will receive regulatory approval and the timeline in which this will occur. This provided a challenge for the Covid-19 vaccine manufacturing system in terms of manufacturing capacity planning.

This study investigated the impact that process flexibility can have in reducing the negative impact of the high demand uncertainty associated with vaccine approval for the Covid-19 vaccine manufacturing system. A discrete-event simulation model was developed in Tecnomatix Plant Simulation to investigate this. The model was verified via a series of model execution tests and the results were used to correct errors in the model. Further, the model was validated by conducting semi-structured interviews with subject matter experts in the fields of vaccine development and manufacturing. The feedback from the interviews informed improvements to the model.

It was uncovered in this study that process flexibility significantly improves the performance, in terms of throughput, for a manufacturing system with high demand uncertainty when either the long chain or full flexibility configuration is incorporated (the throughput improved between 25% and 119%). The throughput performance for the full flexibility configuration is markedly better than the long chain configuration. The capital costs associated with the full flexibility configuration is often, however, viewed as an unjustifiable expense. Process flexibility investment decisions should thus also consider the capital costs associated with process flexibility configurations.

It was observed that the operating cost per dose for stainless-steel equipment is significantly higher compared to single-use equipment. Many factors, however, contribute to the manufac-

turing costs for vaccine manufacturing and the observations in terms of the operating cost per dose for the vaccine manufacturing facilities in other circumstances may significantly differ.

This study's results did indicate that process flexibility can potentially improve the performance of a facility utilising stainless-steel equipment. It is, however, required that aspects such as regulatory approval, equipment capabilities, and capital costs are considered to determine the feasibility of a flexible stainless-steel equipment facility. This study can inform the decision on whether to further investigate the feasibility of incorporating process flexibility in a manufacturing facility utilising stainless-steel.

The model developed in this study could be adjusted to investigate other research problems associated with process flexibility in vaccine manufacturing systems. Three examples of alternative applications have been identified. One of these applications involves investigating a facility that continuously manufactures a routine vaccine product, while some of the manufacturing capacity is reserved for shifting between different epidemic products. The demand for these products will fluctuate based on epidemiological outbreaks.

Opsomming

Die Covid-19 siekte is die eerste keer in Desember 2019 in Wuhan, China, gediagnoseer. Die oordrag van die siekte het teen 'n vinnige tempo plaasgevind wat ontwrigting van die wêreld se gesondheidstelsels en die wêreldekonomie veroorsaak het. Dit het 'n aansporing geskep om vinnig 'n doeltreffende entstof teen Covid-19 te ontwikkel. Om die entstofprodukte te vervaardig en aan die wêreldvraag te voldoen, vereis grootskaalse vervaardigingskapasiteit. Verskeie entstofplatforms, gebaseer op verskillende antigeen produksiestelsels, is aangewend in die soektog na effektiewe entstofprodukte. Weens die vinnige tempo waarteen die ontwikkeling van entstofprodukte plaasvind, word groot onsekerheid geassosieer met watter platforms regulatoriese goedkeuring sal ontvang en die tydlyn waarin dit sal plaasvind. Dit het 'n uitdaging gebied vir die Covid-19-entstofvervaardigingstelsel in terme van die beplanning van vervaardigingskapasiteit.

Hierdie studie het die impak wat prosesbuigsaamheid kan hê om die negatiewe impak van die hoë aanvraag-onsekerheid te verminder in verband met entstofgoedkeuring vir die Covid-19-entstofvervaardigingstelsel ondersoek. 'n Diskrete-gebeurtenis-simulasiemodel is in Tecnomatix Plant Simulation ontwikkel om dit te ondersoek. Die model is geverifieer deur middel van 'n reeks model-toetse en die resultate is gebruik om foute in die model reg te stel. Die model is gevalideer deur middel van semi-gestruktureerde onderhoude met vakkundiges op die gebied van entstofontwikkeling en -vervaardiging te voer. Die terugvoer van die onderhoude het verbeteringe aan die model ingelig.

Dit is in hierdie studie ontdek dat prosesbuigsaamheid die werkverrigting, in terme van deurset, aansienlik verbeter vir 'n vervaardigingstelsel met hoë aanvraag-onsekerheid wanneer óf die langketting- óf volle buigsaamheidskonfigurasie toegepas is (die deurset het tussen 25% en 119% verbeter). Die deursetprestasie van die volle buigsaamheidskonfigurasie is aansienlik beter as die langkettingkonfigurasie. Die kapitaalkoste verbonde aan die volle buigsaamheidskonfigurasie word egter dikwels as 'n te duur uitgawe beskou. Beleggingsbesluite oor prosesbuigsaamheid moet dus ook die kapitaalkoste wat met prosesbuigsaamheidskonfigurasies geassosieer word, in ag neem.

Daar is waargeneem dat die bedryfskoste per dosis vir vlekvrye staal toerusting aansienlik hoër is in vergelyking met enkelgebruik toerusting. Baie faktore dra egter by tot die vervaardigingskoste

vir entstofvervaardiging en die waarnemings in terme van die bedryfskoste per dosis vir die entstofvervaardigingsfasiliteite in ander omstandighede kan aansienlik verskil.

Hierdie studie se resultate het wel aangedui dat prosesbuigsaamheid moontlik die werkverrigting van 'n fasiliteit wat vlekvrye staal toerusting gebruik, kan verbeter. Dit word egter vereis dat aspekte soos regulatoriese goedkeuring, toerustingvermoëns en kapitaalkoste oorweeg word om die uitvoerbaarheid van 'n buigsame vlekvrystaaltoerustingfasiliteit te bepaal. Hierdie studie kan die besluit om die uitvoerbaarheid van die inkorporering van prosesbuigsaamheid in 'n vervaardigingsfasiliteit wat vlekvrye staal gebruik verder te ondersoek, inlig.

Die model wat in hierdie studie ontwikkel is, kan aangepas word om ander navorsingsprobleme wat verband hou met prosesbuigsaamheid in entstofvervaardigingstelsels te ondersoek. Drie voorbeelde van alternatiewe toepassings is geïdentifiseer. Een van hierdie toepassings behels die ondersoek van 'n fasiliteit wat voortdurend 'n roetine-entstofproduk vervaardig terwyl 'n gedeelte van die produksiekapasiteit toegeken word aan die vervaardiging van epidemiese produkte. Sommige van die vervaardigingskapasiteit word dus verskuif tussen verskillende epidemiese produkte. Die vraag sal wissel op grond van epidemiologiese uitbrake.

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Nomenclature

Acronyms

ANOVA	Analysis of variance – a statistical test to evaluate the variability in data distributions
BOM	Bill of material – a complete list of the raw materials and components required to manufacture a product
EPI	Expanded Program on Immunisation – a vaccination programme introduced by the World Health Organization in 1974
IV	Inactivated virus – a vaccine platform using the inactivated live virus
LAV	Live attenuated virus – a vaccine platform using a weakened form of the live virus
SP	Subunit protein – a vaccine platform which involves the expression of pathogenic proteins
VLP	Virus Like Particles – a type of subunit vaccine comprised of viral particles
VV	Viral vector – a vaccine platform using a vector to carry the pathogenic genes
WHO	World Health Organization – an organisation forming part of the United Nations, which governs the international health sector

Greek Symbols

γ	Asymptotic ratio for the expected sales of a long chain and full flexibility

μ	Average demand for product i
$\Phi(z)$	Cumulative distribution function
π	Closed loop feasible policy
$\Pi(M^*)$	Probability that the shortfall of demand for a long chain will be greater than that of full flexibility
σ_i	Standard deviation of the demand for a product i

Roman Symbols

A	A set of facilities and products
$BC(A)$	Backlogging cost for a configuration A
$B_j^{\pi}(t)$	Backlog of product j during period t
C_j	Manufacturing capacity for facility j
D_i	Demand for product i
$E[P(D,A)]$	Expected maximum product output for a configuration A
F_n	full flexibility configuration
G_n	Limited flexibility configuration
L_n	Long chain configuration
M	Subset of products
m	Number of products
M^*	The subset of products that maximises $\Pi(M)$
n	Number of facilities
O_n	Open chain configuration
i	Subset of facilities that can manufacture at least one product in subset M
$P(D,A)$	Maximum product output for a configuration A

S_i	Demand shortfall for product i
U	Expected shortfall for a configuration A
X_{ij}	Demand met for product i by facility j

Subscripts

i	Product
j	Facility
n	System size

Terminology

Active drug substance	The active drug substance is the main ingredient in a vaccine and contains the pathegenic components
Antigen Production System	The antigen production system refer to the technologies applied to develop and manufacture vaccine products. Vaccine platforms are associated with specific antigen production systems
Equipment Facility Option	The type of equipment that is utilised in a vaccine manufacturing facility, namely stainless-steel or single-use equipment
Full flexibility	Full flexibility is a process flexibility configuration in which all products can be manufactured by all the facilities in the system
Long Chain	A process flexibility configuration discovered by Jordan & Graves (1995) which is symmetrical and balanced and connect each product to two facilities and each facility to two products
Manufacturing flexibility	Manufacturing flexibility can be incorporated into a manufacturing system to allow the system to reduce the negative impact of uncertainty
Process flexibility	Process flexibility is a manufacturing flexibility classification which allows a system to switch between the manufacturing of products at a production line or manufacturing facility
Vaccine Platform	A vaccine platform refer to a specific manufacturing procedure used to manufacture a vaccine product

Chapter 1

Introduction

This study aims to model the manufacturing of vaccines to determine whether incorporating some degree of flexibility into manufacturing systems has the potential to improve the performance of these systems under conditions where there is significant demand uncertainty. This chapter provides background information on vaccines and flexible manufacturing. The problem statement, objectives, proposed method, study limitations, and expected contributions are presented. Finally, an outline of the remainder of the document is provided.

1.1 Background

The Covid-19 pandemic has caused disruptions to the world's health care sector and the global economy (Prüβ, 2021). Vaccines are very effective at preventing the spread of infectious diseases (Afrough et al., 2019; Hardt et al., 2016; Koff & Schenkelberg, 2021; Koirala et al., 2020; Rottingen et al., 2017; Sparrow et al., 2021; Van der Weken et al., 2021; Zhao et al., 2020). Consequently, since the outbreak of Covid-19, various attempts were made to develop a vaccine to control the pandemic caused by the disease (Ita, 2021; Knezevic et al., 2021; Lozano et al., 2020). The development of vaccines against the virus occurred rapidly (Defendi et al., 2021) and widespread role-out of these vaccines was viewed as an integral step towards minimising the impact of the pandemic.

Particularly during the early phases of the pandemic when vaccines against the virus were still in development, the vaccine manufacturing system faced a significant amount of uncertainty due to various factors (McDonnell et al., 2020). One of the factors contributing to the uncertainty was the possibility of a variety of vaccine products being placed on the market (Bos et al., 2020; McDonnell et al., 2020). Vaccines are generally developed and manufactured using one of a few potential antigen production systems and associated platforms. Figure 1.1 provides an illustration of the relationship between antigen production

systems, platforms, and vaccine products, using the cell-based antigen production system and a non-exhaustive selection of platforms and products as examples. The examples of product were gathered from the U.S. Department of Health Human Services (2021). Facilities for the manufacturing of the active

Antigen production system	Cell-based		
Platform	Live attenuated virus	Inactivated virus	Viral vector
Vaccine product	• Smallpox • Chickenpox • Yellow fever	• Flu • Hepatitis A • Polio	• Ebola • Zika • Covid-19

Figure 1.1: Overview of relationship between antigen production system, platform, and vaccine product

drug substance[1] are often built to produce vaccines of a specific platform. One source of uncertainty in the vaccine manufacturing environment in the early phases of the pandemic, was that it was unclear which vaccine products would be successfully developed. Consequently, it was unclear which type of manufacturing facilities (where *type* is used to refer to the vaccine platform in this case) would be required. In spite of this uncertainty, preparing manufacturing capacity with a view to ensuring that manufacturing could start shortly after vaccine(s) received regulatory approval, would contribute to curtailing the disruption caused by the pandemic, and was therefore desirable. It it likely that incorporating some degree of flexibility into vaccine manufacturing systems could contribute to enabling these systems to respond effectively to uncertainty, enabling the manufacturing systems to meet the demand for products (Jordan & Graves, 1995).

A more detailed introduction to the various topics that are included in the preceding discussion is presented in the remainder of this section.

1.1.1 The role of vaccines

Vaccination is a very cost-effective approach to containing an infectious disease pandemic (Afrough et al., 2019; Kimman et al., 2006). Unlike other pharmaceutical interventions that treat disease, vaccines can prevent disease and significantly reduce the rate of transmission during a pandemic (Afrough et al., 2019; Sheets et al., 2020). Vaccines are developed based on the mechanisms of the natural immune system,

[1]The active drug substance is also commonly referred to as active pharmaceutical ingredient.

protecting against specific pathogens (Loomis & Johnson, 2015). An antigen, comprised of either the entire target pathogen or only a part, is introduced into a host during vaccination (Loomis & Johnson, 2015). When the entire target pathogen is used, it is weakened or inactivated during manufacturing to minimise the risk of infection (Loomis & Johnson, 2015). The pathogen induces a protective immune response in the form of antibody production after vaccination (Loomis & Johnson, 2015).

The first successful vaccine was introduced in 1796 against smallpox, a fatal disease, by Edward Jenner (Brisse et al., 2020; Kyriakidis et al., 2021; Loomis & Johnson, 2015; Souza et al., 2005). A vaccination program against smallpox, eliminating the disease, was executed from 1967 to 1977 (World Health Organisation, 2016). Following the success of the smallpox vaccine, the Expanded Program on Immunization (EPI) was introduced globally in 1974 at the 27th Global Health Assembly (Hardt et al., 2016; World Health Organization, 2021b). Vaccines against six infectious diseases were initially included in the EPI including, among others, polio, measles and tuberculosis (World Health Organization, 2021b). Since the inception of the EPI, vaccines for other infectious diseases have also been developed and included in the programme. According to the World Health Organization (2021d), 20 vaccination programs currently exist against diseases, including hepatitis B, meningitis and influenza type B (World Health Organization, 2021d). The vaccination programs mainly focus on infants and children and are performed routinely (World Health Organization, 2021d). Countries do not necessarily employ all of the vaccine programs, but only those required for the infection risks of the specific country (World Health Organization, 2021d).

1.1.2 Manufacturing of vaccines

The development of vaccines is a complex process that can take months or even years to complete (Borriello et al., 2021; Defendi et al., 2021; Detoc et al., 2020; Haq et al., 2020). It consists of several steps and phases, including identifying an appropriate antigen, establishing the vaccine design, experimental animal trials, human clinical testing, manufacturing and application for approval (Gomez & Robinson, 2013; Haq et al., 2020; Sheets et al., 2020). The facilities manufacturing vaccines are highly specialised and complex, and only a limited number of facilities that can produce vaccines exist (Gomez & Robinson, 2013).

Different vaccine platforms have been developed over the years (Bos et al., 2020). Each of these vaccine platforms has specialised development and manufacturing steps and different mechanisms of operation (McDonnell et al., 2020). Traditional vaccine platforms include inactivated virus vaccines, subunit vaccines and live-attenuated virus vaccines (Brisse et al., 2020). New vaccine technologies include using the pathogen's genetic information in the manufacturing of vaccines (Brisse et al., 2020). These technologies include nucleic acid vaccines, DNA-based or RNA-based vaccines, and viral vector vaccines (Ita, 2021; Mathew et al., 2021; Ulmer et al., 2012).

A description of the general manufacturing process of vaccines is given. The main steps include the generation of the drug substance, purification, quality testing, and fill and finish (McDonnell et al., 2020). The method of generating the antigen, which is the main component of the drug substance, is dependent on the vaccine platform used (McDonnell et al., 2020). The process can either entail the growth and recovery of a pathogen, in which the pathogen is inactivated or isolated, manufacturing of a recombinant protein, or genome sequencing (Gomez & Robinson, 2013).

After the manufacturing or growth phase is completed, the antigen is recovered and purified (McDonnell et al., 2020). Purification can comprise of processes, such as chromatography, filtration or inactivation of the pathogen (McDonnell et al., 2020). Impurities and remaining substrate components are removed from the recovered antigen (Gomez & Robinson, 2013). The vaccines are formulated in mixing vessels (Gomez & Robinson, 2013). In addition to the antigen, ingredients such as adjuvants, stabilisers and/or preservatives may be added to the mixing vessels (Gomez & Robinson, 2013). Adjuvants are added to enhance the immune response induced by the vaccine (Liang et al., 2020).

Quality testing is performed on the vaccine products to ensure the quality and safety aspects adhere to the regulations (Sheets et al., 2020; Silveira et al., 2021). The final step of the manufacturing process is the filling and finishing of the vaccine product (McDonnell et al., 2020). Vaccines are filled either into vials or syringes and stored according to the requirements of the specific vaccine formulation (Gomez & Robinson, 2013).

Manufacturing facilities for the active drug substance can incorporate either stainless-steel equipment, single-use equipment, or a combination of the two (Rogge et al., 2015).

There is little uncertainty in the annual demand that must be met when manufacturing vaccines for vaccination programs. Demand estimates for these vaccination programs is based on historical data on the target population and the previous demand (World Health Organization, 2021c). Demand for new vaccines developed for emerging infectious diseases can not be estimated based on this historical data, and the uncertainty in the demand for these vaccines thus contributes to an unstable manufacturing environment.

1.1.3 Towards a vaccine for Covid-19

The first case of the emerging coronavirus disease (Covid-19) was recorded in December 2019 in Wuhan, China. Since the outbreak of the virus, infections spread rapidly, leading to the World Health Organization's (WHO) decision to declare a global pandemic (Blakney et al., 2021; Bos et al., 2020; Defendi et al., 2021; Haq et al., 2020; Kyriakidis et al., 2021; Mahmood et al., 2021; Pandey et al., 2020; Wang et al., 2020; Zhao et al., 2020). Worldwide, millions of people have been infected, with many requiring treatment and even hospitalisation (Detoc et al., 2020; Ita, 2021). The initial intervention strategies included social distancing, travel restrictions, and regional and/or national lock-downs in severe instances (Prüβ, 2021; Sparrow et al.,

2021; Zhao et al., 2020). This led to the exhaustion of many countries' health systems and the disruption of the global economy (Belete, 2021; García & Cerda, 2020; Liang et al., 2020; Mahmood et al., 2021; Mara et al., 2021; Mathew et al., 2021; Prüβ, 2021; Zhou et al., 2020). As of 2021, approximately four million Covid-19-related mortalities have been reported while lasting complications have been noticed for many who have recovered from Covid-19 (Pettersson et al., 2021; Prüβ, 2021).

No vaccines or other pharmaceutical interventions against Covid-19 existed before the pandemic outbreak (Ghaebi et al., 2020; Haq et al., 2020; Ita, 2021; Mahmood et al., 2021; Sparrow et al., 2021; Wang et al., 2020; Zhao et al., 2020). Pharmaceutical companies have made various attempts to develop a vaccine that can induce an immune response to sufficiently slow down the fast transmission rate of the virus and consequently contain the impact of the pandemic globally (Detoc et al., 2020; García & Cerda, 2020; Ita, 2021; Koirala et al., 2020; Kyriakidis et al., 2021; Pandey et al., 2020; Tregoning et al., 2020; Wang et al., 2020).

A challenge facing the development process of Covid-19 vaccines is that vaccines are urgently required on a large scale to meet the global demand (Ghaebi et al., 2020; Kis et al., 2021; Liang et al., 2020; Mara et al., 2021). The urgent need for a vaccine against Covid-19 led to a rapid development pace compared to previous vaccines (Defendi et al., 2021; Kyriakidis et al., 2021; Sparrow et al., 2021; Tregoning et al., 2020; Ura et al., 2020). Belete (2021) estimated the development period of a vaccine against Covid-19 to be approximately 15 to 18 months, while Sparrow et al. (2021) and Kyriakidis et al. (2021) estimated a time period of 12 to 18 months. In contrast, conventional vaccine development could take up to 10 – 15 years (Silveira et al., 2021). The rapid development process for Covid-19 vaccines can be ascribed to significant advances that have been made in vaccine technologies and platforms (Belete, 2021).

A variety of different vaccine platforms have been used in the attempt to develop an effective vaccine for Covid-19 (Belete, 2021; Knezevic et al., 2021; Kyriakidis et al., 2021; Liang et al., 2020; Mahmood et al., 2021; Zhou et al., 2020). According to the WHO, prior to the 18^{th} of February 2021, seven different vaccines were accepted for manufacturing and distribution (World Health Organisation, 2021), including Pfizer/BioTNech and Moderna's mRNA-based vaccines (Prüβ, 2021). At this same date, more than 200 other Covid-19 vaccines were in the development and testing phases (World Health Organisation, 2021).

Due to the unconventional fast development process of the Covid-19 vaccines, some vaccines applying for approval may not be licensed for full-scale manufacturing and distribution (Kis et al., 2021). The pathogen of the virus is not entirely understood, and new and more effective vaccines may be required over time. New emerging virus strands may also require a new vaccine formulation (Brisse et al., 2020; Kis et al., 2021). Some vaccine platforms may also require the construction of additional manufacturing facilities if the current facilities have insufficient capacity to produce the necessary quantities (McDonnell et al., 2020; Zhou et al., 2020). To meet the global demand, it may be required that a variety of vaccines, with different formulations and requiring different manufacturing methods, be produced (McDonnell et al.,

2020). Consequently, various production lines and manufacturing facilities may be required to manufacture a variety of vaccines (McDonnell et al., 2020).

1.1.4 Flexible manufacturing

Flexibility can be added to a manufacturing system to allow the system to cope with uncertainty in the demand for products (Chen et al., 1992; Gupta & Buzacott, 1989; Jain et al., 2013; Shang & Sueyoshi, 1995). Increasing the flexibility, however, requires capital investment (Chandra et al., 2005; Gupta & Goyal, 1989; Jordan & Graves, 1995; Sethi & Sethi, 1990; Shang & Sueyoshi, 1995; Slack, 1988; Yang et al., 2016). Capital costs include the purchasing of multi-purpose machinery and other manufacturing equipment (Olhager, 1993). Consequently, expending capital to add flexibility to a manufacturing system can only be justified if the flexibility is associated with benefits that justify the investment, for example, if flexibility increases the overall profitability of operations (Olhager, 1993).

Process flexibility considers the configuration of products at certain production lines or manufacturing facilities (Browne et al., 1984). Full process flexibility is defined as the ability to produce every product at every production line or manufacturing facility (Chou et al., 2011; Jordan & Graves, 1995; Simchi-Levi & Wei, 2012). Although full flexibility provides the optimal benefits for a manufacturing system, having a fully flexible system is generally an unjustifiable expense (Chou et al., 2010; Simchi-Levi & Wei, 2012; Wang et al., 2019). On the other hand, having no flexibility can result in significant losses due to unfilled demand (Simchi-Levi & Wei, 2012; Wang et al., 2019; Yang et al., 2016). Jordan & Graves (1995) propose that only a limited degree of flexibility is required to achieve benefits similar to full flexibility for the manufacturing process. Chou et al. (2010), Shi et al. (2019),Wang et al. (2019), and Yang et al. (2016) agree that a limited degree of flexibility can create an effective response against uncertainty. In applying only a limited degree of flexibility, a trade-off can be made between the benefits of flexibility and the added expense associated with increased flexibility (Benjaafar, 1994). Benjaafar (1994) suggest that the trade-off can be evaluated by comparing the benefits of flexibility with the increase in cost to determine an appropriate degree of flexibility. The degree of manufacturing flexibility that achieves favourable performance will be the point after which the increase in the system's performance, for added flexibility, is minimal (Jordan & Graves, 1995). Adding more flexibility will result in an unnecessary increase in investment costs (Olhager, 1993).

Jiao et al. (2007) considered the cost of adding flexibility to the manufacturing process and developed a model to assess the optimal trade-off between the cost and benefits of increased flexibility. From the study, it was observed that increased flexibility provided benefits in variable manufacturing systems (Jiao et al., 2007). The high cost associated with increased flexibility was less significant for high product variety and uncertainty scenarios since the increased flexibility led to profitable operations (Jiao et al., 2007). However,

adding flexibility to a manufacturing system with little product variety or uncertainty did not justify the cost of increasing flexibility (Jiao et al., 2007). De Groote (1994) agrees that flexibility becomes beneficial for a diverse manufacturing system.

Quantitative modelling can be used to predict the behaviour of a manufacturing system under different conditions and to evaluate the trade-off between flexibility and cost (Chang, 2012). Different quantitative modelling approaches have been used in literature to model manufacturing systems, as discussed in the reviews written by Beach et al. (2000), Jain et al. (2013), and Sethi & Sethi (1990). An influential article in modelling limited process flexibility for a manufacturing system is that of Jordan & Graves (1995). Jordan & Graves (1995) evaluate the benefits of limited flexibility against that of full flexibility by deriving a model to predict the probability that the shortfall of demand for a manufacturing facility with limited flexibility will be greater than the shortfall of demand for a manufacturing system with full flexibility. The results showed that limited flexibility, and specifically a so-called *long-chain configuration* (described in more detail in subsequent chapters), can have similar benefits to full flexibility, given that the flexibility is configured appropriately and that the level of demand uncertainty is not excessively high (Jordan & Graves, 1995).

A variety of factors would jointly contribute to the feasibility of incorporating process flexibility into the manufacturing of active drug substances, including: technical considerations that relate to the manufacturing process, regulatory considerations, and financial considerations. Single-use equipment has been designed to allow flexibility in the manufacturing of products and some facilities that utilise single-use equipment do currently employ process flexibility (Rogge et al., 2015). In contrast, no instances of stainless-steel facilities that implement process flexibility have been uncovered in this study. Stainless-steel equipment is typically designed to be dedicated to manufacturing a single product (Rogge et al., 2015).

1.1.5 Process flexibility and vaccine manufacturing

Jack & Powers (2004) developed a framework based on strategies of flexibility that are applied in the healthcare sector. The flexibility allows the healthcare sector to better respond to the demands of patients and improve the utilisation of resources (Jack & Powers, 2004). Having flexibility in the healthcare sector can contribute to maintaining the well-being of patients and preventing deaths (Jack & Powers, 2004).

During the early phases of the Covid-19 pandemic, the manufacturing system of Covid-19 vaccines was highly uncertain, and a possibility existed that a variety of vaccines would be made available to the market at an unknown future date. It is reasonable to assume that, in spite of the uncertainty, there was a desire to start preparing manufacturing capacity for Covid-19 vaccines with a view to making these available for wide-spread use as soon as possible. This represents an instance where adding process flexibility to the vaccine manufacturing system could offer benefits in terms of overcoming uncertainty that is present in the manufacturing system. Another example of an instance where process flexibility can be beneficial to

overcome uncertainty within a vaccine manufacturing system is for the manufacturing of products with demand that fluctuates in response to epidemiological outbreaks.

In the derivation of their model, Jordan & Graves (1995) assumed that the demand uncertainty was relatively stable, as has been briefly mentioned before. When the manufacturing of vaccines for Covid-19 is considered, the uncertainty regarding the successful development of vaccines from the different vaccine platforms greatly adds to the demand uncertainty already associated with a vaccine manufacturing system. This may result in the realistic range of demand uncertainty for the manufacturing system, as described by Jordan & Graves (1995), being exceeded. If this is the case, Jordan & Graves's conclusion on the favourable performance of a long-chain network, may no longer hold true.

1.2 Problem statement and research questions

The Covid-19 pandemic caused significant disruption globally (Ita, 2021; Prüβ, 2021), and consequently a search for an effective vaccine against Covid-19 was urgently launched (Defendi et al., 2021). Several factors contribute to the uncertain environment of the Covid-19 vaccine manufacturing system (McDonnell et al., 2020). Different degrees of process flexibility can be added to the manufacturing system with a view to overcoming some of the negative impacts of the manufacturing system's uncertainty. However, depending on the degree of process flexibility incorporated, increasing capital costs are required. The main research question that is considered in this study is as follows: Can process flexibility reduce the negative impact of the high demand uncertainty in the Covid-19 vaccine manufacturing system, caused by the uncertainty associated with the approval of vaccine products, to increase the throughput?

The system considered in this research is a theoretical system in which process flexibility is incorporated for the Covid-19 vaccine manufacturing. Both stainless-steel and single-use equipment are considered for the manufacturing system. The Covid-19 vaccine manufacturing system is faced with unprecedented high demand uncertainty. An important process flexibility configuration discovered by Jordan & Graves (1995) is the long chain configuration. Jordan & Graves (1995) observed that this configuration performs similarly to a full flexibility configuration for systems with low demand uncertainty. The long chain may prove to be significantly less effective for the high demand uncertainty associated with the Covid-19 vaccine manufacturing system.

The sub-research questions considered in this study are:

1. How does the performance, measured in terms of throughput and operating cost, of the long chain configuration compare to the no flexibility configuration and to the full flexibility configuration, for the Covid-19 vaccine manufacturing instance being considered?

2. How does the performance, measured in terms of throughput and operating cost, of different equipment facility options (mentioned in Subsection 1.1.2), compare across different process flexibility degrees for the Covid-19 vaccine manufacturing instance being considered?

1.3 Aims and objectives

The study's aim is three-fold. First, it aims to investigate whether process flexibility can reduce the negative impact of high demand uncertainty on the Covid-19 vaccine manufacturing system's throughput and operating cost. Second, if process flexibility does prove to be beneficial, the study aims to investigate whether the long chain configuration, as defined by Jordan & Graves (1995), provides similar results as a full flexibility configuration. Third, the study aims to gain insights into the likely performance of manufacturing networks that incorporate different equipment options. To achieve the aim, the following objectives are defined:

1. Perform a literature review on the following topics:
    - Vaccine manufacturing: with a view to gain insight on the feasibility of incorporating process flexibility in a vaccine manufacturing system;
    - Manufacturing flexibility: with a view to understanding the principles of incorporating process flexibility in a manufacturing system; and
    - Modelling manufacturing systems: with a view to guide the selection of a modelling approach for this research by considering models used in literature.
2. Define the the Covid-19 vaccine manufacturing system in terms of its elements;
3. Develop a quantitative model that represents the operation of a Covid-19 vaccine manufacturing system with process flexibility;
4. Verify the model developed in Objective 3 by performing a series of model execution tests and make corrections and adjustments to the model based on the verification results;
5. Validate the model developed in Objective 3 with a view to ensuring that the model incorporates an accurate understanding of vaccine manufacturing by interviewing subject matter experts;
6. Refine the model based on the validation results and repeat the verification process, where required;
7. Derive a set of manufacturing data that can be used as input to the modelling of the Covid-19 active drug substance manufacturing system. Run the model using the aforementioned data and determine the number of replications of each scenario that will be run. Run the required number of replications

and use the data that is generated to evaluate scenarios with different degrees of process flexibility and different types of equipment facilities included in the manufacturing system;

8. Make recommendations regarding the implementation of flexibility in the manufacturing system of Covid-19 vaccines.

1.4 Research approach and methodology

The philosophical perspective that is employed in a research study, influences the research approach that is formulated. Consequently, the philosophical perspective that is employed in this study is briefly reflected on in Subsection 1.4.1 . Next, the approach that is employed in the study is outlined in Subsection 1.4.2. Finally, specific aspects of the approach are discussed in more detail. The research approach evolved, and was adjusted, as the understanding of the problem developed. Thus, though the use of discrete-event simulation to model the manufacturing system is described in Subsection 1.4.4, the decision to employ a discrete-event simulation modelling approach was only made based on detailed literature reviews that are presented in subsequent chapters.

1.4.1 Philosophical perspective

Three prominent epistemological perspectives are briefly described, followed by a reflection on the perspective employed in this research.

The focus of the positivism research approach is that knowledge must solely be based on science (Bryman et al., 2016). The research approach only considers facts and all data must be measurable (Bryman et al., 2016). The realism research approach acknowledges that the perceived world (e.g. through observation and measurements) may differ from the real world (Bryman et al., 2016). Two forms of this approach exist, namely: empirical and critical (Bryman et al., 2016). Empirical realism states that all aspects of the real world can be understood (Bryman et al., 2016). The critical realism rather states that all aspects of the real world cannot be observed and the unobserved aspects influence the perceived world (Bryman et al., 2016). The interpretivism research approach contrast with the positivism approach by incorporating subjective perspectives into research. The approach is mainly focused on qualitative analysis (Bryman et al., 2016).

The epistemological perspective that is employed in this research is the critical realism research approach. The research is mainly based on science and facts, it however, will include the opinions of subject matter experts with knowledge in the desired fields. It is also acknowledged that all aspects of the real-world cannot be understood and measured by this research.

1.4.2 Research approach

The research approach followed in this study is as follows:

1. Review literature related to:
   (a) vaccine manufacturing;
   (b) the state of Covid-19 vaccine development and manufacturing;
   (c) flexibility in manufacturing systems;
   (d) economic considerations of manufacturing systems;
   (e) measurement approaches for flexibility in manufacturing systems; and
   (f) modelling approaches used to represent flexible manufacturing systems.
2. Analyse the vaccine manufacturing process to define the elements of the Covid-19 vaccine manufacturing system.
3. Select an appropriate modelling approach which can be used to represent the vaccine manufacturing system at the level that would be required to evaluate the impact of process flexibility, based on the elements of the system, as identified in Step 2.
4. Design and develop a model to adequately represent the vaccine manufacturing system with process flexibility which also takes the factors of uncertainty into account. Verify and refine this model.
5. Interview experts on vaccine manufacturing and process flexibility to gather information with which the model can be validated. Improve the model developed in Step 4 based on validation results and repeat elements of the verification process, as required.
6. Use the model developed in Step 4 to assess the impact of different process flexibility configurations on the vaccine manufacturing system by performing multiple replications of each scenario.
7. Rank the different process flexibility configurations according to the system's performance.
8. Make recommendations on incorporating process flexibility into the manufacturing of vaccine active drug substances with a view to alleviating some of the impacts of high demand uncertainty.

1.4.3 Literature review and analysis of vaccine manufacturing process

The documents used for the review of literature will be obtained by performing several searches in databases, such as Scopus and Web of Science. Relevant documents will be obtained from these databases by applying different approaches (e.g. general searches and structured reviews). To ensure that articles published in highly rated journals are included in the review, relevant journals will be identified from the Scimago Journal and Country Rank (SJR) site. A specific search will also be conducted to identify articles from these journals in the chosen databases.

The qualitative data analysis software Atlas.ti (Atlas.ti (2022)) will be utilised to extract data from the documents obtained during the searches in the databases. The extracted data will be grouped according to topics using the coding function in Atlas.ti.

1.4.4 Model development

The manufacturing system of Covid-19 vaccines will be represented as a discrete-event simulation model via the simulation software Tecnomatix Plant Simulation (TPS) (Siemens (2022)). This step will result in a preliminary model, which will be adjusted through the process of verification and validation, as explained in Subsection 1.4.5, before it will be used to run different process flexibility configurations for the system to evaluate the impact of process flexibility on the system.

1.4.5 Model verification and validation

The model, developed as described in Subsection 1.4.4, will be verified and validated via two separate steps. The verification of the model will be executed internally by performing several tests on the model in the TPS software. Each section of the model will first be verified separately, whereafter, the entire model will be verified. Different scenarios will be simulated via manual manipulation for each model section. The output for each scenario will be known and can be used to compare and verify the model results. The model will also be allowed to operate without any manipulation to ensure that all aspects of the model function as expected. The results from the verification step will be used to adjust the model until all results are as expected.

Validation of the model will be executed after the internal verification process has been completed. The validation process will consist of interviews with subject matter experts in fields such as vaccine manufacturing and development and/or implementing process flexibility in manufacturing systems. The interviews will be conducted to obtain insight into the vaccine manufacturing process, vaccine approval, and considerations for implementing process flexibility in a manufacturing system. The feedback from the expert participants will firstly be used to validate that the assumptions derived and approaches applied to develop the model are appropriate. Furthermore, the feedback from the expert participants will be used to

validate that the model is a realistic representation of the real system and to guide any improvements to the model.

The interviews will be conducted in a semi-structured format, using an interview guide that will be made available to the expert participants prior to the interview.

1.4.6 Scenario execution and analysis

The scenario analysis step will be performed once the model has been verified and validated. Data will be collected by performing runs in the TPS software of different process flexibility configurations and equipment facilities. Each process flexibility configuration will be executed a number of times to accurately represent the impact of a specific configuration. The results from the runs will be used to assess the effect of process flexibility on the manufacturing system of Covid-19 vaccines.

1.5 Ethical considerations

Ethical clearance for this research was received through the Stellenbosch University's Research Ethics Committee. The main ethical considerations for this study relate to the interviewing of subject matter experts as part of the validation process and include:

- An interviewee is allowed to withdraw from the research at any given time. In such an event, all the information relating to the interviewee will be discarded, with no information incorporated into the research and all written or recorded data destroyed; and
- Interviewees provide inputs to the research in their personal capacity, and not as representatives of specific organisations with whom they may be (or have been) affiliated.

1.6 Research boundaries and limitations

According to Pori (2011), the vaccine manufacturing process is divided into an upstream and a downstream section. The upstream section involves the manufacturing of the bulk product, while the downstream section involves the formulation, filling, and finishing of the final product (Pori, 2011). For this study, only the bulk product manufacturing will be considered.

According to Jordan & Graves (1995), the process flexibility that can be added to a system depends on factors such as the number of products considered, the available facilities, the manufacturing capacity of each facility, and the demand and uncertainty in the manufacturing system. The study is limited in that it only considers adding process flexibility to the manufacturing system of Covid-19 vaccine products.

The uncertainty that the manufacturing system may face can either be internal or external (Chen et al., 1992; Chryssolouris, 1996; Gupta & Goyal, 1989; Wahab & Stoyan, 2008). Internal uncertainties include equipment failure, delays in manufacturing and resource shortages (Chryssolouris, 1996; Gupta & Goyal, 1989; Sethi & Sethi, 1990). Uncertainty in the demand for products, price of the input materials and/or the availability of the input materials are all external uncertainties (Chryssolouris, 1996; Gupta & Goyal, 1989; Sethi & Sethi, 1990). In this study, only the uncertainty in the demand for products will be considered since it is seen as one of the primary sources of uncertainty for manufacturing systems (Gupta & Goyal, 1989; Jain et al., 2013; Kemmoe et al., 2014; Wang et al., 2019). Furthermore, in this research the uncertainty in the demand for products is limited to considering the uncertainty linked to the regulatory approval of vaccine products for Covid-19. The approval of vaccines determines which products are available to the market and consequently impacts the demand for products. Uncertainty in the demand for products linked to all other contributing factors are excluded for this study. Contributing factors may include: epidemiological outbreaks, changes in the vaccine market, discovery of a new disease variant, and demographic changes.

This study considers a theoretical problem to determine the potential impact of process flexibility on the Covid-19 vaccine manufacturing system. Many of the flexible manufacturing networks that are modelled do not exist in reality, and consequently data on the construction of vaccine manufacturing facilities with process flexibility is not available for all the considered equipment facility options. Capital costs for vaccine manufacturing facilities are thus excluded for this study. The impact of process flexibility on the cost associated with facility operation and vaccine product manufacturing is, however, considered.

1.7 Expected contributions

The outcome of the study is expected to contribute to literature on flexible manufacturing, especially in the health care sector. Based on a systematic literature review presented in Chapter 4, no study was uncovered that considered incorporating process flexibility into a vaccine manufacturing system. Though the research specifically considers the case of Covid-19 vaccine manufacturing, some of the findings, for example on the performance of manufacturing networks that incorporate different types of equipment, are applicable to vaccine manufacturing in general. Furthermore, other instances of high demand uncertainty in vaccine manufacturing also exist, including where demand for a vaccine product increases and decreases in line with epidemic outbreaks, the findings of this research are therefore expected to also provide insights on designing resilient vaccine manufacturing networks in a more general sense.

Current research on process flexibility considers relatively low demand uncertainty for products. This research contributes to the process flexibility literature in that it considers the impact of a high level of demand uncertainty. More specifically, it evaluates the performance of two different flexibility configurations in mitigating the impact of the high demand uncertainty associated with the approval of Covid-19 vaccine

products on the manufacturing system. The performance of the long-chain configuration, relative to a full flexibility configuration, under the high demand uncertainty conditions, is expected to be of particular interest.

No instances were uncovered of stainless-steel equipment facilities that incorporates process flexibility. This research will contribute in that it provides insight into the expected benefits of incorporating process flexibility into stainless-steel equipment facilities. In turn, this can inform decisions on whether to dedicate resources to further investigating the feasibility of developing flexible stainless-steel equipment facilities.

1.8 Report structure and outline

Chapter 1 served as an introduction to the study by simultaneously providing background information and the proposed approach to achieving the study's aim. This is achieved via the problem statement, objectives, research methodology, limitations for the research and expected contributions.

An overview of literature on vaccine manufacturing is provided in Chapter 2. A more detailed description of the manufacturing procedure for each vaccine platform will be provided, along with the benefits and drawbacks for each platform. Chapter 3 contains an overview of manufacturing flexibility. The definitions and classifications as found in literature is provided and discussed. Different perspectives of adding flexibility is mentioned and different authors' approaches for each of these perspectives will be discussed. Flexibility measurements, along with the benefits of flexibility, is mentioned.

Chapter 4 contains a high level discussion on modelling approaches that can be used to model a system, along with examples of models used by authors in previous studies. The selection process for the appropriate model to represent the vaccine manufacturing system, will be provided.

The model is developed in Chapter 5, with a discussion of the verification and validation process in Chapter 6. The results obtained from the model will be presented, analysed and discussed in Chapter 7. A summary of the conclusions for the study along with recommendations will be provided in Chapter 8.

1.9 Conclusion: Chapter 1

The chapter provided an introduction for the remainder of this study. Information regarding the need for Covid-19 vaccines and the uncertain environment that the Covid-19 vaccine manufacturing is faced with were provided. Adding flexibility to the manufacturing system as a solution to overcome the uncertainty, was discussed. It was identified that specifically process flexibility can potentially impact the performance of a system with demand uncertainty. The problem statement, research aims and objectives, along with the proposed research methodology, were provided. The boundaries of the study were defined. Finally, the

proposed structure outline of the report is presented. The next chapter contains a discussion of vaccine manufacturing.

Chapter 2

Vaccine Manufacturing

Chapter 1 provided an introduction to the need for flexibility in the manufacturing of Covid-19 vaccines to reduce the impact of the pandemic. This chapter provides a discussion of the manufacturing process for vaccines. First, an overview of the manufacturing system and main manufacturing steps for vaccine products is provided. This is followed by a high-level description of six vaccine platforms, accompanied by process flow diagrams. An overview of equipment facility options for vaccine manufacturing is provided. Lastly, the state of vaccine development for April 2021 and October 2022 is provided.

2.1 Overview

The manufacturing of vaccines is a complex process (Borriello et al., 2021) and is divided into upstream and downstream sections (Pori, 2011). The upstream section generally includes the manufacturing and harvesting of the antigen, while the downstream section includes the purification of the antigen, and the formulation, filling, and finishing of the final product (Pori, 2011). As described in the previous chapter, this research focuses specifically on the manufacturing of the active drug substance, which includes manufacturing and harvesting of the antigen as well as the purification of the antigen.

In addition to the various specialised processing steps, the manufacturing process is also susceptible to the conditions in the manufacturing system (Plotkin et al., 2017). The manufacturing process and the final product must conform to strict regulatory requirements. Any changes in the processing steps or the environmental conditions can cause these requirements not to be met (Plotkin et al., 2017).

2.2 Vaccine platforms

As mentioned in Section 1.1, several different antigen production systems and associated platforms exist, each with unique manufacturing steps (Bos et al., 2020; McDonnell et al., 2020). Examples of antigen

production systems include cell-based, bacterial, plant-based, and egg-based. Specific platforms are associated with specific antigen production systems, although some platforms are associated with more than one production system.

Six vaccine platforms are considered in this study, namely:

1. Live attenuated virus vaccine (LAV);
2. Inactivated virus vaccine (IV);
3. Viral vector (VV);
4. Subunit protein vaccine (SP);
5. DNA vaccine; and
6. RNA vaccine.

These six platforms are considered as they were used in the probability of success modeling study of Covid-19 vaccine platforms performed by McDonnell et al. (2020). They are also frequently referred to in other literature, including: Belete (2021); Kyriakidis et al. (2021); Mahalingam et al. (2020); Zhao et al. (2020).

According to Plotkin et al. (2017), the different vaccine platforms may require similar equipment, such as bio-reactors and purification equipment. Still, the order of the processing steps and equipment used for finishing the product generally differ. Before proceeding with the research, it is prudent to obtain insight into the extent to which the manufacturing processes of the different platforms have some commonalities. Although this does not provide a conclusive indication that it would be feasible to construct flexible manufacturing facilities that have the ability to switch manufacturing between these platforms, it does give an indication of whether this might be feasible in theory. Obtaining an overview of the different manufacturing steps also provides background information on the manufacturing of active drug substances to contextualise the research.

Literature on the manufacturing of the different vaccine platforms was analysed to obtain information regarding the manufacturing process for each vaccine platform. The information gathered from the literature was used to draw up preliminary process flow diagrams for the aforementioned six vaccine platforms. The process flows contain information on the processing steps, the equipment used at each step, and the specific process name of each step. Advantages and drawbacks of each platform were also considered. Limited literature on the manufacturing of the different vaccine platforms is available, and the preliminary process flow diagrams had several incomplete sections. The process flows were subsequently verified through interviews with subject matter experts, and were updated based on the feedback received. The verification process is described in detail in Chapter 6.

For the sake of brevity, only the live attenuated virus vaccine platform's manufacturing process is discussed in the main document (refer to Section 2.2.1). Similar discussions for the other five platforms are provided in Appendix A.

2.2.1 Live attenuated virus vaccine manufacturing process

The process flow diagram depicting the manufacturing processing steps for the live attenuated virus vaccine is shown in Figure 2.1. The manufacturing of live attenuated virus vaccines entails the manufacturing of live viruses which are weakened prior to the formulation of the vaccine (Kyriakidis et al., 2021; Tregoning et al., 2020). Although the development process for this vaccine platform is time consuming, the cost of large-scale manufacturing is relatively low (Kyriakidis et al., 2021; Mahalingam et al., 2020; Tregoning et al., 2020).

Virus seeds are used to infect micro-organisms or mammalian cells, which have previously been amplified in seed bioreactors (Chin et al., 2021; Gomez & Robinson, 2013; McDonnell et al., 2020). The virus propagates as the infected cells are allowed to replicate on cell lines in micro-cultures (Chin et al., 2021; Kyriakidis et al., 2021; McDonnell et al., 2020). The fluid containing the virus is harvested from the cells via centrifugation (Gomez & Robinson, 2013; Josefsberg & Buckland, 2012; McDonnell et al., 2020). Cell lysis may be required for intra-cellular viruses (Josefsberg & Buckland, 2012; McDonnell et al., 2020). The harvested virus may be clarified and purified using filtration, buffer exchange and chromatography (Chin et al., 2021; McDonnell et al., 2020; Pori, 2011). The drug substance is stored in bulk before it is processed further (McDonnell et al., 2020).

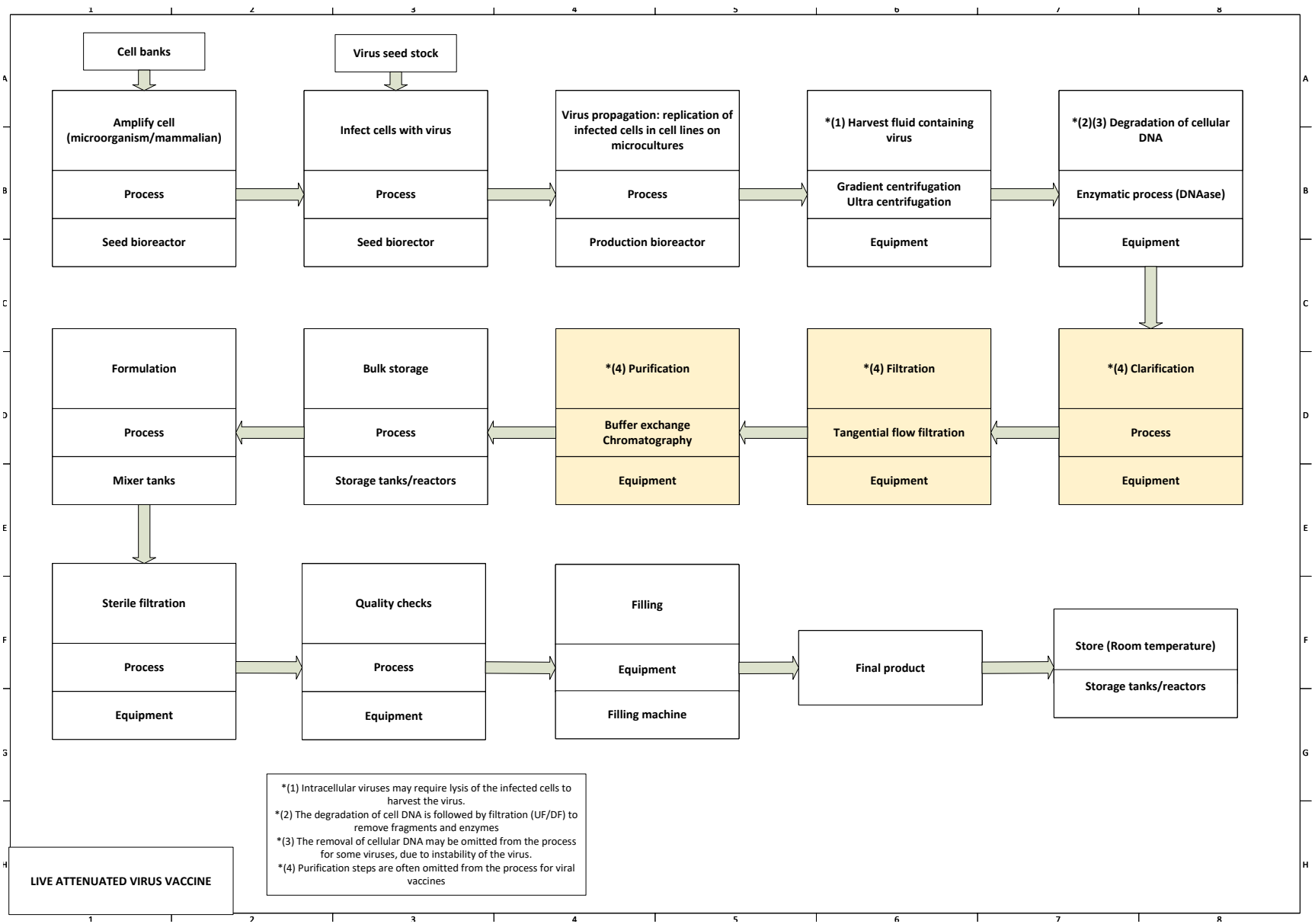

Figure 2.1: Manufacturing process for the live attenuated virus vaccine

The drug substance is formulated in mixers (Gomez & Robinson, 2013; McDonnell et al., 2020). It is then filtered to ensure high sterility before quality checks are performed to ensure that regulations are met (Silveira et al., 2021). Filling and finishing of the final product are completed, after which the final product is stored at approximately -80°C until distribution (Chin et al., 2021; Gomez & Robinson, 2013; McDonnell et al., 2020).

The advantages and drawbacks of the live attenuated virus vaccine platform are presented in Table 2.1.

Table 2.1: Advantages and drawbacks of the live attenuated virus vaccine platform (adapted from McDonnell et al. (2020))

Advantages	**Drawbacks**
Well-established method	Timely development
Success with previous vaccines	Can revert back to pathogenic form
Induces a strong and long-lasting immune response	Can cause infection in the pathogenic form
Available large-scale manufacturing capacity	Not suited for immuno-compromised patients
Requires no adjuvants	Timely safety evaluation
Requires only a single dose	Risk for vaccine-enhanced disease
Low-cost manufacturing	Requires refrigeration

2.2.2 Commonalities in vaccine platform manufacturing processes

The upstream sections of the live attenuated virus, inactivated virus, and viral vector vaccine platforms are almost identical. An unique step for the inactivated virus vaccine is the inactivation step performed via heat or chemical treatments, refer to Appendix A.1. The viral vector vaccine platform is produced using a foreign non-pathogenic virus as a vector rather than the target virus, refer to Appendix A.2.

The manufacturing processes for the subunit protein, DNA, RNA, and viral vector vaccine platforms all involve genetically engineered plasmid DNA, refer to Appendix A. For the viral vector platform, the DNA plasmid is inserted into micro-organisms or mammalian cells. For both the DNA and subunit protein platforms, the plasmid DNA may be inserted into bacterial cells (e.g. *E.coli*), after which the bacterial cells are amplified. The plasmid DNA for the subunit protein platform may also be inserted in mammalian cells, which makes its manufacturing requirements more similar to that of the live attenuated virus, inactivated virus, and viral vector vaccine platforms. The DNA plasmid is linearised and used for the enzymatic transcription in the RNA vaccine platform's manufacturing process.

Based on an analysis of the process flows, it is reasonable to conclude that it may be feasible to create a manufacturing system that manages to incorporate flexibility between the live attenuated virus, inactivated

virus, and viral vector platforms in a manner that is financially feasible, given the extent of similarities in the process flows. Using the same logic, it may furthermore be feasible to incorporate the manufacturing of the subunit protein platform into this flexible manufacturing system for the case where the DNA plasmid is inserted into mammalian cells.

Finally, based on the same reasoning, another theoretically feasible manufacturing system would be one that incorporates flexibility in the manufacturing of the DNA and subunit protein platforms for the case where the DNA plasmid is inserted into bacterial cells.

2.2.3 Equipment facility options

Two types of equipment exist for the manufacturing of vaccine products (Nivsarkar, H., 2022; Rogge et al., 2015). According to Nivsarkar, H. (2022) and Rogge et al. (2015), manufacturing facilities can be equipped with one of three equipment options, namely: single-use, stainless-steel, and a combination of stainless-steel and single-use equipment.

Single-use equipment is predominantly employed by contract developers and manufacturers (Rogge et al., 2015). Contract manufacturers require the ability to manufacture a variety of products which are not necessarily from the same platform (Rogge et al., 2015). This requires a flexible manufacturing facility design, which is made possible with single-use equipment (Nivsarkar, H., 2022; Rogge et al., 2015). This significantly reduces the risk for cross-contamination between batches (Rogge et al., 2015). Stainless-steel equipment is very restricted in terms of the manufacturing flexibility that it allows (Nivsarkar, H., 2022; Rogge et al., 2015). The stainless-steel facilities generally have dedicated designs (Rogge et al., 2015).

Stainless-steel equipment require intensive cleaning between the manufacturing of products (Nivsarkar, H., 2022). This is eliminated for the single-use equipment via disposable equipment that is replaced between each batch (Rogge et al., 2015). Single-use equipment thus allows for a quicker change-over between the manufacturing of products compared to the stainless-steel equipment (Rogge et al., 2015). Stainless-steel equipment, however, allows for significantly larger scale operation (Nivsarkar, H., 2022; Rogge et al., 2015). The maximum stainless-steel bioreactor capacity is 20 000 L, while the capacity for single-use equipment bioreactors can only reach a maximum of 5 000 L (Nivsarkar, H., 2022).

Single-use equipment is associated with lower capital costs and increased operating costs (Rogge et al., 2015). The increased operating costs is ascribed to the replacement of the disposable equipment between batches (Rogge et al., 2015).

Currently, stainless-steel equipment is predominant in industry with approximately 90% of pharmaceutical facilities employing it (Nivsarkar, H., 2022). Both Nivsarkar, H. (2022) and Rogge et al. (2015) mention that facilities employing a combination of the two equipment types are becoming more prevalent.

2.2.4 Vaccine platforms for Covid-19

As mentioned in Subsection 1.1.3, various vaccine platforms are used to develop a Covid-19 vaccine (Ita, 2021). The WHO records all the vaccines entering pre-clinical and clinical trials (World Health Organization, 2021a) as well as all approved vaccines. Table 2.2 shows the number of Covid-19 vaccine products of each platform, recorded by the WHO on 20 April 2021, in either the pre-clinical or the clinical trials. The table further shows the number of approved Covid-19 vaccine products of each platform as recorded by the Covid-19 vaccine tracker on 04 October 2022. Various observations can be made based on the data presented in the table. The ratio of the total number of approved vaccines to those in pre-clinical or clinical phases after a period of 18 months is approximately 1:6. Furthermore, variation in this ratio across different platforms can also be observed, e.g. the ratio is particularly high for inactivated virus vaccines and particularly low for DNA vaccines. Drawing specific conclusions on the success rate of vaccine research and development or on the suitability of different platforms for vaccines that target different pathogens, is beyond the scope of this research; these observations do, however, give an indication of the uncertainty that is inherent to the research and development process for vaccines, and that is conceptualised as a form of demand uncertainty when considering the design of manufacturing networks in this research.

Table 2.2: State of Covid-19 vaccine development and approval April 2021 and October 2022 (adapted from World Health Organization (2021a))

Vaccine platforms	Number of candidates in pre-clinical phase April 2021	Number of candidates in clinical phase April 2021	Number of candidates approved October 2022
Live attenuated virus	4	2	0
Inactivated virus	10	13	11
Protein subunit	70	29	17
Virus-like particles [1]	17	5	1
Viral vector (NR) [2]	22	15	9
Viral vector (R) [3]	20	6	0
DNA	16	10	1
RNA	24	13	8
Cellular based [4]	1	0	0
Total	184	93	47

Notes:

[1] Virus-like particles are included in the subunit protein platform, refer to Appendix A.3.

[2] *NR* refers to the use of a non-replicating viral vector, refer to Appendix A.2.

[3] *R* refers to the use of a replicating viral vector, refer to Appendix A.2.

[4] The cellular-based vaccine platform employs "engineered human mesenchymal stem cells" (Liu et al., 2022) and is not included in one of the six platforms that are focussed on in this research.

2.3 Conclusion: Chapter 2

This chapter provided a detailed description of the manufacturing processes, as well as the benefits and drawbacks of the following vaccine platforms: LAV, IV, SP, VV, DNA, and RNA. Process flow diagrams for the manufacturing of each of these vaccine platforms have been developed and verified via interviews with SMEs. From the manufacturing process descriptions and diagrams, it was identified that the following two platforms combinations may potentially be feasible for the incorporation of process flexibility. The first combination include the live attenuated virus, inactivated virus, and viral vector platforms. The subunit protein platform can be included in this combination if mammalians cells are used. The second combination include the DNA platform and the subunit platform given that bacterial cells are used.

An overview of the equipment options for vaccine manufacturing facilities were provided. Finally, the state of Covid-19 vaccine development for April 2021 and October 2022 was provided. The next chapter will discuss manufacturing flexibility in a manufacturing system.

Chapter 3

Flexible Manufacturing

Chapter 2 provided a discussion of vaccine manufacturing, with the focus on the specific manufacturing processes for six vaccine platforms. In this chapter flexibility in the manufacturing environment is discussed by considering aspects such as: the classification of flexibility; different perspectives on adding process flexibility to a system; measurements of flexibility; and the benefits associated with flexibility. Finally, the elements that contribute to manufacturing costs are discussed.

3.1 Flexible manufacturing

As mentioned in Section 1.6, uncertainty in the demand for products is a significant concern for manufacturers (Gupta & Goyal, 1989; Jain et al., 2013; Kemmoe et al., 2014; Wang et al., 2019). Uncertainty in product demand can arise from various sources, including (Angkiriwang et al., 2014): a change in the number of customers; and changes to orders such as, adjustments to the required delivery dates or the type and/or quantity of products. In order to efficiently adapt to these changes, alterations to various manufacturing resources might be required (Sethi & Sethi, 1990). For example, achieving the changes might require (Co, 2001): adjusting the available manufacturing capacity; making use of different transportation modes; and/or adjusting the time required to change the manufacturing set-up. Thus, responding to changes in demand for products requires flexibility in manufacturing systems. Creating a flexible manufacturing system is a complex process, since it requires establishing several interactions between the resources in the system (Co, 2001).

3.1.1 Levels of flexibility

The term 'flexibility' has been defined and categorised in several ways within manufacturing literature. Various reviews have been conducted to obtain a coherent definition and classification structure for flexibility (Chang, 2012; Sethi & Sethi, 1990). A general definition for flexibility can be constructed as *the ability*

to adapt to changes in the manufacturing system (Chandra et al., 2005; Gerwin, 1993; Gregory et al., 2019; Gupta & Buzacott, 1989; Gupta & Goyal, 1989; Jordan & Graves, 1995; Ramasesh & Jayakumar, 1991; Sethi & Sethi, 1990). Chryssolouris et al. (1998) state that the changes should be able to occur quickly. Furthermore, Mishra et al. (2014) and Upton (1994) propose that the general definition be extended to include that *the ability to adapt should occur without requiring significant changes to cost, time, performance or set-up*.

A few authors have classified manufacturing flexibility into different *levels*. The classifications provided by Taymaz (1989), Sethi & Sethi (1990), and Koste & Malhotra (1999) are summarised and compared in Table 3.1.

Table 3.1: Classification of flexibility levels

Taymaz (1989)	**Sethi & Sethi (1990)**	**Koste & Malhora (1989)**
Component level Considers basic flexibilities for manufacturing components	**Component level** Considers basic flexibilities for manufacturing components	**Individual resource level** Considers flexibility of individual resources **Floor shop level** Considers flexibility associated with manufacturing
Operational level Considers integration of component level flexibilities	**System level** Considers flexibility built on component level flexibilities	**Plant level** Considers flexibility associated with manufacturing facilities
System level Considers overall manufacturing flexibility	**Aggregate level** Considers overall manufacturing flexibility	**Functional level** Considers overall manufacturing flexibility

As shown in Table 3.1, Taymaz (1989) and Sethi & Sethi (1990) each define three corresponding levels, though their use of the "system" label is contradicting. The labels as defined by Taymaz (1989) are referred to for the remainder of this study. At the component level, flexibility is defined in terms of each individual component of a product (Sethi & Sethi, 1990; Taymaz, 1989). In turn, the operational level flexibility is built on the component level flexibilities. Thus, for operational level flexibilities to be achieved in a manufacturing system, it is required that some degree of component level flexibility is also available (Jain et al., 2013). Finally, the overall manufacturing system's flexibility is considered at the system level (Taymaz, 1989). As shown in Table 3.1, Koste & Malhotra (1999) classify flexibility into four levels rather than three. Their individual and shop levels correspond to Taymaz (1989)'s component level; their plant level corresponds to Taymaz (1989)'s operational level; and their functional level corresponds to Taymaz (1989)'s systems level.

3.1.2 Categories of flexibility

Proceeding to a more granular classification, several different *categories* of flexibility in manufacturing have been defined in literature. A summary of the categories defined by the following authors is provided in Table 3.2: Browne et al. (1984); Sethi & Sethi (1990); Sawhney (2006); Chen et al. (1992); and Koste & Malhotra (1999). Both Sawhney (2006) and Chen et al. (1992) grouped the categories that are defined. Sawhney (2006) groups the categories of flexibility into three stages, namely: process flexibility stage, output flexibility stage and input flexibility stage. On the other hand, Chen et al. (1992)'s approach is to group the categories of flexibility into three overarching categories, namely: production flexibility, market flexibility and infrastructural flexibility.

The *categories* of flexibility in manufacturing, as depicted in Table 3.2, have also been mapped to the three *levels* of manufacturing flexibility as defined by Taymaz (1989) and Sethi & Sethi (1990). Some categories of flexibility (e.g. infrastructural flexibility) are not explicitly associated with a specific level, as shown in Table 3.2.

One category of flexibility that is defined by all the studies included in Table 3.2, is process flexibility. Process flexibility is viewed as an effective approach to overcoming some of the uncertainties associated with the demand for products, especially for systems with varying demands for the different products (Chou et al., 2010; Jordan & Graves, 1995; Shi et al., 2019; Wang et al., 2019; Yang et al., 2016). Each of the categories of flexibility included in Table 3.2 are reviewed in some detail. As process flexibility is the category of manufacturing flexibility that is relevant to this research, its description is included in the main document, while the descriptions of the remaining 17 categories of process flexibility are provided in Appendix B.

Table 3.2: Categories of flexibility

	Author				
	Browne et al. (1984)	Sethi & Sethi (1990)	Chen et al. (1992)	Koste & Malhotra (1999)	Sawhney (2006)
Component level	Machine Routing Operation	Machine Routing Operation Material handling	Machine Routing Material handling Manpower[2]	Machine Routing Operation Material handling Labour	Equipment[1] Routing Material handling Labour
Operations level	Process Product Volume Expansion	Process Product Volume Expansion	Process Product Volume Expansion Mix	Mix[3] Product Volume Expansion	Process New product Volume Expansion Mix
System level	Production	Production Program Market	Production Program Market		
			Infrastructural		Input quality Delivery Input Output

3.1.3 Process flexibility

As shown in Table 3.2, process flexibility is associated with the operational flexibility level. Various different definitions for process flexibility have been defined in previous literature. Broockman et al. (2021) define process flexibility as the system's ability to produce different products of the same set via different operational approaches. Products in the same set may require different materials but are similar in form and machine operations (Broockman et al., 2021; De Toni & Tonchia, 1998). Adding manufacturing flexibility to products in the same set may be more beneficial since it will require less change over time than products from different sets (Co, 2001). Sethi & Sethi (1990) similarly define process flexibility as the ability to produce other products of the same set without requiring significant changes to the manufacturing system.

Process flexibility is similarly defined as "job flexibility" by Buzacott (1982) and as "mix flexibility" by Gerwin (1982). Both Chandra et al. (2005) and Das & Nagendra (1993) refer to process flexibility as "product-mix" flexibility. A definition provided by Wang et al. (2019) is that process flexibility allows a fast response to rapidly changing demand without incurring a significant cost increase.

According to Jordan & Graves (1995), process flexibility is the ability to adjust the output volume of a product according to the requirements set by the market. Hua & He (2010)'s definition of process flexibility is slightly different from that of Jordan & Graves (1995), Sethi & Sethi (1990) and Browne et al. (1984), namely: the ability of a production line to manufacture different products simultaneously. The definition of Yang et al. (2016) is in agreement with that of Hua & He (2010). According to Hua & He (2010), the definition of process flexibility includes some aspects of product flexibility, defined by Chryssolouris (2013). Product flexibility is defined by Chryssolouris (2013) in Section B.6 as the ability to quickly and without incurring a significant cost increase change to the manufacturing of new products. In contrast, Beckman (1990), defines process flexibility as a measure that can deal with internal uncertainties, while product flexibility deals with product output volume and minimising the cost of shifting between different resources.

Both process and product flexibility are classified under the operational flexibility level (Chang, 2012). Having process and/or product flexibility reduces potential bottlenecks and delays in the manufacturing processes (Benjaafar, 1994). This role of both process and product flexibility in addressing bottlenecks in manufacturing processes as a whole supports Chang (2012)'s placement of both these categories of flexibility at the operational level.

Based on the definitions and perspectives from literature presented here, process flexibility can, in summary, be defined as the ability to shift the available manufacturing capacity of a manufacturing system between products without incurring significant cost increases or loss of time, to meet the changing demand for products. According to both Benjaafar (1994) and Browne et al. (1984), a system with process flexibility will require some degree of machine flexibility, defined in Appendix B.1.

3.1.4 Adding process flexibility to a system

Using its definition as a reference, process flexibility can be achieved in a manufacturing system by producing more than one product at a single production line or manufacturing facility and/or producing a single product at more than one production line or manufacturing facility (Jordan & Graves, 1995). The decision of which products should be produced at a specific production line or manufacturing facility accompanies the design of a process flexible manufacturing system (Jordan & Graves, 1995; Wang et al., 2019).

The manufacturing flexibility achieved for a manufacturing system falls within a flexibility spectrum, with no flexibility at the one end and full flexibility at the other end (Jordan & Graves, 1995; Shi et al., 2019). Between the two ends of the spectrum, various flexibility degrees can be achieved, each having a different product-plant configuration (Jordan & Graves, 1995; Shi et al., 2019).

Different perspectives on adding process flexibility to manufacturing systems are seen in literature. The process flexibility can either be added to the manufacturing system by only considering the operational level or by considering the operational and the component levels separately (Hua & He, 2010; Jordan & Graves, 1995). Process flexibility is added between different production lines and/or manufacturing facilities when only the operational level is considered (Jordan & Graves, 1995). When both the operational and component levels are considered, machine flexibility is considered at the production lines in addition to the process flexibility added to the system (Hua & He, 2010). The machine flexibility forms the basis on which the process flexibility can be added, and the flexibilities become integrated when the overall system flexibility is considered (Hua & He, 2010).

Jordan & Graves (1995), Shi et al. (2019), and Wang et al. (2019) are examples of authors adding process flexibility to manufacturing systems by only considering the operational level and the approach is discussed in Subsection 3.1.4.1. In the study of Hua & He (2010), process flexibility was added to manufacturing systems via the operational and component levels approach. The approach is further discussed in Subsection 3.1.4.2.

3.1.4.1 Operational-level perspective

Different approaches may be used to solve a process flexibility problem for a manufacturing system (Chou et al., 2008). The most well-known approach is that of chaining, first applied by Jordan & Graves (1995) in an attempt to solve the process flexibility configuration for a manufacturing system. From an operational-level perspective, the process of chaining is performed by adding links between products and manufacturing facilities to form chains (Jordan & Graves, 1995). An example of adding flexibility to create a chain is indicated in Figure 3.1. According to Jiao et al. (2007), the flexibility increases with each link that is added.

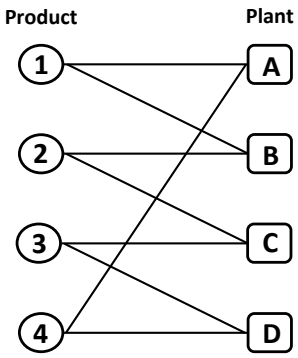

Figure 3.1: An example of product configuration to create a single chain (adapted from: Jordan & Graves (1995)).

Linking the products to create a longer chain increases the benefits and allows a better response to uncertainty (Jordan & Graves, 1995). The manufacturing of products can be shifted within the chain (Hua & He, 2010; Jordan & Graves, 1995; Shi et al., 2019). Consequently, products with high demand can utilise the available manufacturing capacity of products with lower demand (Hua & He, 2010; Kaminsky & Wang, 2019; Simchi-Levi & Wei, 2012). These products do not have to be directly connected to utilise the manufacturing capacities but merely form part of the same chain (Jordan & Graves, 1995). When considering a specific chain, only products in the chain can be produced by the manufacturing facilities in that chain, while no product in the chain can be produced by a manufacturing facility outside of the chain (Jordan & Graves, 1995). Iravani et al. (2005a) assumed that the manufacturing capacity of a production line and/or manufacturing facility can be completely shifted from one product to another when only the operational level is considered.

Different degrees of process flexibility are defined in Wang et al. (2019) and configurations of the degrees of flexibilities are shown in Figure 3.2.

Many authors including Jordan & Graves (1995), Shi et al. (2019), Wang et al. (2019), and Yang et al. (2016) studied the benefits of adding limited process flexibility to a manufacturing system via the process of chaining and found that chaining may provide an effective response to demand uncertainty. The chain allows shifting of product manufacturing between the available capacity in the chain and consequently improves the responsiveness to changes in demand (Jordan & Graves, 1995; Shi et al., 2019; Wang et al., 2019). Limitations to the benefits of chaining have, however, also been noticed. Yang et al. (2016) noticed that chaining may not provide optimal benefits for an unbalanced and asymmetric system, while Shi et al. (2019) and Simchi-Levi & Wei (2012) noticed that the benefits of chaining are reduced for systems with a large number of products and plants.

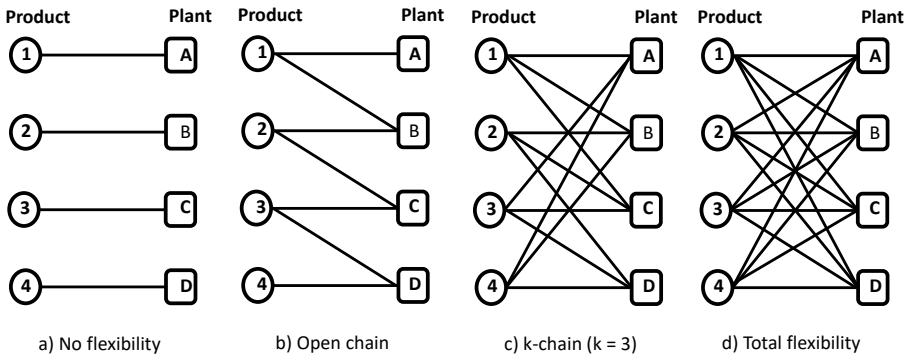

Figure 3.2: Classification of degrees of process flexibility (adapted from: Wang et al. (2019)).

Jordan & Graves (1995) provide the following guidelines on how to create process flexibility, with optimal benefits, in a manufacturing system using the principle of chaining:

1. assign the products such to have approximately equal available manufacturing capacity;
2. assign the products to achieve approximately equal product demand for each plant;
3. link plants and products to create the least number of chains; and
4. attempt to create a closed loop, if possible.

Assigning the products to have approximately equal capacity available for each product and approximately equal product demand at each manufacturing facility creates a balanced and symmetric configuration (Wang et al., 2019). The chain shown in Figure 3.1 is defined as a long chain (Wang et al., 2019) since each manufacturing facility can manufacture two products, and each product can be produced by two manufacturing facilities in a single, closed chain. The long chain configuration and the other configurations in Figure 3.2 are viewed as balanced since each configuration contains an equal number of products and manufacturing facilities (Shi et al., 2019). Having a balanced and symmetric configuration eases the process of shifting the available manufacturing capacity between products to meet the demand for each product.

Creating fewer and longer chains allows for a greater ability to shift manufacturing capacity between different products and consequently increases the demand that can be met (Chou et al., 2008; Jordan & Graves, 1995). Figure 3.3 shows both a configuration of longer and fewer chains and a configuration of shorter and more chains. As shown in Figure 3.3 for the shorter and more chains configuration, the manufacturing capacity can only be shifted between the two products included in each chain. In contrast

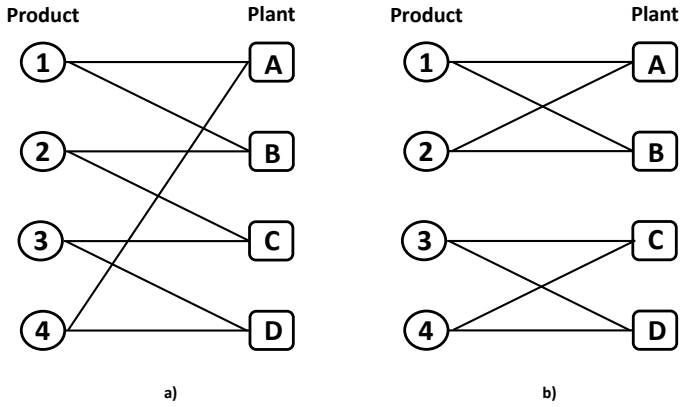

Figure 3.3: Examples of both a single chain configuration and multiple chains configuration (adapted from Wang et al. (2019)).

to this, for the longer and fewer chain configuration, the manufacturing capacity can be shifted between all four products included in the single chain.

Creating a closed loop also allows the ability to better shift the manufacturing capacity between the manufacturing of the different products (Jordan & Graves, 1995). An open chain configuration is shown in Figure 3.2, labeled as "b)", while a closed chain configuration is shown in 3.1. For the open loop configuration, no capacity can be shifted to fulfil the unmet demand of product "4". Adding the final link to create a closed loop adds great value to the flexibility of the system (Jordan & Graves, 1995)

3.1.4.2 Operational and component levels perspective

According to Hua & He (2010), process flexibility should be considered separately on the production line, and the manufacturing system levels since the flexibility at the two levels differ. The production line and the manufacturing system levels are similar to the component and operation levels defined by Taymaz (1989), respectively.

Hua & He (2010) added a bill of material (BOM) constraint to their study of process flexibility in manufacturing systems. Under this constraint, it cannot necessarily be assumed that the full capacity of a production line or manufacturing system can be shifted between products (Hua & He, 2010). The manufacturing of the individual product components is also considered, and the BOM constraints of products may result in only limited ability to shift manufacturing capacity between products (Hua & He, 2010). For a product to be produced at a specific production line, the machinery of the production line have to be able to manufacture every component of the product (Hua & He, 2010). Thus, when the flexibility of a production line is considered, the ability to shift the manufacturing of different product components between the machinery becomes essential (Hua & He, 2010). Figure 3.4 presents an example of adding

machine flexibility to a production line.

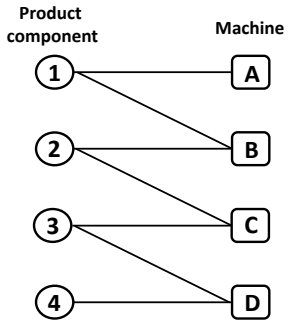

Figure 3.4: Classification of degrees of process flexibility (adapted from Hua & He (2010)).

In contrast, when the system's flexibility is considered, the ability to shift the manufacturing of different products between production lines or manufacturing facilities is considered (Hua & He, 2010).

3.1.5 Measurement of flexibility

Flexibility measures create the ability to evaluate the impact of manufacturing flexibility on a manufacturing system to guide decision-making processes (Ramasesh & Jayakumar, 1991). The discussion on flexibility measurement approaches in this section will consider approaches applied to manufacturing flexibility in general, as these measurements are applicable to a wide range of manufacturing flexibility categories, and a manufacturing flexibility category is not limited to a specific measurement approach.

According to Gupta (1993), the measurements of flexibility should consider aspects such as the equipment's capabilities, the set-up of the system's components and the uncertainty that the system faces. Different measurement approaches for flexibility have been applied in previous studies, and these flexibility measurements can either be qualitative or quantitative (Jain et al., 2013). Qualitative measures generally focus on the flexibility strategies applied in the system, while quantitative measures consider specific aspects of manufacturing (Beach et al., 2000). Quantitative measures often involve the development of mathematical models (Beach et al., 2000).

De Toni & Tonchia (1998) state that flexibility can either be measured with direct, indirect or synthetic methods. The methods are further subdivided as shown in Figure 3.5. Direct, indirect, and synthetics measures are discussed in more detail in the following subsections.

3.1.5.1 Direct measuring approaches

As shown in Figure 3.5, De Toni & Tonchia (1998) categorise direct methods for measuring flexibility into:

- objective methods, which focus on either:

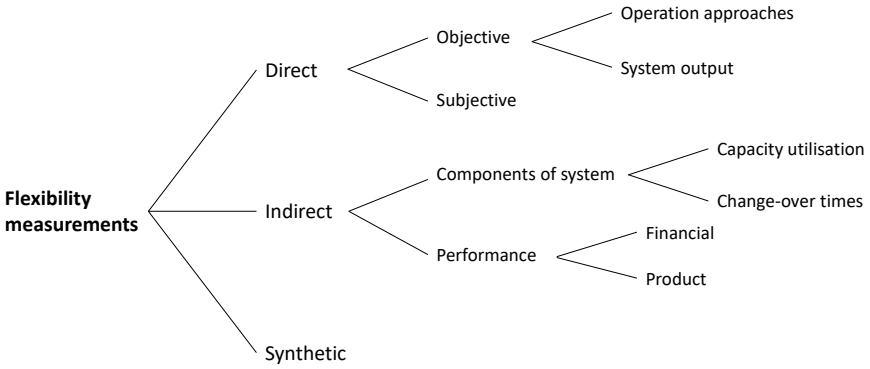

Figure 3.5: Classification of flexibility measurements (adapted from: De Toni & Tonchia (1998)).

  - the different operational approaches; or
  - the system's output; and

- subjective methods.

The entropy measure is an example of a direct objective measuring method for flexibility considering the different operational approaches (Chryssolouris, 1996; De Toni & Tonchia, 1998). The entropy measure is based on the concept that greater flexibility in a system is achieved when any of the following criteria are met Chang et al. (2001): the system produces a greater variety of products, the system can operate at different output volumes, or the system can produce products via different operation approaches. Authors that have used the entropy measurement for various categories of flexibility include Kumar (1987), Yao (1985) and Benjaafar (1994). According to Chang et al. (2001), Correa (1994) and Chandra et al. (2005), the entropy measure, as used by these authors, is not a complete measure for flexibility. This is because the entropy measure lacks the evaluation of the efficiency and reliability of the system (Chang et al., 2001).

Measuring manufacturing flexibility by considering aspects of the system's output involves using quantitative data from the system over time (De Toni & Tonchia, 1998). Authors that have used this method to investigate the impact of a systems size on the benefits associated with volume flexibility is Fiegenbaum & Karnani (1991). De Toni & Tonchia (1998) mention that the method applied by Fiegenbaum & Karnani (1991) is limited in that is does not indicate whether the variability in the product output is due to improved system performance or adjusted parameters in the system.

The direct subjective measures are based upon opinions on the state of a system's flexibility (De Toni & Tonchia, 1998). According to De Toni & Tonchia (1998), the direct measuring approaches have difficulties associated with it, leading to authors rather applying indirect measures. No explicit discussion is, however, provided on the difficulties with these measures.

3.1.5.2 Indirect measuring approaches

As shown in Figure 3.5, De Toni & Tonchia (1998) categorise indirect methods for measuring process flexibility as focusing either on:

- the performance of the system evaluated in terms of:
  - financial aspects; or
  - product quality and development; or
- components of the system, evaluated in terms of aspects such as:
  - capacity utilisation; or
  - changeover times.

According to De Toni & Tonchia (1998), the manufacturing flexibility in a manufacturing system can be measured in terms of its financial aspects by considering any of the following: increase in system's sales; additional costs associated with the manufacturing flexibility; and lost sales due to the inability to shift capacity appropriately to meet product demand.

Gupta & Buzacott (1989) use an indirect method, which is based on financial performance, to measure flexibility. In their measurement, they consider the required expenditures and sales associated with different degrees of flexibility (De Toni & Tonchia, 1998). Another indirect method based on the financial performance of a system is used by Buzacott (1982). In this method, the expected economic loss at low degrees of flexibility is considered for a changing environment (De Toni & Tonchia, 1998). The cost considered in the measurement of flexibility is directly related to the changes that occur in the environment (Gupta, 1993). Flexibility has also been measured by considering the discounted cash flow and combining it with the benefits associated with a certain degree of flexibility (Chryssolouris, 1996).

According to De Toni & Tonchia (1998), measuring the system's performance without considering financial aspects may include considering the system's productivity level during system failures, the time required to develop or deliver products, and the quality of products. Chryssolouris (1996) evaluated machine flexibility by measuring the number of products that can be produced by the system during downtime.

In addition to the change-over times mentioned by De Toni & Tonchia (1998) as an indirect measure considering the components of the system, Ettlie et al. (1994) also propose two other measuring approaches in this category. The first approach is to count the number of product part sets that the system can manufacture (De Toni & Tonchia, 1998; Ettlie et al., 1994). The second method is to measure the number of different product parts that the system is capable of producing (De Toni & Tonchia, 1998; Ettlie et al., 1994).

Examples of indirect measures considering the components of the system can be found in Chryssolouris (1996), Hua & He (2010), Koste & Malhotra (1999), and Sethi & Sethi (1990). Sethi & Sethi (1990) and Koste & Malhotra (1999) measured the process flexibility of a system by counting the number of different products that the system can produce without requiring significant changes. Hua & He (2010) measured process flexibility of a system by evaluating the ability of a system or production line to produce different products by shifting the manufacturing capacity to meet demand. Flexibility can also be measured by considering the fraction of product demand that can be fulfilled by the system (Chryssolouris, 1996).

3.1.5.3 Synthetic measuring approaches

The synthetic measurements of flexibility are new methods constructed to take the different components of flexibility into consideration (De Toni & Tonchia, 1998). Sarker et al. (1994) similarly defined this flexibility measure as an aggregate approach. The approach is a combination of flexibility measurements and is used to measure the flexibility of a system (Jain et al., 2013).

A synthetic measuring approach was applied by Jordan & Graves (1995) to measure process flexibility. This involved predicting the probability that the demand will not be met for a certain degree of flexibility (De Toni & Tonchia, 1998).

Another synthetic measure was applied by Brill & Mandelbaum (1989). They developed a function from which a machine's performance can be evaluated by considering either the number of components produced by the machine over a period or the quality of the products (De Toni & Tonchia, 1998). The quality is assessed by the number of components that are rejected (De Toni & Tonchia, 1998). The percentage decrease in the performance of a machine, when faced with changes in the environment compared to its optimal performance, is used to measure flexibility (De Toni & Tonchia, 1998).

Son & Park (1987) created a method to measure flexibility in terms of financial aspects by combining different flexibility measures. The final example of a synthetic measure is the development by Ramasesh & Jayakumar (1991). The measure considers various aspects associated with flexibility. Flexibility is measured by considering the system's ability to be profitable in a highly uncertain environment.

3.1.6 Benefits

Similar to the preceding discussion on measuring flexibility, the benefits that are associated with flexibility will also be discussed for manufacturing flexibility in general, rather than for process flexibility specifically.

The benefit most frequently associated with flexibility is that it allows a company to be competitive in markets faced with great uncertainty or turbulence (Chou et al., 2008; Gupta & Goyal, 1989; Jordan & Graves, 1995; Mara et al., 2021). When a system has some degree of flexibility in the manufacturing process, adjustments can be made to correspond to the current state of the market (Chen et al., 1992;

Gupta, 1993). Several other benefits have been mentioned in literature and Table 3.3 summarises benefits that have been articulated in 16 previous studies.

Adding flexibility to a system can allow the system to meet the demand for products (Chou et al., 2008; Mara et al., 2021; Shi et al., 2019; Simchi-Levi & Wei, 2012). Improved responsiveness enables the system to adjust the product output as required by the market, and consequently, the fraction of demand that can be fulfilled increases (Jordan & Graves, 1995; Sethi & Sethi, 1990). This results in increased sales, along with savings for the manufacturers (Wang et al., 2019). As the demand that is fulfilled increases, there is a reduced need to offer customers discounts as compensation for unfilled demand (Wang et al., 2019).

Flexibility also increases the lifetime of manufacturing facilities (Boyle (2006); Gupta & Goyal (1989)) and makes it more likely that the facilities will be capable of meeting future demand (Wahab & Stoyan (2008)). Finally, flexibility improves the productivity of facilities (Gupta (1993); Mohamed et al. (2001)) and facilitates more effective capacity usage (Gupta & Goyal (1989); Jordan & Graves (1995); Ojha et al. (2013); Simchi-Levi & Wei (2012); Wang et al. (2019)).

Table 3.3: Benefits of flexibility according to different authors

	Benefits							
Author	**Increases sales**	**Meet future demand**	**Coping with uncertainty**	**Effective capacity usage**	**Meet product demand**	**Improves productivity**	**Increased facility lifetime**	**Improved performance**
Gupta & Goyal (1989)			X	X			X	
Sethi & Sethi (1990)			X		X			
Chen & Adam (1991)			X					
Gupta & Sameer (1992)			X			X		
Jordan & Graves (1995)	X		X	X	X			
Mohamed et al. (2001)			X			X		
Boyle (2006)			X		X		X	
Wahab & Stoyan (2008)		X	X		X			
Chou et al. (2008)					X			
Chou et al. (2010)			X		X			
Ojha et al. (2013)			X	X	X			X
Simchi-Levi & Wei (2012)			X	X	X			
Jain et al. (2013)			X		X	X		X
Shi et al. (2019)			X		X			
Wang et al. (2019)	X		X	X	X			X
Mara et al. (2021)			X		X			

3.2 Economic considerations for manufacturing

Adding flexibility to a system increases the manufacturing and investment costs for the system (Jordan & Graves, 1995). In order to have flexibility between production lines or manufacturing facilities, it may be required that (Van Biesebroeck, 2007): existing equipment is adjusted; specialised equipment are acquired; and/or the facilities are expanded. Furthermore, an increase in flexibility may cause an increase in the labour costs due to additional quality control requirements, training of personnel, and additional engineering and programming requirements (Chen & Adam, 1991).

3.2.1 Vaccine manufacturing costs

Plotkin et al. (2017), Clendinen et al. (2016) and Munira et al. (2019) specified the costs associated with the manufacturing of vaccines and a synthesis of these costs is presented in Table 3.4. The main expenditures for vaccine manufacturing, as shown in Table 3.4, are product development, facilities and equipment, direct labour, overhead, materials, filling and regulatory.

The cost required for product development will depend on the types of vaccines produced (Plotkin et al., 2017). This cost can be significantly reduced if well-established technologies from other manufacturing companies can be obtained (Plotkin et al., 2017). The facilities and equipment are fixed costs but require continuous maintenance (Clendinen et al., 2016; Munira et al., 2019; Plotkin et al., 2017). If the necessary equipment is unavailable locally, it may have to be imported (Plotkin et al., 2017).

Direct labour costs are the wages paid to employees performing work for the different components of the manufacturing process (Clendinen et al., 2016). The overhead costs include costs associated with the material handling, loading, and unloading, and administrative and management costs (Clendinen et al., 2016; Jiao et al., 2007).

According to Clendinen et al. (2016) and Munira et al. (2019), the raw materials include all the materials required for manufacturing, while the filling costs are all the costs associated with filling and finishing the product. The raw materials for producing vaccines are often obtained from biological processes and may be very specialised (Plotkin et al., 2017). The regulatory cost is expenditures associated with obtaining licensure and meeting quality control requirements (Plotkin et al., 2017).

The required capacity at the facilities depends on the market's requirements and directly impacts the investment cost for the system (Laengle et al., 1994). The investment in capacity occurs prior to any manufacturing of products (Hagspiel et al., 2016).

3.2.2 The cost of process flexibility

According to Jordan & Graves (1995), adding flexibility to a system does not have to be accompanied by a significant increase in either the manufacturing or investment costs. Chaining allows products with similar

Table 3.4: Costs for vaccine manufacturing

Costs	Examples	References
Product development	R&D laboratories and equipment	Munira et al. (2019); Plotkin et al. (2017)
	R&D personnel	Munira et al. (2019); Plotkin et al. (2017)
Facilities and equipment	Land	Plotkin et al. (2017)
	Buildings	Munira et al. (2019); Plotkin et al. (2017)
	Equipment	Clendinen et al. (2016); Munira et al. (2019); Plotkin et al. (2017)
	Maintenance	Plotkin et al. (2017)
	Utilities	Plotkin et al. (2017)
Direct labour	Manufacturing	Plotkin et al. (2017)
	Quality control	Clendinen et al. (2016)
	Regulatory	Clendinen et al. (2016)
	Filling	Clendinen et al. (2016)
	Supervision	Clendinen et al. (2016)
Overhead	Factory	Clendinen et al. (2016)
	Administrative	Clendinen et al. (2016)
	Management	Plotkin et al. (2017)
	Quality systems	Plotkin et al. (2017)
	IT systems	Plotkin et al. (2017)
Raw materials	Materials required for manufacturing	Clendinen et al. (2016); Plotkin et al. (2017)
Filling	Vials	Clendinen et al. (2016); Munira et al. (2019)
	Syringes	Clendinen et al. (2016); Munira et al. (2019)
	Stoppers	Clendinen et al. (2016); Munira et al. (2019)
	Packaging	Clendinen et al. (2016); Munira et al. (2019)
	Quality checks	Munira et al. (2019)
Regulatory	Expenses to comply with requirements	Plotkin et al. (2017)

manufacturing processes to be produced at a specific production line or manufacturing facility (Jordan & Graves, 1995). Applying the guideline of Jordan & Graves (1995) creating long chains removes the need to produce various products at the same production line or manufacturing facility, which reduces the need to make expensive adjustments to the manufacturing system.

When flexibility is added, different optimal trade-off scenarios of benefits and costs can be achieved, depending on the different plant and facility configurations (Jiao et al., 2007; Jordan & Graves, 1995).

3.3 Conclusion: Chapter 3

This chapter considered manufacturing flexibility via discussion on the following topics: classification, adding process flexibility to a system, measurements, and benefits. An important process flexibility configuration discussed in this chapter is the long chain configuration. Several studies have proven the long chain configuration to provide benefits similar to the full flexibility configuration. These studies considered relatively stable demand uncertainty. Lastly, the costs associated with vaccine manufacturing and flexible manufacturing were discussed.

The next chapter contains an overview on the modelling of manufacturing systems. Examples found in literature are presented and finally the selection process of a modelling approach is discussed.

Chapter 4

Modelling manufacturing systems

Chapter 1 provided background on the purpose of this study, while Chapter 2 provided literature on vaccine manufacturing and Chapter 3 provided the classification of manufacturing flexibility topics. This chapter will expand on the literature reviewed in Chapter 3 by specifically considering the modelling of systems. This guides the selection of an appropriate model to represent the specific research problem. The research problem will be defined in terms of its characteristics. A typology of modelling approaches and techniques will be defined and discussed. To provide context on the modelling literature, examples of modelled systems are provided and discussed. The modelled systems include aspects of vaccine product life cycles and manufacturing flexibility. This is followed by the selection of an appropriate modelling approach to represent the specific research problem.

Section 4.4 contains text that has been published as a conference paper. In line with the copyright agreement, the citation to this paper is provided here: Spamer, M., Bam, L. (2022). "Modelling manufacturing process flexibility: A systematic review." Accepted for publication in: Proceedings of the 2022 IEEE 28th International Conference on Engineering, Technology and Innovation (ICE/ITMC) & 31st International Association For Management of Technology (IAMOT) Joint Conference, 19^{th} - 23^{rd} of June 2022, Nancy, France

4.1 Defining the research problem: Covid-19 vaccine manufacturing system

Models represent the operations of a system and allow the ability to evaluete the system's behaviour without requiring expensive and time-consuming experiments on the real system (Buzacott & Mandelbaum, 2008; Buzacott & Yao, 1986; Chryssolouris et al., 1998; Kochikar & Narendran, 1994; Mishra & Pandey, 1989). A model is an abstract representation of a real system for which the considered components, the level

of detail, and the assumptions regarding these components of the system can be adjusted (Buzacott & Mandelbaum, 2008; Kochikar & Narendran, 1994).

According to authors such as Chryssolouris et al. (1998), Ervural et al. (2019), and Gupta (1993), manufacturing systems are often complex and may consequently be difficult to accurately represent.

As mentioned in Section 1.2, the research problem is modelling the Covid-19 vaccine manufacturing system with demand uncertainty linked to the approval of vaccine products. The model that is being developed will represent a theoretical system to assess the expected impact of process flexibility. The model has to incorporate all six of the vaccine platforms discussed in Section 2.2, namely: LAV, IV, SP, VV, DNA, and RNA. As mentioned in Section 1.6, only the manufacturing of the active drug substance (i.e. the bulk product) is considered. The system will be faced with uncertainty in the demand for the aforementioned vaccine platforms, which may result in the under-utilisation (or in some cases no utilisation) of specific vaccine platforms' facilities. As mentioned in Subsections 3.1.3, process flexibility can be implemented in a manufacturing system to allow the shifting of capacity between products, consequently increasing the overall utilisation of available manufacturing capacity. The concept of process flexibility must thus be incorporated into the model. This will allow the shifting of manufacturing capacity between the vaccine platforms.

With reference to Subsection 3.1.6 the expected benefits of process flexibility in the manufacturing system of Covid-19 vaccines include: coping with uncertainty in the demand, effective utilisation of manufacturing capacity, and improved system performance. Based on the potential benefits of process flexibility for the system, and with reference to Subsection 3.1.5, it may be beneficial to consider any or a combination of the following measuring approaches: the increased sales for the system (which can also be considered as the system's throughput), or the additional cost associated with process flexibility as an indirect measure of the system's performance; and the system's capacity utilisation as an indirect measure of the components of the system. The model will have to be capable of considering different process flexibility configurations to assess the impact of process flexibility on the system.

Buzacott & Mandelbaum (2008) identified two modelling strategies that are typically used when representing a manufacturing system, namely: a decision-making model, used for the design or planning of a system; or a model used to evaluate the impact of different parameters, such as changes in the environment, on the performance of the system. The Covid-19 vaccine manufacturing system model is developed to assess the impact of process flexibility on the system. The insight gained from this model may be used to guide future developments of manufacturing systems and networks.

4.2 Typology of modelling approaches

Different modelling approaches will be referred to throughout this chapter. As an introduction to these discusions, a typology of different modelling approaches, typically used to model manufacturing systems, is presented and discussed in this section.

Various modelling approaches and techniques can be used to represent a manufacturing system. Different classifications of models for manufacturing systems can be found in literature. According to Viswanadham et al. (1992), modelling approaches can be classified into two main categories, namely: qualitative and quantitative. As mentioned in Section 4.1, the system may be measured in terms of the model's throughput, the additional costs associated with process flexibility, or the utilisation of manufacturing capacity over time, which all require the use of quantitative measures. Thus, qualitative models are not suitable, and only quantitative modelling approaches will be considered further.

Lingervelder (2017) created a typology of modelling approaches for supply chains, based on the classification by authors such as Beamon (1998), Riddalls et al. (2000), Biswas & Narahari (2004), and Thierry et al. (2010). The author classified the approaches into three main categories, namely (Lingervelder, 2017):

1. Analytic measures and modelling;
2. Physical experiments; and
3. Simulation and emulation.

Though this typology was created for application to supply chains, it is also relevant to the application of modelling a manufacturing system since most, if not all, of the modelling approaches presented in the typology are also mentioned in manufacturing systems literature. Physical experiments are used to physically evaluate the performance of the real system (Lingervelder, 2017). As mentioned in Section 4.1 the model being developed for the Covid-19 vaccine manufacturing system will represent a theoretical system, and physical models are thus not applicable.

The modelling typology created by Lingervelder (2017) is used as a basis for the typology presented in this study. Additional classifications and modelling approaches found in literature are incorporated into Lingervelder's typology, and the adjusted typology is shown in Figure 4.1.

Lingervelder's typology does not include qualitative models, with the exception of petri nets[1]. Although some authors (e.g. Viswanadham et al. (1992)) view petri nets as a qualitative modelling approach, others (e.g. Bause (1993) and Kochikar & Narendran (1994)) classify petri nets as both a qualitative and a quantitative modelling approach. As exclusively qualitative modelling approaches such as conceptual and

[1]Petri nets are used to represent a system graphically (Viswanadham et al., 1992). The model comprises of a series of arcs connecting different components of a system and can be used to assess the performance of flexible manufacturing systems (Viswanadham et al., 1992)

theoretical frameworks (Green, 2014) are not considered applicable to this study, the category is also excluded from the typology presented in Figure 4.1.

Various authors categorise quantitative models into different approaches. Perrone & Noto La Diega (1996) categorise manufacturing system models into four modelling approaches, namely: queueing models, simulation models, multi-criteria models, and mathematical programming models. Yadav & Jayswal (2018) instead classify manufacturing system models into six different approaches, namely: mathematical models, artificial intelligence models, hierarchical models, multi-criteria decision-making models, petri nets and simulation models.

The typology presented in this study comprises of five quantitative modelling approaches, namely: analytical modelling, simulation, multi-criteria, artificial intelligence and financial modelling. The multi-criteria and artificial intelligence approaches are included in the typology since several examples of modelling a manufacturing system with techniques from either of the two approaches can be found in literature. Even though financial modelling is not explicitly defined as a modelling approach in literature, it is included in the typology due to the mention of flexibility investment models in literature.

In addition to the modelling techniques presented in Lingervelder (2017)'s typology, other techniques that are also used in literature to represent manufacturing systems are briefly discussed. Mathematical programming models are often mentioned in literature, and although it is not explicitly indicated in Lingervelder (2017)'s typology, it forms part of the operations research modelling approach. According to Viswanadham et al. (1992), Markov chains and queueing networks are also considered to be examples of analytical modelling techniques. In addition to the simulation techniques presented in Lingervelder (2017)'s typology, authors such as Law (2004) and White & Ingalls (2009), also consider Monte Carlo simulation to be a simulation technique. The multi-criteria modelling approach did not form part of Lingervelder (2017)'s typology, however authors such as Yadav & Jayswal (2018) and Perrone & Noto La Diega (1996) do consider it to be a modelling approach and includes techniques such as the analytical hierarchy process (AHP) and the data envelope analysis (DEA) as modelling techniques.

The main quantitative modelling approaches presented in Figure 4.1 are briefly discussed in the remainder of this section.

Approaches	Quantitative										Multi-criteria	Artificial intelligence	Financial
	Analytical modelling		Simulation										
Techniques	Operations research	Statistical models	Analytics	Discrete event		Business games		Agent-based	Continuous	Hybrid	Monte Carlo			
			- Prescriptive - Descriptive - Predictive	Event based	Time based	Strategic game	Operational game						
Examples	Mathematical programming Queueing networks Markov networks Game theory Fuzzy set theory	Regression analysis Correlation analysis		Discrete event dynamic system	Spread-sheet simulations	The Beer game	Production Schedule training		Systems dynamics	Combination of analytical modelling and simulation		Analytical hierarchy process Data envelope analysis	Game programming	Real option

Figure 4.1: Typology of quantitative modelling approaches for manufacturing systems (adapted from: Lingervelder (2017)).

4.2.1 Analytical modelling

The analytical modelling approach uses mathematical models, comprised of equations and functions, to represent the operations of a system (Lingervelder, 2017; Wahab & Stoyan, 2008). According to Viswanadham et al. (1992), analytical models often do not have the ability to incorporate all the complexity of a system since high levels of detail can present difficulty when solving a problem analytically. The considered system may be required to be simplified to solve the problem analytically (Lingervelder, 2017).

4.2.2 Simulation

The simulation modelling approach makes use of computer-based models to represent a system (Fone et al., 2003; Lingervelder, 2017). Simulation models can be developed to describe the complex operations of a manufacturing system and generally provide a very accurate prediction of the system's expected performance for different scenarios (Fone et al., 2003; Viswanadham et al., 1992; Yadav & Jayswal, 2018). Simulation modelling can be costly and time-consuming due to the need for simulation tools and the iterative nature of this type of modelling approach (Fone et al., 2003; Yu et al., 2015).

4.2.3 Multi-criteria models

The multi-criteria modelling approach uses evaluation criteria to assess aspects of a manufacturing system (Petroni & Bevilacqua, 2002; Shang & Sueyoshi, 1995; Yadav & Jayswal, 2018). The criteria used to evaluate aspects of the manufacturing system consider different system elements simultaneously to assist the decision-making process for selecting alternative strategies (Petroni & Bevilacqua, 2002; Shang & Sueyoshi, 1995; Yadav & Jayswal, 2018). The multi-criteria models can also be described as decision-making models and are typically used when choosing between alternative options for a system (Petroni & Bevilacqua, 2002; Shang & Sueyoshi, 1995; Yadav & Jayswal, 2018).

4.2.4 Artificial intelligence

The artificial intelligence modelling approach makes use of different algorithms and is typically used for the design of a manufacturing system with flexibility (Yadav & Jayswal, 2018). The model can accommodate the human aspects that may be inherent in systems, and simulation is often used in conjunction with the artificial intelligence modelling approach to represent the human aspects of a system (Chan et al., 2002; Shang & Sueyoshi, 1995; Yadav & Jayswal, 2018).

4.2.5 Financial modelling

The financial modelling approach uses various evaluation techniques, which may include the net present value and discounted cash flow, to assess investment strategies for a system (Jiao et al., 2007). A financial

modelling technique, used to assess investment options for flexibility in a manufacturing system, is the "real option" model (Hagspiel et al., 2016; Jiao et al., 2007). The modelling approach can be used to determine the optimal strategy, regarding the time and intensity, for manufacturing flexibility investment (Hagspiel et al., 2016). The optimal investment strategy is determined by assessing the benefits of manufacturing flexibility in a changing environment (Jiao et al., 2007). Often a variety of uncertainty factors are considered in these assessments (Jiao et al., 2007).

4.2.6 Conclusion: Typology of modelling approaches

The categories of modelling approaches defined in the typology will be used when reviewing modelling instances documented in literature in the remainder of this chapter.

4.3 Contextualisation: Modelling of vaccine product's life cycle and manufacturing flexibility

This section contains narrative reviews on the modelling of systems representing aspects of vaccine product life cycles and systems with manufacturing flexibility. This is merely presented to provide general context on the modelling of: vaccine products; and manufacturing systems with flexibility, in general. Structured reviews were not performed on these topics as the topics do not directly contribute to the main theme of the research problem, which is the modelling of a manufacturing system with process flexibility specifically. However, insight can still be gained on the potential applicability of modelling approaches to the research problem. The narrative reviews for systems representing vaccine product life cycles and manufacturing systems with manufacturing flexibility are discussed in Subsections 4.3.1 and 4.3.2, respectively.

4.3.1 Vaccine product life cycles

The models presented in Table 4.1 are examples of modelling approaches used to solve aspects of vaccine product life cycles. The examples in Table 4.1 specifically include the evaluation of different strategies or the prediction of scenario outcomes associated with the manufacturing and distribution of vaccines. Strategies that were evaluated include vaccine allocation, improvement of immunization programs and procurement contracts. For the examples in Table 4.1, conceptual models were used to evaluate different strategies, while the analytical, simulation and financial modelling approaches were used to predict outcomes of scenarios.

Although the examples in Table 4.1 provide insight into considerations of specific aspects of vaccine products, the examples do not provide guidance to the modelling of Covid-19 vaccine manufacturing.

Table 4.1: Examples of models for aspects of the vaccine's life-cycle

Application	**Problem description**	**Modelling technique**	**Citation**
Approach: Analytical			
Willingness to pay for Covid-19 vaccine	The model determines how willing individuals in Ecuador are to acquire a vaccine against Covid-19. The factors that influence individuals' valuation of vaccines were also taken into account.	Online survey Regression model	Carpio et al. (2020)
Approach: Simulation			
Priority of vaccine allocation	The model, which was built on an existing mathematical model, is used to simulate possible scenarios that may occur during a pandemic. The model considered the health care requirements for different target groups in these scenarios. The results from the model were used to develop an ethical framework for the allocation of vaccines to target groups.	Not specified	Fielding et al. (2020)
Approach: Financial			
Willingness to pay for the Covid-19 vaccine	The model determines how willing individuals are to acquire a vaccine against Covid-19. The factors that influence individuals' valuation of vaccines were also considered.	Discrete choice model	García & Cerda (2020)

4.3.2 Manufacturing flexibility

Examples of the modelling of systems with manufacturing flexibility are presented in Table 4.2, refer to Section 3.1.1 for descriptions of manufacturing flexibility topics. As previously mentioned, the examples presented in Table 4.2 are only based on a narrative review of systems with manufacturing flexibility, and no conclusions can be made regarding the prevalence of modelling approaches and research themes.

Table 4.2: Examples of models for manufacturing systems with flexibility

Application	Problem description	Modelling technique	Citation	Flexibility
Approach: Analytical				
Financial benefits of flexible capacity	The model is developed to evaluate the long-term financial benefits of having flexibility in the available capacity for a manufacturing system. The financial benefits are determined by comparing the net present value of a system with full flexibility with a system with limited flexibility.	Dynamic programming	Laengle et al. (1994)	Capacity
Performance of FMS with machine and routing flexibility	The model assesses the performance of a manufacturing system with machine and routing flexibility. The model also considers several technological attributes often associated with a manufacturing system.	Mathematical models	Wahab & Stoyan (2008)	Machine, routing
Flexible capacity and delivery lead time for a supply chain	The model is used to evaluate different scenarios of flexible capacity and delivery lead time for a supply chain comprised of a supplier and a customer. The customer demand is considered dependent on the supplier's lead time. It is further evaluated how certain parameters influence the different scenarios.	Continuous Gauss process model	Altendorfer (2017)	Capacity
Flexibility measurement	The model is used to measure the flexibility of a manufacturing system by comparing the cost and time required to increase the capacity levels for different manufacturing systems.	Mixed integer programming model	Bordoloi et al. (1999)	FMS

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Application	Problem description	Modelling technique	Citation	Flexibility
Competitive advantages of technology acquisition	The model assesses the advantage that a company can obtain by acquiring new technology that reduces manufacturing costs. The acquisition of technology is made in response to the actions of competitors, and the interactions between companies are considered.	Game theoretical model	Gaimon (1989)	Technology
Scheduling of FMS	The model is used to determine certain aspects required for scheduling a manufacturing system. These aspects include the components' selection, the sequence in which they should be manufactured, and the machine utilization for the operations.	Multi-level integer program	Sawik (1990)	FMS
FMS design faced with uncertainty	The model is used in designing an FMS and considers minimizing the cost and maximizing the sales for increased flexibility. Aspects such as the degree of flexibility, the output volume, and the available capacity level are considered in the design of the FMS.	Fuzzy set theory	Perrone & Noto La Diega (1996)	FMS
Measurement of flexibility	The model is used to measure the overall flexibility of a manufacturing system by considering the effect of the different degrees of flexibility in the measurement. The measurement is based on the sales that the manufacturing system can achieve in different environments.	Stochastic mathematical programming	Ramasesh & Jayakumar (1991)	Overall
Approach: Simulation				
Flexible costing for FMS	The models are used to assess the performance of the FMS. The results from the models are used to develop a new method for allocating overhead costs.	manufacturing planning model Discrete event simulation	Koltai et al. (2000)	FMS (cost)

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Application	Problem description	Modelling technique	Citation	Flexibility
Performance of system with sequencing flexibility	The model is used to assess the impact of sequencing flexibility on a manufacturing system's performance. Different aspects of sequencing flexibility are considered. The model results are used to develop a new measure for the performance of a system with sequencing flexibility.	Not specified	Benjaafar (1994)	Routing
Performance of FMS	The model is used to assess the impact of routing and 'part sequencing' flexibility on an FMS's performance. The performance of the FMS is assessed by considering factors such as the processing time of parts.	Discrete event simulation Regression based meta-models	Joseph & Sridharan (2012)	Routing, sequencing
Manufacturing system design	The model is used to compare the effect of different manufacturing system designs on the volume, mix, product and production flexibility that can be achieved for the system. The necessity for a trade-off of different flexibilities is considered.	Not specified	Shewchuk & Moodie (2000)	Volume, mix
Benefits of flexibility	The model evaluates whether an increase in flexibility results in increased benefits. The model considers aspects of the machines, such as processing and change-over time, that form part of the manufacturing system.	Not specified	Chan et al. (2006)	FMS
Performance of flexibility in discrete manufacturing	The model is used to assess the performance of flexibility in a discrete manufacturing system. The flexibility is assessed by comparing the order lead time for a system with that of a system with a high degree of flexibility.	Not specified	Seebacher & Winkler (2014)	FMS
Performance of manufacturing system with machine flexibility	The model is used to assess the performance of a manufacturing system with machine flexibility for components with similar features. Different scenarios of machine configurations are considered.	Not specified	Singholi et al. (2012)	Machine

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Application	Problem description	Modelling technique	Citation	Flexibility
Impact of personnel flexibility on manufacturing flexibility	The model assesses the impact of personnel flexibility on the manufacturing system's flexibility. Different uncertainty scenarios and personnel flexibility strategies are considered.	Hybrid model	Ren et al. (2021)	Personnel
Performance of supply chain flexibility	The model assesses the performance of supply chain flexibility by considering the trade-off between benefits and costs associated with the flexibility. Two aspects of the supply chain, namely: safety stock levels; and manufacturing outputs, are evaluated.	Discrete event simulation	Pfeiffer et al. (2013)	Supply chain
Performance of batch job shop type FMS	The model is used to assess the performance of batch job shop type FMS for different scenarios of operating conditions. The results of the model were used to develop empirical models which can determine the average utilization of machines of the FMS.	Not specified	Mishra & Pandey (1989)	FMS
Performance of a manufacturing system with flexibility	The model is used to assess the impact of routing, machine and product-mix flexibility on the performance of a system. Scenarios with different combinations of these flexibilities were considered, and the system's performance was evaluated in terms of processing time and inventory levels.	Not specified	Das & Nagendra (1993)	Machine Routing Product-mix
Flexibility trade-off	The model is used to assess the trade-off between different flexibilities that can be made for a manufacturing system. The performance of the manufacturing system is evaluated for different scenarios.	Not specified	Gupta & Sameer (1992)	All flexibilities
Approach: Multi-criteria				
FMS comparison	The model is developed to compare flexible manufacturing systems (FMS) and considers both quantitative and qualitative factors. The model's results can assist the process of choosing a specific FMS.	Data envelope analysis (DEA)	Sarkis & Talluri (1999)	FMS

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Application	Problem description	Modelling technique	Citation	Flexibility
Improving flexibility	The models are used to assess the uncertainty associated with the manufacturing system and provide a method to implement the required improvements for the flexibility to deal with the uncertainty.	Quality function deployment (QFD), Analytical hierarchy process (AHP), Grey relational analysis (GRA)	Chang (2012)	FMS
Identification of elements of efficient FMS	The model was used to compare the efficiency of different FMSs. The results were used to distinguish between efficient and non-efficient strategies of flexibility and to identify what aspects of flexibility are generally present in companies that have implemented an efficient FMS. The trade-off between different flexibilities is also considered.	DEA	Petroni & Bevilacqua (2002)	FMS
Selection of an FMS strategy	The model is used to evaluate flexible manufacturing system strategy by considering trade-offs between various aspects of the manufacturing system.	Non-linear optimization model	Kuula & Stam	FMS
Selection of FMS	The models are used to evaluate FMS strategies to generate a framework which can guide the choice of a strategy for a specific scenario. Aspects such as the benefits and required costs are considered in the models	AHP Simulation DEA	Shang & Sueyoshi (1995)	FMS
Approach: Financial				
Cost of FMS options	The model is used to compare different manufacturing options for an FMS. The various uncertainties that may be associated with a manufacturing system, as well as the cost associated with flexibility, are considered.	Real option theoretic approach	Jiao et al. (2007)	FMS investment

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Application	Problem description	Modelling technique	Citation	Flexibility
Capacity investment under uncertainty	The model is used to assess the capacity investment that should be made for manufacturing systems with volume flexibility facing uncertainty. A system with no flexibility is compared with a flexible system.	Real option theoretic approach	Hagspiel et al. (2016)	Volume

Examples of the following modelling approaches are presented in Table 4.2: analytical, simulation, multi-criteria, and financial. The simulation and analytical modelling approaches were applied to either evaluate the performance of a system with manufacturing flexibility or assess the benefits associated with aspects of a flexible manufacturing system. As mentioned in Section 4.1, the Covid-19 vaccine manufacturing system may be measured in terms of the system's performance by considering the model's throughput. From the examples in Table 4.2, both the analytical and simulation modelling approach may apply to the Covid-19 vaccine manufacturing system.

The multi-criteria modelling approach was applied to evaluate and compare different strategies of flexible manufacturing flexibility to assist the choice of strategy for a specific system. As mentioned in Section 4.1, different process flexibility configurations will be considered and compared for the Covid-19 vaccine manufacturing model. The multi-criteria model is often applied when alternative options for a system have to be evaluated by considering different elements simultaneously, refer to Subsection 4.2.3. It may thus be beneficial to apply the multi-criteria model in conjunction with either the analytical or simulation model if the system is measured in terms of multiple elements simultaneously.

The financial model was applied to evaluate the investment in manufacturing flexibility. For the Covid-19 vaccine manufacturing system being modelled in this research, the investment required to enable process flexibility will not specifically be considered.

4.4 Systematic review: Modelling of manufacturing systems with process flexibility

As mentioned in Section 4.1, process flexibility will be incorporated into the model of the Covid-19 vaccine manufacturing system that is developed in this research. Wang et al. (2019) propose a classification of modelling approaches based on the type of manufacturing capacity allocation strategy used for the system. The possible capacity allocation strategies are summarized in a capacity allocation matrix presented in Figure 4.2. A manufacturing system's manufacturing capacity can be allocated either independently or

dependently over time (Wang et al., 2019). Whether the allocation is independent or dependent over time is determined by two variables, namely (Wang et al., 2019): the mode of allocation; and the unmet demand.

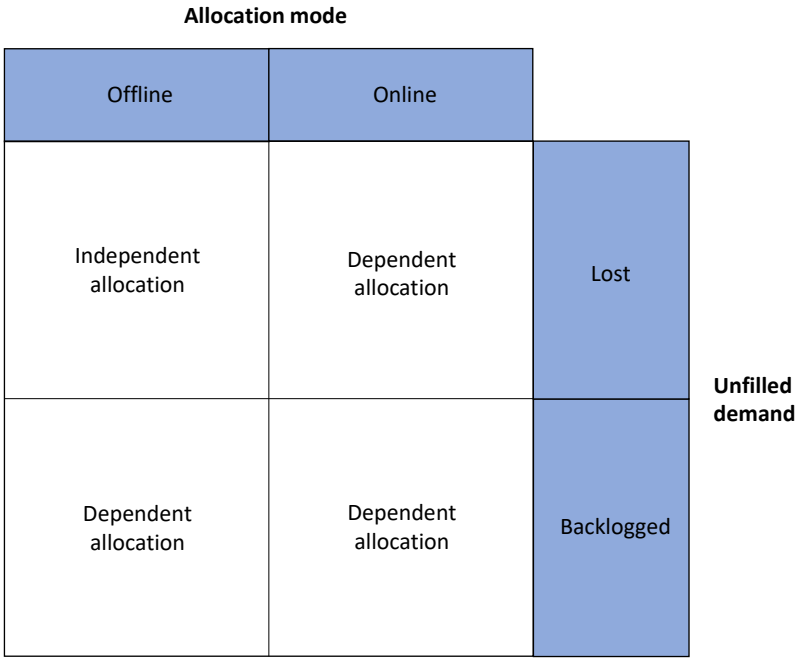

Figure 4.2: Process flexibility capacity allocation matrix (diagram constructed based on information presented in Wang et al. (2019)).

The mode of allocation can either be (Wang et al., 2019): off-line, with the allocations made at the start of every period and no adjustment made during a period; or online, with the allocations made dynamically during the period as the demand is realised. Offline allocations are typically in systems where the demand is known prior to the start of manufacturing (Wang et al., 2019).

The unmet demand can be dealt with in two ways, namely (Wang et al., 2019): it can be considered as lost, or it can be backlogged to the next period and possibly incur waiting costs.

The capacity allocation for a system is independent over time for an off-line allocation where the unmet demand is discarded. The allocation decisions in a certain period do not influence the successive periods (Wang et al., 2019). The capacity allocation for the three remaining strategies is dependent over time. Any allocation decision that is made in a certain period can affect all the successive periods, and each allocation decision is thus very important for the entire manufacturing horizon (Wang et al., 2019).

This classification of modelling approaches, as defined by Wang et al. (2019), will be applied when examples for manufacturing systems with process flexibility are considered.

4.4.1 Structured literature review approach

A structured review was conducted to obtain a comprehensive overview of the literature concerning the modelling of manufacturing systems with process flexibility. The structured review was conducted in line with the eight steps proposed by Thomé et al. (2016), namely:

1. Identifying the research problem and goal;
2. Conducting the search;
3. Assessing the data quality;
4. Extraction and compilation of the data;
5. Interpretation;
6. Presenting results; and
7. Updating the review.

4.4.2 Research problem and goal

The structured review was conducted to gather documents from which information on modelling manufacturing systems with process flexibility can be extracted. The following research objectives were defined to achieve this goal:

1. Inductively derive a set of categories that describe the research themes that have been considered in the modelling of process flexibility; and
2. Categorise the existing literature on modelling of manufacturing systems according to: modelling technique, capacity allocation strategy, and the research theme considered.

4.4.3 Conducting the search

Thomé et al. (2016) recommend the use of at least two databases when conducting the literature search. The search platforms *Scopus* and *Web of Science* were employed in this systematic review. Scopus and Web of Science were identified as appropriate sources for the systematic review as the two platforms jointly cover many prominent abstract- and citation databases.

The keyword search phrase constructed for this systematic review is as follows: "("process flexibility" or "mix flexibility" or "job flexibility") and model". Process flexibility is most frequently used to describe manufacturing flexibility that allows a system to shift capacity between products, however, the terms *mix*

flexibility and *job flexibility* have also been used to describe this concept in literature and are therefore also included in the keyword search phrase.

Structural adjustments were made to the keyword search phrase to meet the requirements of both the Scopus and Web of Science platforms. The search phrase used to conduct a search for documents in the title, abstract, and keywords section in Scopus is as follows: ((“process flexibility” OR “mix flexibility” OR “job flexibility”) w/5 (model*)). This primary search in Scopus resulted in 49 documents. The search phrase used to conduct a search for document titles in Web of Science is as follows: TS = (“process flexibility” NEAR model* OR “mix flexibility” NEAR model* OR “job flexibility” NEAR model*). This primary search in Web of Science resulted in 75 documents. The Scopus and Web of Science searches uncovered 29 identical documents. Thus, a total of 95 unique documents were uncovered.

The 95 documents were screened based on their titles and keywords to assess their relevance to modelling a manufacturing system with process flexibility. No limitations, for example, the languages and publication dates, were implemented when the search was conducted. Documents were only included if one of the following criteria were met:

- Specific mention of process flexibility, or related terms, is made; or
- Mention of a modelling approach is made.

21 documents were selected for a subsequent round of screening, where the abstracts were reviewed. In the abstract screening round, documents were selected for inclusion if the study involved evaluating a manufacturing system with process flexibility via a specific modelling approach. 13 relevant documents were identified.

Thomé et al. (2016) recommend the use of backward and forward searches of the selected documents to identify relevant documents that were not initially uncovered. As a backward search, the references of the 14 documents that were identified as relevant from the primary search were screened. As a forward search, documents referencing the aforementioned 13 documents were also screened. An additional 15 documents were selected for inclusion in the data set based on the forward and backward searches. Thus a data set of 28 documents was obtained from the systematic review process.

4.4.4 Assessing the data quality

Thomé et al. (2016) recommend an evaluation of the reliability of the selection process and the quality of the selected data. An iterative approach was employed to ensure the quality of the results.

27 of the 28 documents in the data set have been published in journals. Several highly regarded journals are represented in the data set, including: *Operations Research* (10 documents), *Flexible Service and Manufacturing Journal* (three documents), *Management Science* (two documents), *International*

Journal of Production Research (two documents), and *International Journal of Production Economics* (two documents).

4.4.5 Extraction and compilation

The papers were reviewed to extract relevant data. In a limited number of instances, a single paper describes more than one independent instance of modelling process flexibility. Each instance of modelling process flexibility (rather than each paper) was defined as a unique data point in the data set. The data set includes a total of 30 data points. Each of these data points is referred to as a case in the remainder of the discussion. These 30 cases are presented as examples of manufacturing systems with process flexibility in Table 4.3.

Table 4.3: Examples of models for manufacturing systems with process flexibility.

Problem description	**Modelling technique**	**Citation**	**Allocation mode**		**Unmet demand**		**Research theme**			
			Off-line	Online	Lost	Backlog	Design	Performance	Benefits	Investment
Analytical										
The model aims to prove that limited flexibility can provide similar benefits to full flexibility. The model predicts the probability that the unmet demand for a balanced system with limited flexibility will be greater than that of the system with full flexibility. Simulation experiments are also performed to validate the results of the model.	Linear programming model	Jordan & Graves (1995)	X		X				X	
The model is used to evaluate the performance of a manufacturing system in a supply chain network. The results are used to present design guidelines. Simulation experiments are performed to prove the accuracy of the results.	Linear programming	Graves & Tomlin (2003)	X		X			X		
The model is used to evaluate the performance of a manufacturing system with process flexibility under the bill of material constraint to improve the process flexibility configuration, measured in terms of the shortfall of demand. Computational experiments are performed to validate the results.	Linear programming model	He & Xu (2009)	X		X			X		

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Problem description	Modelling technique	Citation	Allocation mode		Unmet demand		Research theme			
			Off-line	Online	Lost	Backlog	Design	Performance	Benefits	Investment
The model is used to evaluate the performance of different configurations of process flexibility for a manufacturing system, measured in terms of the demand shortfall and capacity utilisation. The model considers varying demand for a product throughout its lifetime. Numerical experiments are performed to prove the accuracy of the results.	Stochastic programming	Francas et al. (2009)	X		X			X		
The model is used to evaluate the trade-off between the benefits and cost of process flexibility for a symmetrical and balanced manufacturing system.	Stochastic integer programming	Mak & Shen (2009)	X		X				X	
The model is used to evaluate the performance of a balanced manufacturing system with process flexibility in a supply chain. Uncertainty in both the demand and manufacturing capacity is considered.	Linear programming model	Zhou et al. (2009)	X		X			X		
The model proves that limited flexibility can have similar benefits to that of full flexibility. This is done by evaluating the performance of a system with limited flexibility, in terms of expected sales, for different demands. The model is further used to develop a range of conditions in which limited flexibility can achieve near-optimal benefits.	Stochastic programming model	Chou et al. (2010)			X		X		X	

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Problem description	Modelling technique	Citation	Allocation mode		Unmet demand		Research theme			
			Off-line	Online	Lost	Backlog	Design	Performance	Benefits	Investment
The model is used to develop a process flexibility design for a manufacturing system, under worst-case demand, that can meet demand more effectively than in previous literature. Graph expansion is utilized in the modelling of the system. Numerical experiments are performed to assess the accuracy of the results.	Graph theory	Chou et al. (2011)	X		X		X			
A flexibility fit index is developed to determine a system's required process flexibility degree. The performance of process flexibility in a manufacturing system is analytically determined, and the results are used to develop the flexibility index. Simulation models are used to assess the effectiveness of the fit index.	Operations research model	He et al. (2012)	X					X		X
The model is used to assess the effectiveness of the long chain configuration for a manufacturing system with process flexibility. A balanced system configuration is considered, and the performance is measured in terms of the expected sales.	Linear programming model	Simchi-Levi & Wei (2012)	X		X				X	

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Problem description	Modelling technique	Citation	Allocation mode		Unmet demand		Research theme			
			Off-line	Online	Lost	Backlog	Design	Performance	Benefits	Investment
The model is used to evaluate two capacity allocation strategies for a manufacturing system to assess the best approach to minimize total costs for the associated process flexibility. For the first strategy, the allocation of capacity is done at the beginning of the manufacturing horizon, while for the second strategy, the allocations are done at the beginning of each period.	Stochastic integer programming	Tanrisever et al. (2012)	X			X		X		
The model is used to evaluate the financial impact associated with process flexibility by considering both the cost and profit associated with a degree of process flexibility. Furthermore, the model also determines the optimal degree of process flexibility.	Operations research model	Afflerbach et al. (2013)		X	X			X		
The model evaluates the benefits of a process flexibility configuration by considering both the costs and the profits associated with the flexibility degree. Furthermore, the model also determines the optimal degree of process flexibility. The model is applied to a case study of an insurance broker company.	Operations research model	Afflerbach et al. (2014)		X	X			X		

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Problem description	Modelling technique	Citation	Allocation mode		Unmet demand		Research theme			
			Off-line	Online	Lost	Backlog	Design	Performance	Benefits	Investment
The model is used to evaluate the performance of a symmetrical and unbalanced manufacturing system, with partial manufacturing postponement, where some of the capacity allocation decisions are performed prior to any demand realizations. A long chain configuration is considered.	Linear programming	Chou et al. (2014)	X		X			X		
The model is used to evaluate the trade-off between process flexibility and inventory flexibility for a manufacturing system. Stochastic processing times and demands are considered for the products. Scenarios with different capacity levels and costs are also considered.	Markov model	Iravani et al. (2014)		X	X			X		
The model is used to evaluate the performance of an unbalanced manufacturing supply chain with volume and process flexibility and safety stocks. The costs associated with a flexible configuration are also considered. To validate the results, numerical experiments are performed.	Mixed integer linear programming	Kemmoe et al. (2014)	X		X			X		

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Problem description	Modelling technique	Citation	Allocation mode		Unmet demand		Research theme			
			Off-line	Online	Lost	Backlog	Design	Performance	Benefits	Investment
The model is used to develop a process flexibility design for a symmetrical and balanced manufacturing system with a high probability of achieving (1-ε) fraction of the performance of total flexibility. New probabilistic graph expanders are developed in the modelling of the system. Simulation studies are performed to prove the accuracy of the results.	Linear programming Graph theory	Chen et al. (2015)	X		X				X	
The model is used to evaluate the performance of a symmetrical and balanced manufacturing system with process flexibility under worst-case demand. A long chain configuration is considered.	Linear programming	Simchi-Levi & Wei (2015)	X		X				X	
The model is used to evaluate the performance of a symmetrical and balanced manufacturing system with process flexibility in a k-chain configuration. A lower bound for the asymptotic ratio, developed by Chou (2010), is developed.	Linear programming	Wang & Zhang (2015)	X		X				X	
The model is used to assess the performance of a system with process flexibility by considering the worst-case scenario of the expected sales for changing demand. Both a balanced and an unbalanced chaining system configuration is evaluated.	Linear programming model	Bidkhori et al. (2016)	X		X			X		

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Problem description	Modelling technique	Citation	Allocation mode		Unmet demand		Research theme			
			Off-line	Online	Lost	Backlog	Design	Performance	Benefits	Investment
The model developed by Jordan & Graves (1995) is used to evaluate whether the long chain configuration for a manufacturing system with process flexibility is beneficial for all scenarios. A balanced system configuration is considered.	Linear programming model	Désir et al. (2016)	X		X			X		
The model is used to evaluate different configurations for both balanced and unbalanced manufacturing systems with process flexibility. The model's results can be used to design a system.	Mathematical programming	Yang et al. (2016)	X		X		X			
The model is used to evaluate different process flexibility strategies for the design of an unbalanced manufacturing system. The impact of facility uniformities and product similarities on the design for such a system is also considered.	Stochastic integer programming model	Feng et al. (2017)		X	X		X			
The model is used to assess the benefits of limited flexibility in a manufacturing system with an unbalanced configuration over multiple periods. The model considers uniform costs for the backlogged demand of different products. Numerical experiments are used to assess the accuracy of the model.	Optimization dynamic model	Shi et al. (2019)	X			X			X	

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Problem description	Modelling technique	Citation	Allocation mode		Unmet demand		Research theme			
			Off-line	Online	Lost	Backlog	Design	Performance	Benefits	Investment
The model is used to evaluate the relationship between process flexibility and inventory levels for manufacturing systems with a K-chain configuration. Different process flexibility strategies are considered, and the optimal inventory level is determined for each strategy. The results are verified by performing numerical experiments.	Two-stage optimization model	Simchi-Levi et al. (2018)	X		X			X		
The model is used to develop a process flexibility design for a symmetrical and unbalanced manufacturing system with a high probability of achieving (1-$)-fraction of the performance of total flexibility. Graph expanders are utilized in the modelling of the system.	Linear programming Graph theory	Chen et al. (2019)	X		X		X			
The model is used to assess design strategies for balanced manufacturing systems with process flexibility in a bio-pharmaceutical supply chain. Furthermore, the best trade-off scenario between process flexibility and inventory levels is also considered.	Deterministic linear programming	Kaminsky & Wang (2019)	X		X			X	X	
Simulation										

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Problem description	Modelling technique	Citation	Allocation mode		Unmet demand		Research theme			
			Off-line	Online	Lost	Backlog	Design	Performance	Benefits	Investment
The model is used to evaluate the performance, measured in terms of expected sales and capacity utilization, of limited process flexibility for a balanced and symmetrical manufacturing system. The results are used to present design guidelines.	Not specified	Jordan & Graves (1995)	X		X			X		
The model is used to investigate whether large supply chain systems requires a higher degree of flexibility.	Not specified	Graves & Tomlin (2003)	X		X			X		
Measures for process flexibility of a system under bill of material constraints are developed. Simulation experiments are used to assess the effectiveness of these measures.	Not specified	Hua & He (2010)	X		X			X		

In line with the research objectives of the systematic review, the following data were captured for each case in the data set:

- Detailed problem description, including a description of the objectives of the research;
- Modelling approach and specific technique (where specified);
- Research theme; and
- Type of capacity allocation strategy.

The extraction of data was an iterative process which consisted of three steps. The first step involved extracting a description of the problem that was considered in each case and the research objectives associated with each case. This information was used to inductively derive four main research themes for the modelling of systems with process flexibility, namely:

- Performance of a system with process flexibility;
- Benefits of ideal limited process flexibility;
- Design of alternative process flexibility structures; and
- Process flexibility investment.

With these research themes in mind, the data set was re-evaluated, and the cases were each categorized into one of the research themes.

4.4.6 Interpreting and presenting results

From the examples in Table 4.3, it can be seen that the research theme most frequently investigated for manufacturing systems with process flexibility is the performance of a system with process flexibility, followed by benefits of ideal limited process flexibility. The least frequently investigated research theme is flexibility investment.

The analytical modelling approach was favoured (27 of 30 cases), with authors most frequently applying an operations research technique. As seen in Table 4.3, the analytical model has been applied to model all four of the research themes. Three examples of simulation models are presented in Table 4.3. The research theme for all three of these cases was the performance of a system with process flexibility. All the cases applying the analytical modelling approach used some form of operations research modelling techniques. Many of the cases utilising the analytical modelling approach make use of additional approaches to verify the analytical results, including numerical and simulation experiments. In some cases where an analytical

modelling approach has been applied, the authors mention the need to either simplify the system or reduce the scope of the system in order to solve the problem analytically.

As shown in Table 4.3, the majority of the modelling cases (20 of the 30 cases) investigated systems for which the capacity allocation strategy involved an off-line capacity allocation mode with the unmet demand being discarded (Q1). Two cases considered a slightly more complex capacity allocation strategy comprising of an off-line allocation mode coupled with unmet demand that is backlogged (Q4). Five of the 30 cases considered a significantly more complex capacity allocation strategy comprising of an online allocation mode and the unmet demand being discarded (Q2). No case was presented that considered the most complex capacity allocation strategy comprising of an online allocation mode and the demand being backlogged (Q3). Many real systems do however, implement this capacity allocation strategy and it may be valuable to gain insight to effective management approaches and potential decision-making heuristics for such systems.

In Section 4.3.2, both the analytical and simulation modelling approaches were identified as potential modelling approaches for the Covid-19 vaccine manufacturing system. This is further motivated by the examples presented in Table 4.3. As mentioned in Section 4.1, the Covid-19 vaccine manufacturing system may be measured in terms of the system's performance. As shown in Table 4.3, the performance of a system with process flexibility has been modelled by both the analytical and simulation modelling approaches.

4.5 Important developments in process flexibility literature

Evaluating the efficiency of chaining to construct the configuration of a system with process flexibility has been dealt with several times in literature. Jordan & Graves (1995) first introduced the concept and various other publications have since built on their work. Some of the most influential developments with the analytical and simulation modelling approaches in this field are discussed in this section.

4.5.1 Analytical approaches

Jordan & Graves (1995) studied the benefits of chaining by predicting the probability that a system with a specific limited process flexibility configuration will have a greater demand shortfall than a system with full flexibility. To predict this probability, they developed a linear programming function (Jordan & Graves, 1995).

A manufacturing system with n facilities and m products with a balanced configuration is considered (Jordan & Graves, 1995). For the long chain configuration, used by Jordan & Graves (1995), two adjacent products are assigned to each facility, as indicated in Figure 3.1. The set of connected facilities and products is denoted by A and a product i can be produced by a facility j if $(i, j) \in A$ (Jordan & Graves, 1995). The configuration of the system is constructed in a way that minimises the total shortfall of demand (S_i)

for the system (Jordan & Graves, 1995). This can be re-expressed as maximising the demand that is met (X_{ij}) . It is assumed that the capacity allocation is performed off-line and that any unmet demand is lost (Jordan & Graves, 1995).

According to Jordan & Graves (1995), the minimum predicted shortfall for a configuration A, denoted by U, can be expressed by the function

$$U = \min \sum_{i=1}^{m} S_i \tag{4.1}$$

$$\sum_{(i,j)\in A} X_{ij} + S_i \geq D_i ... i = 1, 2, ..., m,$$

$$\sum_{(i,j)\in A} X_{ij} \leq C_j ... i = 1, 2, ..., n.$$

The shortfall of the demand is affected by two variables, namely the capacity (C_j) for each facility and the demand (D_i) for each product (Jordan & Graves, 1995). The objective of Jordan & Graves (1995)'s model is to predict the probability that the expected shortfall of demand for a system with limited flexibility will be greater than the expected shortfall of demand for a system with full flexibility (Jordan & Graves, 1995). For a specific subset of products M, Jordan & Graves (1995) denotes this probability by $\Pi(M^*)$, with M^* as the subset of products that will maximise the probability, and express it as a linear programming function

$$\Pi(M^*) = Pr[\{\sum_{i\in M} D_i - \sum_{j\in P(M)} C_j\} > \max\{0, \sum_{i=1}^{m} D_i - \sum_{j=1}^{n} C_j\}]. \tag{4.2}$$

The subset of facilities that can produce at least one of the products in subset M is denoted by $P(M)$(Jordan & Graves, 1995).

For a system with limited flexibility to have similar benefits to that of a system with full flexibility, it is required that $\Pi(M^*)$ is small (Jordan & Graves, 1995). According to Jordan & Graves (1995), if the value is less than 0.05, it can be assumed that the degree of flexibility is sufficient, and any additional flexibility will not add many benefits.

The function presented in (4.2) is difficult to solve and Jordan & Graves (1995) simplified it by denoting

$$a = \sum_{i\in M} D_i - \sum_{j\in P(M)} C_j$$

and

$$b = \sum_{i=1}^{m} D_i - \sum_{j=1}^{n} C_j.$$

It is also assumed that the demand is an independent, normally-distributed random variable and Jordan & Graves (1995) rewrote the function in (4.2) in the form of

$$\Pi(M^*) = [1 - \Phi(z_1)]\Phi(z_2), \tag{4.3}$$

with $z_1 = -\mu[a]/\sigma[a]$, $z_2 = -\mu[b]/\sigma[b]$, and $\Phi(z)$ as the cumulative distribution function.

Chou et al. (2010) considered a different approach to measure the benefits associated with chaining for a manufacturing system with process flexibility by considering the maximum product output for the system of infinite size. The objective is to compare the performance of limited flexibility in a long chain configuration with that of full flexibility (Chou et al., 2010).

A balanced system with equal number of products and facilities (n) with independent demand [$D = \mu_i$] is considered (Chou et al., 2010). It is assumed that the capacity allocation is performed off-line, and any unmet demand is lost (Chou et al., 2010). The asymptotic ratio γ between the expected sales for a system with limited flexibility and a system with full flexibility, developed by Chou et al. (2010), can be expressed by the function

$$\gamma = \lim_{n\to\infty} \frac{E[P(D, L_n)]}{E[P(D, F_n)]}, \tag{4.4}$$

with $P(D, A)$ the maximum output of products for a configuration A, L_n the configuration of a system with limited flexibility, and F_n the configuration of a system with full flexibility.

Chou et al. (2010) made several observations from their results. Firstly, they observed that the performance of a long chain configuration decreases as the system size is increased (Chou et al., 2010). Furthermore, a system with a long chain configuration, evaluated under worst-case demand, can still achieve approximately 90% of the performance of a system with full flexibility when the demand distribution has an equal probability of being any value between 0 and $2C_j$ (Chou et al., 2010). Finally, they observed that a system with a long chain configuration could achieve near-optimal benefits when the system is faced with little demand uncertainty (Chou et al., 2010).

Chou et al. (2010) also considered the flexibility for an open chain configuration (O_n) for a system with infinite size and developed a function that indicates the relationship between the performance of an open chain and a long chain, presented by

$$\lim_{n\to\infty} \frac{E[P(D, O_n)]}{n} = \lim_{n\to\infty} \frac{E[P(D, L_n)]}{n}. \tag{4.5}$$

The "greedy algorithm" is used in the evaluation of the performance of the open chain (Chou et al., 2010). All the required capacity from facility i is first utilised to meet the demands for product i (Chou et al., 2010). Any remaining capacity of facility i can thereafter be used for the demand of product $i+1$ (Chou et al., 2010). If more capacity is required for product i, the remaining demand should be met by utilising capacity from facility $i+1$ (Chou et al., 2010).

Chou et al. (2011) consider graph expansion in their evaluation of the performance for a balanced and symmetric system with limited flexibility under worst-case demand. They aimed to prove that a limited flexibility configuration can be created that always achieves performance close to that of full flexibility

(Chou et al., 2011). It is assumed that the capacity allocation is performed off-line and that any unmet demand is lost (Chou et al., 2011).

An assumption was made that the demand is restricted to a range around its mean (Chou et al., 2011). The function

$$P(D, G_n) \geq (1 - \varepsilon)P(D, F_n) \tag{4.6}$$

is used to prove that a limited flexibility configuration G_n with O(N) links can achieve performance similar to full flexibility for any demand (D) in the restricted range (Chou et al., 2011). Chou et al. (2011) observed that a chain configuration no longer achieves favourable performance for a system with limited process flexibility when more than two products are assigned per plant.

Furthermore, Chou et al. (2011) also considered the evaluation of systems with unbalanced and non-symmetric configurations and used the results to provide guidelines for the design of an unsymmetrical system. Simchi-Levi & Wei (2012) evaluated the performance, measured in terms of expected sales, for a system with limited flexibility, configured in a long chain with two products assigned to each facility. It is assumed that the capacity allocation is performed off-line and that any unmet demand is lost (Simchi-Levi & Wei, 2012).

Simchi-Levi & Wei (2012) used the concept of supermodularity to prove that adding a link and consequently increasing the degree of flexibility has marginal benefits. Furthermore, Simchi-Levi & Wei (2012) developed a lower bound for the asymptotic ratio of the expected sales for a long chain and full flexibility, with mean demand (μ_i) equal to the available manufacturing capacity, given by the function

$$\frac{E[P(D, O_n)]}{E[P(D, F_n)]} \geq 1 - (1 - \gamma)\frac{n\mu}{E[P(D, F_n)]}. \tag{4.7}$$

Simchi-Levi & Wei (2012) made two observations from their results. Firstly, they observed that a long chain configuration consistently performs better than a configuration with a series of short chains (Simchi-Levi & Wei, 2012). Secondly, the results indicated that for a system with a size greater than two, the long chain configuration could achieve approximately 96% of the performance of full flexibility (Simchi-Levi & Wei, 2012).

Shi et al. (2019) evaluated the performance of systems that backlogs any unmet demand over multiple periods with the capacity allocations performed off-line. Shi et al. (2019) used the average backlogging cost, $BC(A)$, to quantify the performance of a system with backlog for a configuration A, as given by the function in

$$\mathrm{BC}(A) = \min_{\pi}\mathrm{limsup}_{(\mathrm{T}\to\infty)}\frac{1}{T}E[\sum_{t=1}^{T}\sum_{j=1}^{n}B_j^{\pi}(t)], \tag{4.8}$$

with π as the closed-loop feasible policy and $B_j^{\pi}(t)$ the backlog of product j in time period t. The system under consideration has m products and n facilities with normalized capacity for each plant, denoted by q_i.

The demand is independent, with mean demand μ_i and standard deviation σ_i. The system is considered over multiple periods t.

Shi et al. (2019) also developed the generalized chaining gap (GCG) to design a limited flexibility configuration for an unbalanced system that can meet most of the demand. A configuration that is constructed according to the GCG will achieve performance similar to that of full flexibility Shi et al. (2019).

4.5.2 Simulation approaches

As seen in Table 4.3, only three cases were uncovered that investigated process flexibility with the simulation modelling approach. The developments made in each of these cases are briefly discussed.

Jordan & Graves (1995) investigated the performance of an ideal manufacturing system with process flexibility by considering the expected sales and the capacity utilisation of the system. Different systems were considered to evaluate the impact of process flexibility via simulation experiments. The specific simulation modelling technique applied was not specified.

The first system that was considered comprised of two products and two manufacturing facilities (Jordan & Graves, 1995). The total available manufacturing capacity for the system is 200 units (Jordan & Graves, 1995). The demand for the products is random and independent, varying between 50, 100, and 150 (Jordan & Graves, 1995). Both full flexibility and no flexibility scenarios were considered, and the results are shown in Table 4.4. It is evident from the simulation experiments that process flexibility improves the performance

Table 4.4: Comparison of *no flexibility* and *full flexibility* for a two product and two facilities system (adapted from Jordan & Graves (1995)).

	No flexibility	**full flexibility**
Expected sales	167	178
Lost sales	33	22
Capacity utilisation (%)	83	89

of a manufacturing system.

Another system that was considered by Jordan & Graves (1995), involved considering a system with 10 products and 10 manufacturing facilities. Each manufacturing facility is assigned an available manufacturing capacity of 100 units (Jordan & Graves, 1995). The expected demand for each product is 100 (standard = 40, minimum = 20, and maximum = 180) (Jordan & Graves, 1995). For a simulation experiment, the demand for each product is randomly selected, and the manufacturing of the products is assigned

to manufacturing systems, as allowed by the process flexibility configuration (Jordan & Graves, 1995). The simulation run was repeated numerous times to obtain accurate estimates (Jordan & Graves, 1995). The results for different process flexibility configurations are shown in Figure 4.3. From the simulation

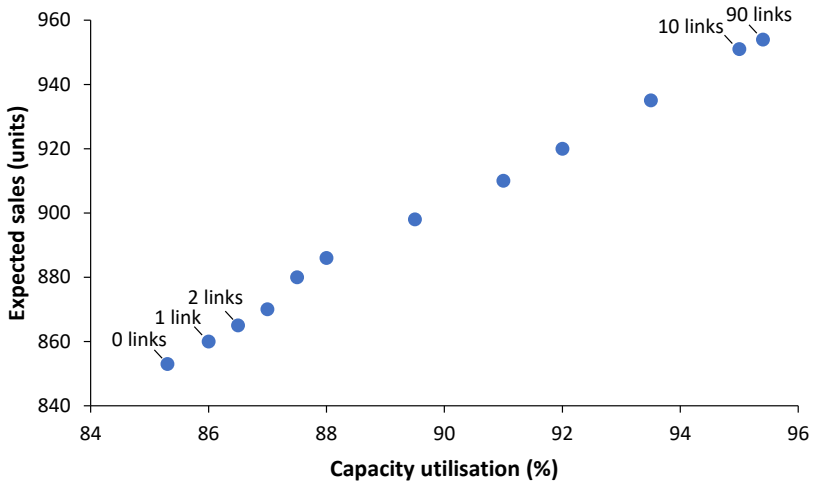

Figure 4.3: Comparison of different process flexibility degrees for a system with 10 products and 10 manufacturing facilities (adapted from: Jordan & Graves (1995)).

experiments, Jordan & Graves (1995) observed that the performance of the system only improved until the 10th link was added, any further links resulted in very little improvement.

According to Jordan & Graves (1995), the desired number of links for a system will depend on the system's number of products and manufacturing facilities, the available manufacturing capacity, the demand for products, and the uncertainty in the demand.

Graves & Tomlin (2003) performed simulation experiments to investigate whether large supply chains require a greater degree of process flexibility than small supply chains. The system's performance was measured by considering the excess available manufacturing capacity and the expected unmet demand for a system (Graves & Tomlin, 2003). Graves & Tomlin (2003) consider a flexibility measure for supply chain networks, denoted by g. A detailed description for the flexibility measure can be found in Graves & Tomlin (2003).

For small supply chain networks, a flexibility measure of $g = 1$ provided sufficient performance, while larger supply chain networks required g to be larger than one (Graves & Tomlin, 2003). Figure 4.4 shows the performance of different sized supply chain networks with $g = 1$. As seen from Figure 4.4, the performance of supply chains with $g = 1$ decreases as the number of products increases.

Graves & Tomlin (2003) investigated increasing g to two for large supply chain networks and observed significant improvement. Graves & Tomlin (2003) proved that limited process flexibility can provide benefits

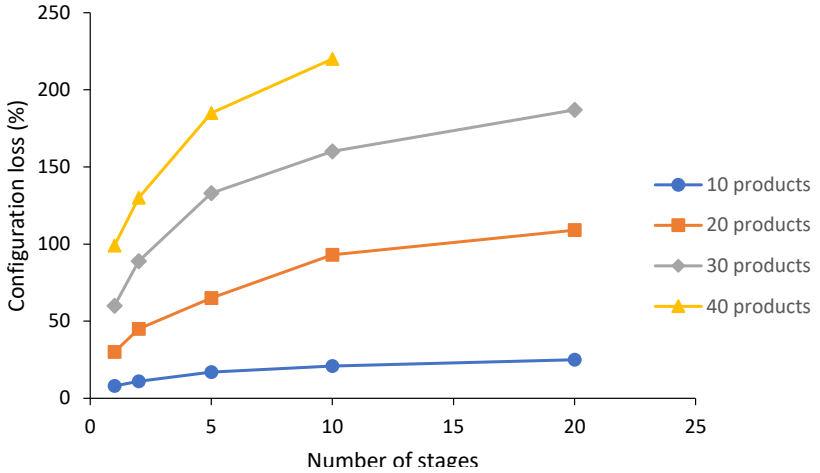

Figure 4.4: The performance of supply chain networks (g=1) with increasing number of products (adapted from: Graves & Tomlin (2003)).

similar to that of full process flexibility even for large supply chain networks.

Hua & He (2010) performed simulation experiments to evaluate the effectiveness of their proposed measures and guidelines for process flexibility in a manufacturing system under BOM constraints. The system and production line levels are considered separately (Hua & He, 2010). The performance of the system level is measured by considering the expected unmet demand for the system (Hua & He, 2010). For the simulation experiments, Hua & He (2010) considered manufacturing systems comprising of four assembly lines. Each of the assembly lines are comprised of five different machines capable of producing three product types (Hua & He, 2010). An example of three product sets assembled from five part types for three different BOM constraint cases is presented in Table 4.5

Table 4.5: A system of three products and five-part types under three different BOM constraints (adapted from Hua & He (2010))

Case	Product	Part p_1	Part p_2	Part p_3	Part p_4	Part p_5
1	i_1	5	15	20	8	12
	i_2	10	7	15	3	15
	i_3	25	11	9	32	23
2	i_1	12	25	23	0	0
	i_2	21	0	18	0	11
	i_3	35	0	0	27	38
3	i_1	28	10	22	0	0
	i_2	12	7	28	0	3
	i_3	14	21	5	40	20

Hua & He (2010) considered both scenarios where the machine capacity is deterministic and where the machine capacity is random and normally distributed. If the capacity was considered to be deterministic, each machine was assigned a capacity of 1 000 products for the manufacturing horizon (Hua & He, 2010). If the capacity was considered to be random and normally distributed, a machine's capacity could range between 800 and 1 200 products for the manufacturing horizon (Hua & He, 2010). The scenarios with random and normally distributed capacity were considered to assess how internal uncertainties affect the proposed measures and guidelines (Hua & He, 2010).

The experiments were executed by first randomly sampling demands for the products and capacities for the machines based on their respective distributions (Hua & He, 2010). The demand for the three product types was considered to be Poisson distributions, with the respective modes being 80, 100, and 120 (Hua & He, 2010).

Hua & He (2010) compared the results obtained from the proposed measures to that of the J&G index and stated that their measure is appropriate and effective in measuring process flexibility for a manufacturing system under BOM constraints.

4.6 Selection of modelling approach

As seen in Section 4.4, only analytical and simulation modelling approaches have been used to represent the manufacturing systems with process flexibility in Table 4.3. In these examples, the analytical modelling approach was highly favoured. However, the Covid-19 vaccine manufacturing system is expected to face unusually high levels of uncertainty associated with the approval of different vaccines, as mentioned in Subsection 1.1.3. This stochastic element creates a complex system that may present difficulties when solving analytically. As discussed in Section 4.2.2, the simulation modelling approach can represent complex systems (Fone et al., 2003; Viswanadham et al., 1992; Yadav & Jayswal, 2018). It can thus be assumed that a simulation modelling technique is an appropriate choice to represent the manufacturing system of Covid-19 vaccines.

As presented in Figure 4.1, the main simulation modelling techniques include discrete event simulation, business games, continuous simulation, agent-based simulation, hybrid simulation and Monte Carlo simulation. A brief overview of each modelling technique is presented in Subsection 4.6.1 to 4.6.6. An appropriate simulation modelling technique will be identified in Subsection 4.6.7.

4.6.1 Discrete-event simulation

The discrete event simulation technique considers each individual entity that is transported through the system and takes part in the processes (Kersten & Saeed, 2014; Mielczarek & Uziałko-Mydlikowska, 2012). The system is comprised of several events that occur at discrete points in time, each causing the system's

state to change (Ahmadi, 2012; Kersten & Saeed, 2014). In between two events, the state of the system is stationary. The technique can either be time-driven or event-driven (Lingervelder, 2017). For the time-driven scenario, time is divided into equal increments, and each event is considered at the discrete point in time that it occurs (Lingervelder, 2017). For the event-driven scenario, only the discrete point in time when an event occurs is considered (Mielczarek & Uziałko-Mydlikowska, 2012). Different output values have to be estimated for both the time- and event-driven scenarios to evaluate the system's behaviour (Ahmadi, 2012).

4.6.2 Business games

The business games simulation techniques are used to evaluate different aspects of a system by representing the system in a game format that can incorporate human behaviour (Kersten & Saeed, 2014; Lingervelder, 2017). Essential players in the system, such as managers or partners, are allowed to participate in the simulated system and apply their knowledge and skills to obtain a solution (Lingervelder, 2017). Two types of business games exist, namely (Kersten & Saeed, 2014; Lingervelder, 2017): the strategic game and the operational game. The strategic game involves several teams that have to compete for a set number of rounds, while for the operational game only a single team is allowed to interact for a set number of rounds (Kersten & Saeed, 2014; Lingervelder, 2017).

4.6.3 Agent-based simulation

The agent-based simulation technique is capable of representing complex systems (Lingervelder, 2017; Luke & Stamatakis, 2012). The technique involves the creation of agents that each represents certain aspects of a system (Fioretti, 2013; Lingervelder, 2017; Luke & Stamatakis, 2012). The agents are capable of imitating the behaviour of the real object(s), which includes making decisions and interacting with other agents in the system (Fioretti, 2013; Kersten & Saeed, 2014; Lingervelder, 2017; Luke & Stamatakis, 2012). Interaction between different levels of the system can also be considered (Luke & Stamatakis, 2012). The model is used to evaluate the system's behaviour under different scenarios and assists in the decision-making process (Luke & Stamatakis, 2012).

4.6.4 Continuous simulation

The continuous simulation technique does not consider individual entities but rather considers flows, such as material, resources and information, and stocks that form part of the system (Ahmadi, 2012; Lingervelder, 2017; Luke & Stamatakis, 2012; Mielczarek & Uziałko-Mydlikowska, 2012). The model's focus is to understand a complex system and the interaction between its components via feedback loops and non-linear relationships (Kersten & Saeed, 2014; Lingervelder, 2017; Mielczarek & Uziałko-Mydlikowska, 2012). The

modelling technique can also evaluate the interaction between different levels in the system (Luke & Stamatakis, 2012). The time is divided into equal continuous-time increments, and the system's state is continuously adjusted (Lingervelder, 2017). The technique is comprised of both a qualitative and quantitative modelling phase (Kersten & Saeed, 2014).

4.6.5 Hybrid simulation

The hybrid simulation model often involves the use of analytical techniques in conjunction with the simulation techniques (Lingervelder, 2017; Viswanadham et al., 1992). Two different hybrid approaches exist. The first approach is to develop simulation sub-models to assist in the solving of an analytical model (Viswanadham et al., 1992). The second approach is to use the results from a simulation and analytically solve the problem, reducing the need for iterative simulations (Viswanadham et al., 1992).

4.6.6 Monte Carlo simulation

The Monte Carlo simulation technique can simulate complex systems by performing multiple random samples and statistical analysis to gain insight into the system's behaviour (Harrison, 2009; Raychaudhuri). It is a static technique (i.e time-independent) and obtains values for its input variables by randomly sampling from statistical distributions, and output values are obtained by performing a simulation run (Raychaudhuri). The simulation has to be performed several times to obtain an sufficient estimate for the output variable, and statistical analysis is often performed on the output values (Raychaudhuri).

4.6.7 Selection of simulation modelling technique

The choice of a simulation modelling technique is based on certain system elements. These elements are presented in Figure 4.5. The state of a system with dynamic time dependency will change over time, while the state remains stationary over time for a system with static time dependency (Bekker, 2020). A system with discrete-time increments is modelled at the discrete points in time when events occur with no change in the system's state between any two points in time (Bekker, 2020). A system with continuous-time increments will have constantly changing variables with an infinite number of changes that occur between any two points in time (Bekker, 2020).

The manufacturing system for Covid-19 vaccines can be defined in terms of its elements according to the structure of simulation modelling shown in Figure 4.5. As previously discussed, the Covid-19 manufacturing system is expected to be a complex system. An element of the system that significantly contributes to the system's complexity is the approval of vaccine platforms. Limited historical data is available for the prediction of the Covid-19 vaccine platforms' success rate due to the novelty of the virus (McDonnell et al., 2020). The approval of the vaccine platforms is thus a **stochastic variable**.

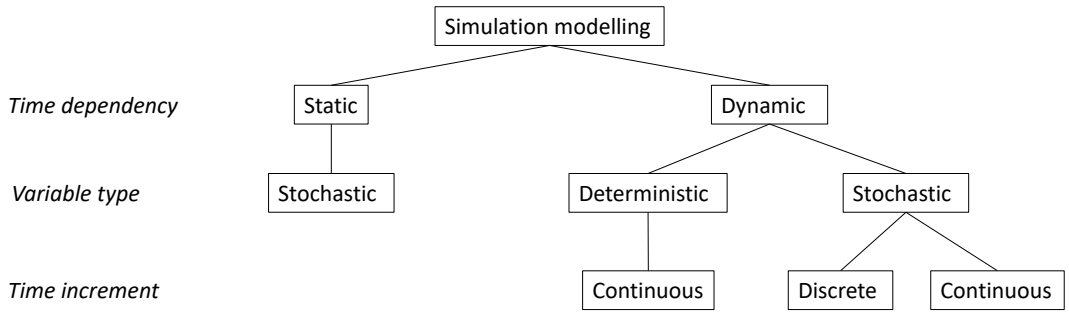

Figure 4.5: Elements of the system that governs the choice of modelling technique (adapted from: Bekker (2020)).

The number of vaccine platforms that are approved for manufacturing can vary over time, and the system has a **dynamic time dependency**.

The manufacturing of a vaccine product is a discrete event, as it starts at a point in time and ends at a point in time. The Covid-19 vaccine manufacturing system can thus be considered in **discrete-event time increments**.

As mentioned in Section 4.6.1, the discrete-event simulation is sub-divided into two types, namely (Lingervelder, 2017): time-driven and event-driven. Tecnomatix Plant Simulation (TPS) was chosen as the simulation software for the development of the Covid-19 vaccine manufacturing system for the following reasons:

- It is licensed to the department;
- Support is available from the vendors; and
- Expertise and support are available from the academic staff.

The TPS simulation software is an a **event-driven** discrete-event simulation application.

From this point forward, referring to the simulation model used for the Covid-19 vaccine manufacturing system will imply that it is an event-driven discrete-event simulation model.

Periods with equal time increments (e.g. a month) will be considered for the system. Changes to the system (e.g. approval of vaccine platforms, activation of vaccine's manufacturing etc.) will only be considered at the start of a period, with no changes to the state of the system considered during any period.

The capacity allocation strategy selected for this system is an off-line allocation mode with the unmet demand being backlogged ((Q4) in Figure 4.2 refer to Section 4.4). Both the approval of new vaccine platforms and the allocation of capacity to manufacturing facilities will occur at the start of a period.

The demand for a specific manufacturing facility will thus be known when capacity allocation is being performed, and an off-line allocation mode can be considered. The model aims to meet the global demand faster by considering different process flexibility configurations. Unmet demand for a period can thus not be discarded but must instead be considered as backlogged.

4.7 Conclusion: Chapter 4

This chapter provided an overview of the modelling of manufacturing systems in literature. The purpose is to identify an appropriate modelling approach for this study's research problem. A modelling approach typology was presented for systems with process flexibility, based on the typology for supply networks by Lingervelder (2017). To provide some context to the modelling literature of vaccine products and manufacturing systems with flexibility, examples gathered via narrative reviews were considered for these topics. A systematic review was conducted to obtain a comprehensive overview of the modelling of manufacturing systems with process flexibility. Some important work in the modelling of process flexibility was also discussed. Based on the system definition, it was identified that an discrete-event simulation modelling technique is an appropriate modelling technique for the considered system.

The next chapter contains a detailed description of the model development for the Covid-19 vaccine manufacturing system.

Chapter 5

System definition and model development

Chapter 4 provided an overview of manufacturing systems modelling to guide the selection process of a modelling approach for this study's research problem. This chapter will discuss in detail the development process of a model for the considered system. The discussion will include defining the system in terms of its world-view and concept model, and building the simulation model in TPS. The model description presented in this section is of the final model after verification and validation steps have been performed. The original model description is presented in Appendix D.

5.1 Defining the system

To conceptualise the Covid-19 vaccine manufacturing system as a simulated model, the system discussed in Section 4.1 can be defined at a higher level by considering its world-view and constructing a concept model. The system's world-view is discussed in Subsection 5.1.1, while the concept model is presented and discussed in Subsection 5.1.2.

It should be noted that standard SI units are considered for the development of the model, e.g. time will be modelled in seconds.

5.1.1 World-view of model

The system can be defined by considering six aspects of the system. These aspects will be defined and discussed for the Covid-19 vaccine manufacturing system. Furthermore, the model assumptions and inputs and outputs will also be addressed.

The first aspect of the system that is considered is its entities. Entities are the objects that move through the system and participate in the process and compete for resources (Bekker, 2020; Ingalls, 2013; Shannon, 1975). The entity for the Covid-19 vaccine manufacturing system is the demand for vaccine products.

The attributes describe a specific aspect of an entity (Bekker, 2020; Shannon, 1975). These aspects may be physical (e.g. mass or volume) or a classification (e.g. type) (Bekker, 2020). In any period of the Covid-19 vaccine manufacturing system, the demand for vaccine products only includes the vaccine platforms already approved at the start of the specific period. This will change periodically.

Resources process the entities that move through the system (Bekker, 2020; Ingalls, 2013; Shannon, 1975). The entities are assigned to resources based on their availability (Bekker, 2020; Ingalls, 2013; Shannon, 1975). The resources for the Covid-19 vaccine manufacturing system are the vaccine platform manufacturing facilities. For any period, only the manufacturing facilities that have an approved vaccine product or which are connected to an approved vaccine platform are available. This will change periodically.

The conditions govern the operation of the system (Bekker, 2020; Ingalls, 2013; Shannon, 1975). Entities can only move through the system if the appropriate conditions are met (Bekker, 2020; Shannon, 1975). The conditions for the Covid-19 vaccine manufacturing system include the following:

- A vaccine platform can only be approved in a specific period if a drawn random number is smaller than its probability of success value for that period;
- A vaccine platform must be approved before it can be manufactured; and
- Only activated facilities (either approved platform or connected with an approved platform) can manufacture products.

Events are moments during the simulation run time when changes to the entities and, consequently, the system state occurs (Bekker, 2020; Ingalls, 2013; Shannon, 1975). Events can include, amongst others, the arrival or departure of an entity at a process and the start or end of the simulation run time (Bekker, 2020). The events for the Covid-19 vaccine manufacturing system include the following:

- If a new vaccine platform is approved, it is added to the approved vaccine list;
- A newly approved vaccine platform's manufacturing facility is activated, and the facility's manufacturing starts;
- If a newly approved vaccine product is connected with an idle manufacturing facility, a change-over time is implemented where after the idle manufacturing facility's capacity is shifted to the approved vaccine platform's facility;
- If a vaccine platform, for which its manufacturing facility's capacity is shifted, is approved, the capacity is shifted back to the newly approved platform after a change-over time has been implemented; and
- Vaccines are manufactured, and completed products leave the system.

The last aspect of the system being considered is the system's state, which is dependent on variables that change over time (Bekker, 2020; Ingalls, 2013; Shannon, 1975). The utilisation of the available capacity and the number of vaccine throughput at a specific time are both system state variables for the Covid-19 vaccine manufacturing system.

The assumptions for the Covid-19 vaccine manufacturing system include the following:

- Complete ability to switch over from one product to the next (Iravani et al., 2005b)
  - If a facility is connected to a product, it can produce each component of the product; and
  - Considering only operational level (Not component level as well).
- Offline allocation of capacity Wang et al. (2019)
  - Demand for vaccine platforms is known at the start of a period; and
  - Considering capacity allocation at discrete points in time;
- All manufacturing capacity has already been constructed prior to the start of the manufacturing horizon;
- The system has unlimited demand for vaccine products;
- The system is faced with no upstream supply restrictions;
- A month is comprised of 30 days; and
- All facilities operate 24 hours per days and no maintenance time is included.

The inputs for the Covid-19 vaccine manufacturing system include the following:

- Probability of success distribution for each vaccine platform;
- Flexibility configuration for a specific simulation run;
- Processing times for each vaccine platform;
- Operating cost for each vaccine platform;
- Change-over times for capacity shift; and
- Number of production lines for each manufacturing facility (capacity).

Lastly, the system's outputs are considered. The model has three outputs, namely the throughput of vaccine products per platform, the operating cost for a scenario, and the change-over cost for a scenario.

5.1.2 Concept model

A concept model is typically formulated to translate the elements of the considered system to a programmable format prior to developing the digital model (Bekker, 2020). The concept model is formulated on paper and considers required data inputs and logic of the proposed model (Bekker, 2020). It furthermore, assists in identifying any insufficient information (Bekker, 2020). A concept model was developed for the Covid-19 vaccine manufacturing system, and is shown in Figure 5.1.

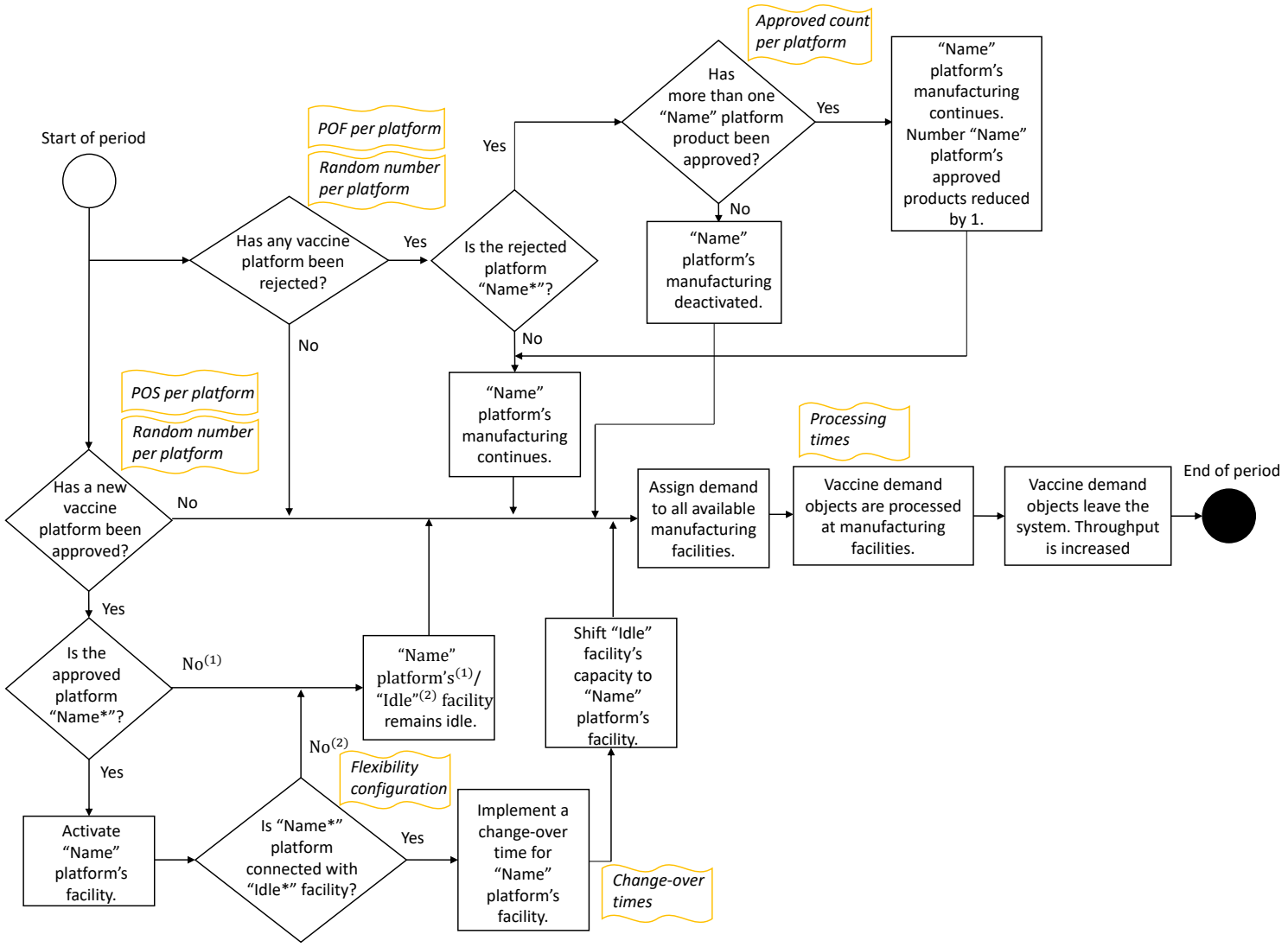

Figure 5.1: Concept model for the Covid-19 vaccine manufacturing system

5.2 Simulating the system

The main sections included in the model are the approval section, rejection section, manufacturing of vaccines, and the shifting of capacity. For the sake of brevity, the detailed model description for the dynamic and stochastic discrete-event simulation model, as developed in Tecnomatix Plant Simulation (TPS), is provided in Appendix C. Two portions of this detailed model description, namely an introduction as well as a description of the vaccine approval section, are however repeated in the main thesis document to provide sufficient insight into the modelling aspect of the work. The model, as it is described here and in Appendix C, incorporates adjustments that were made based on insights derived from the validation process that is described in Chapter 6[1].

5.2.1 Introduction

The goal of the model is to evaluate the impact of different manufacturing process flexibility configurations on the manufacturing system of Covid-19 vaccines. The manufacturing system consists of six vaccine platforms, namely: Live attenuated virus (LAV), Inactivated virus (IV), Subunit protein (SP), Viral vector (VV), DNA, and RNA. The model is divided into four main sections, namely: the approval of vaccines, the rejection of vaccines, the manufacturing of vaccines, and capacity shifting.

A brief overview of the model is provided with detail regarding the operations of each section within the model discussed later. The model considers the manufacturing of vaccines over a time horizon (e.g. five years), which is divided into equal periods of 30 days. The time is indicated in the following manner in TPS: dxd:hh:mm:ss.00, with dd indicating the number of days, hh indicating the number of hours, mm indicating the number of minutes and ss.00 indicating the number of seconds. The first period starts at 00:00:00:00 and ends at 30:00:00:00, while the second period will start at 30:00:00:00 and end at 60:00:00:00. Actions regarding the approval, rejection, and manufacturing of vaccines and the reconfiguration of the manufacturing system can only occur at the start of such a period. Vaccines are approved based on a pre-determined probability of success distribution. Once at least one vaccine product of a platform is approved, the manufacturing of the platform is activated. Manufacturing throughput is measured on a platform level only. Thus, if a second vaccine product of a specific platform is approved, this has no impact as all available manufacturing capacity for the given platform will already have been activated. Approved vaccines may also be rejected based on a pre-determined probability of failure distribution. The manufacturing of a specific vaccine platform will only cease if all previously approved vaccine products of the platform have subsequently been rejected. The manufacturing section is represented as six manufacturing subsections,

[1]For the sake of transparency, a detailed discussion in Appendix D describes the original model before any adjustments were implemented. All of the aspects that are addressed in this appendix are, however, also addressed in Appendix C and readers that are interested in the detailed model description need therefore only read the latter.

each producing one of the six vaccine platforms mentioned previously, with set manufacturing capacity (i.e. a set number of production lines) available to each manufacturing subsection. Each manufacturing subsection is comprised of two facilities equipped with different equipment, namely: stainless-steel, and single-use. The two types of equipment types were only uncovered during the validation interviews and subsequently incorporated into the model.

Process flexibility configurations can be created by setting the production lines of a specific manufacturing facility to have the capability to manufacture more than one vaccine platform. The capacity of an idle vaccine platform's manufacturing facility can be used to manufacture an approved vaccine platform, given that the process flexibility configuration allows it. The shifting of manufacturing capacity from one product to another results in a time delay, which differs for the two different equipment facilities. The model's output is the throughput of vaccine products, operation cost, and switch-over cost and is used to evaluate the performance of a specific process flexibility configuration. Flexibility can be separately incorporated into the manufacturing system for the two different equipment facilities. Figure 5.2 represents a process flexibility configuration in which the LAV platform manufacturing facility's (A) capacity can be shifted to produce the SP and RNA vaccine products, respectively. Each of these platform's facilities is

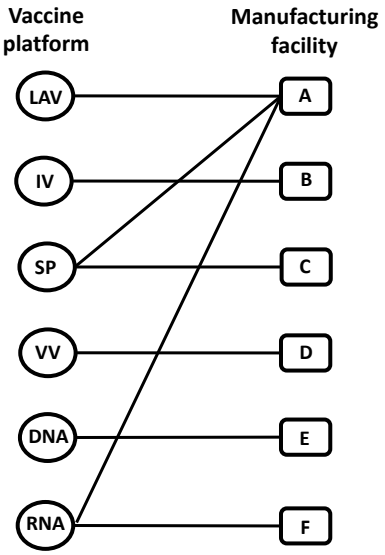

Figure 5.2: A flexibility configuration for vaccine platforms

initially assigned 10 production lines. If, for example, at the start of period 9 of the model run time, the LAV platform has not been approved for manufacturing, but both the RNA and SP platforms are approved, the 10 production lines initially assigned to the RNA platform will immediately start manufacturing RNA vaccine products, and the 10 production lines initially assigned to the SP platform will immediately start manufacturing SP vaccine products. The LAV platform facility's production lines that can be shifted to the

RNA and SP facilities will be divided equally between the two platforms. Both the RNA and SP platforms can thus each receive five additional production lines. Due to the time delay associated with the capacity shifts, these additional production lines will only start producing the RNA and SP vaccine products once the respective time delays have been enforced. If, for example, the LAV platform is then approved at the start of period 17, the five additional LAV production lines assigned to the manufacturing of RNA vaccine products as well as the five additional LAV production lines assigned to the manufacturing of SP vaccine products will immediately be shifted back to the manufacturing of LAV vaccine products. Manufacturing of the LAV products will only start once the associated time delay for switching the production lines back to the LAV facility has been enforced. The model is not a perfect representation of reality. In deciding whether and how to implement simplifications, the ability to accurately investigate the substantive research questions was the primary consideration. For example, in reality, it is likely that, for a variety of reasons, the manufacturing of a vaccine would not commence at the same time as regulatory approval. However, incorporating a delay for this commencement will not clarify insights on the impact of process flexibility. Especially if this delay is variable, incorporating it may obscure model outputs that can assist in drawing clear conclusions on the impact of process flexibility.

The model aims to consider the impact of process flexibility on the throughput of vaccine products over time, given the relatively high "demand" uncertainty created by the approval of vaccines. (Returning to the example in Figure 1 to illustrate, if no LAV, SU, or RNA vaccines were approved during a model run time, all 10 production lines of manufacturing facilities A, C, and F would have remained idle throughout.) To ensure that the findings on the throughput performance of various process flexibility configurations under the approval uncertainty are not obscured, unlimited demand for approved vaccines is assumed. Thus, all available manufacturing capacity is utilised to manufacture approved vaccines. The possibility of vaccine rejection is included in the model to represent the reality of the system. As mentioned previously, the goal of the model is to investigate the impact of process manufacturing flexibility on the throughput of vaccine manufacturing. Considering the rejection of vaccine platforms may obscure the results obtained for the flexibility configurations. It is expected to be highly unlikely that a vaccine product will be rejected once approved for manufacturing. The possibility of vaccine product rejection can be ignored in the model by assigning all the platforms a probability of failure value of zero. To further represent the reality of the system, the manufacturing of a system will only be de-activated if a platform has no approved product at the time since the manufacturing for a specific platform will not be terminated if only one of its products becomes rejected.

5.2.2 Vaccine approval

The graphical representation of the vaccine platform approval section as it has been implemented in TPS is shown in Figure 5.3. The vaccine platform approval section operates in a loop structure. The

VaccineApproval source creates a single object *ApprovedVaccine*, at the start of the model run time and the *ApprovedVaccine* object remains within the loop structure for the remainder of the model run time.

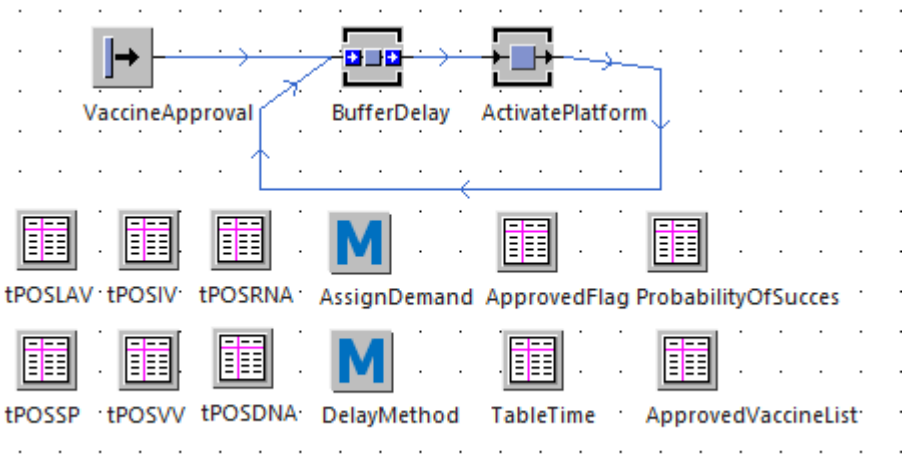

Figure 5.3: Graphical representation of the approval of vaccines

The *BufferDelay* buffer ensures that the *ApprovedVaccine* object remains stationary until the start of a period via the *DelayMethod* method, using the code (SimTalk in TPS) shown in Figure 5.4. When the object arrives at the *BufferDelay* buffer, the code checks if the current time of the simulation, *eventcontroller.SimTime*, is equal to the start of a period. The time value for the start of each period is given in the *TableTime* table; a section of the *TableTime* table is shown in Figure 5.5. If the object arrives at the start of a period, the *BeginPeriod* variable is assigned a true value. Otherwise, the variable is assigned a false value, and a delay time is assigned to the *TimeWait* variable. Suppose the *BeginPeriod* variable has a true value. In that case, the object can proceed to the *ActivatePlatform* station. In contrast, if the *BeginPeriod* variable has a false value, the object is delayed for a time equal to the value of the *TimeWait* variable before it is allowed to proceed to the *ActivatePlatform* station.

The ActivatePlatform has a processing time of one second, and its function is two-fold. It firstly controls which vaccine platform(s) are approved at the start of a period. Secondly, the ActivatePlatform station controls the activation of approved vaccine platforms' manufacturing.

5.2.3 Approval of vaccine platforms

The approval of vaccine platforms at the start of a period is achieved via the *AssignDemand* method. As an example, the code used to control the approval of the LAV platform is shown in Figure 5.6. The approval of the other vaccine platforms is achieved via a similar code.

Simulation experiments performed by McDonnell et al. (2020) generated an estimation of the number of vaccine products for each platform that will be approved over a three-year time horizon. These results

```
for var y:= 1 to TableTime.ydim
    if eventController.simtime = TableTime[1,y] then
        BeginPeriod := true
        exitloop
    elseif eventController.simtime < TableTime[1,y] then
        BeginPeriod := false
        TimeWait := TableTime[1,y] - eventController.simTime
        exitloop
    end
next

if BeginPeriod = true then
    @.move
else wait TimeWait
    @.move
end
```

Figure 5.4: Code used in *DelayMethod* to delay the *ApprovedVaccine object*

were utilised to create a probability of success (POS) distribution over time for each vaccine platform using the cumulative exponential function, given in (5.1). The distribution for each platform is recorded in a *POS* table (e.g. *tPOSSP*). As an example, a graphical representation of the probability of success distribution for the SP platform is given in Figure 5.7, while a section of the *tPOSSP* table is shown in Figure 5.8.

$$\mathrm{POS}_{\mathrm{Platform}}(t) = [1 - e^{-t/beta}] \tag{5.1}$$

When the *ApprovedVaccine* object arrives at the *AssignDemand* station, a random number (e.g. *L*) is created. The random number is an integer of any value between 0 and 100. For each period, the random number is compared to the probability of success value for that period in the *tPOSPlatform* table. If the random number is smaller than the probability of success value for that period, the vaccine platform becomes approved. A true value is assigned to the Approved status column in the *ProbabilityOfSuccess* table; a section of the *ProbabilityOfSuccess* table is shown in Figure 5.9. Record is kept of the number of vaccine products per platform that would have been approved if the approval was considered on a product level by incrementing the *TotalPlatformApproved* (e.g. *TotalLAVApproved*) variable by one when a platform's random number is smaller than its probability of success value for a period.

As discussed in the Vaccine Manufacturing section, capacity can be shifted between platforms. Capacity shift loops control this. When a platform is approved, an object is created at the buffer of its capacity shift loop to activate it (e.g. *.UserObjects.CapacityDecrease.create (LAVBuffer)*), as shown in the code in Figure 5.6. To ensure that only one object is created per loop, the object is only created if the *PlatformCreate* (e.g. *LAVCreate*) variable has a false value. The *PlatformCreate* variable initially has a false value and is assigned a true value after the object has been created.

	time 1
1	0.0000
2	30:00:00:00.0000
3	60:00:00:00.0000
4	90:00:00:00.0000
5	120:00:00:00.0000
6	150:00:00:00.0000
7	180:00:00:00.0000
8	210:00:00:00.0000
9	240:00:00:00.0000
10	270:00:00:00.0000
11	300:00:00:00.0000
12	330:00:00:00.0000
13	360:00:00:00.0000
14	390:00:00:00.0000
15	420:00:00:00.0000
16	450:00:00:00.0000
17	480:00:00:00.0000

Figure 5.5: A section of the *TableTime* table

5.2.4 Activation of vaccine platforms

The *ActivatePlatforms*tation controls the activation of approved vaccine platforms' manufacturing via the *AssignDemand* method. The activation of all the vaccine platforms' manufacturing is achieved similarly. Only the code used to activate the manufacturing of the LAV platform is shown in Figure 5.10.

The code used to activate the manufacturing of a platform can only be executed if the platform has an approved product (i.e. when the platform has a true value in the Approved status column of the *ProbabilityOfSuccess* table, refer to Figure 5.9). Since the model only considers one vaccine product per platform at any given time, *ApproveFlag[2,y]* (e.g. *ApproveFlag[2,1] for the LAV platform*) variable is used to prevent more than one vaccine product of a platform from being approved simultaneously. A section of the *ApproveFlag* table is shown in Figure 5.11. Thus, for example, a new vaccine product can be recognised as approved only when the *ApproveFlag[2,y]* variable has a false value. The *ApproveFlagLAV* variable has an initial value of false and is assigned a true value after the approval of the first LAV vaccine product. If the *ApproveFlag[2,y]* variable has a true value, the approval of the additional vaccine products will not be considered.

As shown in the code in Figure 5.10, an approved vaccine platform's manufacturing is activated by

```
var L: integer
L := floor(z_uniform(1,1,100))
Ltable[1,Ltable.ydim+1] := eventController.simtime
Ltable[2,Ltable.ydim] := L
LTable[4,LTable.ydim] := MTable[1,1]
LTable[5,LTable.ydim] := ProbabilityOfFailure[2,1]
for local y := 1 to tPOSLAV.ydim
    If eventController.SimTime = tPOSLAV[1,y] + 0:01 then
        Ltable[3,Ltable.ydim] := tPOSLAV[2,y]
        If L < tPOSLAV[2,y] then
            ProbabilityOfSucces[3,1] := true
            TotalLAVApproved := TotalLAVApproved +1
            If LAVCreate = false then
            .UserObjects.CapacityDecrease.create(LAVBuffer)
            LAVCreate := true
            end
        end
    end
next
```

Figure 5.6: Code used in *AssignDemand* to control the approval of LAV vaccine products

assigning a true value to the *ConnectPlatform* (e.g. *ConnectLAV*) variable. The number of approved vaccine products is counted by increasing the value of the *ApprovedVaccineCnt* by one when a vaccine platform is approved. Further, an entry is made in the *ApprovedVaccineList* table, shown in Figure 5.12. In the first column of the table, the name of the vaccine platform is entered (*.UserObjects.LAVPlatform*), the status of the vaccine platform is changed to *Approved* in the second column, and the time at which the platform is approved is entered in the third column.

As mentioned previously, the model makes provision for a platform that was once approved to be rejected in future. This is described in more detail in Subsection C.3. After a vaccine platform has been rejected, a new vaccine product for the platform may be approved. A probability of failure value is thus assigned to the platform in the *POF* column of the *ProbabilityOfFailure* table. This is discussed in more detail in Subsection C.3.1.

A section of the *DelayTimes* table referred to in the code in Figure 5.10, is shown in Figure 5.13. The *DelayTimes* table contains the delay (i.e. switchover time) for each platform's manufacturing facilities when capacity is shifted between products. Separate delay times are given for the stainless-steel and the single-use equipment facilities. This is discussed in greater detail in Subsection C.4. Once a vaccine platform has been approved, the code searches for the platform in the *DelayTimes* table and assigns a true value to the *ApprovedStatus* column of the *DelayTimes* table (e.g. textitDelayTimes[4,3] for the LAV platform), which represents the same variable as *ConnectPlatform* (e.g. *ConnectLAV*).

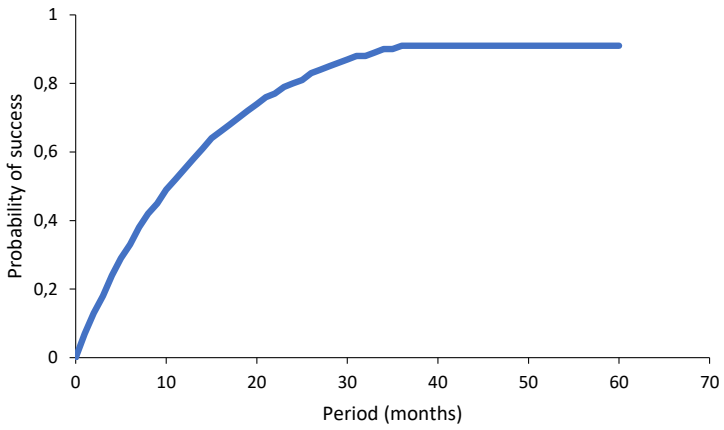

Figure 5.7: Graphical representation of the probability of success values for the SP platform over three years

The code includes a section that relates to the approval of a vaccine product for a platform that has previously been both approved and rejected and for which the capacity was not shifted during the rejected state (e.g. *LAVApprovedCnt* >= 2 and *LAVLines* = *Lines[2,1]*). The code is explained in this section as presented in Figure 5.9. However, reference is made to the shifting of capacity and the number of production lines assigned to a manufacturing system which are discussed in Subsection C.4. If a vaccine platform, which matches the aforementioned criteria, is approved, its manufacturing facility can start manufacturing without delay (*LAVFacilitySS.entrancelocked := false*). The manufacturing facility is assigned its initial number of production lines (*LAVFacilitySS.xdim := Lines[2,1]*). The example only refers to the stainless-steel (SS) equipment facility, but the same action will also be performed for the platform's single-use (SU) equipment facility, as seen in Figure 5.10.

	time 1	integer 2
1	0.0000	0
2	30:00:00:00.0000	7
3	60:00:00:00.0000	13
4	90:00:00:00.0000	18
5	120:00:00:00.0000	24
6	150:00:00:00.0000	29
7	180:00:00:00.0000	33
8	210:00:00:00.0000	38
9	240:00:00:00.0000	42
10	270:00:00:00.0000	45
11	300:00:00:00.0000	49
12	330:00:00:00.0000	55
13	360:00:00:00.0000	55
14	390:00:00:00.0000	58
15	420:00:00:00.0000	61
16	450:00:00:00.0000	64
17	480:00:00:00.0000	66

Figure 5.8: A section of the *tPOSSP* table

	string 1	real 2	boolean 3
string	Platform		Approved
1	.UserObjects.LAVPlatform	0.00	false
2	.UserObjects.IVPlatform	0.00	false
3	.UserObjects.SPPlatform	0.00	false
4	.UserObjects.VVPlatform	0.00	false
5	.UserObjects.DNAPlatform	0.00	false
6	.UserObjects.RNAPlatform	0.00	false

Figure 5.9: Section of the *ProbabilityOfSuccess* table

```
If ProbabilityOfSucces[3,1] = true then
    If ApprovedFlag[2,1] = false then
        ConnectLAV := True
        For local y:= 1 to DelayTimes.ydim
            if DelayTimes[1,y] = "LAV" then
                DelayTimes[4,y] := true
            end
        next
        LAVApprovedCnt := LAVApprovedCnt + 1
    if LAVApprovedCnt >= 2 and LAVLines = Lines[2,1] then
        LAVFacilitySS.entrancelocked := false
        LAVFacilitySU.entrancelocked := false
        LAVFacilitySS.xdim := Lines[2,1]
        LAVFacilitySU.xdim := Lines[2,1]
    end
    ApprovedVaccineList[1, ApprovedVaccineList.ydim+1] := .UserObjects.LAVPlatform
    ApprovedVaccineList[2, ApprovedVaccineList.ydim] := "Approved"
    ApprovedVaccineList[3, ApprovedVaccineList.ydim] := eventController.simTime
    LAVApproval := eventController.simTime
    ApprovedVaccineList[6, ApprovedVaccineList.ydim] := false
    ApprovedVaccineCnt := ApprovedVaccineCnt +1;
    ProbabilityOfFailure[2, ProbabilityOfFailure.ydim-5] := POFTable[2,1]
    ApprovedFlag[2,1] := True
    end
end
```

Figure 5.10: Code used in *AssignDemand* to activate the manufacturing of the LAV platform

	string 1	boolean 2
string	Platform	Approved status
1	LAV	false
2	IV	true
3	SP	false

Figure 5.11: A section of the *ApproveFlag* table

	object 1	string 2	time 3
string	MU	Approved	Period
1	*.UserObjects.LAVPlatform	Approved	1.0000
2			
3			

Figure 5.12: A section of the *ApprovedVaccineList* table

	string 1	time 2	time 3	boolean 4	boolean 5
string	Platform	Delay Time (SS)	Delay Time (SU)	ApprovedStatus	ApprovedFlag
1	RNA	59:23:59:56.0000	29:23:59:56.0000	false	false
2	SP	59:23:59:56.0000	29:23:59:56.0000	false	false
3	LAV	59:23:59:56.0000	29:23:59:56.0000	false	false
4	IV	59:23:59:56.0000	29:23:59:56.0000	true	false

Figure 5.13: A section of the *DelayTimes* table

5.3 Conclusion: Chapter 5

This chapter provided a detailed description of the development of the discrete-event simulation model for Covid-19 vaccine manufacturing system. The simulation model was first conceptually defined by considering its world-view and constructing a concept model. The simulation model was then developed in Tecnomatix Plant Simulation.

The next chapter will describe the verification and validation process followed for the simulation model.

Chapter 6

Model verification and validation

The verification and validation process of the developed model, defined and discussed in Chapter 5, is discussed in this chapter. A two-step process was performed to ensure that the model meets the specified requirements and represents a realistic system.

6.1 Verification and validation approach

Verification can be described as identifying whether a product's development has been performed correctly (Srai et al.; Thacker et al., 2004). It generally only considers the operation of the product and does not consider the link between the product output and the research question, the latter is assessed via validation (Srai et al.). Validation is furthermore also performed to assess the reliability and the quality of the model output that can be obtained (Srai et al.).

The overarching verification and validation process logic is depicted in Figure 6.1.

Each verification and/or validation process depicted in the figure consist of two phases, namely: an evaluation phase, and an amendment phase. The evaluation phase for verification comprised of several model execution tests. If required, troubleshooting and corrections were performed after an execution test, forming the amendment phase for verification. The evaluation phase for validation comprised of interviews with SMEs. Feedback from the experts was used during the amendment phase to make adjustments and/or improvements to the model.

The verification and validation processes are described in significantly more detail in Sections 6.2 and 6.3, respectively. For the sake of brevity, the verification process is described only once, although tests were executed in several iterative rounds, following successive rounds of changes to the model. Similarly, for the sake of brevity, only one set of verification tests is described in the main text of the document, whilst the remainder of the tests that employ similar logic to test other aspects of the model logic, are described in Appendix E.

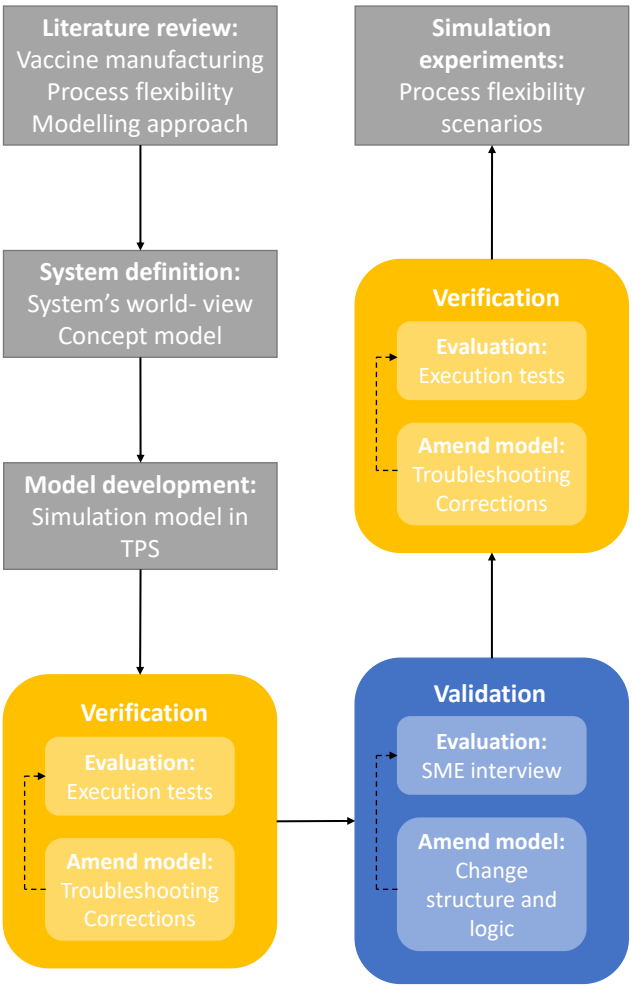

Figure 6.1: Verification and validation process logic

6.2 Desktop verification

The verification process is discussed in detail in this section. This includes an overview of the objectives of the verification process as well as the approach employed. Finally, as an example of the implementation of the verification process, the execution testing of the approval section is described in detail.

6.2.1 Verification motivation

The verification process was performed to ensure that the model functions properly. This involved ensuring that the following objectives were met:

- Ensure that the code used to control the model contains no errors;

- Verify that each model section's code is executed as intended; and
- Verify that the model as a whole functions correctly when all the model sections are combined.

6.2.2 Verification approach

The verification objectives mentioned in Subsection 6.2.1 were achieved by performing several model execution tests. The model was considered in its different sections, namely: approval section, rejection section, manufacturing system, and capacity shift and time delay. Each of the sections were first verified separately, where-after some sections were verified in parallel. During the preliminary verification process, issues in the model were noticed. These issues were rectified, and new verification runs were performed. Verification tests were also performed to ensure that the two types of equipment facilities (stainless-steel and single-use, refer to 5.2) can be operated independently.

The testing of the approval section is described in full detail in Subsection 6.2.3. As detailed descriptions of the verification of the other model sections is not provided in the main document, an overview of the approach employed for each model section is provided here. The troubleshooting process performed during the verification runs is discussed in Subsection 6.2.4.

6.2.2.1 Verification approach for rejection section

The rejection section was verified via two approaches. The first approach involved manipulating both the random number and the probability of failure values for a platform (refer to Subsection C.3.1 for a description of how the random number and probability of failure values are used in the rejection logic). The second approach involved the manipulation of only the probability of failure value for the platform, while the random number was allowed to be generated by the simulation software. A detailed description of the verification of the rejection section is provided in Section E.1.

6.2.2.2 Verification approach for manufacturing section

The verification of the manufacturing section was relatively complex and five approaches were employed, as described in Section E.2. The first approach involved considering only the operation of the manufacturing subsections. The approval of a vaccine platform was manually controlled via manipulation of the *ConnectPlatform* variable to ensure that the activation of the manufacturing subsections and the processing of objects in the subsections function correctly. The second approach incorporated the approval section. The approval of vaccine platforms was manually controlled via the manipulation of the probability of success and random number U values. The third approach incorporated the approval and rejection sections. The approval of vaccines were manipulated in the same manner as approach two. The rejection of vaccine platforms were manually controlled via the manipulation of the probability of failure and random number

M values. For the fourth approach, only the approval section was incorporated. The random number U was manipulated to create more than one period in which the platform would be approved to ensure that a platform is approved only the first time. For the final approach, the approval and rejection sections were incorporated. No manipulation was performed and the random numbers U and M were allowed to be generated by the simulation software.

6.2.2.3 Verification approach for capacity shifts and time delays

The implementation of capacity shifts and time delays was verified by combining the manufacturing section and the approval and rejection sections whilst manually adjusting the random numbers, the probability of success and the probability of failure values for a platform to create different scenarios for which the outcome can be predicted without relying on the model. The scenarios were designed to increase in complexity, by increasing the number of platforms considered. For each combination of platforms, several distinct cases were designed and the model behaviour was predicted and evaluated over successive time periods. A total of 27 cases were tested. The verification of capacity shifts and time delays is described in detail in Section E.3.

6.2.2.4 Types of equipment facilities

The two types of equipment facilities were only incorporated into the model after the validation interviews and did not form part of the initial verification tests. To ensure that the two types of equipment facilities operate independently, two approaches were employed. For the first approach, only the stainless-steel equipment facilities were allowed to operate. For approach two, both the stainless-steel and the single-use equipment facilities were allowed to operate. Only the single-use equipment facilities were allowed to be flexible. Several distinct cases were designed for the two approaches and the model behaviour was predicted and evaluated over successive time periods. A total of 27 cases were tested.

6.2.3 Verification of the approval section

As an example of the implementation of the verification process, the execution testing of the approval section is described in detail in this section.

The approval section makes use of pre-determined probability of success values over time to control the approval of vaccine platforms. At the start of a period, a random number is generated for each vaccine platform and compared to its probability of success value for that period. Only one product per platform is considered at a specific time, thus while the manufacturing for a product is active, the approval of other products for the same platform is not considered. The manufacturing of vaccines is thus only considered on the platform level, not on the individual product level.

The approval section adds an approved platform to the *ApprovedVaccineList* table by indicating the name of the platform (e.g. *UserObjects.LAVPlatform*) and the time at which the platform was assigned an *Approved* status. The approval section also controls the following variables: *ProbabilityOfSucces[3,y]*, *ApprovedFlagPlatform*, *ConnectPlatform*, *PlatformApprovedCnt*, and *ApprovedVaccineCnt*. When a platform is approved, the following variables are assigned a *true* value: *ProbabalityOfSuccess[3,y]*, *ConnectLAV*, and *ApprovedFlagPlatform*. The *PlatformApprovedCnt* variable is incremented by one when the platform's random number is smaller than its probability of success value for that period. The *ApprovedVaccineCnt* variable is incremented by one when a platform has been approved. When the first product for a platform is approved, the approval section activates the creation of an object at the platform's capacity control line. The approval section controls the *PlatformCreate* variable to ensure that this only occurs when the first product is approved.

The approval section was verified via two approaches. The first approach involved the manipulation of both the random number, referred to as U in the results presented in Table 6.1 and Table 6.2, and the probability of success values for a platform. The second approach involved the manipulation of only the probability of success value for the platform, while the random number was allowed to be generated by the simulation software.

6.2.3.1 Approach one

The random number and probability of success values for a platform were manipulated to create different scenarios for which the outcome can be predicted and verified. The results obtained for the different scenarios for the RNA platform are shown in Table 6.1.

Case one represents the scenario where the random number U is smaller than the probability of success value. It is thus expected that the RNA platform will be approved, assigning a true value to the following variables: *ProbabilityOfSucces[3,6]*, *ApprovedFlagRNA*, and *ConnectRNA*. Both the *RNAApprovedCnt* and *ApprovedVaccineCnt* variables should be incremented by one.

Case two represents the scenario where the RNA platform has already been approved, and the random number is smaller than the probability of success value. Since only one product per platform is considered at a time, no change to the variables, except *RNAApprovedCnt*, is expected.

Case three represents the scenario where the random number U is larger than the probability of success value, and it is thus expected that the platform will not be approved, and no changes to any of the variables are expected.

Case four represents the scenario where a platform that has previously been rejected has a random number that is smaller than its probability of success value. The results are expected to be the same as that of case one.

Table 6.1: Results for RNA platform for manual verification of approval section

Case 1		
Conditions	**Expected Results**	**Results**
Plan A: *POSRNA* = 100%,	*ProbabilityofSucces[3,6]* = *true*	✓
U = 45	*ConnectRNA* = *true*	✓
Plan B: *POSRNA* = 75%,	*ApprovedVaccineList*: *RNAPlatform* Approved	✓
U = 45	*ApprovedVaccineCnt* = 1	✓
Plan C: *POSRNA* = 50%,	*ApprovedFlagRNA* = *true*	✓
U = 45	*RNAApprovedCnt* = 1	✓
Case 2		
Conditions	**Expected Results**	**Results**
POSRNA = 100%	*ProbabilityofSucces[3,6]* = *true*	✓
U = 45	*ConnectRNA* = *true*	✓
ApprovedFlagRNA = true	No new entry in *ApprovedVaccineList*	✓
(*RNAPlatform* already approved)	*ApprovedVaccineCnt* = 1	✓
	ApprovedFlagRNA = true	✓
	RNAApprovedCnt = 2	✓
Case 3		
Conditions	**Expected Results**	**Results**
Plan A: *POSRNA* = 50%,	*ProbabilityofSucces[3,6]* = *true*	✓
U = 50	*ConnectRNA* = *false*	✓
Plan B: *POSRNA* = 25%,	No new entry in *ApprovedVaccineList*	✓
U = 45	*ApprovedVaccineCnt* = 0	✓
Plan C: *POSRNA* = 0%,	*ApprovedFlagRNA* = *false*	✓
U = 45	*RNAApprovedCnt* = 0	✓
Case 4		
Conditions	**Expected Results**	**Results**
POSRNA = 100%	*ProbabilityofSucces[3,6]* = true	✓
U = 45	*ConnectRNA* = *true*	✓
RejectedFlagRNA = *true*	*ApprovedVaccineList*: *RNAPlatform* Approved	✓
(*RNAplatform* already rejected)	*ApprovedVaccineCnt* = 1	✓
	ApprovedFlagRNA = *true*	✓
	RejectedFlagRNA = *false*	✓
	RNAApprovedCnt = 1	✓

6.2.3.2 Approach two

In this approach, the random number was not manipulated, and the results are shown in Table 6.2. For case one, the probability of success value was set to 100% for all the platforms, and it is expected that all the platforms will be approved, given that the random number is smaller than 100%. For case two, the simulation was allowed to run over four consecutive periods with the probability of success value initially set at 75%. All platforms with a random number smaller than their probability of success value are expected to be approved at the start of a period. In the results presented in Table 6.2, an approved platform is assigned a zero probability of success value at the start of the next period. It is not executed in the simulation software in this manner, but it is simply done to indicate that another product will not be approved for this platform regardless of the value of the random number. If a platform is approved, the platform will be added to the *ApprovedVaccineList* table, while no action will occur if a vaccine is not approved. After a platform has been approved, the platform will remain approved for the remainder of the run.

6.2.4 Troubleshooting process

As mentioned in Section 6.1, errors in the model were identified after the preliminary verification tests. These errors and the process of troubleshooting to rectify the errors are discussed in this section.

Many errors were identified during the verification process that occurred due to typing errors in the code, causing the expected results to not be achieved. An example of such a typing error is to change the order of the word or letters in a variable's name (e.g. *ConnectPlatform* rather than *PlatformConnect*). Another example of a typing error is to refer to the wrong column in a table (e.g. *PlatformConnect[3,y]* rather than *PlatformConnect[1,y]*). A final example of typing errors that occurred is that sections of code were copied to achieve the same action for the different platforms, however, the names of the variables were not adjusted accordingly.

The code controlling the entries in the *ApprovedVaccineList* table had to be adjusted to avoid the repetition of an entry in the table. Originally, the code was developed to create a new entry in the *ApprovedVaccineList* table in the event that any of the variables in *ProbabilityOfSucces[3,y]* column had a true value. However, this action is performed at the start of each period. Consequently, for every period after the approval of a platform, an entry was made for that platform in the *ApprovedVaccineList* table. This was rectified by introducing the *ApprovedFlagPlatform* variable in the *AssignDemand method*. The *ApprovedFlagPlatform* variable ensures that each approved platform only receives one entry in the *ApprovedVaccineList* table. The *ApprovedFlagPlatform* variable has an initial value of *false* and is assigned a *true* value after the first entry in the *ApprovedVaccineList* table for the approved platform is made.

An adjustment was required to the approach of removing additional capacity from a platform that became rejected. The capacity was initially removed by assigning the platform's original number of produc-

Table 6.2: Results for verification of approval section with no manipulation of random number

Case 1				
Platform	**POS**	**U**	**Status**	**Action**
LAV	100	93	Approved	Added to *ApprovedVaccineList*
IV	100	99	Approved	Added to *ApprovedVaccineList*
SP	100	43	Approved	Added to *ApprovedVaccineList*
VV	100	91	Approved	Added to *ApprovedVaccineList*
DNA	100	92	Approved	Added to *ApprovedVaccineList*
RNA	100	10	Approved	Added to *ApprovedVaccineList*
Case 2				
Period 1				
Platform	**POS**	**U**	**Status**	**Action**
LAV	75	88	Not approved	No action occurs
IV	75	84	Not approved	No action occurs
SP	75	73	Approved	Added to *ApprovedVaccineList*
VV	75	76	Not approved	No action occurs
DNA	75	76	Not approved	No action occurs
RNA	75	3	Approved	Added to *ApprovedVaccineList*
Period 2				
Platform	**POS**	**U**	**Status**	**Action**
LAV	75	1	Approved	Added to *ApprovedVaccineList*
IV	75	75	Not approved	No action occurs
SP	0	98	Already approved	Remains approved
VV	75	15	Approved	Added to *ApprovedVaccineList*
DNA	75	88	Not approved	No action occurs
RNA	0	23	Already approved	Remains approved
Period 3				
Platform	**POS**	**U**	**Status**	**Action**
LAV	0	22	Already approved	Remains approved
IV	75	69	Approved	Added to *ApprovedVaccineList*
SP	0	48	Already approved	Remains approved
VV	0	3	Already approved	Remains approved
DNA	75	37	Approved	Added to *ApprovedVaccineList*
RNA	0	8	Already approved	Remains approved
Period 4				
Platform	**POS**	**U**	**Status**	**Action**
LAV	0	4	Already approved	Remains approved
IV	0	54	Already approved	Remains approved
SP	0	7	Already approved	Remains approved
VV	0	29	Already approved	Remains approved
DNA	0	60	Already approved	Remains approved
RNA	0	39	Already approved	Remains approved

tion lines to its facility immediately after the platform had become rejected. This created an error as these production lines were still busy processing objects at the time the platform became rejected, and the lines could not immediately be removed. This was rectified by creating a variable *RemovePlatformWait*. When a platform is rejected, the *RemovePlatformWait* variable is assigned the value of the facility's processing time via the *RemoveVaccines* method. A time delay equal to the value of the *RemovePlatformWait* variable is enforced before the number of production lines for the facility is changed.

Finally, an error was identified with the implementation of the time delay when a previously rejected platform became approved again. When a platform which can receive capacity from an idle facility is approved a second time, the capacity was immediately shifted to the approved platform with no time delay being enforced. During the troubleshooting process, it was identified that the *ChangeOverPlatformTime* variable remains *true* after the platform has been terminated. Consequently, the code implementing the time delay for the newly approved platform is never executed. This was rectified by assigning a *false* value to the *ChangeOverPlatformTime* variable in the *RemoveVaccines* method after a platform has been terminated.

6.3 Validation

The validation process is discussed in this section. This includes an overview of the motivation for validation, the validation methodology, the interview procedure, and the analysis and interpretation of the data gathered through the validation interviews.

6.3.1 Validation motivation

As mentioned in Section 4.1, the model was developed to investigate a theoretical Covid-19 vaccine manufacturing system to obtain insights into the real-world system. Validation of the model development process is required to ensure that the model represents a realistic system. As discussed in Subsection 2.2, the process flows diagrams depicting the manufacturing process of the active drug substance for different vaccine platforms contain several incomplete sections, due to limited detail in the description of these processes in literature. Consequently, these are also validated to ensure an accurate understanding of the manufacturing processes.

The following objectives are defined for the validation process:

- Ensure that the current vaccine manufacturing systems are understood correctly at a basic level;
- Investigate whether the assumptions made during model development are realistic; and
- Obtain realistic estimates for input parameters.

Understanding the current vaccine manufacturing systems at a basic level provides insight into aspects such as: how vaccine manufacturing facilities are currently operated; what the main considerations are when designing a vaccine manufacturing facility, and which process flexibility configurations could potentially be feasible.

Some assumptions made during the initial model development were based on knowledge gained from the limited available literature. These assumptions may lead to an inaccurate representation of the realistic system. Therefore, these assumptions must be validated by experts with knowledge of the vaccine manufacturing industry.

The model requires data for the following input parameters: production time per platform; available capacity per platform; operating cost per platform, and change-over cost and -time per platform. Obtaining estimates from experts will contribute to the representation of a realistic system.

6.3.2 Validation methodology

The validation objectives mentioned in Subsection 6.3.1 were achieved by performing semi-structured interviews with SMEs in the fields of vaccine manufacturing and vaccine development. The intent was to also include SMEs in the field of process flexibility, but unfortunately no SMEs from this field agreed to participate in the validation process. This is not viewed as a serious limitation, however, as the literature on process flexibility that informs the research is comprehensive, and none of the objectives of the validation process relate specifically to process flexibility.

During the first round of invitations, SMEs were identified as the corresponding authors of relevant articles published in 2010 or later. Invitation to six SMEs in the fields of vaccine manufacturing and vaccine development was extended, while five invitations to SMEs in the field of process flexibility were extended. Two SMEs in the fields of vaccine manufacturing and vaccine development agreed to participate, while no SMEs in the field of process flexibility agreed to participate. During the interviews with SMEs, contact details to other potential SMEs were received, and invitations were extended to an additional nine SMEs in the fields of vaccine manufacturing and vaccine development. Five of these SMEs agreed to participate, resulting in a total of seven SME participants. Background information of the participants is given in Table 6.3. As indicated, each SME has extensive, relevant experience and several of the SMEs occupy senior positions in the field of vaccine manufacturing and development. ID codes are used to refer to the participants to allow for anonymous reporting.

Table 6.3: Background information on participating SMEs

			Relevant experience		
No	**Affiliation**	**Academic qualifications**	**Vaccine manufacturing**	**Process flexibility**	**Years of experience**
1	Vice-chair at pharmaceutical foundation developing vaccines	BSc(Chemical Engineering) MSc(Chemical Engineering)	✓		43
2	Technical officer, focusing on vaccine product development, at a global health organisation	BSc(Biotechnology and Genetics) MSc(Public health)	✓		15
3	Acting executive director of manufacturing and supply chain at pharmaceutical foundation developing vaccines	BEng(Chemical)	✓		30
4	Director of manufacturing and supply chain networks at pharmaceutical foundation developing vaccines	BscHons(Industrial Biology), PhD(Biochemical Engineering)	✓		25
5	Group leader of downstream processing at vaccine manufacturing company	PhD(Synthetic Organic Chemistry)	✓		15
6	Deputy director at a global foundation focusing on CMC strategies and enhancing vaccine development	BSc(Chemical Engineering), PhD(Biochemical Engineering)	✓		25

Continued on next page

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			Relevant experience		
No	**Affiliation**	**Academic qualifications**	**Vaccine manufacturing**	**Process flexibility**	**Years of experience**
7	Chief investment officer at a biotechnology company	MA(Hons) Philosophy, Politics, and Economics Master of Public Administration	✓		3

The data gathered during the SME interview process was analysed via a three-step process, which included identifying topics (or themes), coding the interview transcripts using these topics, and finally interpreting and summarising the information obtained on each topic. This process described in more detail in Subsection 6.3.4.

6.3.3 Interview procedure

As mentioned in Subsection 6.3.2, semi-structured interviews were performed as this allows flexibility during the interview for both the interviewer and the SME to deviate from the interview guide at any time during the interview. Welman et al. (2005) argue that, because unstructured interviews are not limited to pre-determined questions, they allow a conversation to evolve more naturally based on a specific topic. Advantages of this type of interview include: that questions can be adjusted or added as required; and that further clarification on discussion areas can be obtained (Welman et al., 2005). This allows an opportunity to obtain greater insights on specific topics.

All SMEs were invited via email. The interview guide (refer to Appendix F) and informed consent documents accompanied the invitation. The interview guide provided SMEs with background on the model that was developed and an indication of the topics that will be discussed. Willing SMEs provided their consent to participate via email.

All the interviews were conducted on the online platform Microsoft Teams. The interviews followed the following procedure:

1. The interviewer presented an overview of the study and the model that has been developed for the participant.

2. The interviewer asked for permission to record the interview to capture the participant's input.

3. The participant was asked to provide background on their experience and knowledge in the field of vaccine manufacturing and vaccine development.

4. A discussion proceeded, in line with the interview guide.

5. Follow-up questions were asked by the interviewer if further clarification was required on a specific topic.

The questions in the interview guide were structured around meeting the validation objectives defined in Subsection 6.3.1. Questions related to the following main topics were included: contextual perspective, vaccine manufacturing, process flexibility, and the approval and rejection of vaccines.

The contextual perspective questions were focused on gaining insight into the current vaccine manufacturing systems. This included gaining insight into what challenges the vaccine manufacturing systems faced during the Covid-19 pandemic and how they responded. Furthermore, questions were focused on understanding whether manufacturing facilities are generally constructed for only one product or platform or whether some flexibility has already been incorporated into the industry.

The vaccine manufacturing questions were focused on gaining insight into different aspects of the vaccine manufacturing process. This involves questions on production times, output measurements, and manufacturing capacity. These questions are directly related to the appropriate development of the model.

The process flexibility questions were focused on understanding how process flexibility in vaccine manufacturing systems can be implemented. Questions regarding feasible flexibility configurations for vaccine platforms and the implications of the change-over process in the vaccine manufacturing systems were included. Furthermore, the questions were focused on obtaining estimates for input parameters, such as production cost, construction cost, production time, and change-over time.

The measurement of flexibility questions were focused on validating that the output measurement for the model is appropriate. This included gaining insight into the measurement approaches typically used to measure the performance of vaccine manufacturing systems in industry.

The approval and rejection of vaccines questions were focused on obtaining estimates for the likelihood that vaccine platforms may become approved for Covid-19 and the likelihood of products being removed from the market after approval.

The preliminary process flow diagrams were made available to the SMEs during the unstructured interviews. SMEs provided guidance on how to improve the process flow diagrams, including by providing information on aspects of the process flows that could not be clearly discerned from descriptions in literature. The guidance and information provided by the SMEs were used to draw up the complete process flow diagrams, presented in Section 2.2.

6.3.4 Data analysis and interpretation

As was briefly mentioned before, data gathered during the SME interview process was analysed via a three-step process. The first step in analysing the data gathered from the interviews consisted of reading through

the interview transcripts and identifying topics that were addressed during the interviews. Six main topics were identified, namely: contextual perspective, equipment, manufacturing of vaccines, measurement of a system, manufacturing flexibility, and participant information. Each topic was sub-divided into more topics as indicated in Table 6.4.

The second step involved coding the data, using the Atlas.ti software package. Coding involved labelling sections of the transcript according to the topics presented in Table 6.4. The coding step is performed to organise the SME's input to allow easier data interpretation. A section may have multiple labels assigned to it, depending on the topics that are addressed in the section.

The third and final step involved the interpretation and reporting of the data. The feedback from the SMEs will be discussed in the remainder of this section. The participant information topic is not discussed in this section, as a summary of each participant's background has already been provided in Table 6.3.

6.3.4.1 Contextual perspective: Covid-19 context and pandemic preparedness

The manufacturing network is faced with many challenges and experienced even more challenges during the Covid-19 pandemic. SME 6 mentioned that one of the challenges that arose during the pandemic was a shortage in the supply of specialised single-use bags. The suppliers of these bags were not prepared to upscale to meet the demand. SME 1 ascribed this to insufficient flexibility in the supply chains of vaccine manufacturing.

Several approaches can be followed when preparing capacity for the event of a pandemic. According to SME 6, constructing and preparing new facilities for manufacturing vaccines can take several years, typically around four years. Using existing facilities can greatly contribute to making capacity available more timeously. SME 1 also mentioned that constructing capacity solely for pandemic preparedness is not a feasible strategy as this may result in the facility being idle for some time, while no products are required. Such an approach would lead to operational costs that are associated with maintaining idle facilities, that can not be sustainably financed.

SME 6 mentioned that an approach to being prepared for capacity during a pandemic can be to use existing facilities that are continuously manufacturing products, such as the vaccine for measles, to produce pandemic-related products if required. Both SME 2 and SME 6 mentioned that a challenge arising from this approach is that the original product still has to be manufactured, but its manufacturing capacity would be temporarily lost.

According to SME 6, an approach that was considered for the Covid-19 pandemic was the use of seasonal flu vaccine manufacturing facilities as these vaccines are only required seasonally, and the capacity can be made available to pandemic vaccine manufacturing during off-season periods. Unfortunately, this did not work as well as planned. According to SME 2, studies have also been performed to consider using

Table 6.4: Categorisation of topics addressed during interviews

Main topic	Code
Contextual perspective	African context
	Approval
	Challenges: Facilities
	Challenges: Operation
	Contract manufacturers
	Contract vs pharmaceutical companies
	Covid-19 context
	Information shared with contract manufacturers
	Preparing for pandemic
	Regulatory
	Rejection of vaccines
	Single product vs many
Manufacturing of vaccines	DNA vaccine
	Manufacturing processes
	Processing time
	RNA vaccine
	Types of platforms
	Technology platforms
	Unit of measurement
Equipment	Bioreactor
	Other equipment
	Single-use bioreactor
	Single-use vs fixed equipment
Measurement of a system	Cost facilities
	Cost production
	Fixed cost
	Fixed vs Change-over cost
	Grants
	Manufacturing cost
	Performance
	Troughput measurement
Manufacturing flexibility	Flexibility in industry
	Labour flexibility
	Process flow diagrams
Participant information	Background participant
	Participant experience

the facilities for seasonal influenza vaccines to manufacture pandemic influenza vaccines. Exactly the same process is used for manufacturing the two types of influenza vaccines, but the composition of the two products differ. It is also required that cleaning and validation processes are performed between the two products.

Another approach for pandemic preparedness, mentioned by SME 6, was attempted by the US government, which funded the construction of manufacturing facilities that can be used for the manufacturing of other products, and in the event of a pandemic, the capacity can be converted to pandemic product manufacturing. SME 6 described that this approach also did not work very well during the Covid-19 pandemic, and that millions of doses of vaccine products had to be discarded due to the impact of poorly trained staff.

Both SME 1 and SME 6 suggest that the ideal model for pandemic preparedness could comprise of having manufacturing facilities continuously operating at very low capacity (e.g. 25%) and then up-scaling in the event of a pandemic. This allows for trained staff and equipment that is maintained and calibrated. SME 6 mentioned that this will still have a high operating cost per unit associated with it during normal operation. Additionally, SME 1 proposed that the approach could be improved by incorporating the capability to manufacture a broad variety of products across a network of manufacturing companies.

According to SME 5, producing vaccines for a pandemic is not sustainable in the long run. Sustainability in the vaccine manufacturing systems is achieved via the manufacturing of EPI vaccines as this is needed every day regardless of pandemics. The manufacturing of EPI vaccines is mainly controlled by multinational companies.

6.3.4.2 Contextual perspective: Approval and rejection of vaccines

According to SME 1, SME 2, and SME 6, it is very difficult to obtain good probability of success estimates for the approval of Covid-19 vaccines. Both SME 1 and SME 2's motivation for this is that the probability of success for a vaccine can only really be determined once clinical studies have been performed. Clinical studies to determine the efficiency of vaccines are expensive to perform. According to SME 1, for a pandemic such as Covid-19, it is easier to quickly obtain a successful vaccine as the number of active cases is very high. Clinical trials may take years to complete for other diseases with low incidence numbers. SME 6's motivation for why it is difficult to gather probability of success values for the Covid-19 vaccines is that the reason for vaccines not making it to the market is often business strategies rather than the inefficiency of the platform or regulatory issues. According to SME 6, if a vaccine had not already received regulatory approval for Covid-19 by mid-2022, then the manufacturers are likely to withdraw the product due to the lack of market that is available. SME 6 suggested that historical probability of success values for other cases can be applied to overcome the challenge of obtaining good probability of success values for each platform for Covid-19.

According to both SME 2 and SME 6, vaccine products approved for Covid-19 may be removed from the market if they become ineffective against the current variant. SME 2 mentioned that for most diseases the mutations would not occur at such a rapid pace, and the required vaccine can be predicted with relative accuracy. For viruses such as Covid-19 and influenza, it is more difficult to accurately predict what the active variant will be in a few months time, due to the rapid rate of the virus' mutation. This may result in some products being ineffective once the development and manufacturing phases have been completed.

6.3.4.3 Contextual perspective: General vaccine manufacturing challenges

Both SME 1 and SME 5 describe the main challenge associated with vaccine manufacturing as ensuring a sustainable market for the vaccine product. SME 1 also mentions that obtaining funding, and hiring and training staff, are some of the other big challenges facing vaccine manufacturers.

SME 5 explained that when constructing a new facility for a specific product, it is crucial to consider the facility's sustainability in the event the product no longer has a demand. A large investment will already have been made in terms of the construction cost, which may be in the region of 250 to 500 million Rand, hiring and training staff, and operating costs that will already have been incurred. The facility will then have to be able to manufacture another product to avoid the loss of investment. Incorporating flexibility in a facility would increase the possibility of utilising the facility for another product.

SME 1 agrees that it is beneficial to construct a facility to be capable of producing more than one product. In the event that the demand for one product is reduced, the manufacturing system can campaign to rather manufacture another product. Single-use technologies are especially valuable to achieve such a system. A challenge arises when a manufacturing facility is producing, for example, two products and the demand for both becomes high. This scenario might necessitate a choice between which product to discontinue manufacturing at the facility to allow sufficient capacity for the other product.

According to SME 1, the choice of constructing a facility for a specific product or having the capability to manufacture different products will depend on the company and its marketplace. Facilities in the USA and Europe are generally constructed to be single-product focused. This is often due to the difficulty of managing two products' demands. SME 2 mentioned that manufacturers tend not to switch between the manufacturing of different bulk products but often do have shared spaces for the filling and finishing, and quality systems of different products.

6.3.4.4 Contextual perspective: Contract vaccine manufacturers

Pharmaceutical companies do sometimes employ contract manufacturers for the manufacturing of products. Both SME 1 and SME 6 mentioned that this involves a technology transfer from the pharmaceutical

companies to the contract manufacturers. According to SME 6, big pharmaceutical companies are motivated to use contract manufacturers to avoid the capital expense associated with capacity. It is easier to spread the capital costs across multiple different points and have the clients take up all the capacity costs. Contract manufacturing was not very common 20 years ago, and manufacturers were only used when companies did not have the required specialised equipment or expertise. According to SME 1, many contract manufacturers use single-use equipment in their facilities, and for viral vaccines it is usually comprised of 2000 L single-use bioreactors. SME 1 and SME 6 agree that the process in a contract manufacturing facility will be very similar to that of the pharmaceutical company as an attempt is made to avoid any differences during the technology transfers. Any difference in the process will have to be explained to regulators.

According to SME 1, the benefit of companies manufacturing their own product rather than outsourcing is that the process can continually be improved over time, and especially human resource efficiency can be obtained. The continual improvements generally do not occur as any significant changes to the process will have to be reported and approved by regulators and may even require new clinical studies. If the clinical trials are ineffective it will result in the product being discontinued. This often results in manufacturers continuing to use the same equipment for years, even if new equipment exists that is more cost- and time effective.

6.3.4.5 Contextual perspective: Challenges for developing countries

SME 1 and SME 5 mentioned that another challenge vaccine manufacturers face is obtaining procurement contracts. If a company misses a procurement contract for the manufacturing of a vaccine product, this can result in two or three years in which the company receives no new business. Many countries, especially African countries, receive GAVI funding, and the procurement is mainly performed by UNICEF at low costs to provide these countries with low-cost products. Manufacturers providing products at low cost and high volume are generally successful in obtaining procurement contracts from UNICEF. The Gates foundation and GAVI provide funding to companies for establishing new facilities, but these companies will have to be able to become sustainable in the markets.

According to both SME 1 and SME 5, there might be a stigma that products developed by vaccine manufacturers in developing countries are of lower quality than those of big pharmaceutical companies in developed countries. SME 5 further mentioned that the stigma will probably remain until these countries can commercially manufacture and vaccinate people. If these manufacturers can guarantee good regulatory processes, then there should be no difference in product quality. SME 1 mentioned that countries from developing countries often do not have the capability to supply all the equipment, consumables, raw materials, etc. that is required for the manufacturing of vaccines and thus often struggle to compete in the global market. According to SME 5, currently, the majority of the vaccines procured by UNICEF and

GAVI are manufactured by a company in India which is also a developing country. It should be possible for manufacturers from other developing countries, such as African countries, to also compete in the global market, but this might take a few years and will require governmental support.

According to SME 5, Africa has very limited vaccine manufacturers, with only one in Southern Africa, which currently only has formulation and fill and finish capabilities. SME 1 suggests that the African countries should focus on establishing a regional approach for vaccine manufacturing and employ local people to form part of the process. Both SME 1 and SME 7 suggested that the best strategy for the African continent in terms of vaccine manufacturing and procurement would be to have the vaccine products for the continent be controlled at the African Union level with the African CDC driving the operation. SME 7 agrees with the regional approach and mentioned that single-use equipment makes this possible as it has lower capital costs associated with it. Both SME 1 and SME 7 mentioned that having more manufacturers worldwide will reduce the economies of scale, but it will allow better access and distribution to countries that are currently under-served. According to SME 7, the vaccine manufacturing industry is currently dominated by five main pharmaceutical companies. This used to be a larger number in the past but was reduced due to the high manufacturing costs associated with vaccine manufacturing. SME 7 mentioned that countries such as China have been able to reduce manufacturing costs by using low-cost labour, but that is not a sustainable solution. The manufacturing costs can rather be reduced by implementing low-cost single-use equipment technologies.

6.3.4.6 Manufacturing of vaccines: Antigen production systems and manufacturing processes

According to SME 1, there are three types of manufacturing facilities, namely: cell-based facilities, which are used for viral live attenuated-, viral inactivated-, and viral vector vaccines; recombinant facilities, which are used to manufacture subunit protein- and DNA vaccines; and RNA vaccines. Some cell-based facilities may also be used to manufacture subunit proteins. SME 1 mentioned that some of the steps in the manufacturing of the active substance, the formulation, and fill and finish processes are the same across all of the platforms, but the platforms are separated due to biosafety requirements. The manufacturing times of vaccine products within the same platforms are also expected to be very similar. The differences in the manufacturing processes for the viral platforms include that the live attenuated virus is slowed down, the inactivated virus is killed, and the viral vector virus carries foreign genes instead of its own.

SME 5 and SME 6 agreed that all the viral vaccine platforms can potentially be manufactured in the same manufacturing facility due to the similar biosafety requirements. According to SME 6, the subunit protein platform is kept separate from the viral platforms due to differences in biosafety requirements. SME 5 further mentioned that RNA products could potentially be manufactured in bacterial facilities as it does not require cell culture for the manufacturing, but rather uses enzymes. If facilities are set up correctly

to manage the biosafety of the products then there should be no reason why RNA products cannot be manufactured in existing bacterial facilities. Manufacturers, however, tend to keep the manufacturing separate to avoid implementing the required regulatory systems.

According to SME 1, the upstream section of vaccine manufacturing often takes longer to complete than the downstream. For example, the upstream section for the viral products may require a couple of weeks, while the downstream may only require a couple of days. SME 1 mentioned that a single downstream process can support multiple upstream bioreactors.

SME 5 agrees with the classification of the types of manufacturing facilities but also considers the antigen production system. The four main antigen production systems include: plant-based, cell-based, egg-based, and bacterial systems. For each of these antigen production systems, different equipment are required. SME 5 further mentions that viral products cannot be manufactured in non-viral facilities. Bacterial system facilities will only manufacture bacterial vaccines. This is based on the current GMP of the vaccine manufacturing industry, and it will be very difficult to follow another structure.

According to SME 1, two types of cells can be used for the cell-based systems, namely: suspension or adherent. The adherent cells grow on surfaces such as glass beads, while the suspension cells remain suspended in the growing media. The adherent cells tend to grow at a slower pace than the suspension cells as the growing process for the adherent cells requires multiple transfers to new culture media and growing surfaces as the cells are expanding.

According to SME 2, the viral inactivated and live attenuated platforms are potentially the best vaccines as the entire virus is used, and antibodies can be generated against multiple targets. For the vaccine platforms, such as DNA, RNA, viral vector, and subunit protein platforms, only a specific antigen is targeted, and it may sometimes be difficult to determine an effective target for a disease.

According to SME 5, a challenge with the viral vector vaccine is that the same vector is often applied to several different viral vector vaccine products. Humans, therefore, have most likely already been pre-exposed to the vector and have built up immunity against it. Even when a new direct target is introduced in the same vector, there is a great uncertainty regarding the response it will induce in humans.

6.3.4.7 Manufacturing of vaccines: Measurement of bulk product

According to SME 6, litres are only used as a unit of measurement for the bulk product when cells are grown in suspension. When cell cultures in fixed bed bioreactors are considered, litres can no longer be used as a unit of measurement. The media in the bioreactors is replaced everyday, and according to SME 6, it no longer makes sense to consider litres. A better unit of measurement for this case is to consider the particles in the bulk product. It is difficult to measure the output of the bulk product as it depends on the method to quantify the potency of the product.

6.3.4.8 Manufacturing of vaccines: DNA vaccine

SME 1 and SME 2 mentioned that the DNA platform does not have a good chance of being approved for Covid-19. SME 1 ascribes this to several challenges the platform still faces. One of these challenges is finding a better transportation system for the DNA into a cell's nucleus, where it is transcribed. According to both SME 1 and SME 2, the DNA platform currently requires electroporation or something similar to allow the DNA to enter the nucleus. SME 2 mentioned that the electroporation devices are quite expensive. The DNA platform for the vaccine product is manufactured in *E.coli*, which is commonly also applied to manufacture subunit protein products. SME 2 further mentioned that there is a risk associated with introducing the DNA into the cell nucleus. This risk is avoided for the RNA platform as it only needs to enter a cell's cytoplasm. According to SME 1, the transportation of the cytoplasm is achieved via the incorporation of lipid nanoparticles in the formulation of the RNA platform's vaccine products.

6.3.4.9 Manufacturing of vaccines: RNA vaccine

According to SME 1, the manufacturing process for the RNA vaccine differs from the rest of the platforms in that it is a chemical process rather than a biological process. The process is still based on biology as it requires a DNA template which is grown in *E.coli* at very small scale. The DNA template manufacturing process is very simple and often outsourced to contract manufacturers. The DNA template is linearised and used as a template to transcribe the RNA. The manufacturing of the RNA involves adding the correct amino acids to transcribe for the correct RNA. According to both SME 5 and SME 6, producing the antigen for the RNA vaccine is currently very expensive. Besides the expensive raw materials, another aspect that contributes to the expense is the need for cold chain distribution at -80°C. This also requires very expensive storage facilities. Both SME 1 and SME 5 mentioned that the RNA platform performed well for the Covid-19 virus since it was easy to identify the antigen for the disease. This may, however, not be so easy for other diseases, and the platform may not be feasible beyond Covid-19. According to SME 1, some companies that had success with the mRNA platform are investing in expanding their capacity in the event the platform may be applicable to other diseases. These companies made such a big revenue with the Covid-19 product, that it is a risk worth taking.

6.3.4.10 Equipment: Bioreactors

According to SME 1, SME 5, SME 6, and SME 7, the main equipment used in the manufacturing of vaccines are bioreactors. According to SME 6, the type of bioreactors used for cell-based facilities depends on whether suspension or adherent cells are used. SME 1 mentioned that big pharmaceutical companies tends to use traditional stainless-steel equipment, although newly developed single-use equipment allows for flexibility in a manufacturing facility.

6.3.4.11 Equipment: Single-use equipment overview

According to SME 6, there are two different types of single-use equipment. The first type is disposable bags, which can only be used for suspension cells. The second type of single-use equipment is fixed-bed bioreactors.

According to SME 6, single-use equipment was mainly applied for the manufacturing of Covid-19 vaccines, with only a few manufacturers applying the traditional stainless-steel equipment. SME 6 mentioned an example of the manufacturing of a viral vector Covid-19 vaccine was the utilisation of suspension cells in 1 000 L disposable bags.

SME 6 mentioned two companies manufacturing different types of single-use bioreactors. Both SME 1 and SME 7 discussed one of these companies' single-use bioreactors. The bioreactor is a fixed-bed bioreactor which can accommodate both adherent and suspension cell cultures. This is achieved by entrapping the cells and operating the bioreactor in perfusion mode, allowing constant oxygen and nutrient supply to all the cells simultaneously. SME 7 explained the operation of the single-use bioreactor in more detail. The inside of the bioreactor consists of layers of material forming a spiral. This material is very easy to procure. Once cells are introduced into the bioreactor, they attach to the material and media is fed through the bioreactor allowing cells to be fed.

6.3.4.12 Equipment: Single-use equipment vs stainless-steel equipment

Both SME 1 and SME 7 agree that single-use bioreactors can achieve very high cell density for a small surface area. This allows the single-use bioreactor to be much smaller than the traditional stainless-steel bioreactors and consequently reduces the required manufacturing space.

Another benefit of single-use equipment mentioned by SME 5 and SME 6 is that it removes the need of extensive cleaning and validation processes associated with switching between products for stainless-steel equipment. This significantly reduces the time required to change between the manufacturing of products. According to SME 1, there are several regulatory issues associated with manufacturing multiple products in the same facility, and cross-contamination has to be avoided. According to SME 1, these regulatory issues are significantly less when single-use equipment is used. This allows multiple products to be manufactured in the same facility with very little risk of cross-contamination as the equipment is disposable and replaced after each batch.

According to SME 1, a downside of the single-use equipment is that it has lower oxygen and heat transfer rates. Single-use bioreactors are therefore not very effective for products that require high oxygen demands, for example, products grown on *E.coli* or yeast.

SME 5 mentioned that although single-use equipment provides flexibility in manufacturing systems and allows for faster campaigning of products, it may not always be an appropriate option due to the high

operation costs associated with the disposable equipment that has to be replaced between each batch. SME 5 further mentioned that it is very important to consider the country or region and the available market when designing a manufacturing facility. For a country which does not have a local supply of the disposable equipment, and which supplies products to low-income markets, such as African countries with GAVI support, having single-use equipment facilities may not be feasible. The high cost of importing the equipment may result in the manufacturing cost to be too high for local manufacturers to compete with global manufacturers. Even though the stainless-steel equipment facilities require high initial capital investment due to the expensive equipment, it may be more profitable and sustainable in such a case. as mentioned in Subsection 6.3.4.5, funding is available for the construction of manufacturing facilities.

6.3.4.13 Measurement of a system: Throughput and performance measurement

According to SME 1, the throughput of a system is an important performance indicator, but it is also linked to many other aspects of the system. Two of these aspects include: first-time quality, and schedule adherence. The schedule adherence considers whether a batch is started according to schedule. This can only be achieved by having the required trained staff and having all the manufacturing supplies, raw materials, etc. from the upstream supply chain. The first-time quality considers whether the required quality can be met the first time. If both criteria are met, the output will also be met at an optimal cost.

6.3.4.14 Measurement of a system: Manufacturing system costs

According to SME 1, SME 5, SME 6, and SME 7, both the fixed and variable cost of a system is important to consider. According to both SME 1 and SME 6, the fixed costs for the manufacturing system are distributed across all the doses manufactured per year in the facility.

According to SME 7, the size of the manufacturing facility will affect the facility's capital and operational costs. Beyond the larger initial capital expense associated with a larger facility, the manufacturing cost per year will also be negatively affected due to a high depreciation cost.

6.3.4.15 Measurement of a system: Facility-dependent costs

According to SME 1, SME 2, and SME 6, an important aspect for manufacturers to consider from a financial point is unused capacity during low demand periods. Unused capacity for a manufacturing facility will increase the operating cost per unit as operating the facility is associated with certain fixed costs, such as facility and equipment maintenance, overhead, and regulatory. These costs will be distributed across fewer units if the capacity is underutilised. According to SME 6, the magnitude of the unused capacity's impact on the operating cost depends on the vaccine product. A product for which the raw materials mainly dominate the overall cost, such as RNA, will be less affected by lower utilisation than a product for

which the overall cost is mainly dominated by capital and operating costs. The viral vaccines are, however, dominated by capital and operation costs and these vaccines will have high manufacturing costs if the used capacity is reduced. This cost will further vary depending on the level of functionality that the facility is operated at, for example, if all the operators are maintained even at the lower manufacturing levels. SME 5 also mentioned that keeping facilities compliant with the GMP standards greatly affects the facility's operation costs.

SME 1 suggests that a good economic strategy may include only building the capacity that is immediately required but to have the space available to quickly add more capacity over time as required. This allows for lower initial capital costs and incremental costs as capacity is added.

According to SME 1, single-use equipment will have no change-over costs associated with it when switching the manufacturing from one product to the next. Single-use equipment requires the replacement of disposable equipment regardless if the equipment is completely dedicated to one product or whether the equipment is used for the campaigning of products. The cost associated with the replacement of equipment is already incorporated in the operating cost for single-use equipment facilities.

6.3.4.16 Measurement of a system: Country-dependent costs

According to SME 5 and SME 7, both the capital and operating costs could be significantly affected by whether a manufacturing facility is situated in a developing or developed country. Developed countries have local suppliers for the manufacturing input requirements, such as raw materials, disposable equipment, consumables, etc., while developing countries often have to import most or even all of the manufacturing requirements resulting in a high transportation cost for the manufacturers of developing countries. This may increase both the capital and manufacturing costs. Other aspects that may affect the cost when comparing manufacturers from developing and developed countries are labour, water, and utility costs. Both SME 6 and SME 7 mentioned that these costs, especially labour, may often be less expensive in developing countries.

6.3.4.17 Measurement of a system: Product-dependent costs

SME 7 mentioned that different products from the same platform for the same disease may differ in terms of the dosage of active substance in the product. An example is the RNA vaccine products for Covid-19. Moderna, BioNTech/Pfizer and CureVac have all developed a RNA vaccine for Covid-19, but the dosages in their products are 100 μg, 30 μg, and 12 μg, respectively. The number of serotypes may also differ for different products of the same platform. The difference in dosage and serotypes affects the quantity of the required raw material and consequently influences the operating costs for the products.

SME 7 also mentioned that the product yield achieved for viral vaccines depends on both the growth media and the virus used to manufacture the active drug substance. A lower yield will increase the operating cost per unit as increased quantities of the media and virus will be required to achieve the required product output.

6.3.4.18 Manufacturing flexibility: Flexibility in industry

As mentioned in Subsection 6.3.4.14, the under-utilisation of capacity has a high operating cost associated with it. According to SME 6, in the case of under-utilisation of capacity, it may be beneficial to consider switching the manufacturing to another product to reduce the manufacturing cost per unit. The challenge that then arises is the decision of when to switch to making a new product. SME 6 further mentioned that the switching capabilities between platforms are limited, especially for the upstream section. The downstream section can be shifted more easily, as the processes are much more similar for the different platforms. The inactivated virus vaccine can be filled in the same lines as the bacterial vaccines since the inactivated form of the virus requires low bio-safety levels. However, the live attenuated virus will still have to be separated from the bacterial vaccines due to the higher bio-safety level requirements for the live attenuated virus vaccines.

SME 2 agreed that switching between products could be difficult due to differences in the equipment and manufacturing process requirements, and flexibility in manufacturing facilities may be more feasible for small-scale manufacturing than multinational companies manufacturing millions of doses per year. An example of the small-scale manufacturing is a local manufacturer only supplying vaccines to its own country and some neighbouring countries.

6.3.4.19 Manufacturing flexibility: Labour flexibility

According to SME 1, it may also be beneficial for manufacturers to invest in labour flexibility for the manufacturing system. Even when the output for a product is low, the labour cost will still have to be covered. A solution is to have staff trained to be capable of participating in more than one manufacturing process. Suppose the manufacturing system is comprised of more than one product and the demand for one product becomes low, while it increases for another, than the trained staff can be moved from one manufacturing process to the next. This removes the need to quickly hire and train new staff for the manufacturing of the product with high demand, and allows the opportunity to rather incrementally hire and train staff as required.

6.3.5 Changes made to the model based on SME feedback

As mentioned in Chapter 4, the model discussed in Appendix C is the final version after the completion of the verification and validation process. The discussion of the original model is presented in Appendix D. The main differences between the model in Appendix D and Appendix C is discussed in this section.

The feedback from the SMEs indicated that the model presented in Appendix D did not incorporate an important aspect of the vaccine manufacturing system, namely distinguishing between the different equipment technologies that a manufacturing system is equipped with. The different equipment technologies that should be considered include stainless steel equipment, and single-use equipment.

The model was adjusted by considering separate facilities for stainless-steel- and single-use equipment in each platform's manufacturing subsection. Three different scenarios can be created in terms of the types of equipment technologies that are consider for the facilities, namely only stainless steel equipment facilities, only single-use equipment facilities, and a combination of stainless-steel and single-use equipment facilities.

If both the stainless-steel and single-use equipment facilities are considered, then each facility only receives half of the total available capacity for that platform.

Furthermore, the model was adjusted to separately control process flexibility for the stainless-steel and single-use equipment facilities. This allows both types of equipment facilities to be actively manufacturing vaccines while only one type of equipment facility has flexibility incorporated.

Lastly, the model was adjusted to allow the change-over time to differ based on the type of equipment facility, rather than the platform considered.

6.4 Conclusion: Chapter 6

This chapter provided an overview of the two-step verification and validation process that was followed for the simulation model developed in Tecnomatix Plant Simulation, discussed in Chapter 5. The verification process involved performing simulation runs to ensure that the model is performing as expected. The validation process involved conducting interviews with SMEs to ensure that the model represents a realistic system. Finally, the changes made to the model, based on the feedback from the SMEs are discussed. The most significant change made to the model is the incorporation of separate manufacturing facilities that utilise stainless-steel and single-use equipment.

The next chapter will discuss the execution of simulation experiments and the interpretation of the results.

Chapter 7

Model execution and results analysis

Chapter 6 provided a detailed description of the verification and validation process followed to ensure that the developed simulation model for the Covid-19 vaccine manufacturing system functions as expected and represents a realistic system. In this chapter, the execution of simulation runs is discussed. Firstly, the simulated scenarios are defined, followed by a discussion of the model execution approach in Tecnomatix Plant Simulation. Finally, the scenario results are reported and discussed.

7.1 Scenario definition

As mentioned in Section 1.2, this study aims to investigate the potential benefits of process flexibility in reducing the negative impact of the unusually high demand uncertainty associated with a pandemic outbreak where there is a need to prepare vaccine manufacturing capacity before a specific vaccine has received regulatory approval. The manufacturing of the active drug substance for Covid-19 vaccines represents a real-world instance where there was a need to prepare manufacturing capacity whilst there was high uncertainty regarding which vaccines would be successfully developed to the point of receiving regulatory approval. Thus, in line with the approach employed in Chapters 4 and 6, data relating to the manufacturing of the active drug substance for Covid-19 vaccines dictates the scenario definition. The interviews with the SMEs described in Subsection 6.3.4, provided insight into the real-world complexities of vaccine manufacturing systems. Some of the significant factors contributing to these complexities include:

- The manufacturing of vaccine platforms must be separated based on the antigen production system used for the manufacturing of the active drug substance;
- Within a specific antigen production system, vaccine platforms must be separated based on the biosafety and regulatory requirements;

- Stringent regulatory procedures have to be followed when switching between the manufacturing of products within a facility;
- A vaccine manufacturing facility can either be equipped with single-use or stainless-steel equipment, and the two types of equipment technologies have very different fixed and operating costs associated with them;
- The fixed and operating costs for vaccine platforms must be product- and facility-specific.

In selecting modelling scenarios, there is a need to incorporate sufficient complexity into the model to ensure that the findings are valid and applicable to real-world systems whilst simultaneously ensuring that the stochastic elements that are incorporated into the model do not obscure the observations that can be made regarding the impact of process flexibility on the system. The scenarios considered for the simulation experiments are defined in Subsection 7.1.1, whilst the input data for the various scenarios are defined in Subsection 7.1.2.

7.1.1 Scenarios for simulation experiments

The scenarios considered for the simulation experiments are depicted in Figures 7.1 and 7.2. The considered antigen production systems are limited to the cell-based and the bacterial antigen production systems, as these have both been used to manufacture approved Covid-19 vaccines. The plant-based and egg-based antigen production systems are not considered for the scenarios. The egg-based antigen production system does not have many applications beyond flu vaccines, while the plant-based antigen production system is a relatively new method, and very few vaccines using this antigen production system have been developed. Furthermore, as indicated in the figures, both stainless-steel and single-use equipment facilities are considered.

As illustrated, nine scenarios each are considered for the cell-based and for bacterial antigen production systems, respectively. For each system, three flexibility configurations are considered by incorporating the chaining approach first introduced by Jordan & Graves (1995), namely no flexibility, limited flexibility achieved via the long-chain approach, and full flexibility. Each of these flexibility configurations is considered with three different equipment options incorporated into the manufacturing system, namely only single-use equipment, only stainless-steel equipment, and a combination of single-use and stainless-steel equipment. When a combination of single-use and stainless-steel equipment is considered, only the single-use equipment facilities are assumed to be capable of flexibility. This modelling decision is informed by the characteristics of the real-world system where switching between the manufacturing of products is more common for single-use equipment than for stainless-steel equipment. From the perspective of process flexibility, the set of nine cell-based antigen scenarios is identical to the set of nine bacterial antigen scenarios. This

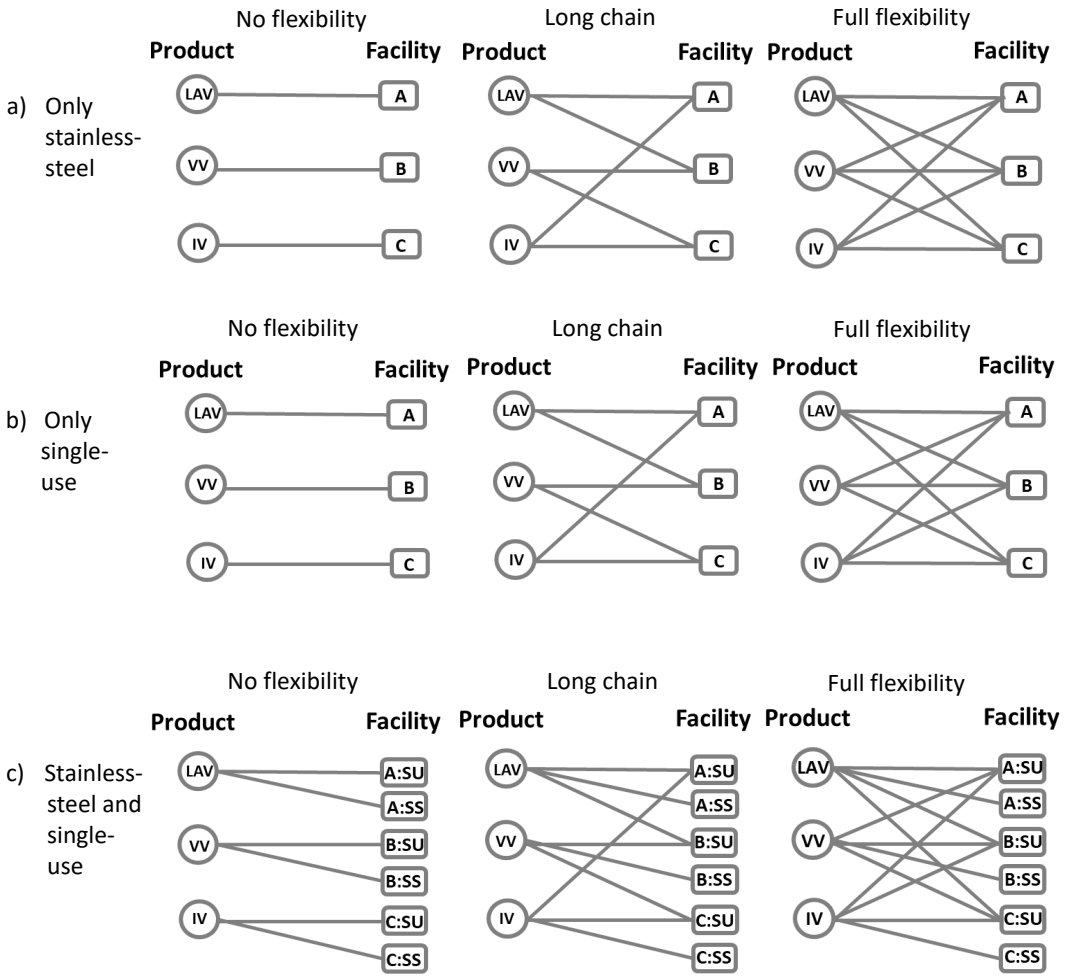

Figure 7.1: Modeling scenarios for the cell-based antigen production system considered in the model

strengthens the ability to draw conclusions on the impact of different process flexibility configurations from the simulation results.

To perform the simulation experiments for these scenarios, certain input data is required, such as the probability of vaccine platform approval, manufacturing time of the vaccine platforms, the operating cost, and the switch-over time and cost. This is discussed in the next section.

7.1.2 Input data for simulation experiments

Two sets of input data is used for the simulation experiments. The first input data set is the probability of approval for vaccine platforms. The second set of input data is the manufacturing input data, which includes manufacturing time and costs. The two input data sets are discussed in greater detail in the remainder of this section.

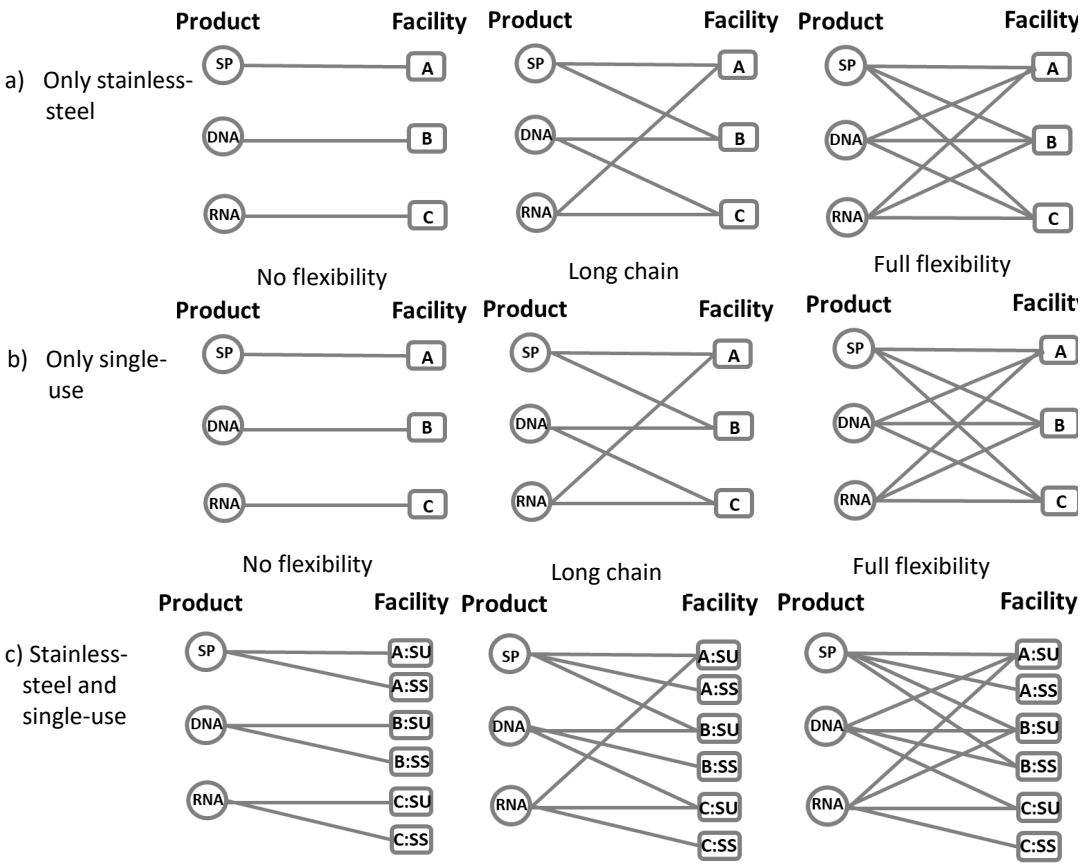

Figure 7.2: Modeling scenarios for the bacterial antigen production system considered in the model

7.1.2.1 Probability of approval input data

The Covid-19 vaccine manufacturing system is faced with high demand uncertainty. One of the biggest factors contributing to the demand uncertainty is which vaccine platforms will be approved and the timeline in which this will occur.

As mentioned in Subsection 6.3.4.2, it is difficult to obtain probability of success values for the approval of vaccine platforms for Covid-19. McDonnell et al. (2020) performed mathematical modelling to predict the probability of approval for Covid-19 vaccine platforms. The results from the study include the time-to-approval and the number of successes over a three-year time-span for each vaccine platform. The results are provided in Table 4.3.

The number of approvals for a platform, as provided in Table 7.1, were used to create a probability of success distribution for each vaccine platform. The distribution is created via the function

$$POS_{Platform(t)} = (1 - e^{(-t)/\beta}),$$

with t as the time at the start of each period and β as the average time between approvals for a platform.

Table 7.1: Results from simulation runs of McDonnell et al. (2020) for each vaccine platform

	Months to first success	Number of successes
Live attenuated virus	-	-
Subunit protein	20,9	2,42
Inactivated virus	11,6	1,63
RNA	12,8	1,75
Non-replicating viral vector	14,6	1,76
Replicating viral vector	27,9	1,14
DNA	30,4	1,06

The average time between approvals is calculated as 36 months divided by the number of successes for the platform, indicated in Table 7.1. The intention is to run the simulation over a five-year timespan and create the distribution by extending the results of McDonnell et al. (2020)'s work from 36 months to 60 months.

7.1.2.2 Manufacturing input data

To date, Covid-19 vaccine products have not yet been approved for all of the platforms considered in the scenarios. Very limited or no manufacturing data is available for the approved products. Assumptions are thus required to determine a complete manufacturing data set on the Covid-19 vaccine manufacturing systems defined in the 18 scenarios described in the preceding section. Manufacturing data was obtained from two sources, namely literature and the SuperPro Designer simulation software. The data does contain some grey literature, as not all the sources are peer-reviewed publications. As mentioned in Section 1.6, the construction costs is not available for all the considered facilities with process flexibility as many of the facilities do not exist in reality. Capital costs are excluded in this study and the impact of process flexibility on only the operating cost is considered.

As discussed previously, a variety of factors can cause the costs for similar vaccines to differ significantly even though similar manufacturing processes are followed (refer to Subsection 6.3.4), including: the size of the manufacturing facility; the facility's capacity utilisation; whether the manufacturing facility is situated in a developing or developed country; the dosage and serotypes for a vaccine product; and the production yield of the facility. The manufacturing data can either be processed to create deterministic data (e.g. using the average value for all sources) or to create stochastic data. For the stochastic data all the data sources can be included in the model as a cumulative empirical distribution, creating variability between observations. If deterministic data is used, a sensitivity analysis can be performed to investigate the impact on the model results. To not obscure the observations that can be made regarding the impact of process flexibility on the system, deterministic rather than stochastic manufacturing data is used in the simulations.

It is recommended that, once conclusions on the impact of process flexibility have been derived, it would be beneficial to incorporate stochastic manufacturing data into future modelling work that informs the design of vaccine manufacturing systems.

Different approaches are implemented to select the deterministic manufacturing data for the cell-based- and bacterial antigen production systems, as discussed in the remainder of this section.

7.1.3 Cell-based antigen manufacturing data

Manufacturing data for the cell-based antigen production systems is presented in Table 7.2. Data for facilities that use stainless-steel equipment is presented in the first portion of the table, while data for facilities that utilise single-use equipment is presented in the second portion of the table. For stainless-steel equipment, data for all three platforms considered in the scenarios (thus LAV, IV, and VV) is presented. For single-use equipment, data for the IV and VV platforms is presented. The costing data presented includes the following values: the number of batches per year, the number of doses per year, the operating cost per year, the operating cost per batch, the operating cost per dose, and the unit manufacturing cost. Data for both Covid-19 vaccines and inactivated polio vaccines is presented. No data were obtained for the switch-over costs for any platforms, and no data were found for the time required to switch between different platforms. The switch-over data presented in Table 7.2 indicate the number of days required before the manufacturing of a new batch for the same product can begin, and can also be referred to as the recipe cycle time.

Table 7.2: Manufacturing data for the cell-based antigen production systems

Source	Platform	Product	Annual operating time (wk/year)	Batch size (g MP)	Batches per year	Doses per year (M)	Unit manufacturing Cost ($/g MP)	Operating cost $/year	Operating cost $/batch	Operating cost $/dose [2]	Switch-over time (days) LAV	Switch-over time (days) IV	Switch-over time (days) VV
Equipment: SS													
SuperPro Intelligen (2022)	LAV / IV / VV	AstraZeneca or Jansen: Covid-19	47.82	125.04	88	400	10 067	110 773 000	1 258 784	0.277	3.5	-	-
Ferreira et al. (2021)[1]	VV	AstraZeneca or Jansen: Covid-19	48.00	124.00	89	400	6 160	68 000 000	764 045	0.170	-	-	3.5
			48.00	124.00	89	400	8 420	93 000 000	1 044 944	0.233	-	-	3.5
Shih (2019)	IV	Sabin-IPV: Polio	-	-	96	48	-	22 823 232	237 742	0.475	-	-	-
Equipment: SU													
Shih (2019)	IV	Sabin-IPV: Polio	-	-	88	48	-	138 79 096	157 717	0.289	-	-	-
Ferreira et al. (2021)[1]	VV	AstraZeneca or Jansen: Covid-19	48.00	124.00	89	400	3 910	43 000 000	483 146	0.108	-	-	3.5
			48.00	124.00	89	400	5 340	59 000 000	662 921	0.148	-	-	3.5

Notes: [1] The study evaluated two different quantities of viral particles for both types of equipment resulting in different manufacturing costs
[2] This value was calculated based on the raw data provided in the various sources.

The deterministic manufacturing data for the cell-based antigen production system employed in the simulation experiments are summarised in Table 7.4. The approach employed to determine the deterministic manufacturing data for the cell-based antigen production systems is set out below.

1. A single set of values is determined for all:

   - cell-based antigen production systems that employ stainless-steel equipment; and
   - cell-based antigen production systems that use single-use equipment.

   Thus, no distinction is made between manufacturing data for the LAV, IV or VV platforms. This approach reflects the similarity in the manufacturing data for platforms of the same antigen production system that utilise the same type of equipment.

2. Only data related to Covid-19 vaccines are used to inform specific manufacturing data values. This approach is informed by the discrepancy between the data obtained for the Covid-19 vaccines and the polio vaccines, using the same manufacturing systems and equipment.

3. For both equipment types, more than one data set was available with the same product yield, and each costing data value is determined as an average value.

4. The manufacturing time for the vaccine platforms is derived from the number of doses per year, even though only the bulk product (i.e. the active drug substance) is considered. The "dose per year" unit of measurement has less variability associated with it. Furthermore, the upstream process may require significantly more time than the downstream process and the unit of measurement thus still provides a reasonable manufacturing time estimate for the bulk product. The manufacturing time is calculated as an estimate for 10 000 doses

5. As no data was obtained for the change-over times between platforms, and the change-over time required for stainless-steel equipment is expected to be significantly greater than that of single-use equipment, the change-over time was assumed to be one modelling period (i.e. one month) for the single-use facilities, and two periods (i.e. two months) for the stainless-steel facilities. A sensitivity analysis of the chosen change-over times are performed and discussed in Subsection 7.3.4.

6. As no data was gathered for the change-over cost, the change-over cost was calculated based on the portion of the non-product operating costs reported in Kis et al. (2021), for the duration of the assumed change-over time (refer to the previous point). The non-product operating costs include facility-related operating costs and labour costs. The ratio reported in Kis et al. (2021) was used as it contains a more comprehensive summary of the operating costs compared to other sources. The operating cost summary as reported in Kis et al. (2021) is shown in Table 7.3. The change-over

cost for the single-use equipment was thus calculated as approximately 7% of the operating cost for one month, while it was calculated as approximately 7% of two months' operating costs for the stainless-steel equipment. It is suggested that a sensitivity analysis of the chosen change-over times are performed.

Table 7.3: Summary of operating cost for producing 100 000 000 Moderna doses

	Costs for 100M Moderna doses
Facility operating cost	4,3
Consumable & single-use equipment costs	59,5
Total raw material cost	162,9
Total labour costs	12,7
Total operating cost	**241,6**

Table 7.4: Cell-based antigen production data used for simulation experiments

Manufacturing time (min/10 000 doses)	**Operating cost per dose SS-facility ($/dose)**	**Operating cost per dose SU-facility ($/dose)**
00:13:36	0.227	0.128

7.1.4 Bacterial antigen production data

Manufacturing data for bacterial antigen production systems is presented in Table 7.5. The table has a similar format to Table 7.2, and the description of the columns is therefore not repeated. In contrast to Table 7.2, Table 7.5 only contains data that relates to Covid-19 vaccines. Furthermore data for only one platform that utilises SS equipment was obtained, namely the DNA platform. Similarly, for SU equipment, only data that relates to the RNA platform was obtained.

Table 7.5: Manufacturing data for the RNA platform

Source	Product	Annual operating time (wk/year)	Batch size (g MP)	Number of batches per year	Doses per year (M)	Unit Manufacturing Cost ($/g MP)	Operating cost ($/year)	Operating cost ($/batch)	Operating cost ($/dose)	Switch-over time (days)		
										RNA	DNA	SP
Equipment: SS, Platform DNA												
SuperPro Intelligen (2022)	Zydus Cadila: Covid-19	47.03	930	324	137	459.65	139 039 000	149 504	1.014	-	1	-
Equipment SU, Platform: RNA												
SuperPro Intelligen (2022)	Pfizer: Covid-19	47.95	95.93	334	970	45 044.66	1 443 294 000	4 321 240	1.488	1	-	-
Kis & Rizvi (2021)	Pfizer: Covid-19	-	-	3 145	8 000	-	5 400 000 000	1717011	0.675	-	-	-
Pardi et al. (2020)	Pfizer: Covid-19	49.29	-	264	100	-	88 100 000	333 712	0.881	-	-	-
Kis & Rizvi (2021)	Moderna: Covid-19	-	-	10 175	8 000	-	17 480 000 000	1 717 936	2.185	-	-	-
Pardi et al. (2020)	Moderna: Covid-19	49.29	-	264	100	-	241 600 000	915 152	2.416	-	-	-
Kis & Rizvi (2021)	Curevac: Covid-19	-	-	1 295	8 000	-	2 220 000 000	1714286	0.278	-	-	-

The approach employed to determine the deterministic manufacturing data for the bacterial antigen production systems is set out below.

1. In contrast to the approach followed for cell-based antigen production systems, separate costing values are considered for the three platforms (DNA, RNA, and SP) that utilise bacterial antigen production systems. The motivation for this approach is that the operating cost of the RNA platform is expected to be significantly higher than that of the other two platforms, and the available data can thus not be combined as a single set.

2. Multiple data sources considering different Covid-19 products and product yields (i.e. the number of doses per year) are available for the RNA platform's single-use equipment. The operating cost per dose for CureVac, Pfizer, and Moderna is depicted in Figure 7.3. The significant difference in the cost between the different RNA products is due to the different dosages (refer to Subsection 6.3.4.17). Since all the data relates to Covid-19 vaccines, it is considered acceptable to use the average operating cost value when modelling the RNA platform's single-use equipment.

3. For the RNA platform, no data for the stainless-steel equipment was uncovered, while no data was uncovered for the DNA platform's single-use equipment. The ratio between the operating costs of the cell-based single-use and stainless-steel equipment (refer to Table 7.4) is thus applied to the DNA platform's stainless steel equipment to estimate the operating cost of the DNA platform's single-use equipment. Similarly, the ratio is applied to the RNA platform's single-use equipment to estimate the operating cost of the RNA platform's stainless steel equipment.

4. Although subunit protein Covid-19 vaccines have been approved, no manufacturing data for the subunit protein platform was uncovered. The platform's manufacturing process is expected to be more similar to the DNA platform than the RNA platform. The DNA platform's manufacturing data is therefore used for the SP platform. It is strongly recommended that future work that informs the design of vaccine manufacturing systems uses manufacturing data for subunit protein platform once this becomes available.

5. Similar to the approach taken for the cell-based antigen production systems, the manufacturing time for the vaccine platforms is derived from the number of doses per year, even though only the bulk product (i.e. the active drug substance) is considered. The manufacturing time is calculated as an estimate for 10 000 doses.

6. Similar to the approach taken for the cell-based antigen production systems, a change-over time of one modelling period (i.e. approximately one month) is assumed for single-use facilities and two periods for the stainless-steel facilities.

7. An identical approach to that described for the cell-based antigen production systems was employed to estimate the change-over costs.

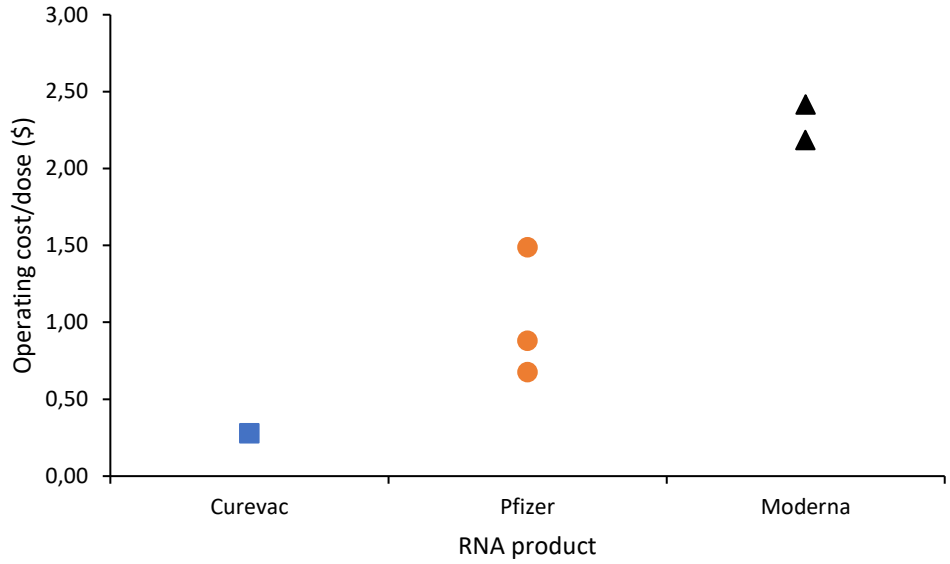

Figure 7.3: Operating cost per dose for different RNA Covid-29 products

The manufacturing time for 10 000 doses, and the operational cost per dose for both the single-use and the stainless-steel equipment facilities, as used in the simulation experiments for the bacterial antigen production system, are presented in Table 7.6.

Table 7.6: Bacterial antigen production data used for simulation experiments

Platform	**Manufacturing time (min/10 000 doses)**	**Operating cost per dose SS-facility ($/dose)**	**Operating cost per dose SU-facility ($/dose)**
DNA	38,36	1,014	0,572
RNA	02:14	2,342	1,321
SP	38,36	1,014	0,572

7.2 Scenario execution

The two sets of modelling scenarios, refer to Subsection 7.1.1, were executed independently in Tecnomatix Pant Simulation via the *ExperimentManager*. The following inputs were adjusted to create nine unique scenarios: which equipment facilities are considered; which equipment facilities are flexible; what process

flexibility configuration is considered; and the switch-over time for each equipment facility type. Two main output variables were defined as the *TotalThroughput* and *TotalOperatingCost* variables. These two variables will be used to analyse and compare the different scenarios.

As mentioned in Section C.1, the rejection of vaccine platforms may obscure the impact of process flexibility on the vaccine manufacturing system. The rejection of vaccine platforms are not thus not incorporated in the executed scenarios.

For each set, nine experiments with 40 observations for the cell-based scenarios and 160 observations for the bacterial scenarios were executed. The number of observations per simulation experiment was determined in accordance with the two-phase method described in Bekker (2020). A trial run was performed with 10 observations per simulation experiment. The number of required observations was calculated by applying the equation

$$n^* = [n(h/h^*)^2], \tag{7.1}$$

with n the sample size for the trial run; h the confidence interval half-width for the trial run; n^* the desired sample size; and h^* the desired confidence interval half-width.

Data for the cell-based scenario that utilises only stainless-steel equipment and does not incorporate any process flexibility was used in the aforementioned equation to determine the required number of observations to be applied to the nine cell-based scenarios. Data for the bacterial scenario that utilises only stainless steel equipment and does not incorporate any process flexibility was similarly used to determine the required number of observations to be applied to the nine bacterial scenarios.

The equation was applied twice for each antigen production system, using h for the *TotalThroughput* variable and the *TotalOperatingCost* variable, respectively. For the cell-based scenarios, it was decided to consider a h^* with half the value of h at 10 observations. This results in a possible error of 2.15% for the *TotalThroughput* variable and a possible error of 2.14% for the *TotalOperatingCost* variable, both of which are considered acceptable. The required number of observations for the cell-based scenarios was thus determined to be 40.

For the bacterial scenarios, it was decided to consider a h^* with quarter of the value of h at 10 observations. The bigger h/h^* ratio was chosen as the bacterial scenarios have significant more variability in the data compared to the cell-based scenarios. This is due to different manufacturing input data (manufacturing time and operating cost per dose) used for the three bacterial scenario platforms, while the same input data was used for the three cell-based scenario platforms. The h/h^* ratio results in a possible error of 0.74% for the *TotalThroughput* variable and a possible error of 0.74% for the *TotalOperatingCost* variable, both of which are considered acceptable. The required number of observations for the cell-based scenarios was thus determined to be 160.

The model run time was set to five years (thus 1800:00:00:00 when the dxd:hh:mm:ss.00 format that TPS employs is implemented, refer to Section C.1), and the output variables were evaluated in terms of confidence intervals. The analysis of the model results will be discussed in Section 7.3.

The model execution time for the experiments is lengthy and required approximately 12 hours per experiment for the cell-based scenarios on a standard computer. A virtual machine was created on Microsoft Azure (Microsoft (2022)) to run the Tecnomatix software on. The specifications of the virtual machine is provided in Table 7.7. The virtual machine slightly reduced the model execution time to approximately nine hours per experiment with 40 observations.

Table 7.7: Specifications of Microsoft Azure virtual machine

Type	General purpose
vCPUs	4
RAM (GB)	16
Data disks	8
Max IOPS	6400
Temp storage (GB)	32

7.3 Simulation results

The analysis of the model results is comprised of three components. The first component involves assessing the credibility of the data generated by the model. The second component involves considering the impact of process flexibility on the system's performance. Finally, the third component considers the best scenario regarding the degree of process flexibility incorporated in the manufacturing system.

As mentioned in Section 1.6, this study considers a theoretical problem and it is important to bear the following in mind when reviewing and interpreting the simulation results:

- The theoretical model set-up involves a network of facilities that are ready and available to start production of Covid-19 vaccines at any point after the start of the five-year modelling period.
- Capital costs to set up the facilities are not included in the modelling[1]. There is significant uncertainty as to what the capital cost of setting up flexible networks would be.
- Operating costs for idle facilities are not included in the modelling.

The aforementioned emphasise that the appropriate use of the data generated by the simulation modelling is limited to comparing the relative performance of the various scenarios.

[1]For single-use facilities, the costs of single-use equipment components that are routinely replaced in the course of production are included in the operating costs, which are considered in the model.

7.3.1 Model results analysis

The model results are considered separately for the cell-based and bacterial scenarios, executed in Tecnomatix Plant Simulation as independent sets. The model results for the *TotalThroughput* variable are provided in Table 7.8 for the cell-based scenarios, and in Table 7.9 for the bacterial scenarios. The model results for the *TotalOperatingCost* are provided in Table 7.10 for the cell-based scenarios, while the results for the bacterial scenarios are provided in Table 7.11. The model results include both output variables' average, standard deviation, and 95% confidence interval. All four of the tables are structured according to the three equipment facility options. The operating cost per throughput (operating cost per dose) values for all the cell-based and bacterial scenarios are provided in Table 7.12.

Table 7.8: Model results for cell-based scenarios' *TotalThroughput* variable

		Throughput (dose)			
	Scenario	Average	Standard deviation	Confidence interval low bound	Confidence interval high bound
SS	No flexibility	3 525 225 000	187 761 099	3 465 160 968	3 585 289 032
	Long chain	5 638 350 000	733 467 513	5 403 716 648	5 872 983 352
	Full flexibility	7 028 537 500	977 501 855	6 715 838 528	7 341 236 472
SU	No flexibility	3 525 225 000	187 761 099	3 465 160 968	3 585 289 032
	Long chain	6 052 550 000	927 168 088	5 755 952 601	6 349 147 399
	Full flexibility	7 706 625 000	821 973 452	7 443 678 948	7 969 571 052
SS/SU	No flexibility	3 525 225 000	187 761 099	3 465 160 968	3 585 289 032
	Long chain	4 788 887 500	513 543 915	4 624 606 836	4 953 168 164
	Full flexibility	5 525 842 500	481 786 128	5 371 721 026	5 679 963 974

As shown in Tables 7.8 and 7.9, an identical total throughput is achieved for the three equipment facility options when no flexibility is incorporated for both the cell-based scenarios (3 525 225 000 doses) and the bacterial scenarios (14 328 140 000 doses). In Tecnomatix, each of the nine scenarios starts with the same random number seed values, and vaccine platforms are therefore approved in the same period within each of the 40 or 160 observations across the nine scenarios for the cell-based and bacterial scenarios, respectively. It is possible to circumvent this operating characteristic of the simulation software, but in this instance it is considered useful as it enables a more direct comparison of the performance of the different manufacturing networks that are being evaluated in each scenario. Importantly, variability in time-to-approval time for each platform is observed from one observation to another within each scenario, as depicted by the box and whisker plots for the cell-based and bacterial scenarios in Figures G.1 and G.2. This indicates that the

Table 7.9: Model results for bacterial scenarios' *TotalThroughput* variable

		Throughput (dose)			
	Scenario	Average	Standard deviation	Confidence interval low bound	Confidence interval high bound
SS	No flexibility	14 328 143 750	687 571 031	14 220 764 346	14 435 523 154
	Long chain	19 635 875 000	6 547 768 643	18 613 296 295	20 658 453 705
	Full flexibility	22 184 478 125	9 915 925 587	20 635 887 315	23 733 068 935
SU	No flexibility	14 328 143 750	687 571 031	14 220 764 346	14 435 523 154
	Long chain	21 371 650 000	6 748 021 507	20 317 797 387	22 425 502 613
	Full flexibility	24 788 559 375	10 732 171 080	23 112 493 801	26 464 624 949
SS/SU	No flexibility	14 328 143 750	687 571 031	14 220 764 346	14 435 523 154
	Long chain	17 849 896 875	3 556 073 633	17 294 537 428	18 405 256 322
	Full flexibility	19 287 831 875	5 631 585 276	18 408 335 440	20 167 328 310

Table 7.10: Model results for cell-based scenarios' *TotalOperatingCost* variable

		Operating cost			
	Scenario	Average	Standard deviation	Confidence interval low bound	Confidence interval high bound
SS	No flexibility	$799 168 508	$42 565 441	$785 551 991	$812 785 024
	Long chain	$1 290 864 340	$170 355 095	$1 236 368 420	$1 345 360 260
	Full flexibility	$1 613 610 083	$221 599 671	$1 542 721 226	$1 684 498 940
SU	No flexibility	$451 228 800	$24 033 421	$443 540 604	$458 916 996
	Long chain	$778 868 776	$120 027 985	$740 472 299	$817 265 253
	Full flexibility	$992 161 622	$105 212 602	$958 504 527	$1 025 818 717
SS/SU	No flexibility	$625 198 654	$33 299 431	$614 546 298	$635 851 010
	Long chain	$791 089 830	$72 835 135	$767 790 158	$814 389 501
	Full flexibility	$886 991 316	$67 860 149	$865 283 123	$908 699 509

Table 7.11: Model results for bacterial scenarios' *TotalOperatingCost* variable

		Operating cost			
	Scenario	Average	Standard deviation	Confidence interval low bound	Confidence interval high bound
SS	No flexibility	$3 193 350 576,25	$160 103 921,00	$3 168 346 812,50	$3 218 354 340,00
	Long chain	$4 433 467 424,00	$1 565 727 517,08	$4 188 944 487,33	$4 677 990 360,67
	Full flexibility	$4 987 745 960,88	$2 371 160 378,50	$4 617 436 891,94	$5 358 055 029,81
SU	No flexibility	$1 801 209 222,50	$90 306 300,33	$1 787 105 898,96	$1 815 312 546,04
	Long chain	$2 706 552 274,63	$908 782 291,49	$2 564 625 846,00	$2 848 478 703,25
	Full flexibility	$3 127 328 650,88	$1 453 390 390,65	$290 049 637,88	$3 354 307 663,87
SS/SU	No flexibility	$2 497 279 899,38	$125 205 110,67	$2 477 726 355,73	$2 516 833 443,02
	Long chain	$2 956 424 899,94	$500 557 723,50	$2 878 251 754,75	$3 034 598 045,13
	Full flexibility	$3 132 523 639,31	$783 905 741,77	$3 010 099 442,28	$3 254 947 836,34

Table 7.12: Cost per throughput for cell-based and bacterial scenarios

		Cost/throughput cell-based ($)	Cost/throughput bacterial ($)
SS	No flexibility	0,227	0,223
	Long chain	0,229	0,226
	Full flexibility	0,230	0,225
SU	No flexibility	0,128	0,126
	Long chain	0,129	0,127
	Full flexibility	0,129	0,128
SS/SU	No flexibility	0,177	0,174
	Long chain	0,165	0,166
	Full flexibility	0,161	0,162

stochastic element built into the approval section, (described in Subsection 5.2.2), functions as expected. Furthermore, the same capacity is made available for the stainless-steel and single-use equipment facilities when only one facility type is considered. This is also equal to the total available capacity when both the equipment facility types are considered. This results in equal throughput for the scenarios within a set when no flexibility is incorporated.

For both the cell-based and the bacterial scenarios, error plots are provided to consider the credibility of the model data. The error plots for the *TotalThroughput* variable are provided in Figure 7.4 and Figure 7.5 for the cell-based and bacterial scenarios, respectively.

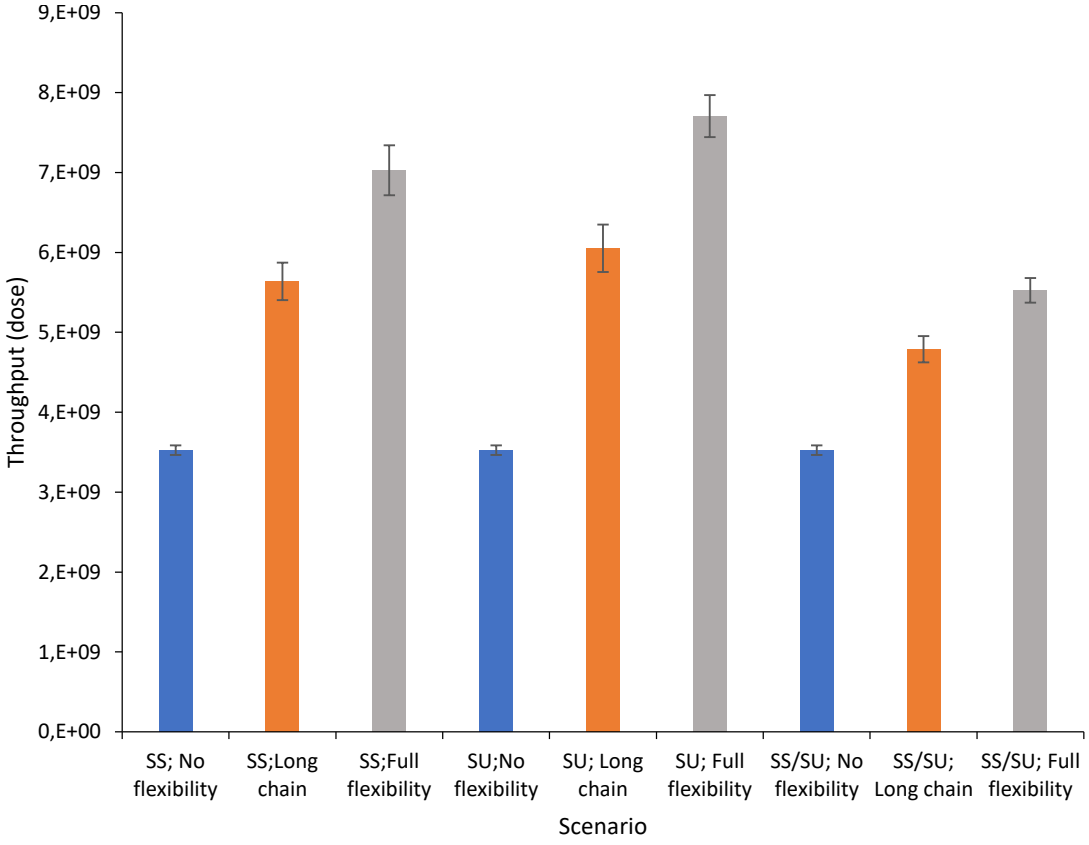

Figure 7.4: Error plot for the cell-based scenarios' *TotalThroughput* variable

The variability in the bacterial scenarios' data is more significant than the cell-based scenarios' data, even with the 160 observations for the bacterial scenarios versus the 40 observations for the cell-based scenarios, refer to Figure 7.4 and Figure 7.5. The higher variability in the bacterial scenarios' data is ascribed to the different input data used for the three bacterial scenario platforms (refer to Section 7.2). For both the bacterial and cell-based scenarios, the confidence intervals are considered small and the variability in the model data is deemed acceptable. The most significant variability for the cell-based scenarios is the scenario

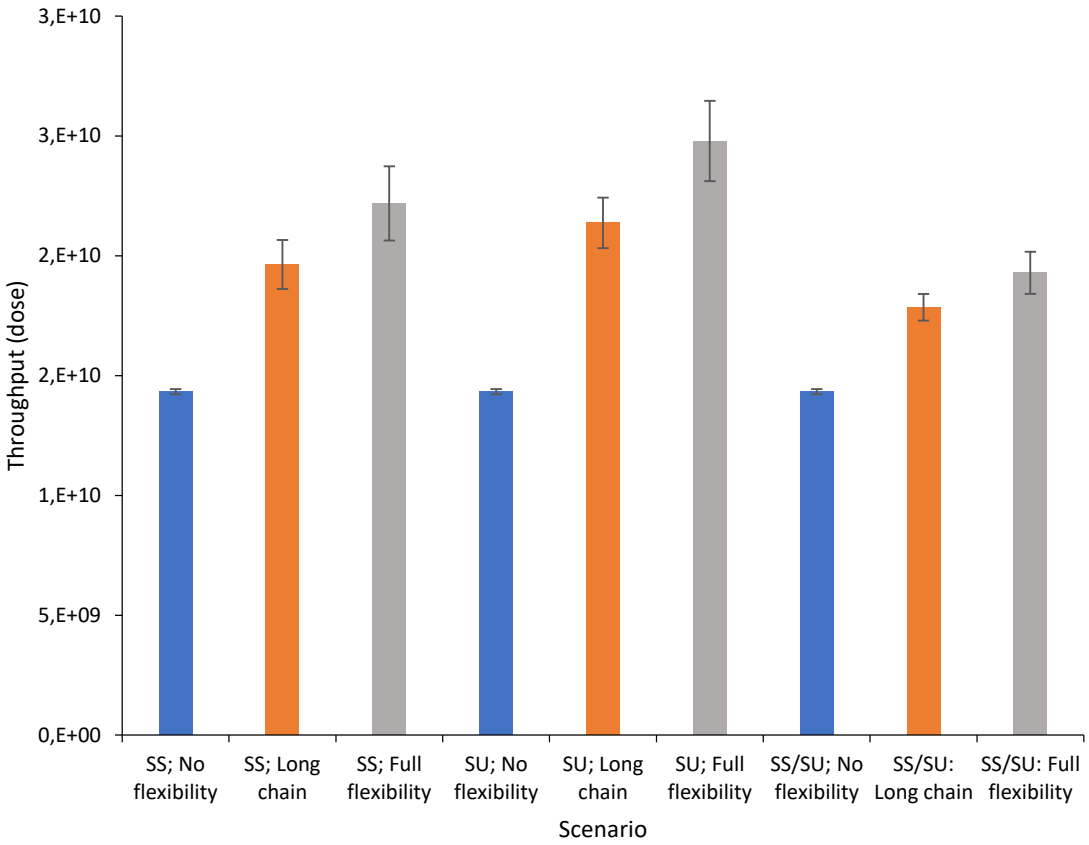

Figure 7.5: Error plot for the bacterial scenarios' *TotalThroughput* variable

which utilises only single-use equipment and incorporates the long chain configuration. This scenario has a possible error of 4.90 %. The most significant error for the bacterial scenarios is the scenario which utilises only stainless-steel equipment and incorporates the full flexibility configuration. This scenario has a possible error of 7.50%. The data that is generated by the model can confidently be deemed credible.

7.3.2 Impact of process flexibility

The impact of the process flexibility configuration on the system's throughput is evaluated in this section. The impact is first evaluated by considering p-value ANOVA tables for both the cell-based and bacterial scenarios' throughput, refer to Subsection 7.3.2.1. The impact of process flexibility is further evaluated by considering the percentage difference in throughput for the three configurations, refer to Subsection 7.3.2.2.

7.3.2.1 Evaluation of process flexibility configurations via ANOVA

Analysis of variance (ANOVA) is used to evaluate quantitative experimental data (Devore, 2016). The evaluation of data involves comparing the means of distributions to determine the variability in the distributions (Devore, 2016). Two types of ANOVA tests can be performed, namely single-factor ANOVA, and multi-factor ANOVA (Devore, 2016). The null hypothesis for the ANOVA test is that the means of different distributions do not differ significantly (Devore, 2016). A specific confidence level is considered when the ANOVA test is performed, for example 90% or 95% (Devore, 2016). The p-value is one of the results from the ANOVA test that can be used to evaluate the variability between distributions (Devore, 2016). If the p-value for two distributions is smaller than the confidence level's $alpha$ value, the null hypothesis is rejected (Devore, 2016).

Single-factor ANOVA tests were performed for both the cell-based and bacterial scenarios' model data. The throughput data is approximately normally distributed with a high number of observations performed for each scenario (40 and 160 observations) (Law, 2004). The p-value ANOVA tables for the *TotalThroughput* variable are presented for the cell-based scenarios in Table 7.13 and in Table 7.14 for the bacterial scenarios, respectively. A 95% confidence interval is considered, and p-values smaller than 0.05 thus indicate that the values differ significantly.

The ANOVA tables, in combination with the model data presented in Subsection 7.3.1 are used to consider two hypotheses formulated in accordance with this study's aims, refer to Section 1.3. Firstly, it is hypothesised that process flexibility will impact the Covid-19 vaccine manufacturing system under the high demand uncertainty. Secondly, it is hypothesised that the long chain configuration will perform similarly to full flexibility. The performance of the system is evaluated in terms of throughput. The first hypothesis is evaluated by comparing the variability in the no flexibility, long chain, and full flexibility configurations for each of the three equipment facility options. The second hypothesis is evaluated by comparing the variability in the long chain and full flexibility configurations for each of the three equipment facility options.

Table 7.13: ANOVA table for the cell-based scenarios' *TotalThroughput* variable

		No flexibility		Long chain			Full flexibility		
		SU	SS/SU	SS	SU	SS/SU	SS	SU	SS/SU
No flexibility	SS	1	1	0	0	0	0	0	0
	SU		1	0	0	0	0	0	0
	SS/SU			0	0	0	0	0	0
Long chain	SS				0,030	0	0	0	0,422
	SU					0	0	0	0,002
	SS/SU						0	0	0
Full flexibility	SS							0,001	0
	SU								0

Table 7.14: ANOVA table for the bacterial scenarios' *TotalThroughput* variable

		No flexibility		Long chain			Full flexibility		
		SU	SS/SU	SS	SU	SS/SU	SS	SU	SS/SU
No flexibility	SS	1	1	0	0	0	0	0	0
	SU		1	0	0	0	0	0	0
	SS/SU			0	0	0	0	0	0
Long chain	SS				0,020	0,003	0,007	0	0,612
	SU					0	0,392	0,001	0,003
	SS/SU						0	0	0,007
Full flexibility	SS							0,025	0,001
	SU								0

From Table 7.8 and Table 7.9, it can be observed that the throughput increases in line with the degree of flexibility for all three equipment facility options of the cell-based and bacterial scenarios. The impact of process flexibility on the system can further be observed from the ANOVA tables for the cell-based and bacterial scenarios in Table 7.13 and Table 7.14, respectively. The p-values indicate that the throughput achieved for the no flexibility configuration differs significantly ($p<0.05$) from both the long chain and the full flexibility configuration. These results indicate that process flexibility has a statistically significant impact on the Covid-19 manufacturing system with its high level of demand uncertainty. The first hypothesis is thus accepted.

When considering the difference in throughput for the long chain and full flexibility configurations, it is observed from the p-values for both the cell-based and bacterial scenarios that the throughput achieved for the long chain configuration differs significantly from the full flexibility configuration ($p<0.05$). Although the long chain configuration provides significantly improved performance compared to the no flexibility configuration, the long chain configuration's performance is not equivalent to that of the full flexibility configuration under the high demand uncertainty that is present in the Covid-19 manufacturing system that has been modelled. The second hypothesis is thus rejected.

7.3.2.2 Throughput improvement for process flexibility configurations

The impact of the three process flexibility options on the manufacturing system is evaluated by considering the percentage difference in the throughput, provided in Table 7.15. The values in the table are calculated based on the average throughput value of each scenario, across all replications.

Table 7.15: Throughput improvement achieved by flexibility configurations

	SS		SU		SS/SU	
	Cell-based	Bacterial	Cell-based	Bacterial	Cell-based	Bacterial
Long chain	60%	37%	72%	49%	36%	25%
Full flexibility	99%	55%	119%	73%	57%	35%

From Table 7.15 it can clearly be seen that both the long chain and full flexibility configurations provide significant improvement in terms of the throughput achieved for the manufacturing system compared to the no flexibility configuration for both the cell-based and the bacterial scenarios, with improvements ranging between 25% and 119%.

For all the scenarios, the full flexibility configuration achieves a substantially greater improvement than the long chain configuration. However, capital costs were not considered in this study, refer to Subsection 7.1.2, and process flexibility investment decisions should not merely be based on the improvement in throughput results achieved in this study. Thus, an informed choice between the long chain and full

flexibility configurations can only be made once realistic estimates of the required capital costs are available so that the cost-effectiveness of the incremental cost associated with both a long chain and a full flexibility configuration can be considered.

The most significant improvement in throughput is observed for the cell-based scenario that utilises single-use equipment, followed by the cell-based scenario that utilises stainless-steel equipment. The cell-based scenarios had much more significant improvement in the throughput for all three the equipment options compared to the bacterial scenarios. This is postulated to be due to the greater variability which is incorporated in the bacterial scenarios with the consideration of different input manufacturing data for the three bacterial scenario platforms.

7.3.3 Determining the best scenario

Throughput versus operating cost per dose graphs were constructed for both the cell-based and bacterial scenarios to evaluate the relative performance of the scenarios and to identify the Pareto set. The operating cost per dose is considered as this provides a comparable measurement. The graph for the cell-based scenarios is provided in Figure 7.6, while the graph for the bacterial scenarios is provided in Figure 7.7.

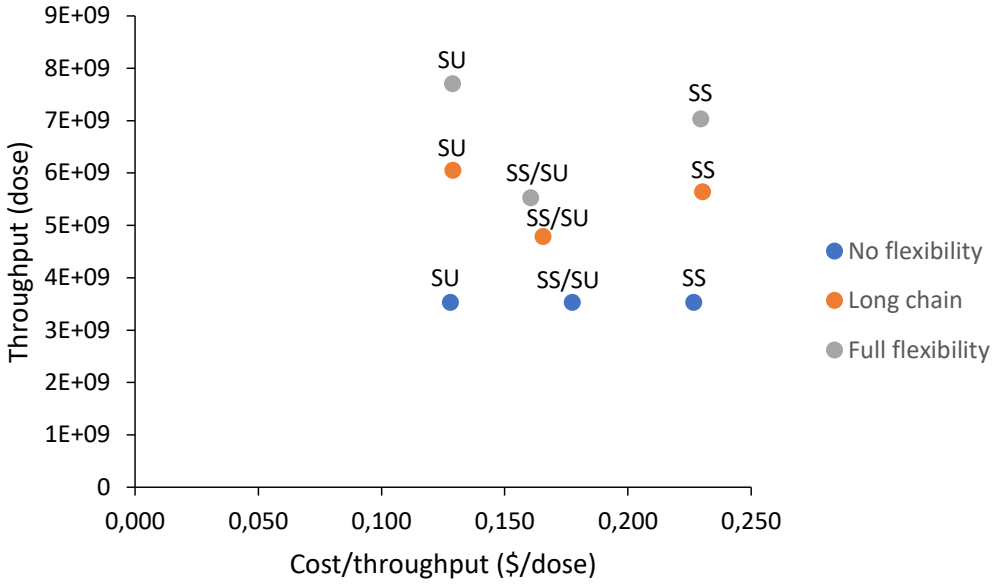

Figure 7.6: Throughput vs cost graph for the cell-based scenarios

7.3.3.1 Evaluation of the throughput for equipment facilities

As seen from Tables 7.8 and 7.9, and Figures 7.6 and 7.7, the highest throughput amongst the three equipment facility options is achieved for the scenarios which utilise only single-use equipment for both the

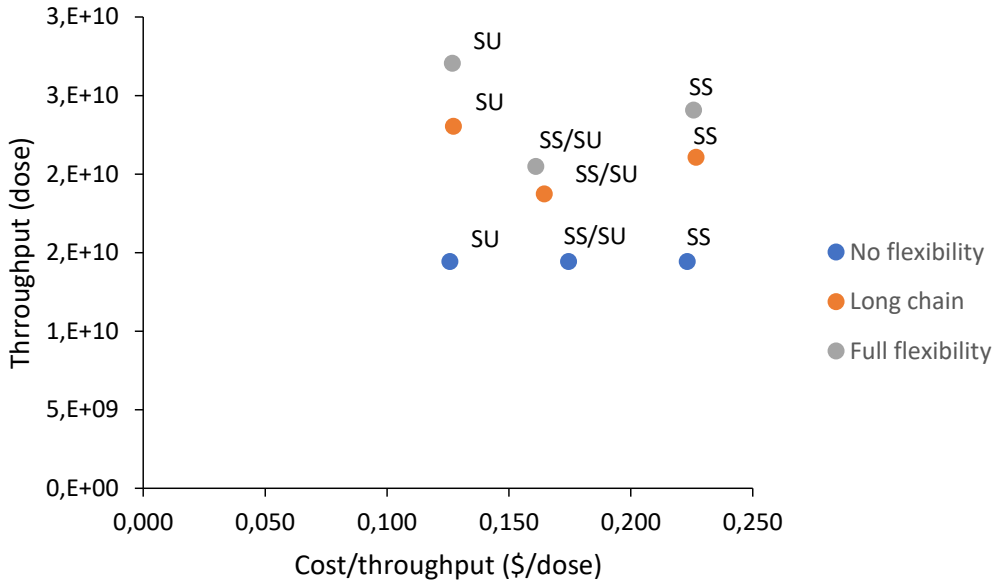

Figure 7.7: Throughput vs cost graph for the bacterial scenarios

cell-based and bacterial scenarios. The single-use equipment facilities have a shorter delay when switching capacity between platforms than the stainless-steel facilities and therefore gain additional manufacturing time. Although the scenarios in which both the stainless-steel and the single-use equipment facilities are utilised also have a shorter delay time for the single-use equipment facilities, the total available capacity is split between its single-use and stainless-steel equipment facilities for these scenarios. The single-use equipment facilities can thus only receive half of the total available capacity from an idle platform's facility. This results in the lowest throughput among the three considered equipment facility scenarios.

7.3.3.2 Evaluation of operating cost for the different scenarios

As seen from Table 7.10 and Table 7.11, the operating cost increases for an increase in flexibility for all three of the cell-based and bacterial scenarios' equipment facility options. This corresponds with the increase in throughput for an increase in flexibility.

As seen from Table 7.12, among the three equipment facility scenarios, the lowest operating cost per dose is achieved for the scenarios which utilise only the single-use equipment. This corresponds with the lower input operating cost per dose for the single-use equipment facilities, refer to Subsection 7.1.4.

The operating cost per dose achieved for all the scenarios utilising both the single-use and stainless-steel equipment lies between that for only single-use and only stainless-steel scenarios. This is expected as a combination of stainless-steel, and single-use equipment facilities' operating cost is considered.

For the no flexibility configuration, a similar result is obtained when comparing the difference in the operating cost per dose for the scenarios utilising only stainless-steel equipment facilities and the scenarios in which both the single-use and stainless-steel equipment facilities are utilised with the difference for the scenarios utilising only single-use equipment facilities and the scenarios in which both the single-use and stainless-steel equipment facilities are utilised. As the flexibility degree increases, the difference in the operating cost per dose value for the scenarios in which both the single-use and stainless-steel equipment facilities are considered become more similar to the only single-use equipment than the only stainless-steel equipment. Due to the increase in the throughput for the single-use equipment with increased flexibility, the operating cost for the single-use equipment becomes more dominant.

7.3.3.3 Pareto data set

From both Figure 7.6 and Figure 7.7, it can be observed that the Pareto data set is the three scenarios that utilise single-use equipment. The single-use equipment dominates among the equipment options in terms of both the throughput and the operating cost per dose, as the throughput is maximised, while the cost per dose is minimised.

7.3.4 Sensitivity analysis for switch-over time

Several assumptions were made to determine the input manufacturing data for both the cell-based and bacterial scenarios, refer to Subsections 7.1.3 and 7.1.4. A sensitivity analysis was performed using the cell-based scenarios' model data to investigate the impact of the switch-over time assumption on the operating cost per dose. The cell-based scenarios' switch-over time ratios for the stainless-steel and single-use equipment were adjusted to create six unique sensitivity analysis experiments. The switch-over time ratios for the six experiments are provided in Table 7.16.

Table 7.16: Switch-over time ratios for sensitivity analysis experiments

	SS switch-over time (months)	SU switch-over time (months)
Base line	2	1
Sensitivity analysis 1	4	2
Sensitivity analysis 2	6	3
Sensitivity analysis 3	8	4
Sensitivity analysis 4	4	1
Sensitivity analysis 5	6	1
Sensitivity analysis 6	8	1

For sensitivity analysis experiments one to three, the switch-over time period for both the stainless-steel and single-use equipment scenarios were incremented with two months at a time. This provides an

indication of the magnitude of the impact that switch-over time has on the model results.

For sensitivity analysis four to six, the switch-over time period for the stainless-steel scenarios was incremented with two months at a time, while it was kept constant for the single-use equipment. This investigates the impact of the case where the required switch-over time for the stainless-steel equipment is significantly longer compared to single-use equipment than initially assumed (refer to Subsection 7.1.3). As described in Chapters 1 and 2, this research did not uncover real-world instances of process flexibility between different vaccine platforms in facilities that use stainless steel equipment. However, it is clear that if such a switch were implemented, comprehensive cleaning and calibrating of the facility would be required. It is therefore prudent to explore the impact of longer switch-over times for stainless steel equipment on the performance of the flexible manufacturing network.

Due to the computing time required to run the 18 simulation experiments using Tecnomatix, the scenarios were evaluated by adjusting the output data obtained for the base line scenarios, rather than by re-calibrating the Tecnomatix model and executing the simulation model again for each sensitivity analysis experiment. For each experiment, the throughput achieved and the switch-over cost for each of the 40 replications of each of the nine base-line scenarios was adjusted, based on the number of times that a switch-over was implemented in each replication. Table 7.17 contains the switch-over cost and throughput per day values used to make the adjustments for the experiments, these align to the model input data provided in Table 7.4.

Table 7.17: Switch-over cost and throughput per day values used for the sensitivity analysis experiments

	Switch-over cost ($)	Throughput/day (doses)
SS	5 060 158	1 058 824
SU	2 856 811	1 058 824

The throughput versus cost per dose for the six sensitivity analysis experiments are depicted in Figure 7.8. From Figure 7.8, it can be seen that the switch-over time ratio between the stainless-steel and the single-use equipment does not greatly impact the observations that can be made for the results. The Pareto set still contains the three scenarios that utilise the single-use equipment.

7.3.5 Discussion of results

The single-use equipment option had both a lower input operating cost per dose and a shorter switch-over time between periods compared to the stainless-steel equipment, refer to Subsections 7.1.3 and 7.1.4. The finding that the scenarios utilising single-use equipment and the scenarios utilising both single-use and stainless-steel equipment dominate the scenarios utilising only stainless-steel equipment in terms of the operating cost per dose, is therefore as expected. As mentioned in Subsection 7.1.2, however, many

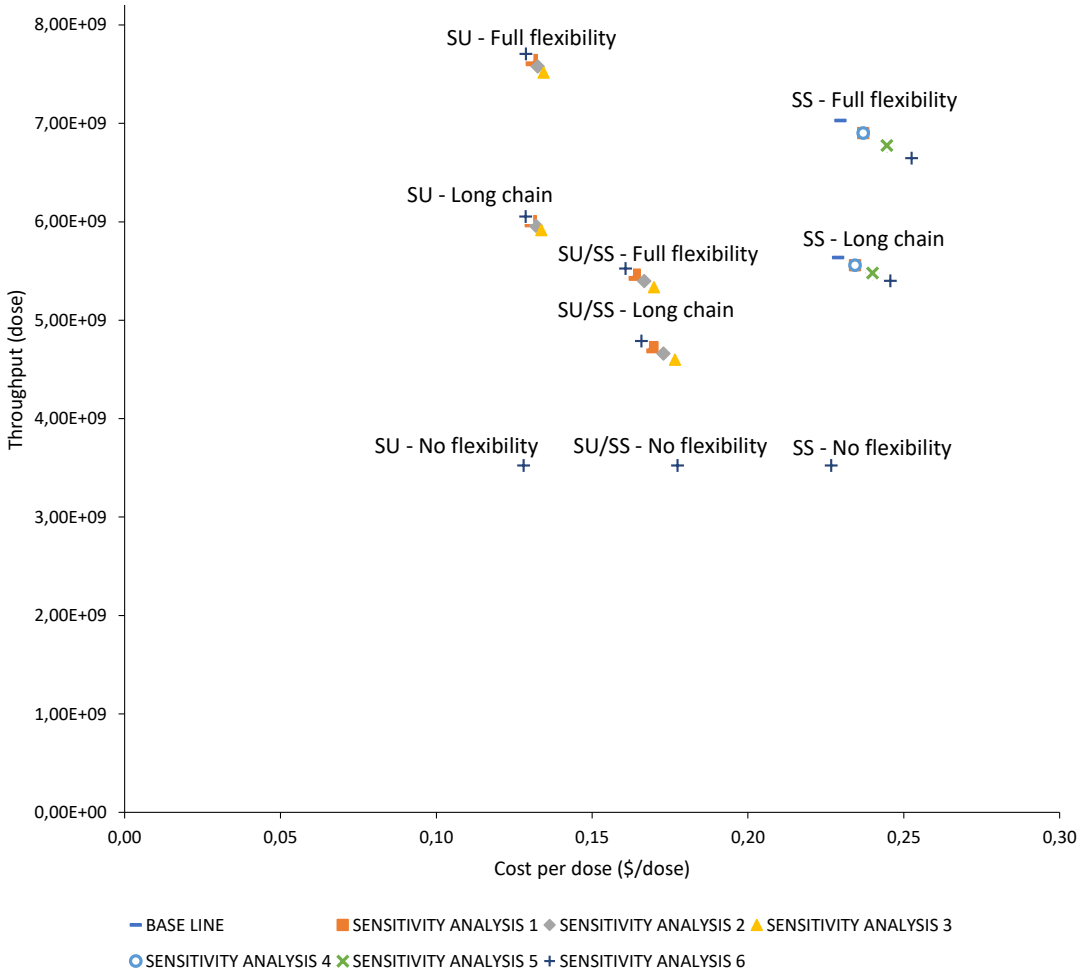

Figure 7.8: Throughput vs cost per dose graph for the cell-based scenarios' sensitivity analysis

factors can cause the cost data for vaccine manufacturing to differ significantly. One factor that greatly contributes to the cost is whether a manufacturing facility is located in a developing or developed country. For vaccine manufacturers in developing countries, the operating cost for the single-use equipment facility may be significantly higher as the disposable equipment which is replaced after each batch is increased by import costs. Therefore, the results from the current modelling are not necessarily applicable for all Covid-19 vaccine manufacturing facilities. It would be beneficial to perform a sensitivity analysis that focuses specifically on the operating cost of single-use equipment facilities in countries where this equipment would need to be imported in future research, especially with a view to better informing the design of flexible vaccine manufacturing networks in developing country contexts. The simulation model that has been developed in this research can be used for such sensitivity analysis by adjusting the "operating cost per dose SU-facility" input data value for each vaccine platform.

An aspect that was not evident prior to the execution of the modelling scenarios was the magnitude of process flexibility's impact on the system (i.e. the difference in the performance obtained for the no flexibility, long chain, and full flexibility configurations), under the high demand uncertainty conditions associated with the approval of vaccines.

From the results it was observed that both the long chain and the full flexibility configurations provide significant improvements in terms of the throughput, and that the full flexibility configuration markedly outperforms the long chain configuration. The maximum throughput improvement that was achieved with the full flexibility configuration is 119%, while the maximum throughput improvement for the long chain configuration is 72%. Across all equipment options, process flexibility did not have a significant impact on the operating cost per dose. For the scenarios utilising both the single-use and the stainless-steel equipment, the operating cost per dose decreased as the degree of flexibility increased. As mentioned in Subsection 1.1.4, full flexibility configurations are often deemed an unjustifiable high expense in literature that considers manufacturing flexibility. The capital costs associated with process flexibility play an important role in shaping this perspective. Capital costs have not been included in this study, and for some of the systems that are considered in the study, there is significant uncertainty as to what the expected capital costs would be as there don't currently appear to be stainless steel facilities that incorporate process flexibility. However, the results of this study can inform decisions on allocating resources to further investigating the feasibility of incorporating process flexibility into vaccine manufacturing networks, either when building new facilities or when retro-fitting existing facilities, by considering aspects such as equipment capabilities, quality considerations, regulatory approval, and capital costs. A trade-off between the throughput and costs will have to be considered for process flexibility investment decisions.

As mentioned in Subsection 6.3.4.12, stringent regulations govern the manufacturing processes of vaccine products. The regulations associated with the cleaning and validation processes between the manufacturing of different platforms may prove the benefits that process flexibility provides to be less substantial when considering the real-world system compared to what was uncovered in this study. It is significantly easier to incorporate process flexibility in facilities that utilise single-use equipment compared to stainless-steel facilities, as the single-use equipment facilities are subject to fewer regulations. The dominance of single-use equipment in terms of performance is thus a valuable finding. Although incorporating process flexibility in facilities that utilise stainless-steel equipment theoretically provides improved benefits, in terms of the throughput achieved, the stringent regulations make this a less favourable solution. The high operating cost per dose further reduces the attractiveness of investing in process flexibility in a facility that utilises stainless-steel equipment.

The assumption of change-over time between platforms was solely based on the knowledge that the change-over time required for the single-use equipment is significantly less than that for the stainless-steel equipment. The sensitivity analysis presented in Subsection 7.3.4 indicated that adjusting the assumed

change-over times in various ways does not greatly impact the conclusions that can be drawn from the model results. The difference in the throughput and cost per dose for the three equipment options are much more significant than the change in the values resulting from the change in switch-over time. It is recommended that a sensitivity analysis is also performed to investigate the impact of the switch-over cost ratio for the stainless-steel and single-use equipment assumption on model results.

Another assumption that may have a significant impact on the observations that can be made from the model results, is the operating cost per dose for the bacterial scenarios. As mentioned in Subsection 7.1.4, the operating cost per dose for the bacterial scenarios was based on the cell-based scenarios' ratio. Suppose this ratio does not represent reality for the bacterial scenarios. In that case, the observations made for these scenarios may be obscured, resulting in the utilisation of single-use equipment proving to be less beneficial compared to stainless-steel equipment. To make a definitive observation regarding the bacterial scenarios' operating cost, future work will have to consider data for both the stainless-steel and single-use equipment facilities for all three of the considered platforms once it becomes available. It is further recommended that future work should include a sensitivity analysis for the impact of the operating cost per dose of the bacterial scenarios.

7.4 Conclusion: Chapter 7

This chapter provided an overview of the scenario execution and the analysis of results. 18 Unique scenarios investigated in this study were first defined. Different equipment options, process flexibility degrees, and antigen production systems were considered in the scenarios. An overview of the selection process for the scenarios' manufacturing data was provided.

The model results and an analysis of the results were also provided. All three this study's aims were met with the analysis of the results. The results indicated that both the long chain and the full flexibility configurations significantly improved the performance of the manufacturing system (improvement ranging between 25% and 119%). It was further observed that the full flexibility configuration provided significantly improvement compared to the long chain configuration under the high demand uncertainty for the Covid-19 vaccine manufacturing system. Finally, it was observed that incorporating process flexibility in facilities utilising stainless-steel equipment had a significantly higher operating cost per dose compared to the single-use equipment for the specific manufacturing data employed in this study. Different observations may be obtained when considering manufacturing data with for facilities in other circumstances (e.g. developing country that has to import disposable equipment)

Chapter 8

Conclusion

Chapter 7 provided a discussion of the model scenario execution and analysis of the model results. This chapter provides an summary of the research. This includes a summary of each chapter, a discussion of the main insights gathered from the research, an overview of this research's contribution to literature, a discussion of this study's limitations and finally recommendations for future work informing the design of vaccine manufacturing systems with process flexibility.

8.1 Overview of research and completed research objectives

The Covid-19 pandemic caused great disruption to the world's health systems and the global economy. The Covid-19 vaccine manufacturing system was faced with high demand uncertainty associated with the approval of vaccine platforms. Vaccine manufacturing systems are complex and process flexibility is not frequently implemented.

The aim for this study is three-fold. The first aim is to investigate the potential benefits that process flexibility can have in reducing the negative impact of high demand uncertainty for the Covid-19 vaccine manufacturing system. The second aim is to investigate the difference in the performance of a long chain configuration and full flexibility configuration for the manufacturing system under high demand uncertainty. The final aim is to investigate the potential benefit of incorporating process flexibility in stainless-steel equipment facilities which are typically designed for the manufacturing of a single product. A discrete-event simulation model was developed and verified in the Tecnomatix Plant Simulation software. The model was also validated via semi-structured interviews with subject matter experts in the fields of vaccine development and manufacturing.

Chapter 1 provided background for this study, including information of vaccine manufacturing, manufacturing flexibility, and modelling of manufacturing systems. The problem statement and research aims and objectives were defined. It was identified from literature that process flexibility has the potential to

reduce the negative impact of demand uncertainty on a manufacturing system. The main research question for this study is as follows: "Can process flexibility reduce the negative impact of high demand uncertainty associated with the approval of vaccine products, to increase the throughput?" The research methodology, limitations, and the contributions were identified. Finally, a summary of the report structure was presented.

Chapter 2 provided an overview of vaccine manufacturing to obtain an understanding of the considerations for a vaccine manufacturing system, as well as the similarities in the manufacturing processes for the six considered platforms, namely: live attenuated virus, inactivated virus, viral vector, subunit protein, DNA, and RNA. Preliminary observations regarding the feasibility of process flexibility configurations within the vaccine manufacturing system was made.

Chapter 3 provided an overview of manufacturing flexibility. The categories of manufacturing flexibility were defined. Process flexibility was particularly discussed in great detail due to its potential of reducing the impact of demand uncertainty for a manufacturing system. The chapter further provided a discussion of the incorporation of process flexibility in a manufacturing system, and the measurement and benefits of manufacturing flexibility. Finally, an overview of manufacturing costs were provided.

Chapter 4 provided an overview of literature on the modelling of systems, to inform the selection process of a modelling approach for this study. The modelling of three types of systems were considered, namely: vaccine product life cycles, systems with manufacturing flexibility, and systems with process flexibility specifically. The Covid-19 vaccine manufacturing system, as considered in this study, was defined on a basic level. Based on the system elements, it was identified that a discrete-event simulation model would be appropriate to model the system.

The discrete-event simulation model for the Covid-19 vaccine manufacturing system development was discussed in Chapter 5. The system was first considered in terms of its world-view. This involved considering its entities, attributes, conditions, events, and the system state. Furthermore, the assumptions, and input and output variables for the system were considered. A detailed description of the model development in Tecnomatix Plant Simulation was provided.

Chapter 6 contains the description of the verification and validation process for the model developed in Chapter 5. The verification process involved the execution of a series of simulation model tests. The results from the verification process were used to make corrections to the model. The validation process comprised of interviews with subject matter experts. The feedback from the SMEs were used to improve the model. The main improvement to the model was distinguishing between single-use and stainless-steel equipment facilities.

Chapter 7 provided an overview of the model scenario and an analysis of the model results. A total of 18 unique scenarios were defined to be investigated. The scenarios differed in terms of the antigen production system considered, the equipment option utilised, and the degree of process flexibility incorporated. The scenarios were designed to achieve all three of this study's aims. The evaluation of different flexibility degrees

indicated that process flexibility does impact the performance of a system. Furthermore, it indicated that the performance of the long chain configuration differs significantly from the full flexibility configuration. Finally, it was uncovered that the incorporation of process flexibility in a manufacturing facility utilising stainless-steel equipment is significantly more expensive per dose compared to single-use equipment facilities. Other factors that contribute to the manufacturing costs, not included in this study, have to be considered to when investigating the feasibility of a flexible stainless-steel equipment facility. These insights are discussed in greater detail in Section 8.2.

8.2 Research insights

The main findings and insights gathered from this research are summarised, also refer to Subsection 7.3.1.

Process flexibility improved the performance of the Covid-19 vaccine manufacturing system, by increasing the total throughput for the system with an increase in the process flexibility degree for all three the equipment options. This was also observed from the p-value ANOVA tables, refer to Tables 7.13 and 7.14. The p-values ($p<0.05$) for the total throughput variable indicated that the no flexibility configuration differed significantly from both the long chain and the full flexibility configurations.

Several existing studies investigating process flexibility have proven that the long chain configuration provides benefits that does not differ significantly from the full flexibility configuration for manufacturing systems facing relatively low demand uncertainty, refer to Section 4.5. In this study, it was observed from the p-value ANOVA tables, refer to Tables 7.2 and 7.14, that the full flexibility configuration achieved significantly better performance compared to the long chain configuration. The full flexibility configuration achieved a throughput improvement ranging between 35% and 119% for the different scenarios, while the long chain configuration achieved a throughput improvement ranging between 25% and 72% for the different scenarios. The capital cost associated with the facilities were not considered in this study. Many studies investigating process flexibility have mentioned that the full flexibility configuration is viewed as an unjustifiable expense due to the high capital costs associated with it, refer to Subsection 1.1.4. The capital costs for a specific configuration should thus form part of any process flexibility investment decision. This study's results only provide an indication of the potential performance associated with the long chain and full flexibility configurations. It can, however, inform the decision to further investigate the cost-effective of the long chain and full flexibility configurations for a vaccine manufacturing system.

This study considered both single-use and stainless-steel equipment. Single-use equipment is designed to allow flexibility in a manufacturing facility. The single-use equipment option dominated in terms of the throughput and the operating cost per dose achieved, refer to Figures 7.6 and 7.7. This was expected due to the lower input operating cost per dose value and shorter switch-over time for the single-use equipment compared to the stainless-steel equipment, refer to Subsections 7.1.3 and 7.1.4. This confirms that it may

be beneficial to include facilities that utilise single-use equipment and incorporates some degree of process flexibility in a manufacturing system, especially under high demand uncertainty. It is important to note that factors, such as the location of the manufacturing facility, may significantly impact the operating cost for a vaccine manufacturing facility and the observations for a manufacturing facility under other circumstances may differ from this study's results.

Process flexibility did show improvement in terms of the throughput achieved for the scenarios utilising stainless-steel equipment from a theoretical perspective, refer to Figures 7.6 and 7.7. No instances of a stainless-steel equipment facility that incorporates process flexibility was uncovered in this study. Commonalities in the manufacturing processes of the vaccine platforms do exist and process flexibility can thus potentially be incorporated in facilities utilising stainless-steel equipment. The results from this theoretical study inform the decision to further investigate the feasibility of either designing new stainless-steel equipment facilities with process flexibility or retro-fitting existing stainless-steel equipment facilities to incorporate process flexibility. Several factors in the real-world contribute to the feasibility of incorporating process flexibility in a manufacturing facility. The main factors uncovered in this study is the technical requirements of the equipment, the regulatory procedures that need to be followed, and the set-up costs associated with flexible equipment and processes.

8.3 Research contributions

This study contributes to both the vaccine manufacturing and flexible manufacturing literature via four main contributions.

No study was uncovered that considered adding process flexibility in a vaccine manufacturing system. **Contribution one** for this study is to provide insight on the potential impact of process flexibility in a vaccine manufacturing system. As mentioned in Chapter 1.1.2, vaccine manufacturing is a complex and expensive process. It is beneficial for the vaccine manufacturing industry to consider the design of effective utilisation of the available vaccine manufacturing capacity. For this study, Covid-19 vaccines were specifically considered due to the high demand uncertainty associated with the approval of the vaccine products for this disease. The uncertainty was elevated due to the rapid vaccine development process compared to the traditional vaccine product development, refer to Subsection 1.1.3. The results are applicable to the manufacturing of other vaccines that adhere to similar circumstances. This includes vaccine products for pandemic diseases which employs the same vaccine platforms in the development of a vaccine product. Furthermore, the disease should have a similar transmission rate as the Covid-19 disease, as the incidence numbers impact the pace at which vaccine products can obtain regulatory approval. For diseases with significantly different prediction of vaccine approval success, the process flexibility results may differ. As mentioned in 7.1.2, operating cost for vaccine manufacturing is very case specific and the

manufacturing input cost data for another disease may significantly differ from the Covid-19 disease and consequently impact the results that can be observed.

As mentioned in Section 1.2, various other demand uncertainty sources, beyond the uncertainty in the approval of vaccine products for a pandemic disease, are present in vaccine manufacturing systems. An example of demand uncertainty in a vaccine manufacturing system is the manufacturing of vaccine products for which the demand is subjected to epidemiological outbreaks, refer to Section 1.6. Although this study indicates that process flexibility can theoretically improve the performance of a vaccine manufacturing system, the manufacturing system for the example differ significantly in terms of the system requirements and consequently the process flexibility considerations. It may be required that a completely new study be performed to inform the process flexibility decisions for such a system.

Contribution two for this study is the high demand uncertainty that is considered. As mentioned in Section 8.2, many studies have compared the performance of the long chain and full flexibility configurations and observed that the long chain configuration performs similarly to the full flexibility configuration for systems with relatively low demand uncertainty. The long chain and the full flexibility configurations were considered under high demand uncertainty in this study. It was uncovered that for high demand uncertainty scenarios the full flexibility configuration does substantially improve the throughput performance for the vaccine manufacturing system compared to the long chain configuration.

Contribution three for this study is the investigation of the potential benefits associated with process flexibility incorporated in a facility that utilises stainless-steel equipment. No instance was uncovered that incorporates process flexibility in a facility that utilise stainless-steel equipment. The results can inform the decision to investigate the feasibility of incorporating process flexibility in a stainless-steel equipment facility from a real-world perspective with the required complexities, such as equipment capabilities, and regulatory considerations, considered.

Contribution four for this study is the discrete-event simulation model which was developed, verified, and validated, refer to Chapters 5 and 6. The model can be adjusted or re-calibrated to represent the manufacturing systems of other diseases or the investigation of other process flexibility problems in vaccine manufacturing systems.

8.4 Limitations

The research has a few noteworthy limitations. Only the upstream manufacturing process for vaccine products were considered. Although incorporating process flexibility for the upstream manufacturing process is significantly more complex than for the downstream manufacturing process, limitations in the process flexibility that can be incorporated in the downstream manufacturing process still exist.

The uncertainty in the demand for products was limited to only considering the uncertainty associated with the approval of vaccine products during a pandemic. Several other factors also contribute to the uncertainty in the demand for products in a vaccine manufacturing system.

Specifically Covid-19 vaccine products were considered. The results for the Covid-19 vaccine products cannot be generalised for all other vaccine manufacturing systems or even all other diseases facing a pandemic. The costs associated with vaccine manufacturing is very case specific.

No capital costs were incorporated in this study. Many of the manufacturing facilities with process flexibility considered in this study do not exist in reality and capital costs are thus not available for these facilities.

The available data on operating costs for vaccine manufacturing does have some limitations and a number of assumptions were made as part of the modelling process. Though steps are taken to limit the potential negative impact of this on the accuracy of the modelling results, most notable through the verification process, this is a noteworthy limitation of the research.

8.5 Recommended future work

Four main aspects have been identified in this study that can be addressed in future work that informs the design of the Covid-19 vaccine manufacturing systems with process flexibility. The improvements of the Covid-19 vaccine manufacturing model is discussed in Subsection 8.5.1. Three alternative vaccine manufacturing system modelling opportunities were identified in this study. The alternative modelling opportunities are discussed in Subsection 8.5.2.

8.5.1 Covid-19 vaccine model improvements

As mentioned in Subsection 7.1.2, several assumptions were made to obtain complete manufacturing input data for the cell-based and bacterial scenarios. In this study, a sensitivity analysis was performed to investigate the impact of the switch-over time assumption. It is recommended that a sensitivity analysis is performed to also investigate the impact of the switch-over cost ratio on the operating cost per dose. This sensitivity analysis will have to be performed via a series of experiments for each of the 18 scenarios in the Tecnomatix Plant Simulation software.

Several factors contribute to variability that can exits in vaccine manufacturing cost data. One of these factors is the location of the manufacturing facility (e.g. developing or developed country). As mentioned in Subsection 7.3.5, it is recommended that a sensitivity analysis of the single-use equipment facility's operating cost is performed to consider the design of single-use equipment facilities in countries that have to import disposable equipment.

Deterministic manufacturing data was considered in this study to not obscure the observations that can be made regarding the impact of process flexibility on the Covid-19 vaccine manufacturing system. It is recommended that a sensitivity analysis is performed on the deterministic manufacturing data used in the model to investigate the impact on the results.

Once data becomes available for all the vaccine platforms with incomplete manufacturing data, it is recommended that the scenario execution is repeated in the Tecnomatix Plant Simulation software with the complete manufacturing data set. This will allow for definitive conclusions to be derived.

8.5.2 Alternative modelling opportunities

The model developed in this study could potentially be adjusted or re-calibrated to consider the alternative modelling opportunities discussed in this section.

The feasibility of a scenario in which a facility continuously operates at low capacity utilisation manufacturing routine vaccines (e.g. EPI vaccines), and for which the capacity is up-scaled for the manufacturing of pandemic products can be investigated. This alternative modelling opportunity was discussed by several SMEs during the validation interviews, refer to Subsection 6.3.4.1.

A scenario in which a facility is dedicated to the continuous manufacturing of a routine vaccine product with the capability to switch over some of the manufacturing capacity for manufacturing of an epidemic product can also be investigated. The demand for the products will fluctuate based on epidemiological outbreaks.

The under-utilisation of capacity results in a very high operating cost and at some point it may be beneficial to rather campaign to manufacture a new product. An investigation can be performed to consider the decision regarding the optimal time to switch to manufacturing a new product. This alternative modelling opportunity was discussed by several SMEs during the validation interviews, refer to Subsection 6.3.4.18.

8.6 Chapter 8: Conclusion

This chapter provided a summary of the research. The main research insights gathered from this study were discussed. The limitations and contributions were also discussed. Finally, recommendations for future work informing the design of process flexibility in a vaccine manufacturing system were discussed.

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Appendix A

Vaccine manufacturing

As mentioned in Section 2.2, the process flow diagrams and description of the inactivated virus, viral vector, subunit protein, DNA, and RNA vaccine platforms' manufacturing processes are provided in this Appendix.

A.1 Inactivated virus vaccine platform manufacturing

The process flow diagram depicting the manufacturing processing steps for the inactivated virus vaccine is shown in Figure A.1.

Manufacturing inactivated virus vaccines entail the manufacturing of live viruses that are inactivated before the vaccine's formulation (Kyriakidis et al., 2021; Tregoning et al., 2020). Inactivated virus vaccines have been used as a vaccine platform for many years, and well-known manufacturing procedures for the platform exist (Mahalingam et al., 2020; Tregoning et al., 2020).

Micro-organisms or mammalian cells, which have priorly been amplified in seed bio-reactors, are infected with virus seeds (Gomez & Robinson, 2013; McDonnell et al., 2020). The infected cells are allowed to replicate on cell lines in micro-cultures, and consequently, the virus is propagated (McDonnell et al., 2020). Centrifugation is used to extract the fluid containing the virus (Gomez & Robinson, 2013; Josefsberg & Buckland, 2012; McDonnell et al., 2020). Cell lysis may be required for intra-cellular viruses (Josefsberg & Buckland, 2012; McDonnell et al., 2020). The harvested virus may be clarified and purified using filtration, buffer exchange and chromatography (McDonnell et al., 2020; Pori, 2011). The virus is inactivated using heat or chemical treatments, typically formalin or UV (Mahalingam et al., 2020; Zhao et al., 2020). The drug substance is stored in bulk before it is processed further (McDonnell et al., 2020).

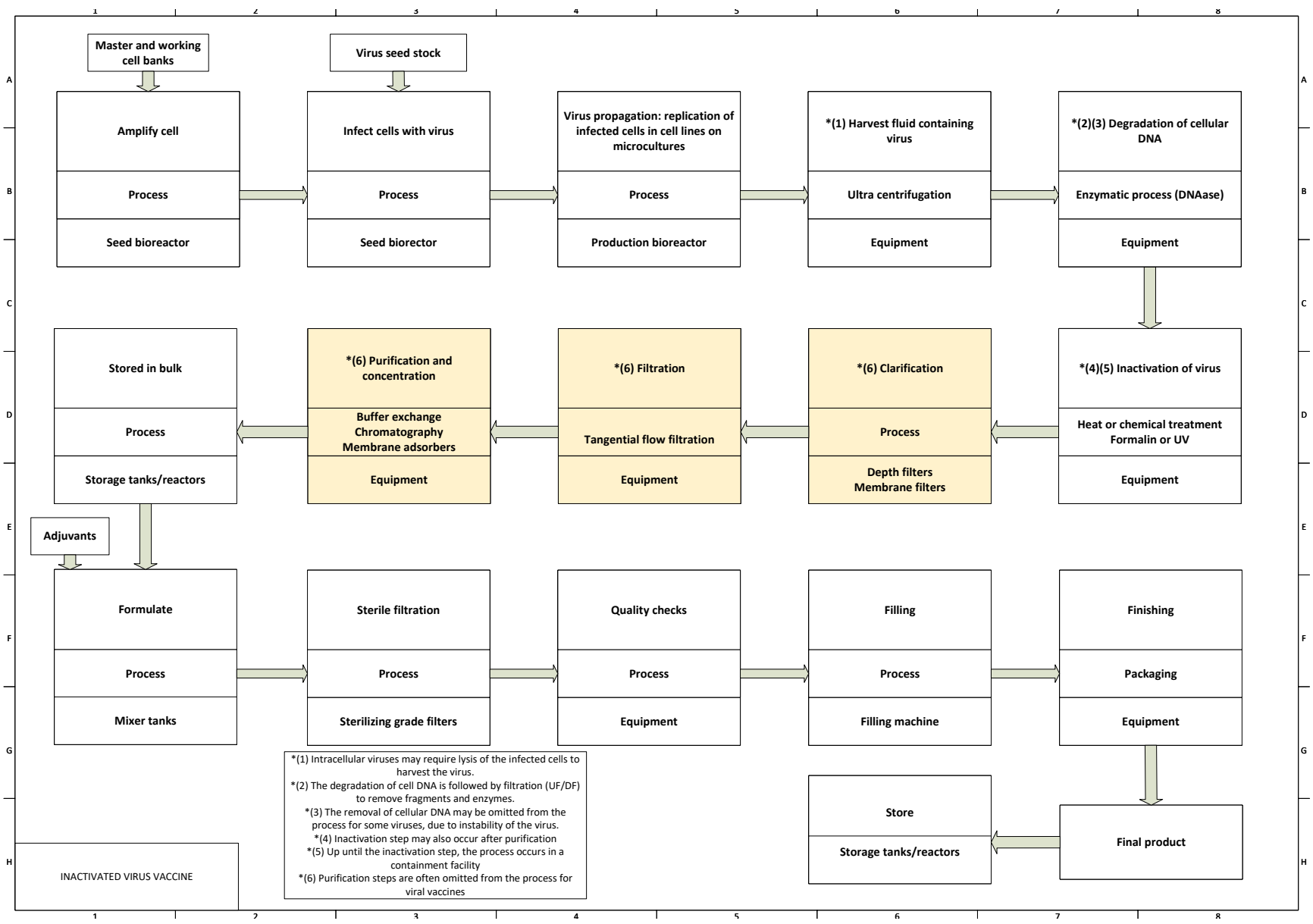

Figure A.1: Manufacturing process for inactivated virus vaccine

The drug substance is formulated in mixers (Gomez & Robinson, 2013; Liang et al., 2020; McDonnell et al., 2020). According to the vaccine design requirements, ingredients such as preservatives and stabilisers may be added (Gomez & Robinson, 2013). It is then filtered to ensure high sterility before quality checks are performed to ensure that regulations are met (Silveira et al., 2021).

Filling and finishing of the final product are performed, after which the final product is stored until distribution (Gomez & Robinson, 2013; McDonnell et al., 2020).

The advantages and drawbacks of the inactivated virus vaccine are presented in Table A.1.

Table A.1: Advantages and drawbacks of the inactivated virus vaccine platform (adapted from McDonnell et al. (2020))

Advantages	**Drawbacks**
Well established method	Requires level 3 bio-containment for growth of live virus
Simple manufacturing process	Timely development
Requires no adjuvants	Timely safety evaluation
Rapid manufacturing	Risk for vaccine enhanced disease
Suitable for immuno-compromised patients	Requires booster doses
	Lower immune response compared to live attenuated virus due to inactivation

A.2 Viral vector vaccine platform manufacturing

The process flow diagram depicting the manufacturing processing steps for the viral vector vaccine is shown in Figure A.2.

Viral vector vaccines are manufactured by producing either a replicating or non-replicating viral vector, which contains genetically engineered viral DNA encoding for a specific antigen (McDonnell et al., 2020; Tregoning et al., 2020; Zhou et al., 2020). A viral vector is non-pathogenic and is generally either micro-organism or mammalian cells (Gomez & Robinson, 2013). Cells are amplified on cell cultures in seed bio-reactors before genetically

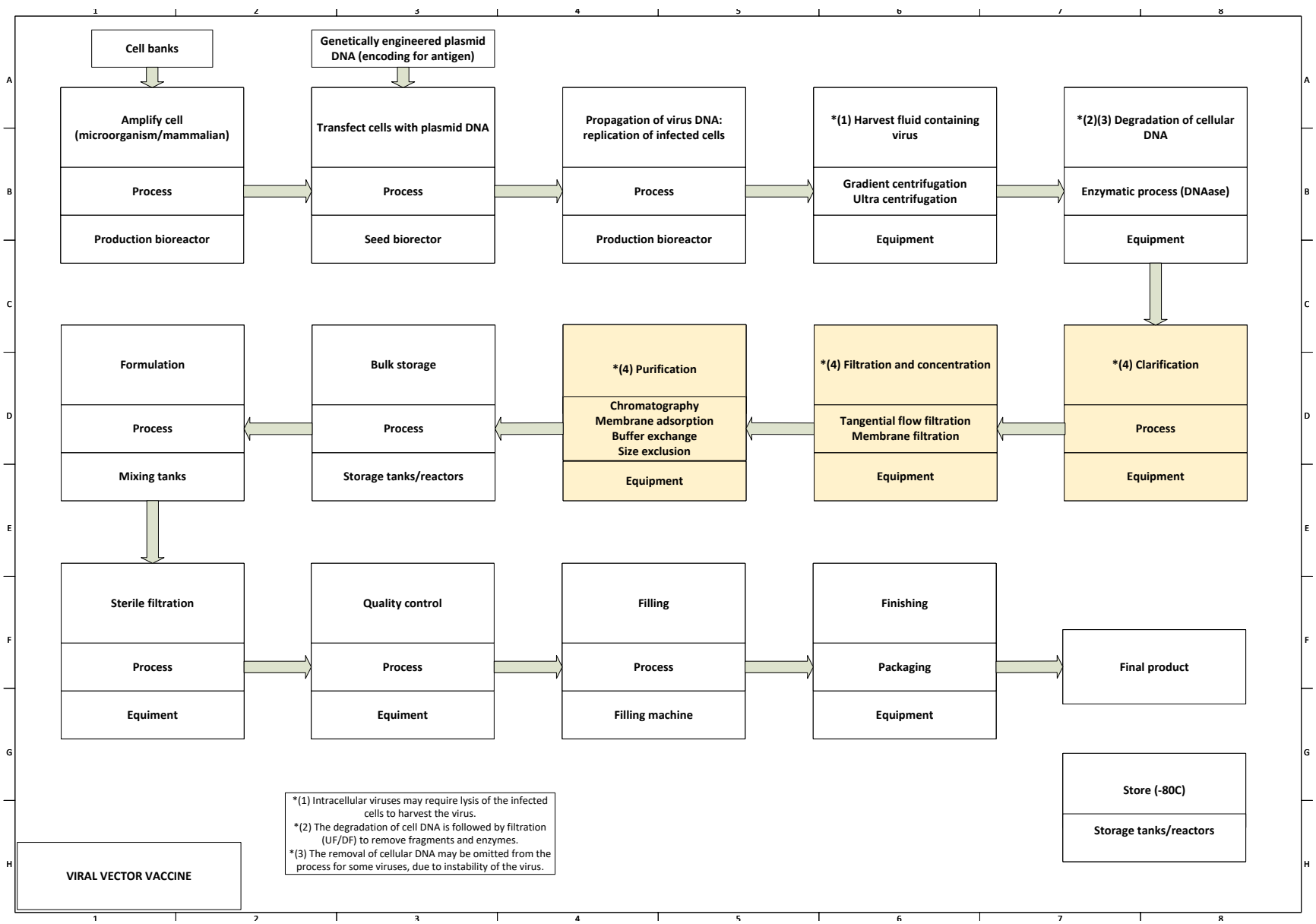

Figure A.2: Manufacturing process for viral vector vaccine

engineered plasmid DNA, encoding for a specific antigen, is inserted into the cells (Chin et al., 2021; Josefsberg & Buckland, 2012; Mahalingam et al., 2020). The viral DNA is allowed to propagate in the cells in manufacturing bio-reactors (McDonnell et al., 2020).

Cell lysis occurs before the cells are harvested, and cell debris is removed via centrifugation (Chin et al., 2021; Josefsberg & Buckland, 2012). The cells may be clarified, followed by filtration and concentration (Ghanem et al., 2013). Further purification may be performed in the form of chromatography before the drug substance is bulk stored (Chin et al., 2021; Josefsberg & Buckland, 2012).

The drug substance is formulated in mixers and filtered to ensure high sterility of the substance (Gomez & Robinson, 2013; Josefsberg & Buckland, 2012). Quality checks are performed on the substance to ensure that regulations are met before filling and finishing the final product is completed (Silveira et al., 2021). The final product is stored at approximately -80°C until distribution (Gomez & Robinson, 2013; McDonnell et al., 2020).

The advantages and drawbacks of the viral vector vaccine are presented in Table A.2.

Table A.2: Advantages and drawbacks of the viral vector vaccine platform (adapted from McDonnell et al. (2020))

Advantages	**Drawbacks**
May require only one dose	Requires storage at -80C
Specific delivery of genes to target cells	May have pre-existing immunity against vector
Induces good immune response	Risk of DNA integrating into host genome
Good safety	
No handling of pathogen	

A.3 Subunit protein vaccine platform manufacturing

The process flow diagram depicting the manufacturing processing steps for the subunit protein vaccine is shown in Figure A.3.

Subunit vaccines are manufactured by producing target proteins or peptides of the pathogen using recombinant DNA technology (Kyriakidis et al., 2021; Pori, 2011). Virus-like particle (VLP) vaccines are included in the subunit vaccine platform.

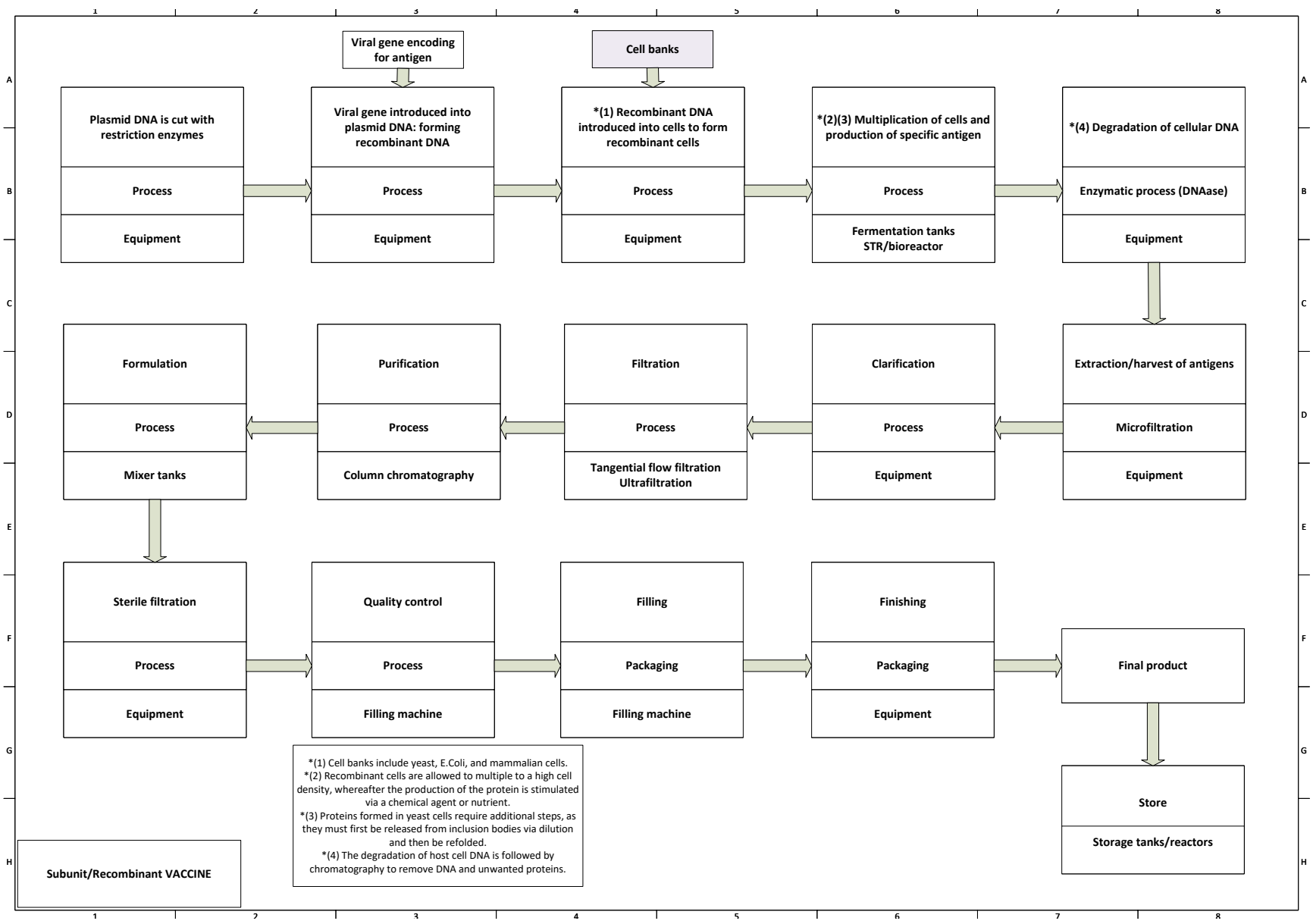

Figure A.3: Manufacturing process for subunit protein vaccine

VLP vaccines are composed of viral particles containing no genetic information, with all or most of the pathogenic proteins on their surface (Kyriakidis et al., 2021; Loomis & Johnson, 2015; Tregoning et al., 2020). Although VLP vaccines are classified as a separate vaccine platform in some literature, the manufacturing of the vaccine corresponds to a subunit vaccine platform (Josefsberg & Buckland, 2012). Authors such as Loomis & Johnson (2015), Josefsberg & Buckland (2012), and Tregoning et al. (2020) also refer to VLP vaccines as a subset of the subunit vaccine platform. The manufacturing of subunit vaccines is timely and relatively expensive (Tregoning et al., 2020).

Genetic engineering techniques are used to isolate and clone a specific DNA segment, encoding for a target antigen (Blakney et al., 2021; Mahalingam et al., 2020; Tregoning et al., 2020). The DNA segment is introduced into a plasmid that has priorly been cut with restriction enzymes to form recombinant DNA (Pori, 2011). The recombinant DNA is inserted into either yeast, bacteria, virus, or mammalian cells to form recombinant cells (Gomez & Robinson, 2013; Josefsberg & Buckland, 2012; Tregoning et al., 2020). The replication of the cells and manufacturing of the target antigen occur in fermentation tanks (Gomez & Robinson, 2013; Josefsberg & Buckland, 2012; Pori, 2011). After sufficient replication of the cells, the antigens are extracted via micro-filtration, and the recovered antigens are clarified and further purified through ultrafiltration and chromatography (Josefsberg & Buckland, 2012; Kyriakidis et al., 2021; McDonnell et al., 2020; Tregoning et al., 2020). The drug substance is stored in bulk until further processing (McDonnell et al., 2020).

The drug substance is formulated in mixers (Gomez & Robinson, 2013). It is often required that adjuvants and delivery mechanisms are added to the vaccine to enhance the immune response and improve vaccine uptake (Blakney et al., 2021; Liang et al., 2020; Zhao et al., 2020). The drug substance is filtered to ensure high sterility before quality checks are performed to ensure that regulations are being met (Silveira et al., 2021). Filling and finishing of the final product are performed, after which the final product is stored until distribution (Blakney et al., 2021; Gomez & Robinson, 2013; McDonnell et al., 2020).

The advantages and drawbacks of the subunit virus vaccine are presented in Table A.3.

Table A.3: Advantages and drawbacks of the subunit vaccine platform (adapted from McDonnell et al. (2020))

Advantages	**Drawbacks**
Established method	Timely development
Simple manufacturing process	May require adjuvant
Not likely to cause adverse effects	May require two doses
Easy to licensure	Risk for vaccine-enhanced disease
Good safety	Induces low immune response
Available large-scale manufacturing capacity	Proteins can become denatured and activate the release of antibodies not targeted.
Suitable for immuno-compromised patients	

A.4 DNA vaccine platform manufacturing

The process flow diagram depicting the manufacturing processing steps for the DNA vaccine is shown in Figure A.4.

DNA-based vaccines are manufactured by producing a viral DNA segment, encoding for a specific antigen in bacterial cells (McDonnell et al., 2020; Pandey et al., 2020; Pori, 2011). The required DNA segment is extracted and isolated using restriction enzymes, after which genetic engineering technologies are used to clone the viral DNA (Pori, 2011). A bacterial DNA plasmid is used as an expression platform for the viral DNA (Pori, 2011; Tregoning et al., 2020). The viral DNA is inserted into the plasmid DNA, which has priorly been cut with restriction enzymes, to form recombinant DNA (Pori, 2011). The recombinant DNA is inserted into cells, typically *E.coli* cells, and allowed to propagate in fermentation tanks (Ghanem et al., 2013; McDonnell et al., 2020; Pori, 2011).

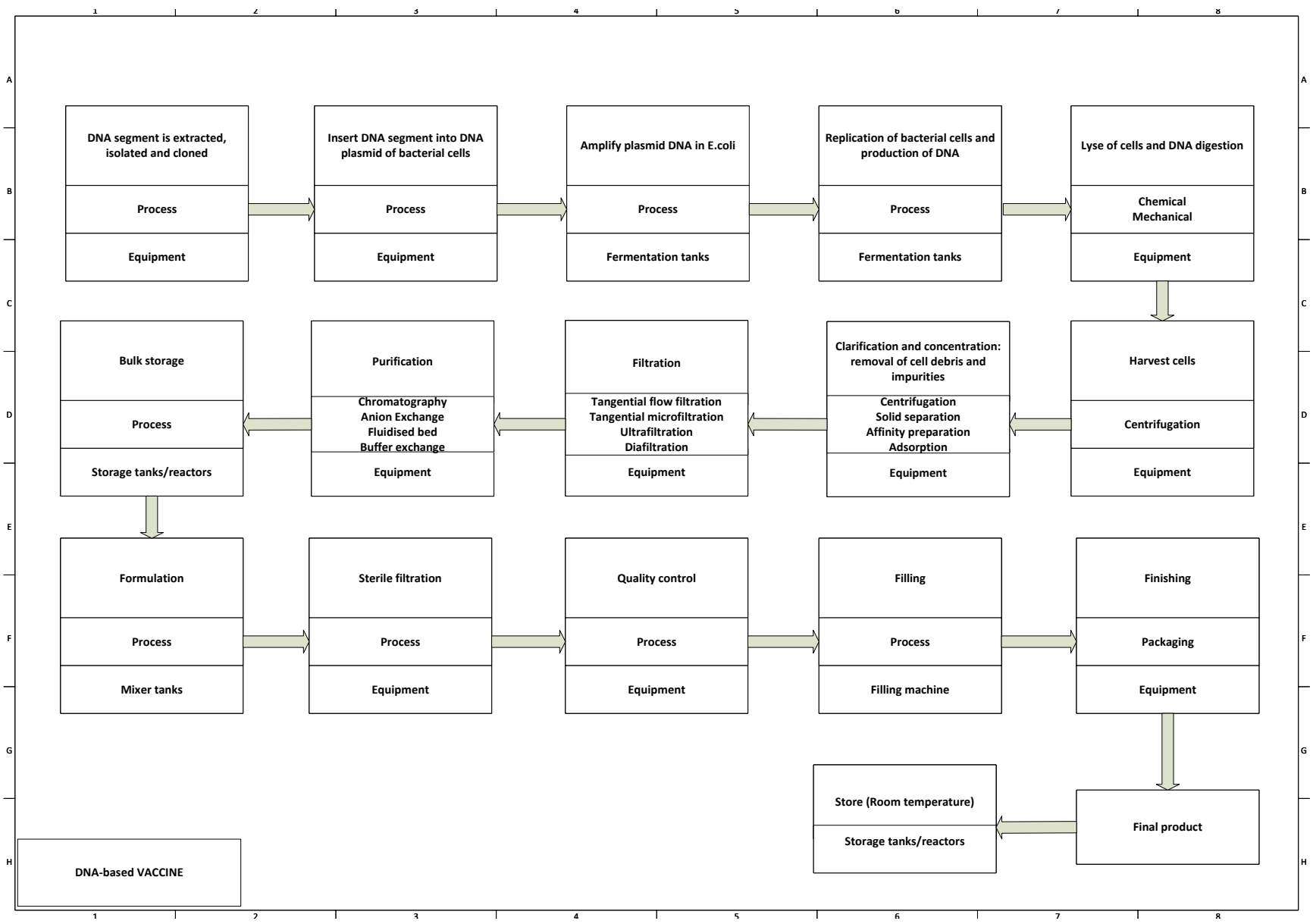

Figure A.4: Manufacturing process for DNA protein vaccine

The DNA plasmids are separated from the rest of the bacterial DNA via cell lysis (Ghanem et al., 2013; Josefsberg & Buckland, 2012; McDonnell et al., 2020). After the manufacturing of multiple bacterial cells, the cells are harvested from the fermentation tanks via centrifugation (Ghanem et al., 2013; Josefsberg & Buckland, 2012). Cell debris and other impurities are removed, and the plasmid DNA is clarified and concentrated (Ghanem et al., 2013). The plasmids are filtered, and further purification is performed via chromatography, anion exchange, and/or a fluidised bed (Josefsberg & Buckland, 2012; Tregoning et al., 2020). The drug substance is stored in bulk until further processing (McDonnell et al., 2020).

The drug substance is formulated in mixers and filtered to ensure sterility of the substance (Gomez & Robinson, 2013; Josefsberg & Buckland, 2012). Quality checks are performed on the substance to ensure that regulations are met before filling and finishing the final product is completed (Silveira et al., 2021). The final product is stored at room temperature until distribution (Gomez & Robinson, 2013; McDonnell et al., 2020).

Although vaccines from the DNA platform can be developed and manufactured faster than the more traditional vaccine platforms requiring culturing, the initial large-scale manufacturing will commence at a slower pace due to the limited manufacturing facilities that were available before the Covid-19 pandemic (McDonnell et al., 2020). The initial large-scale manufacturing of RNA-based vaccines discussed in Section A.5 is subjected to the same restraints as the DNA-based vaccines. The advantages and drawbacks of the DNA-based vaccine are presented in Table A.4.

Table A.4: Advantages and drawbacks of the DNA-based vaccine platform (adapted from McDonnell et al. (2020))

Advantages	**Drawbacks**
Suitable for immuno-compromised patients	No existing human vaccine
Fast manufacturing	Requires delivery device
Low cost manufacturing	Risk of DNA integrating into host genome
Stable	Induces low immune response
No handling of pathogen	May require two doses

A.5 RNA vaccine platform manufacturing

The process flow diagram depicting the manufacturing processing steps for the RNA vaccine is shown in Figure A.5.

RNA-based vaccines are manufactured by producing a segment of RNA that encodes for a specific antigen (Blakney et al., 2021; Pandey et al., 2020). RNA-based vaccines can be synthesised in cell-free environments, reducing the risk of pathogenic contamination (Blakney et al., 2021).

A DNA plasmid template that has been genetically engineered to contain the required RNA sequence is grown in E.coli cells (McDonnell et al., 2020). The plasmid DNA is purified and linearised (Knezevic et al., 2021; McDonnell et al., 2020). The RNA sequence is transcribed to RNA, and the DNA template is digested via enzymatic reactions in a manufacturing bio-reactor (Blakney et al., 2021; Knezevic et al., 2021; McDonnell et al., 2020). The RNA is purified via filtration and chromatography to remove DNA fragments, nucleotides and reagents (Blakney et al., 2021; Knezevic et al., 2021). The RNA is encapsulated in a lipid nanoparticle and formulated, after which it is concentrated and purified using buffer exchange (Blakney et al., 2021; Josefsberg & Buckland, 2012; McDonnell et al., 2020; Zhou et al., 2020). The drug substance is stored in bulk until further processing (McDonnell et al., 2020).

The drug substance is filtered to ensure sterility of the substance (Blakney et al., 2021). Quality checks are performed on the substance to ensure that regulations are met before filling and finishing the final product is completed (McDonnell et al., 2020; Silveira et al., 2021). The final product is stored at approximately -80°C until distribution (Gomez & Robinson, 2013; McDonnell et al., 2020).

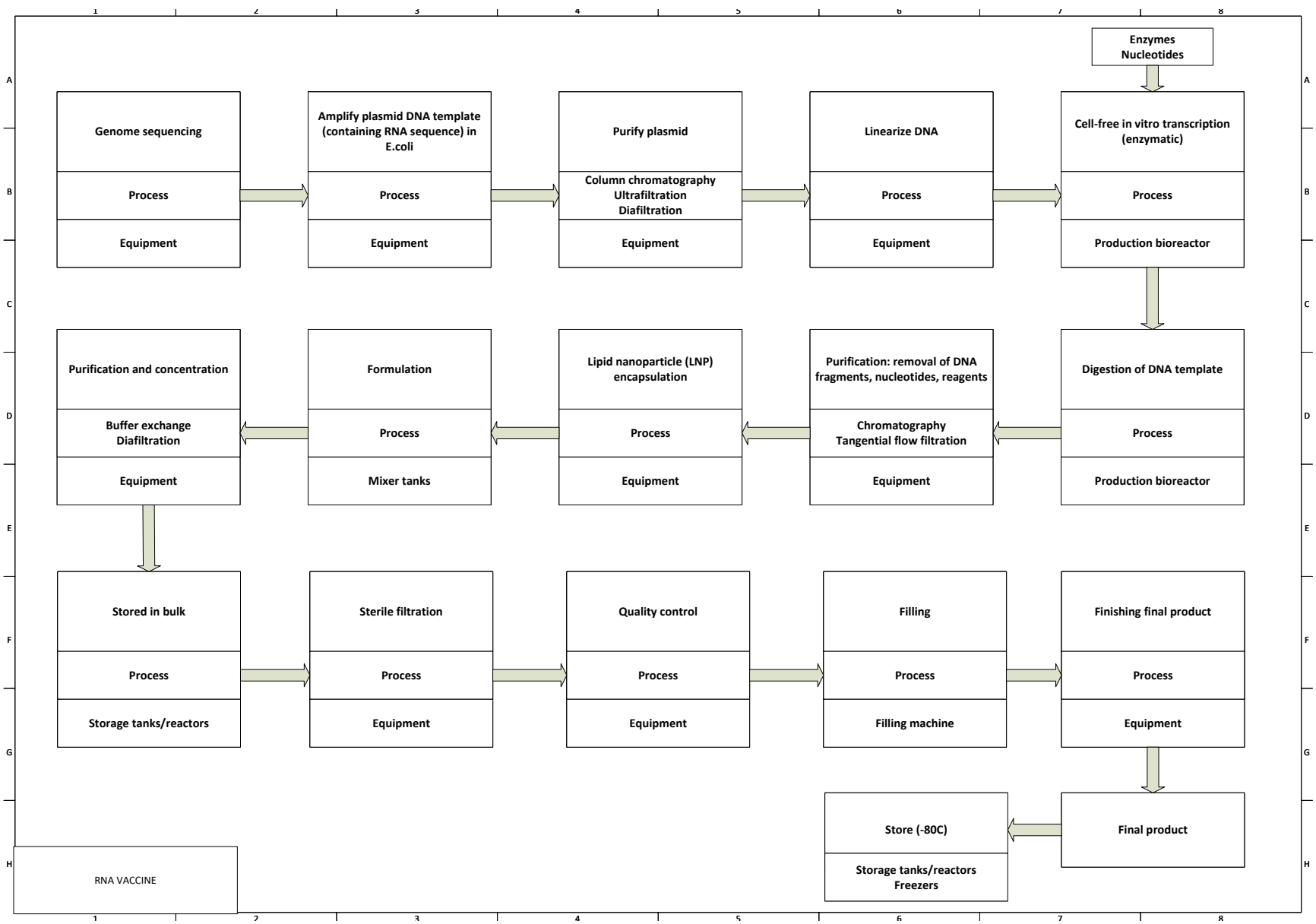

Figure A.5: Manufacturing process for RNA protein vaccine

The advantages and drawbacks of the RNA-based vaccine are presented in Table A.5.

Table A.5: Advantages and drawbacks of the RNA-based vaccine platform (adapted from McDonnell et al. (2020))

Advantages	**Drawbacks**
Fast development and manufacturing	No existing human vaccine
Low cost manufacturing	May require 2 doses
Translation can start in cytosol	May require adjuvants
Good safety	Requires delivery device
No handling of pathogen	LNP delivery system may be toxic
	Unstable
	Requires storage at -80C
	Limited manufacturing capacity
	No information on long-term safety
	Induces low immune response
	Difficulty in sterilisation

Appendix B

Manufacturing flexibility

As mentioned in Section 3.1.1, the remainder of manufacturing flexibilities are defined in this Appendix. The manufacturing flexibilities sections include: machine flexibility, routing flexibility, operation flexibility, material handling flexibility, labour flexibility, product flexibility, volume flexibility, expansion flexibility, mix flexibility, production flexibility, program flexibility, market flexibility, and other flexibilities.

B.1 Machine flexibility

Machine flexibility is associated with the component flexibility level, as shown in Table 3.2. Different definitions for machine flexibility have been defined in literature. A unified definition for machine flexibility is defined by Sawhney (2006), Sethi & Sethi (1990) and Chen et al. (1992), which states that the equipment can perform various processing steps. The definitions by Sethi & Sethi (1990) and Chen et al. (1992) are extended to include that this variety of processing steps should be performed without requiring significant changes to the equipment between different steps. According to Koste & Malhotra (1999), the number of different processing steps that the equipment can perform should also be considered. Browne et al. (1984)'s definition of machine flexibility differs from that of Sawhney (2006), Sethi & Sethi (1990) and Chen et al. (1992) and states that machine flexibility refers to the ability to make changes to the manufacturing equipment that forms part of the system to produce different products without resulting in significant time losses.

Highly flexible machines exist which can produce many or even all the required manufacturing steps of a process. According to Benjaafar (1994), machine flexibility is beneficial for a flexible manufacturing system since it can allow the system to produce different product components simultaneously using various machinery (Co, 2001). Machine flexibility may often be required to achieve other forms of flexibility in the manufacturing system (Sethi & Sethi, 1990).

B.2 Routing flexibility

As shown in Table 3.2, routing flexibility is associated with the component level of flexibility. Different definitions for routing flexibility have been defined in literature. Browne et al. (1984) defined routing flexibility as the ability to produce products despite equipment breakdowns. Other authors' definitions differ from that of Browne et al. (1984). Routing flexibility is instead defined as the ability to produce a product component with different machinery or perform the processing steps in different orders (Sawhney, 2006). Sethi & Sethi (1990), Chen et al. (1992), and Koste & Malhotra (1999) similarly, define routing flexibility in terms of the ability to use alternative operation approaches to produce a component. Gerwin (1982) associates routing flexibility with the configuration of machinery in the manufacturing system.

B.3 Operation flexibility

Operation flexibility is associated with the component level, as shown in Table 3.2. Opposing definitions of operation flexibility have been defined in literature. Browne et al. (1984) define operation flexibility as the ability of a system to change the order in which the manufacturing process of a product is performed. Sethi & Sethi (1990) instead define flexibility as the ability to use different approaches to produce a product component. Finally, in addition to different approaches to producing a product, Koste & Malhotra (1999)'s definition also considers the number of products that can be produced using alternative approaches and the differences between the alternative approaches to manufacturing a product.

B.4 Material handling flexibility

Material handling flexibility is associated with the component level of flexibility, as shown in Table 3.2. Although varying forms of the definition for material handling flexibility exist, the definitions all refer to the transportation of product components within the manufacturing system. Sethi & Sethi (1990) defines material handling flexibility as the ability to efficiently transport product components within the manufacturing facility to subsequently allow the correct processing of the components. Furthermore, in their definition Koste & Malhotra (1999) refer to the number of available transportation routes for product components and the variety of product components that can be transported by these routes. Chen et al. (1992) similarly state that the material handling flexibility is associated with the material transportation system within the manufacturing system. Finally, Sawhney (2006) defines material handling flexibility as the ability to adjust the transportation system to provide the required routes according to the changes in the environment.

B.5 Labour flexibility

As shown in Table 3.2, labour flexibility is associated with the component flexibility level. A unified definition for labour flexibility is defined, which is related to the variety of different tasks that can be performed by the employees in the manufacturing system and the ease of changing between these tasks (Chen et al., 1992; Koste & Malhotra, 1999). Furthermore, it Koste & Malhotra (1999) also considers the number of employees that can perform various tasks as part of the definition of labour flexibility.

B.6 Product flexibility

Product flexibility is associated with the operational level of flexibility, as shown in Table 3.2. Opposing definitions for product flexibility have been defined in literature. A definition for product flexibility that is agreed upon by authors such as Chang (2012), Sawhney (2006) and, Sethi & Sethi (1990), refer to the ability to easily add or replace components to the manufacturing process of a product or to modify existing components. Gerwin (1982) defines this type of flexibility as parts flexibility. Browne et al. (1984) and Chryssolouris (2013) instead refer to product flexibility as the ability to quickly produce new products without significant cost increase. The definition of Koste & Malhotra (1999) is a combination of the aforementioned two views of product flexibility, namely: product flexibility includes both the ability to add new components to products without a significant cost increase and the ability to add new products to the manufacturing system without significant cost increases (Koste & Malhotra, 1999). Some degree of machine flexibility, defined in Section B.1 may be required in a system to enable product flexibility (Browne et al., 1984).

B.7 Volume flexibility

Volume flexibility is associated with the operational flexibility level, as shown in Table 3.2. A holistic definition for volume flexibility is: the ability to adjust the output levels of products whilst remaining profitable (Browne et al., 1984; Koste & Malhotra, 1999; Sethi & Sethi, 1990). Volume flexibility can allow the manufacturing system to respond to high variability in the demand for a product (Jack & Powers, 2004). The output levels can be adjusted according to the market demand without requiring significant changes to the manufacturing set-up (Jack & Powers, 2004). Routing flexibility, defined in Section **??**, is often associated with volume flexibility in a manufacturing system (Browne et al., 1984).

B.8 Expansion flexibility

As shown in Table 3.2, expansion flexibility is associated with the operations level of flexibility. Although the definitions for expansion flexibility vary, they all refer to some form of adjustment made to the system. Browne et al. (1984) refers to expansion flexibility as the ease with which a system can be modified and/or expanded, while both Sawhney (2006) and Sethi & Sethi (1990) refer to expansion flexibility as the ability to adjust the available manufacturing capacity of the system. According to Browne et al. (1984), it is not possible for most existing systems to achieve expansion flexibility. Routing flexibility, defined in Section B.2 can often be associated with systems having expansion flexibility (Browne et al., 1984).

B.9 Mix flexibility

Mix flexibility is associated with the operational level of flexibility as shown in Table 3.2. The different definitions for mix flexibility all relate to the products produced by the manufacturing system. Sawhney (2006) defines mix flexibility as the manufacturing system's ability to produce various products. Gerwin (1982)'s definition is similar to that of Sawhney (2006) but extends to include that the ability of the system to produce a variety of products should be considered within a specific time period. Oke (2005)'s definition differs from that of Sawhney (2006) and Gerwin (1982), namely: mix flexibility is the ability to quickly change the set of products produced by the manufacturing system to a new set of products.

B.10 Production flexibility

As shown in Table 3.2, production flexibility is associated with the system level of flexibility. A holistic definition for production flexibility exists. Browne et al. (1984) refers to production flexibility as the complete set of product components that can be produced by the system. Sethi & Sethi (1990)'s definition is similar to that of Browne et al. (1984), but further states that the product components should be produced without requiring the acquisition of costly equipment. According to Chen et al. (1992), six flexibility categories can be grouped under production flexibility. The categories include (Chen et al., 1992): machine flexibility; process flexibility; routing flexibility; manpower flexibility; material handling flexibility; and programming flexibility. Production flexibility is one of the overarching flexibilities, since it is associated with the overall flexibility of the system (Taymaz, 1989).

B.11 Program flexibility

As shown in Table 3.2, program flexibility is associated with the system level of flexibility. According to Sethi & Sethi (1990) program flexibility is associated with the automation of the system and is defined

as the ability of the system to operate with limited human supervision. The level of program flexibility that can be achieved for a system is based on the process flexibility and especially the routing flexibility available to that system (Jain et al., 2013). Furthermore, it also depends on the process control equipment that forms part of the system, enabling the system to deal with the upsets it faces (Sethi & Sethi, 1990). Program flexibility can reduce the required set-up times of equipment (Sethi & Sethi, 1990).

B.12 Market flexibility

As shown in Table 3.2, market flexibility is associated with the system level of flexibility. According to Sethi & Sethi (1990), the ability of the system to easily adjust to the market requirements is defined as market flexibility. According to Chen et al. (1992), four flexibility categories can be grouped under market flexibility, namely: product flexibility, volume flexibility, mix flexibility and expansion flexibility.

B.13 Other flexibilities

The flexibility categories discussed here include infrastructural flexibility, input-quality flexibility, delivery flexibility, and input and output flexibility stages. These flexibility categories are not broadly defined in literature, and limited definitions are available for each. Furthermore, no flexibility levels are explicitly associated with any of these flexibility categories. According to Chen et al. (1992), infrastructural flexibility is associated with the flexibility that is added to an organisation. Input-quality flexibility is the ability of the system to operate in an environment with various changes occurring to the input of the system (Sawhney, 2006). Delivery flexibility is the ability of the manufacturing system to adjust the delivery date of product according to the market requirements (Oke, 2005). Delivery flexibility is also defined as the ability to deal with changes in the orders made by customers and change the manufacturing schedule (De Toni & Tonchia, 1998; Sawhney, 2006). Sawhney (2006) classified input and output flexibilities, along with process flexibility, as the main stages of flexibility. The input flexibility stage is related to the company's response to changes occurring in the input materials (Sawhney, 2006). The output flexibility stage is related to the flexibility that is added to a system in response to uncertainty in the demands made by customers.

Appendix C

Final model description

The description of the final model developed in Tecnomatix Plant Simulation is described in this Appendix. This model incorporates changes that were made in response to the insights derived from the verification and validation process.

Sections C.1 and C.2 are duplicated in Chapter 5 of this document. They are repeated here so that this appendix constitutes a complete description of the model as it is implemented in Tecnomatix Plant Simulation.

C.1 Introduction

The goal of the model is to evaluate the impact of different manufacturing process flexibility configurations on the manufacturing system of Covid-19 vaccines. The manufacturing system consists of six vaccine platforms, namely: Live attenuated virus (LAV), Inactivated virus (IV), Subunit protein (SP), Viral vector (VV), DNA, and RNA. The model is divided into four main sections, namely: the approval of vaccines, the rejection of vaccines, the manufacturing of vaccines, and capacity shifting.

A brief overview of the model is provided with detail regarding the operations of each section within the model discussed later. The model considers the manufacturing of vaccines over a time horizon (e.g. five years), which is divided into equal periods of 30 days. The time is indicated in the following manner in TPS: dxd:hh:mm:ss.00, with dd indicating the number of days, hh indicating the number of hours, mm indicating the number of minutes and ss.00 indicating the number of seconds. The first period starts at 00:00:00:00 and ends at 30:00:00:00, while the second period will start at 30:00:00:00 and end at 60:00:00:00. Actions regarding the approval, rejection, and manufacturing of vaccines and the reconfiguration of the manufacturing system can only occur at the start of such a period. Vaccines are approved based on a pre-determined probability of success distribution. Once at least one vaccine product of a platform is approved, the manufacturing of the platform is activated. Manufacturing throughput is measured on a platform level only.

Thus, if a second vaccine product of a specific platform is approved, this has no impact as all available manufacturing capacity for the given platform will already have been activated. Approved vaccines may also be rejected based on a pre-determined probability of failure distribution. The manufacturing of a specific vaccine platform will only cease if all previously approved vaccine products of the platform have subsequently been rejected. The manufacturing section is represented as six manufacturing subsections, each producing one of the six vaccine platforms mentioned previously, with set manufacturing capacity (i.e. a set number of production lines) available to each manufacturing subsection. Each manufacturing subsection is comprised of two facilities equipped with different equipment, namely: stainless-steel, and single-use. The two types of equipment types were only uncovered during the validation interviews and subsequently incorporated into the model.

Process flexibility configurations can be created by setting the production lines of a specific manufacturing facility to have the capability to manufacture more than one vaccine platform. The capacity of an idle vaccine platform's manufacturing facility can be used to manufacture an approved vaccine platform, given that the process flexibility configuration allows it. The shifting of manufacturing capacity from one product to another results in a time delay, which differs for the two different equipment facilities. The model's output is the throughput of vaccine products, operation cost, and switch-over cost and is used to evaluate the performance of a specific process flexibility configuration. Flexibility can be separately incorporated into the manufacturing system for the two different equipment facilities. Figure C.1 represents a process flexibility configuration in which the LAV platform manufacturing facility's (A) capacity can be shifted to produce the SP and RNA vaccine products, respectively. Each of these platform's facilities is

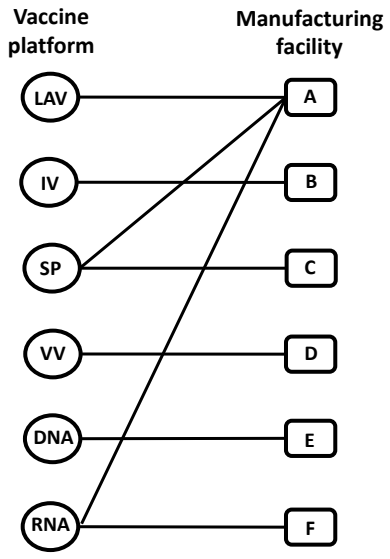

Figure C.1: A flexibility configuration for vaccine platforms

initially assigned 10 production lines. If, for example, at the start of period 9 of the model run time, the LAV platform has not been approved for manufacturing, but both the RNA and SP platforms are approved, the 10 production lines initially assigned to the RNA platform will immediately start manufacturing RNA vaccine products, and the 10 production lines initially assigned to the SP platform will immediately start manufacturing SP vaccine products. The LAV platform facility's production lines that can be shifted to the RNA and SP facilities will be divided equally between the two platforms. Both the RNA and SP platforms can thus each receive five additional production lines. Due to the time delay associated with the capacity shifts, these additional production lines will only start producing the RNA and SP vaccine products once the respective time delays have been enforced. If, for example, the LAV platform is then approved at the start of period 17, the five additional LAV production lines assigned to the manufacturing of RNA vaccine products as well as the five additional LAV production lines assigned to the manufacturing of SP vaccine products will immediately be shifted back to the manufacturing of LAV vaccine products. Manufacturing of the LAV products will only start once the associated time delay for switching the production lines back to the LAV facility has been enforced. The model is not a perfect representation of reality. In deciding whether and how to implement simplifications, the ability to accurately investigate the substantive research questions was the primary consideration. For example, in reality, it is likely that, for a variety of reasons, the manufacturing of a vaccine would not commence at the same time as regulatory approval. However, incorporating a delay for this commencement will not clarify insights on the impact of process flexibility. Especially if this delay is variable, incorporating it may obscure model outputs that can assist in drawing clear conclusions on the impact of process flexibility.

The model aims to consider the impact of process flexibility on the throughput of vaccine products over time, given the relatively high "demand" uncertainty created by the approval of vaccines. (Returning to the example in Figure 1 to illustrate, if no LAV, SU, or RNA vaccines were approved during a model run time, all 10 production lines of manufacturing facilities A, C, and F would have remained idle throughout.) To ensure that the findings on the throughput performance of various process flexibility configurations under the approval uncertainty are not obscured, unlimited demand for approved vaccines is assumed. Thus, all available manufacturing capacity is utilised to manufacture approved vaccines. The possibility of vaccine rejection is included in the model to represent the reality of the system. As mentioned previously, the goal of the model is to investigate the impact of process manufacturing flexibility on the throughput of vaccine manufacturing. Considering the rejection of vaccine platforms may obscure the results obtained for the flexibility configurations. It is expected to be highly unlikely that a vaccine product will be rejected once approved for manufacturing. The possibility of vaccine product rejection can be ignored in the model by assigning all the platforms a probability of failure value of zero. To further represent the reality of the system, the manufacturing of a system will only be de-activated if a platform has no approved product at

the time since the manufacturing for a specific platform will not be terminated if only one of its products becomes rejected.

C.2 Vaccine approval

The graphical representation of the vaccine platform approval section as it has been implemented in TPS is shown in Figure C.2. The vaccine platform approval section operates in a loop structure. The *VaccineApproval* source creates a single object *ApprovedVaccine*, at the start of the model run time and the *ApprovedVaccine* object remains within the loop structure for the remainder of the model run time.

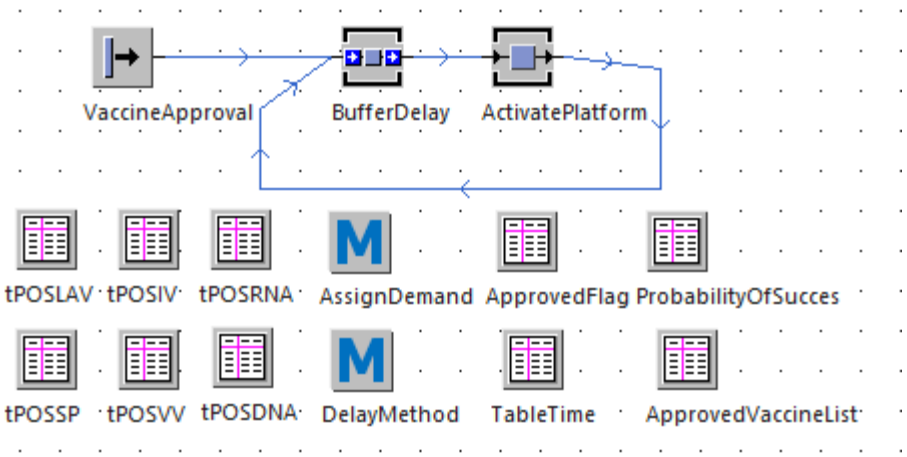

Figure C.2: Graphical representation of the approval of vaccines

The *BufferDelay* buffer ensures that the *ApprovedVaccine* object remains stationary until the start of a period via the *DelayMethod* method, using the code (SimTalk in TPS) shown in Figure C.3. When the object arrives at the *BufferDelay* buffer, the code checks if the current time of the simulation, *eventcontroller.SimTime*, is equal to the start of a period. The time value for the start of each period is given in the *TableTime* table; a section of the *TableTime* table is shown in Figure C.4. If the object arrives at the start of a period, the *BeginPeriod* variable is assigned a true value. Otherwise, the variable is assigned a false value, and a delay time is assigned to the *TimeWait* variable. Suppose the *BeginPeriod* variable has a true value. In that case, the object can proceed to the *ActivatePlatform* station. In contrast, if the *BeginPeriod* variable has a false value, the object is delayed for a time equal to the value of the *TimeWait* variable before it is allowed to proceed to the *ActivatePlatform* station.

The ActivatePlatform has a processing time of one second, and its function is two-fold. It firstly controls which vaccine platform(s) are approved at the start of a period. Secondly, the ActivatePlatform station controls the activation of approved vaccine platforms' manufacturing.

```
for var y:= 1 to TableTime.ydim
    if eventController.simtime = TableTime[1,y] then
        BeginPeriod := true
        exitloop
    elseif eventController.simtime < TableTime[1,y] then
        BeginPeriod := false
        TimeWait := TableTime[1,y] - eventController.simTime
        exitloop
    end
next

if BeginPeriod = true then
    @.move
else wait TimeWait
    @.move
end
```

Figure C.3: Code used in *DelayMethod* to delay the *ApprovedVaccine object*

C.2.1 Approval of vaccine platforms

The approval of vaccine platforms at the start of a period is achieved via the *AssignDemand* method. As an example, the code used to control the approval of the LAV platform is shown in Figure C.5. The approval of the other vaccine platforms is achieved via a similar code.

Simulation experiments performed by McDonnell et al. (2020) generated an estimation of the number of vaccine products for each platform that will be approved over a three-year time horizon. These results were utilised to create a probability of success (POS) distribution over time for each vaccine platform using the cumulative exponential function, given in (C.1). The distribution for each platform is recorded in a *POS* table (e.g. *tPOSSP*). As an example, a graphical representation of the probability of success distribution for the SP platform is given in Figure C.6, while a section of the *tPOSSP* table is shown in Figure C.7.

$$\mathrm{POS}_{\mathrm{Platform}}(t) = [1 - e^{-t/beta}] \tag{C.1}$$

When the *ApprovedVaccine* object arrives at the *AssignDemand* station, a random number (e.g. *L*) is created. The random number is an integer of any value between 0 and 100. For each period, the random number is compared to the probability of success value for that period in the *tPOSPlatform* table. If the random number is smaller than the probability of success value for that period, the vaccine platform becomes approved. A true value is assigned to the Approved status column in the *ProbabilityOfSuccess* table; a section of the *ProbabilityOfSuccess* table is shown in Figure C.8. Record is kept of the number of vaccine products per platform that would have been approved if the approval was considered on a product level by incrementing the *TotalPlatformApproved* (e.g. *TotalLAVApproved*) variable by one when a platform's random number is smaller than its probability of success value for a period.

	time 1
1	0.0000
2	30:00:00:00.0000
3	60:00:00:00.0000
4	90:00:00:00.0000
5	120:00:00:00.0000
6	150:00:00:00.0000
7	180:00:00:00.0000
8	210:00:00:00.0000
9	240:00:00:00.0000
10	270:00:00:00.0000
11	300:00:00:00.0000
12	330:00:00:00.0000
13	360:00:00:00.0000
14	390:00:00:00.0000
15	420:00:00:00.0000
16	450:00:00:00.0000
17	480:00:00:00.0000

Figure C.4: A section of the *TableTime* table

As discussed in the Vaccine Manufacturing section, capacity can be shifted between platforms. Capacity shift loops control this. When a platform is approved, an object is created at the buffer of its capacity shift loop to activate it (e.g. *.UserObjects.CapacityDecrease.create (LAVBuffer)*), as shown in the code in Figure C.5. To ensure that only one object is created per loop, the object is only created if the *PlatformCreate* (e.g. *LAVCreate*) variable has a false value. The *PlatformCreate* variable initially has a false value and is assigned a true value after the object has been created.

C.2.2 Activation of vaccine platforms

The *ActivatePlatform*station controls the activation of approved vaccine platforms' manufacturing via the *AssignDemand* method. The activation of all the vaccine platforms' manufacturing is achieved similarly. Only the code used to activate the manufacturing of the LAV platform is shown in Figure C.9.

The code used to activate the manufacturing of a platform can only be executed if the platform has an approved product (i.e. when the platform has a true value in the Approved status column of the *ProbabilityOfSuccess* table, refer to Figure C.8). Since the model only considers one vaccine product per platform at any given time, *ApproveFlag[2,y]* (e.g. *ApproveFlag[2,1] for the LAV platform*) variable is used

```
var L: integer
L := floor(z_uniform(1,1,100))
Ltable[1,Ltable.ydim+1] := eventController.simtime
Ltable[2,Ltable.ydim] := L
LTable[4,LTable.ydim] := MTable[1,1]
LTable[5,LTable.ydim] := ProbabilityOfFailure[2,1]
for local y := 1 to tPOSLAV.ydim
    If eventController.SimTime = tPOSLAV[1,y] + 0:01 then
        Ltable[3,Ltable.ydim] := tPOSLAV[2,y]
        If L < tPOSLAV[2,y] then
            ProbabilityOfSucces[3,1] := true
            TotalLAVApproved := TotalLAVApproved +1
            If LAVCreate = false then
            .UserObjects.CapacityDecrease.create(LAVBuffer)
            LAVCreate := true
            end
        end
    end
next
```

Figure C.5: Code used in *AssignDemand* to control the approval of LAV vaccine products

to prevent more than one vaccine product of a platform from being approved simultaneously. A section of the *ApproveFlag* table is shown in Figure C.10. Thus, for example, a new vaccine product can be recognised as approved only when the *ApproveFlag[2,y]* variable has a false value. The *ApproveFlagLAV* variable has an initial value of false and is assigned a true value after the approval of the first LAV vaccine product. If the *ApproveFlag[2,y]* variable has a true value, the approval of the additional vaccine products will not be considered.

As shown in the code in Figure C.9, an approved vaccine platform's manufacturing is activated by assigning a true value to the *ConnectPlatform* (e.g. *ConnectLAV*) variable. The number of approved vaccine products is counted by increasing the value of the *ApprovedVaccineCnt* by one when a vaccine platform is approved. Further, an entry is made in the *ApprovedVaccineList* table, shown in Figure C.11. In the first column of the table, the name of the vaccine platform is entered (*.UserObjects.LAVPlatform*), the status of the vaccine platform is changed to *Approved* in the second column, and the time at which the platform is approved is entered in the third column.

As mentioned previously, the model makes provision for a platform that was once approved to be rejected in future. This is described in more detail in Subsection C.3. After a vaccine platform has been rejected, a new vaccine product for the platform may be approved. A probability of failure value is thus assigned to the platform in the *POF* column of the *ProbabilityOfFailure* table. This is discussed in more detail in Subsection C.3.1.

A section of the *DelayTimes* table referred to in the code in Figure C.9, is shown in Figure C.12. The

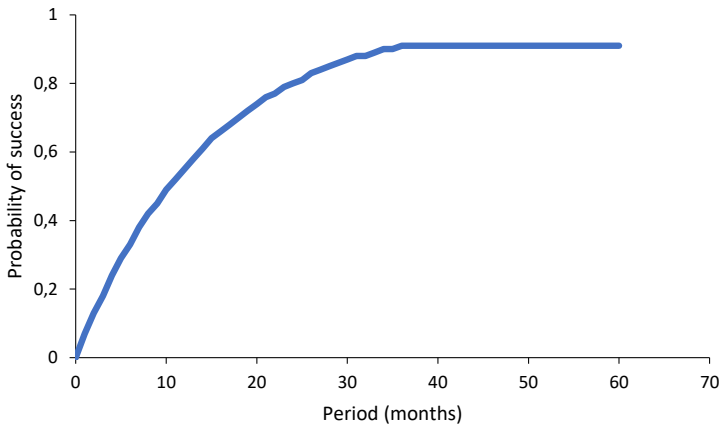

Figure C.6: Graphical representation of the probability of success values for the SP platform over three years

DelayTimes table contains the delay (i.e. switchover time) for each platform's manufacturing facilities when capacity is shifted between products. Separate delay times are given for the stainless-steel and the single-use equipment facilities. This is discussed in greater detail in Subsection C.4. Once a vaccine platform has been approved, the code searches for the platform in the *DelayTimes* table and assigns a true value to the *ApprovedStatus* column of the *DelayTimes* table (e.g. textitDelayTimes[4,3] for the LAV platform), which represents the same variable as *ConnectPlatform* (e.g. *ConnectLAV*).

The code includes a section that relates to the approval of a vaccine product for a platform that has previously been both approved and rejected and for which the capacity was not shifted during the rejected state (e.g. $LAVApprovedCnt >= 2$ and $LAVLines = Lines[2,1]$). The code is explained in this section as presented in Figure C.8. However, reference is made to the shifting of capacity and the number of production lines assigned to a manufacturing system which are discussed in Subsection C.4. If a vaccine platform, which matches the aforementioned criteria, is approved, its manufacturing facility can start manufacturing without delay ($LAVFacilitySS.entrancelocked := false$). The manufacturing facility is assigned its initial number of production lines ($LAVFacilitySS.xdim := Lines[2,1]$). The example only refers to the stainless-steel (SS) equipment facility, but the same action will also be performed for the platform's single-use (SU) equipment facility, as seen in Figure C.9.

	time 1	integer 2
1	0.0000	0
2	30:00:00:00.0000	7
3	60:00:00:00.0000	13
4	90:00:00:00.0000	18
5	120:00:00:00.0000	24
6	150:00:00:00.0000	29
7	180:00:00:00.0000	33
8	210:00:00:00.0000	38
9	240:00:00:00.0000	42
10	270:00:00:00.0000	45
11	300:00:00:00.0000	49
12	330:00:00:00.0000	55
13	360:00:00:00.0000	55
14	390:00:00:00.0000	58
15	420:00:00:00.0000	61
16	450:00:00:00.0000	64
17	480:00:00:00.0000	66

Figure C.7: A section of the *tPOSSP* table

	string 1	real 2	boolean 3
string	Platform		Approved
1	.UserObjects.LAVPlatform	0.00	false
2	.UserObjects.IVPlatform	0.00	false
3	.UserObjects.SPPlatform	0.00	false
4	.UserObjects.VVPlatform	0.00	false
5	.UserObjects.DNAPlatform	0.00	false
6	.UserObjects.RNAPlatform	0.00	false

Figure C.8: Section of the *ProbabilityOfSuccess* table

```
If ProbabilityOfSucces[3,1] = true then
    If ApprovedFlag[2,1] = false then
        ConnectLAV := True
        For local y:= 1 to DelayTimes.ydim
            if DelayTimes[1,y] = "LAV" then
                DelayTimes[4,y] := true
            end
        next
        LAVApprovedCnt := LAVApprovedCnt + 1
    if LAVApprovedCnt >= 2 and LAVLines = Lines[2,1] then
        LAVFacilitySS.entrancelocked := false
        LAVFacilitySU.entrancelocked := false
        LAVFacilitySS.xdim := Lines[2,1]
        LAVFacilitySU.xdim := Lines[2,1]
    end
    ApprovedVaccineList[1, ApprovedVaccineList.ydim+1] := .UserObjects.LAVPlatform
    ApprovedVaccineList[2, ApprovedVaccineList.ydim] := "Approved"
    ApprovedVaccineList[3, ApprovedVaccineList.ydim] := eventController.simTime
    LAVApproval := eventController.simTime
    ApprovedVaccineList[6, ApprovedVaccineList.ydim] := false
    ApprovedVaccineCnt := ApprovedVaccineCnt +1;
    ProbabilityOfFailure[2, ProbabilityOfFailure.ydim-5] := POFTable[2,1]
    ApprovedFlag[2,1] := True
    end
end
```

Figure C.9: Code used in *AssignDemand* to activate the manufacturing of the LAV platform

	string 1	boolean 2
string	Platform	Approved status
1	LAV	false
2	IV	true
3	SP	false

Figure C.10: A section of the *ApproveFlag* table

	object 1	string 2	time 3
string	MU	Approved	Period
1	*.UserObjects.LAVPlatform	Approved	1.0000
2			
3			

Figure C.11: A section of the *ApprovedVaccineList* table

	string 1	time 2	time 3	boolean 4	boolean 5
string	Platform	Delay Time (SS)	Delay Time (SU)	ApprovedStatus	ApprovedFlag
1	RNA	59:23:59:56.0000	29:23:59:56.0000	false	false
2	SP	59:23:59:56.0000	29:23:59:56.0000	false	false
3	LAV	59:23:59:56.0000	29:23:59:56.0000	false	false
4	IV	59:23:59:56.0000	29:23:59:56.0000	true	false

Figure C.12: A section of the *DelayTimes* table

C.3 Vaccine rejection

A graphical representation of vaccine platform rejection as implemented in TPS is shown in Figure C.13. The vaccine platform rejection section operates in a loop structure. The *VaccineRejection* source creates

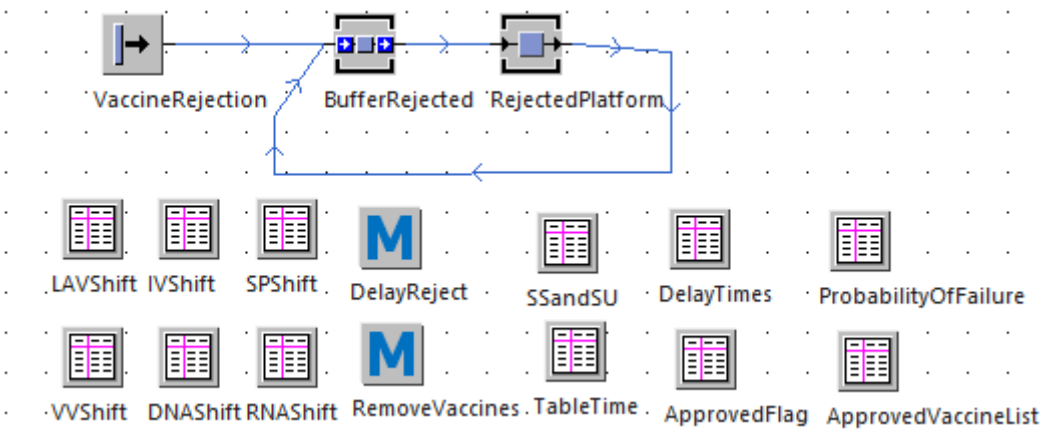

Figure C.13: Representation of the rejection of vaccines

a single object *RejectedVaccine* at the start of the model run time. The *RejectedVaccine* object remains within the loop structure for the remainder of the model run time.

The *BufferRejected* buffer ensures that the *RejectedVaccine* object remains stationary until the start of a period via the *DelayReject* method, using the code shown in Figure C.14. When the object arrives at the

```
for var y:= 1 to TableTime.ydim
    if eventController.simtime = TableTime[1,y] then
        BeginPeriodR := true
        exitloop
    elseif eventController.simtime < TableTime[1,y] then
        BeginPeriodR := false
        TimeWaitR := TableTime[1,y] - eventController.simTime
            exitloop
         end
    next

if BeginPeriodR = true then
    @.move
else wait timewaitR
    @.move
    end
```

Figure C.14: Code used in *DelayReject* to delay the *RejectedVaccine* object

BufferRejected buffer, the code checks whether the current time of the simulation, *eventcontroller.SimTime*,

is equal to the start of a period. If the object arrives at the start of a period, the *BeginPeriodR* variable is assigned a *true* value. Otherwise, the variable is assigned a false value, and a delay time is assigned to the *TimeWaitR* variable. Suppose the *BeginPeriodR* variable has a true value. In that case, the object can proceed to the *RejectedPlatform* station. In contrast, if the *BeginPeriodR* variable has a *false* value, the object is delayed for a time equal to the value of the *TimeWaitR* variable before it is allowed to proceed to the *RejectedPlatform* station.

The *RejectedPlatform* station has a processing time of one second, and its function is two-fold. It firstly controls which vaccine platform(s) is rejected at the start of a period, and secondly controls the de-activation of a vaccine platform's manufacturing.

C.3.1 Rejection of vaccine platforms

The likelihood of a vaccine being rejected is managed using a unique probability of failure (POF) value for each vaccine platform which is stored in the *POFTable* table. As shown in Figure C.9, once a vaccine platform has been approved the *POF* value is assigned to the platform in the *ProbabilityOfFailure* table, depicted in Figure C.16.

The *RejectedPlatform* station controls the rejection of vaccine products via the *DelayReject* method. The code used in the *DelayReject* method is shown in Figure C.15. When the *RejectedVaccine* object

```
var M: integer
for local y:= 1 to ProbabilityOfFailure.ydim
    M := floor(z_uniform(1,1,100))
    Mtable[1,y] := M
    if M <  ProbabilityOfFailure[2,y] then
ProbabilityOfFailure[3,y] := true
    end
next
```

Figure C.15: Code used in *DelayReject* for the rejection of vaccine products

arrives at the *RejectedPlatform* station, a random number is generated for each vaccine platform and compared to its pre-determined probability of failure, given in the *ProbabilityOfFailure* table. A section of the *ProbabilityOfFailure* table is shown in Figure C.16. Suppose a vaccine platform's random number is smaller than its probability of success value. In that case, the vaccine platform becomes rejected, and it is assigned a *true* value in the *Rejected* status column in the *ProbabilityOfFailure* table.

C.3.2 De-activation of vaccine manufacturing

The *RejectedPlatform* station controls the de-activation of a vaccine platform's manufacturing via the *RemoveVaccine*method. As mentioned in Subsection C.2, a record is kept of the number of vaccine

	object 1	integer 2	boolean 3
string	MU	POF	Rejected
1	.UserObjects.LAVPlatform	10	false
2	.UserObjects.IVPlatform	0	false
3	.UserObjects.SPPlatform	0	false
4	.UserObjects.VVPlatform	0	false
5	.UserObjects.DNAPlatform	0	false
6	.UserObjects.RNAPlatform	0	false

Figure C.16: Content of the *ProbabilityOfFailure* table

products that would be approved per platform if the approval were considered on a product-level rather than on a platform level. This is used to limit the de-activation of a platform's manufacturing to instances where no approved vaccine product of a platform remains.

The de-activation of all the vaccine platforms' manufacturing is achieved similarly. Only the code used to de-activate the manufacturing of the LAV platform is shown in Figure C.17 as an example.

When a vaccine product is rejected (e.g. ProbabilityOfFailure[3,1] = true for the LAV platform), the *TotalPlatformApproved* variable is reduced by one. The rejection of the vaccine product is indicated in the *ApprovedVaccineList* by adding to the platform's inscription, as shown in Figure C.18.

The platform is assigned a *true* value in the *Rejected* status column in the *ApprovedVaccineList* table, and the time of rejection is recorded. If the platform is approved again later in the model run time, a completely new inscription will be made in the *ApprovedVaccineList* for the platform's approval.

The de-activation of a vaccine platform's manufacturing will only occur when the *TotalPlatformApproved* (e.g. *TotalLAVApproved*) variable is zero. The manufacturing of the vaccine platform is de-activated by assigning a *false* value to the *ConnectDNA* variable. The code searches for the platform (e.g. "LAV") in the *DelayTimes* table and assigns a *false* value to the *Connect* column (e.g. *DelayTimes[4,1]* for the LAVPlatform) and a textitfalse value to the *ApprovedFlag* column (e.g. *DelayTimes[5,1]*. The platform is assigned a *false* value in the *Approved* status column of the *ProbabilityOfSuccess* table. The platform can no longer be rejected and is assigned a zero probability of failure value in the *ProbabilityOfFailure* table. The number of approved vaccine platforms is adjusted by reducing the value of the *ApprovedVaccineCnt* by one.

To prevent the rejected platform's manufacturing facility (e.g. *LAVFacility*) from manufacturing any further vaccines (i.e. from processing any new *LAVPlatform* objects, for example, as explained in Subsection C.4), the manufacturing facility's entrance is locked by assigning a *true* value to the *PlatfromFacility.entrancelocked* (e.g. *LAVFacility.entrancelocked*) variable. The stainless-steel and the single-use

facilities are considered separately. The entrance lock will only be enforced for the type of equipment facilities considered in a scenario. In other words if only the stainless-steel equipment facilities are considered, then only the stainless-steel equipment facility of the rejected platform will be entrance locked. The type of equipment facility considered in a scenario is indicated at the start of a period by assigning a *true* value to the *Considered* column of the *SSandSU* table for all relevant facilities. These values can either be adjusted manually before the start of the model run time or via the TPS ExperimentManager. A section of the *SSandSU* table is shown in Figure C.19.

To allow a new vaccine product of the platform to be approved, a *false* value is assigned to the platform in the *Approved status* column of the *ApprovedFlag* table (e.g. *ApprovedFlag[2,1]* for the LAV platform).

As previously mentioned, the shifting of capacity is discussed in the Subsection C.4. However, the code in Figure C.17 contains a section that relates to capacity shifting and the associated time delay. A facility's number of production lines is set to the initial value assigned to the facility before the start of the model run time, which is stored in the *Lines* table. A section of the *Lines* table is shown in Figure C.20. This is performed for the case where the facility had received capacity from another facility. At the instance when a platform's manufacturing is de-activated, some object may still be present in the platform's facility. To allow these objects to be processed before the additional capacity is removed, a delay time is enforced. The delay time is set equal to the processing time of the rejected platform's facility (e.g. *RemoveLAVWaitSS* := *LAVFacilitySS.ProcTime* for the LV platform).

The *ChangeOverPlatformTime* (e.g. *ChangeOverLAVTime*) variable controls the initial time delay for a platform after it has been approved. When a platform's manufacturing is de-activated, the time delay that has previously been enforced becomes irrelevant, and a *false* value is thus assigned to the *ChangeOverPlatformTime* variable. To ensure that the removal of a rejected vaccine platform only occurs once, the platform is assigned a *false* value in the *Rejected* status column in the *ProbabilityOfFailure* table, as shown in Figure C.17.

```
if  ProbabilityOfFailure[3,1] = true then
    TotalLAVApproved := TotalLAVApproved -1
    LAVShift[1,LAVShift.ydim+1] := eventcontroller.simTime
    LAVShift[2,LAVShift.ydim] := 0
    LAVShift[3,LAVShift.ydim] := 0
    LAVShift[4,LAVShift.ydim] := 0
    LAVShift[5,LAVShift.ydim] := 0
    LAVShift[6,LAVShift.ydim] := 0
    for var y:= 1 to ApprovedVaccineList.yDim
        if ApprovedVaccineList[1, y] = .UserObjects.LAVPlatform and ApprovedVaccineList[6, y] = false then
            ApprovedVaccineList[4, y] := "Rejected"
            ApprovedVaccineList[5, y] := eventController.simTime
            ApprovedVaccineList[6, y] := true
        end
    next
    IF TotalLAVApproved = 0 then
    ChangeOverLAVTime := false
    RejectedFlagLAV := true
    ConnectLAV := false
    ProbabilityOfSucces[3,1] := false
    ProbabilityOfFailure[2,1] := 0
    For local y := 1 to DelayTimes.ydim
        if DelayTimes[1,y] = "LAV" then
            DelayTimes[5,y] := false
        end
        exitloop
    next
    ApprovedVaccineCnt := ApprovedVaccineCnt -1;
    If SSandSU[2,1] = true then
    LAVFacilitySS.entrancelocked := true
    RemoveLAVWaitSS := LAVFacilitySS.ProcTime
    end
    If SSandSU[2,2] = true then
    LAVFacilitySU.entrancelocked := true
    RemoveLAVWaitSU := LAVFacilitySU.ProcTime
    end
    ApprovedFlag[2,1] := False
    If RemoveLAVWaitSU > RemoveLAVWaitSS then
        Wait RemoveLAVWaitSU
    else RemoveLAVWaitSS
    end
    LAVLines := Lines[2,1]
    If SSandSU[2,1] = true then
        LAVFacilitySS.xdim := LAVLines
    end
    If SSandSU[2,1] = true then
        LAVFacilitySS.xdim := LAVLines
    end
    If SSandSU[2,2] = true then
        LAVFacilitySU.xdim := LAVLines
    end
    end
    ProbabilityOfFailure[3,1] := false
    ChangeOverLAVTime := false
end
```

Figure C.17: Code used in *RemoveVaccine* to de-activate the manufacturing of the LAV platform

	object 1	string 2	time 3	string 4	time 5	boolean 6
string	MU	Approved	Period	Rejected	Period	Removed
1	*.UserObjects.LAVPlatform	Approved	1.0000	Rejected	30:00:00:01.0000	true
2						
3						

Figure C.18: Section of the *ApprovedVaccineList* table

	string 1	boolean 2
string	Platform and technology	Considered
1	LAVSS	true
2	LAVSU	true
3	IVSS	true
4	IVSU	true
5	SPSS	true
6	SPU	true
7	VVSS	true
8	VVSU	true
9	DNASS	true
10	DNASU	true
11	RNASS	true
12	RNASU	true

Figure C.19: Section of the *SSansSU* table

	string 1	integer 2
string	Platform	Production lines
1	LAV	10
2	IV	10
3	SP	10
4	VV	10
5	DNA	10
6	RNA	10

Figure C.20: Section of the *Lines* table

C.4 Vaccine manufacturing

A graphical representation of the vaccine platform manufacturing as implemented in TPS is shown in Figure C.21. Each vaccine platform has a separate manufacturing subsection with a source (e.g. *LAVDemand*) which continuously creates an object (e.g. *LAVPlatform*), given that the platform's manufacturing is activated, as discussed in the Subsection C.2. Each manufacturing subsection has a method (e.g. *MethodLAV*) which delays the creation of objects at a source until the platform's manufacturing is activated. As an example, the code used to achieve this for the LAV platform's manufacturing subsection is shown in Figure C.22.

The buffer (e.g. *BufferLAV*) stores the objects (e.g. *LAVPlatform*) until the manufacturing facilities (e.g. *LAVFacilitySS* and *LAVFacilitySU*) can process the objects. Each manufacturing subsection has a pre-determined capacity for the number of production lines (e.g. $LAVLines = 10$), stored in the *Lines* table, as shown in Figure C.20. If the stainless-steel and the single-use equipment facilities are considered simultaneously, each facility will only have access to half of the capacity available to the manufacturing subsection. The number of production lines can be adjusted as capacity shifts between products; this is discussed in more detail later. When an object has been processed by the manufacturing facility (*LAVFacilitySS*), the object proceeds to a drain (e.g. *LAVDrainSS*), which removes the object from the model. The system's throughput is recorded by counting the number of objects that enter each drain and incrementing the *ThroughputVaccines* variable by 1, as shown in Figure C.23. Each object that enters the drain (e.g. *LAVDrain*) represents 10 000 manufactured vaccine products. The throughput of each vaccine platform is also recorded separately per type of equipment facility by incrementing the appropriate *ThroughputPlatformEquipment* (e.g *ThroughputLAVSS*) variable with 1. The counting of throughput for each platform and specific equipment facility is controlled by separate methods (e.g. LAVCntSS). The method used to control the counting of throughput for the LAV platform with stainless-steel equipment is depicted in Figure C.23.

When a vaccine becomes rejected ($ConnectLAV = false$), its manufacturing subsection will still have objects in the manufacturing facility (*LAVFacility*) station, which the manufacturing facility will still process even though the manufacturing for the subsection has been de-activated. To correct the number of objects that are considered to enter the platform's drain (e.g. *LAVDrainSS*) and consequently the throughput for the system, the ThroughputPlatformEquipment variable is reduced by 1 for each object that enters a de-activated manufacturing subsection's drain.

C.4.1 Process flexibility

Different process flexibility configurations are created by connecting different plant and manufacturing facilities. Each platform has a *PlatformConnect* table (e.g. *LAVConnect*) in which the connections with

its manufacturing facility for a specific configuration are indicated. A section of the *LAVConnect* table is shown in Figure C.24. If the *LAVFacility* can manufacture another platform, a true value is assigned to that platform in the *Configuration* column of the *LAVConnect* table. These values can either be adjusted manually before the start of the model run time or via the TPS ExperimentManager. The example in Figure C.24 indicates that the *LAVFacility*'s production lines can be reassigned to manufacture IV-, SP-, and RNA vaccines. The *Connect* column in the *PlatformConnect* table indicates whether each of the platforms in the *Platform* column has been approved. In the example in Figure C.24, the IV platform has at least one approved vaccine product, but the SP, VV, DNA, and RNA platforms do not have an approved vaccine product. The *LAVFacility*'s capacity can thus be reassigned to the IV platform but not to the SP- or RNA platforms. However, this will only be done if the *LAVFacility* is idle (i.e., there is no approved LAV vaccine). The assignment of values to the Connect column, as shown in Figure C.24, is discussed in the capacity control section Subsection C.4.2.

The incorporation of capacity in a type of equipment facility is controlled with the *flexible* column in the *SSandSU* table. A *true* value is assigned if flexibility is incorporated. These values can either be adjusted manually before the start of the model run time or via the TPS ExperimentManager. A section of the *SSandSU* table is depicted in Figure C.25.

The shifting of capacity from one product to another results in a time delay, which may differ for the different type of equipment facilities. The capacity shift and the accompanying time delay are controlled via seven subsections, as shown in Figure C.26. One of the subsections is the capacity control subsection, while the remaining six are platform control capacity subsections.

C.4.2 Capacity control subsection

The capacity control subsection operates in a loop structure. The *CapacitySource* source creates a single object *Capacity* at the start of the model run time. The *Capacity* object remains within the loop structure for the remainder of the model run time.

The *BufferCapacity* buffer ensures that the *Capacity* object remains stationary until the start of a period via the *CapacityDelay* method, using the code (SimTalk) shown in Figure C.27. When the object arrives at the *BufferCapacity* buffer, the code checks whether the current time of the simulation, event-controller.SimTime, is equal to the start of a period. The time value for the start of each period is given in the *TableTime* table. If the object arrives at the start of a period, the *BeginPeriodC* variable is assigned a true value, otherwise, the variable is assigned a false value, and a delay time is assigned to the *TimeWaitC* variable. Suppose the *BeginPeriodC* variable has a true value. In that case, the object is allowed to proceed to the *CapacityControl* station. In contrast, if the *BeginPeriodC* variable has a false value, the object is

delayed for a time equal to the value of the *TimeWaitC* variable before it is allowed to proceed to the *CapacityControl* station.

The function of the capacity control subsection is three-fold and achieves these functions via the *CapacityMethod* method. The *CapacityControl* source has a processing time of two seconds to allow the approval and rejection of vaccine platforms to be completed before the code in the *CapacityMethod* method is executed.

The first function of the *CapacityControl* source is to consider the number of connections between an idle platform's manufacturing facility and approved platform products. The number of approved platform products which are connected to an idle manufacturing system is recorded and used to divide the capacity of the idle manufacturing facility between the connected products. The code used to achieve this for the LAV platform is shown in Figure C.28. Suppose a only the stainless-steel equipment facilities have flexibility incorporated and a stainless-steel manufacturing facility is idle (e.g. *ProbabilityOfSuccess[3,1] = false*). In that case, the code considers two aspects for each vaccine platform, namely: whether the vaccine platform has been approved (e.g. *ProbabilityOfSucces[3,2] = true*, refer to Figure C.8); and whether the vaccine platform is connected with the idle manufacturing facility (e.g. *LAVConnect[2,1] = true*, refer to Figure C.24). If both these aspects are true, the number of connections (*NumberLAV*) to the idle manufacturing facility is increased by one. As indicated in Figure C.24, a *true* value is assigned for the platform in the *Connect* column of the *PlatformConnect* table of the platform's facility with which it is connected. Suppose an idle manufacturing facility is connected to an approved vaccine platform and its capacity will consequently be shifted. In that case, its number of production lines (e.g. *LAVLines*) is reduced to zero, and the entrance of the manufacturing facility is locked (*LAVFacilitySS.entrancelocked = true*) to prevent any objects from entering the manufacturing facility.

When the manufacturing of one of the approved and connected vaccine platforms become de-activated, it is required that a delay occurs before the capacity can be shifted to the remaining approved and connected platforms. The second function of the capacity control subsection is to consider whether any previously approved and connected vaccine platforms have been terminated to activate the process of enforcing additional time delays for the remaining manufacturing facilities. Suppose a vaccine platform has been terminated (*RejectedFlagIV = true*, refer to Figure C.17) and the vaccine platform is connected with an idle manufacturing facility (*LAVConnect[2,1] = true*, refer to Figure C.24). In that case, the process of time delay is activated by assigning a *true* value to the *FacilityFixVariable* (e.g. *LAVFixVariable*). The *RejectedFlagPlatform* variable is assigned a *false* value to prevent the code from activating the process of additional time delay again.

Due to different lengths of time delays for the different manufacturing facilities, it is necessary to record the time of vaccine platform termination to ensure that the appropriate time delay length can be enforced for each manufacturing facility. This is thus the third function of the capacity control subsection. The

code used to achieve this for the LAV platform is shown in Figure C.29. Suppose the *FacilityFixVariable* variable for a platform's manufacturing system has a true value, the current time, Eventcontroller.SimTime, is recorded. Furthermore, the code considers whether any other vaccine platform(s) is connected with the manufacturing facility (*LAVConnect[2,y]* = *true*, refer to Figure C.24) and has been approved (e.g. *LAVConnect[3,y]* = *true*, refer to Figure C.24). If both these conditions are satisfactory for a vaccine platform, a true value is assigned to the platform in the Delay column of the *LAVConnect* table, shown in Figure C.24.

C.4.3 Shifting capacity between platforms

The shifting of capacity to each platform's manufacturing facility is achieved via its subsection, comprising of a buffer (e.g. *LAVBuffer*) and a station (e.g. *LAVStation*), which operates in a loop structure. As seen in Figure C.5, an object is created at a platform's buffer once approved. After the object has been created at the buffer, the object remains within the loop structure for the remainder of the model run time.

The buffer (e.g. *LAVBuffer*) ensures that the object remains stationary until the start of a period via the *CapacityDelayPlatform* (e.g. *CapacityDelayL*) method, using the code (SimTalk) shown in Figure C.30. When the object arrives at the *PlatformBuffer* (e.g. *LAVBuffer*) buffer, the code checks whether the current time of the simulation, eventcontroller.SimTime, is equal to the start of a period. The time value for the start of each period is given in the *TableTime table*. If the object arrives at the start of a period, the *BeginPeriodCPlatform* (e.g. *BeginPeriodCL*) variable is assigned a *true* value, otherwise, the variable is assigned a *false* value, and a delay time is assigned to the *TimeWaitCPlatform* (e.g. *TimeWaitCL*) variable. Suppose the *BeginPeriodCPlatform* (e.g. *BeginPeriodCL*) variable has a *true* value. In that case, the object is allowed to proceed to the *PlatformStation* (e.g. *LAVStation*) station. In contrast, if the *BeginPeriodCPlatform* (e.g. *BeginPeriodCL*) variable has a *false* value, the object is delayed for a time equal to the value of the *TimeWaitCPlatform* (e.g. *TimeWaitCL*) variable before it is allowed to proceed to the *PlatformStation* (e.g. *LAVStation*) station. When the object is first created, an additional second is added to the entire processing time of the object, and the *CapacityDelayPlatform* (e.g. *CapacityDelayL*) method thus also allows the object to proceed if the eventcontroller.SimTime is equal to the start of a period plus one second.

The code used to control the shift of capacity to a platform's manufacturing facility is comprised of three different sections. The second section is explained first since it controls the initial time delay that is enforced for a manufacturing facility once its vaccine platform has been approved. As an example, the code for the LAV platform is shown in Figure C.31. When a vaccine platform is approved, a time delay, as specified for the platform's manufacturing system in the *DelayTimes* table, is enforced before the manufacturing facility can receive additional capacity from idle manufacturing facilities with which it

is connected. The code searches within the *DelayTimes* table for the appropriate vaccine platform (e.g. "LAV") and ensures that the vaccine platform is both approved (*DelayTimes[4,y]* = true, refer to Figure C.17) and that it has not yet been delayed (*ChangeOverLAVTime* = *false*, refer to Figure C.31). If both the conditions are satisfactory, the delay time is enforced for the platform (e.g. *Wait DelayTimes[2,1]*, refer to Figure C.12). Different time delays are enforced for the stainless-steel and the single-use equipment facilities. After the delay time has elapsed, the *ChangeOverPlatformTime* (e.g. *ChangeOverLAVTime*) variable is assigned a *true* value to prevent the code from enforcing another time delay for the platform, and the shifting of capacity can proceed.

Capacity can be shifted to a manufacturing facility after the initial time delay has been enforced (e.g. *ChangeOverLAVTime* = *true*, refer to Figure C.31). As previously mentioned, when an idle manufacturing facility is connected with more than one approved vaccine platform, and one or/more of these vaccine platforms become terminated, the appropriate time delay must be enforced for each of the remaining manufacturing facilities before their capacities can be increased. When the object enters the *PlatformStation* (e.g. *LAVStation*) station, the first section of the code in the *PlatformMethod* considers whether the platform's manufacturing facility requires a time delay due to the rejection of another vaccine platform. Figure C.32 depicts the code used to consider whether the VV platform's manufacturing facility requires a time delay due to the rejection of another vaccine platform. The code used for the other platforms is similar. For each platform's manufacturing facility, the code checks whether the facility is idle (e.g. *ProbabilityOfSucces[3,4]* = *false*, refer to Figure C.8) and whether the facility is connected with the considered platform (e.g. *VVConnect[2,3]* = *true*, a section of the *VVConnect* table is shown in Figure C.33). Suppose both the conditions are satisfactory for a platform's manufacturing facility. In that case, the code considers whether a time delay is required to shift the manufacturing facility's capacity from a previously approved and connected platform to the considered platform. If no time delay is required for the shift of a manufacturing facility's capacity to the considered platform (e.g. *VVConnect[4,3]* = *false*, refer to Figure C.33), the number of production lines available to the platform is assigned to the *PlatformFacility* (e.g. *LAVV*) variable. This is further explained when the third section of the code is discussed. If a time delay is required for the shift of a manufacturing facility's capacity to the considered platform (e.g. *VVConnect[4,3]* = *true*, refer to Figure C.33), the *FacilityAndPlatformFix* (e.g. *VVAndLAVFix*) is assigned a *true* value, and the shifting of the capacity is dealt with in the third section of the code.

The third section of the code controls capacity shifting after the required time delays have been enforced and are shown in Figure C.34 and Figure C.35.

The code considers whether the platform has been approved (*ConnectLAV* = *true*, refer to Figure **??**) and whether the initial time delay has been enforced (*ChangeOverLAVTime* = *true*, refer to Figure C.32). If both these conditions are satisfactory, the code considers whether capacity can be shifted to the platform for each manufacturing facility. It is again ensured that the manufacturing facility is idle (e.g.

ProbabilityOfSucces[3,4] = *false* refer to Figure C.8) and that the manufacturing facility and the considered platform are connected (e.g. *VVConnect[2,3]* = *true*, refer to Figure C.34). If both these conditions are satisfied, the code then considers whether the platform requires a time delay due to the rejection of another platform. If no time delay is required (e.g. *VVAndLAVFix* = *false*, refer to Figure C.32), the considered platform receives the additional capacity as determined before the initial time delay. If a time delay is required (e.g. *VVAndLAVFix* = *true*, refer to Figure C.32), the code waits until the delay time passes before the additional capacity can be shifted. When the time delay has been enforced, the *FacilityAndPlatformFix* (e.g. *VVAndLAVFix*) is assigned a *false* value to prevent the code from enforcing the delay again. The additional capacity is shifted to the considered platform (e.g. *LAV1* := *VVFacilitySS.xdim/NumberVV*, refer to Figure C.34). The capacity shift is controlled using the different sections of code since the initial time delay and additional time delay, due to the termination of another vaccine platform, may not necessarily start at the same time, and the additional capacity shift may have to occur at a later stage than the initial time delay. If the capacity shifts are not controlled separately, all required capacity shifts will occur once the first delay has been enforced.

For example: Consider a configuration in which both the LAV platform and the IV platform are connected with the RNA platform's facility, and both the LAV platform and the IV platform are approved at the start of period 1, while the facility for the RNA platform remains idle. The LAV platform has a delay of two periods for the shifting of capacity and can thus only receive additional RNA production lines at the start of period three, while the IV platform has a delay of one period for the shifting of capacity and can thus only receive the additional RNA production lines at the start of period two. If, for example, the IV platform's manufacturing becomes de-activated at the start of period two, the LAV platform can receive the additional RNA production lines originally assigned to the IV platform after a delay of two periods for the shifting of capacity has occurred. The LAV platform can thus only receive the additional RNA production lines at the start of period four. If the two different types of capacity shifts are not dealt with independently, all the RNA production lines will be shifted to the LAV platform at the start of period three, when then the initially assigned RNA capacity is shifted to the LAV platform.

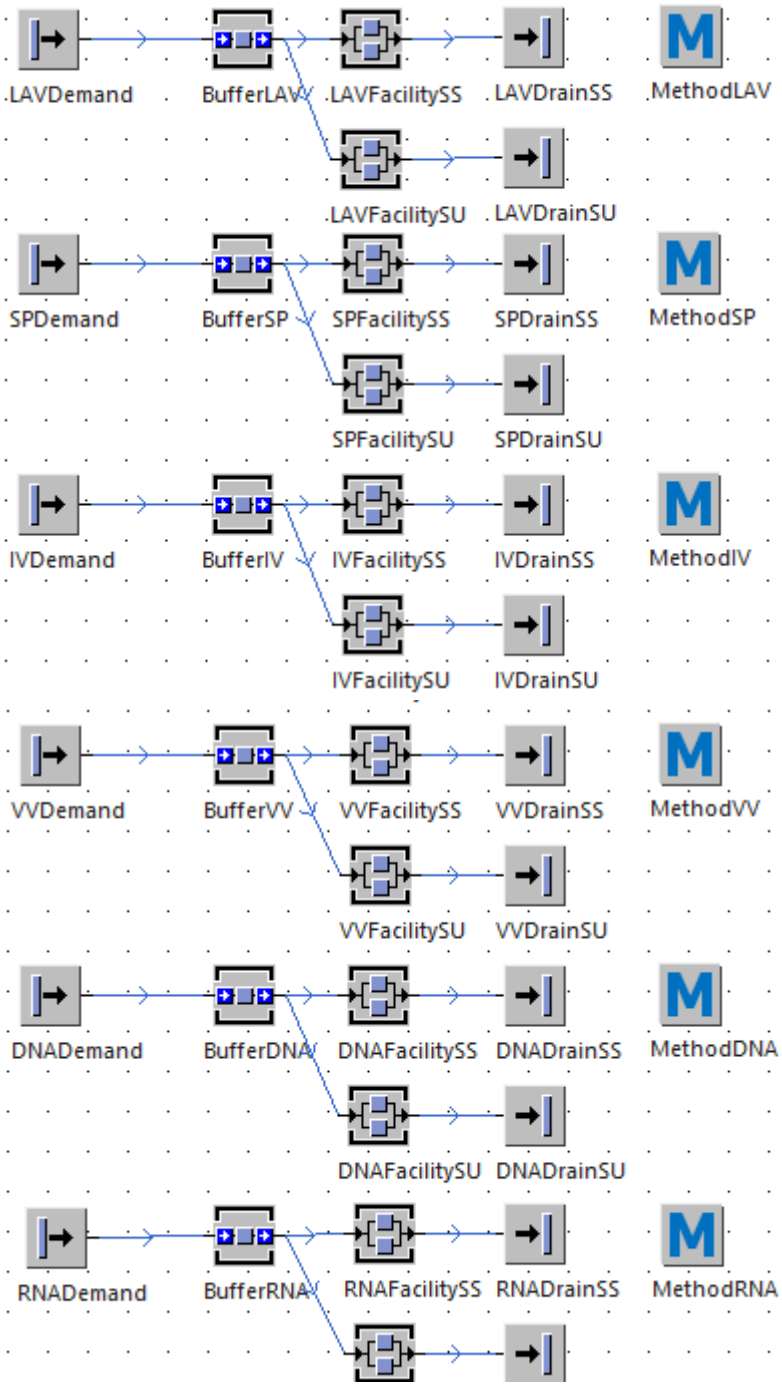

Figure C.21: Representation of the manufacturing of vaccine platforms

```
waituntil ConnectLAV = true
@.move(BufferLAV);
```

Figure C.22: Code used to delay the creation of *LAVPlatform* objects at the *LAVDemand source*

```
ThroughputLAV_SS := ThroughputLAV_SS + 1

ThroughputVaccines := ThroughputVaccines +1

If ConnectLAV = false and @.name = "LAVPlatform" then
    ThroughputVaccines := Throughputvaccines - UnitCount
    end
```

Figure C.23: Code used to count the throughput of LAV vaccine products produced via the stainless-steel facility

	string 1	boolean 2	boolean 3	boolean 4
string	Platform	Configuration	Connect	Delay
1	IV	true	true	true
2	SP	true	false	false
3	VV	false	false	false
4	DNA	false	false	false
5	RNA	true	false	false

Figure C.24: A section of the *LAVConnect* table

	string 1	boolean 2	boolean 3
string	Platform and technology	Considered	Flexible
1	LAVSS	true	false
2	LAVSU	true	false
3	IVSS	true	false
4	IVSU	true	false
5	SPSS	true	false
6	SPU	true	false
7	VVSS	true	false
8	VVSU	true	false
9	DNASS	true	false

Figure C.25: A section of the *SSandSU* table

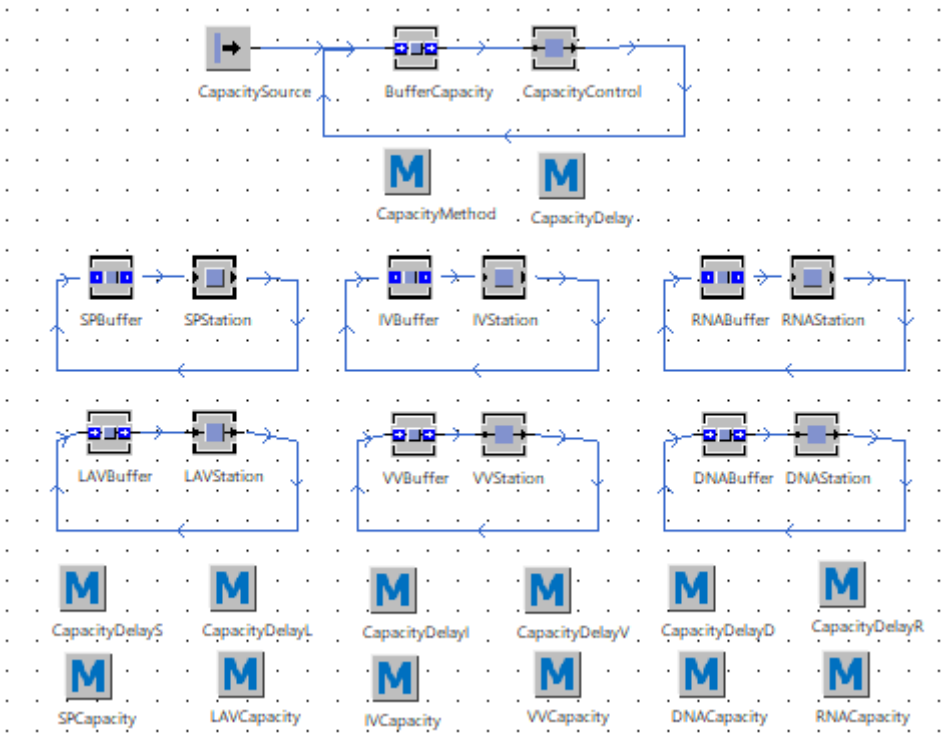

Figure C.26: Representation of the shifting of manufacturing facilities' capacity

```
for var y:= 1 to TableTime.ydim
    if eventController.simtime = TableTime[1,y] then
        BeginPeriodC := true
        exitloop
    elseif eventController.simtime < TableTime[1,y] then
        BeginPeriodC := false
        TimeWaitC := TableTime[1,y] - eventController.simTime
            exitloop
         end
    next

if BeginPeriodC = true then
    @.move
else wait timewaitC
    @.move
    end
```

Figure C.27: Code used in *CapacityDelay* to delay the Capacity object

```
NumberLAV := 0
If ProbabilityOfSucces[3,1] = false then
    If LAVConnect[2,1] = true and ProbabilityOfSucces[3,2] = true then
        NumberLAV := NumberLAV + 1
        LAVEntranceLock := True
        LAVLines := 0
        LAVConnect[3,1] := true
    end
    If LAVConnect[2,1] = true and RejectedFlagIV = true then
        LAVFixVariable := true
        LAVConnect[3,1] := false
    end
    If LAVConnect[2,5] = true and ProbabilityOfSucces[3,6] = true then
        NumberLAV := NumberLAV + 1
        LAVEntranceLock := True
        LAVLines := 0
        LAVConnect[3,5] := true
    end
    If LAVConnect[2,5] = true and RejectedFlagRNA = true then
        LAVFixVariable := true
        LAVConnect[3,5] := false
    end
    If LAVConnect[2,3] = true and ProbabilityOfSucces[3,4] = true then
        NumberLAV := NumberLAV + 1
        LAVEntranceLock := True
        LAVLines := 0
        LAVConnect[3,3] := true
    end
    If LAVConnect[2,3] = true and RejectedFlagVV = true then
        LAVFixVariable := true
        LAVConnect[3,3] := false
    end
    If LAVConnect[2,4] = true and ProbabilityOfSucces[3,5] = true then
        NumberLAV := NumberLAV + 1
        LAVEntranceLock := True
        LAVLines := 0
        LAVConnect[3,4] := true
    end
    If LAVConnect[2,4] = true and RejectedFlagDNA = true then
        LAVFixVariable := true
        LAVConnect[3,4] := false
    end
    If LAVConnect[2,2] = true and ProbabilityOfSucces[3,3] = true then
        NumberLAV := NumberLAV +1
        LAVEntranceLock := True
        LAVLines := 0
        LAVConnect[3,2] := true
    end
    If LAVConnect[2,2] = true and RejectedFlagSP = true then
        LAVFixVariable := true
        LAVConnect[3,2] := false
    end
    else NumberLAV:= 0
end
If LAVEntranceLock = true then
    If SSandSU[2,7] = true and SSandSU[3,7] = true then
        LAVFacilitySS.entrancelocked := true
    end
    If SSandSU[2,8] = true and SSandSU[3,8] = true then
        LAVFacilitySU.entrancelocked := true
    end
end
```

Figure C.28: Code used to count the number of connections for an idle LAV manufacturing facility

```
If LAVFixVariable = true then
    for local y:= 1 to LAVConnect.ydim
        If LAVConnect[2, y] = true and LAVConnect[3, y] = true then
            LAVConnect[4, y] := true
            LAVFixTime := eventController.simTime
        end
    next
end
```

Figure C.29: Code used to record the time when a platform, previously connected to the LAV manufacturing facility, is rejected

```
for var y:= 1 to TableTime.ydim
    if eventController.simtime = TableTime[1,y] then
        BeginPeriodCL := true
        exitloop
    elseif eventcontroller.simTime = TableTime[1,y] +0:01 then
        BeginPeriodCL := true
        exitloop
    elseif eventController.simtime < TableTime[1,y] then
        BeginPeriodCL := false
        TimeWaitCL := TableTime[1,y] - eventController.simTime
            exitloop
        end
    next

if BeginPeriodCL = true then
    @.move
else wait timewaitCL
    @.move
    end
```

Figure C.30: Code used in *CapacityDelayL* to delay the object

```
For local y:= 1 to DelayTimes.ydim
    If DelayTimes[1,y] = "LAV" then
        If DelayTimes[4,y] = true then
            If ChangeOverLAVTime = false then
                If SSandSU[3,1] = true then
                    LAVTime := DelayTimes[2,y]
                    wait DelayTimes[2,y]
                    LAVEntranceLock := false
                    ChangeOverLAVTime := true
                end
                If SSandSU[3,2] = true then
                    LAVTime := DelayTimes[3,y]
                    wait DelayTimes[3,y]
                    LAVEntranceLock := false
                    ChangeOverLAVTime := true
                end
            end
        end
        exitloop
    end
next
```

Figure C.31: Code used in *LAVMethod* to control the initial time delay for the *LAVFacility*

```
if VVConnect[2,3] = true and ProbabilityOfSucces[3,4] = false then
    If VVConnect[4,3] = false and VVAndLAVFix = false then
        If SSandSU[3,1] = true then
            LAVV := VVFacilitySS.xdim/NumberVV
        end
        If SSandSU[3,2] = true then
            LAVV := VVFacilitySU.xdim/NumberVV
        end
    end
    If VVConnect[4,3] = true then
            VVAndLAVFix := true
            VVConnect[4,3] := false
    end
```

Figure C.32: Code used in *LAVMethod* to determine whether time delays are required due to platform termination

string 1	boolean 2	boolean 3	boolean 4
Platform	Configuration	Connect	Delay
IV	false	false	false
SP	false	false	false
LAV	true	false	false
DNA	false	false	false
RNA	false	false	false

Figure C.33: Section of the *VVConnect* table

```
If ChangeOverLAVTime = true and ConnectLAV = true then
    if VVConnect[2,3] = true and ProbabilityOfSucces[3,4] = false then
    If VVAndLAVFix = false
        LAV1 := LAVV
    end
    If VVAndLAVFix = true then
        If eventcontroller.simTime = VVFixTime + LAVTime +0:05 then
            VVAndLAVFix := false
            If SSandSU[3,1] = true then
                LAV1 := VVFacilitySS.xdim/NumberVV
            end
            If SSandSU[3,2] = true then
                LAV1 := VVFacilitySU.xdim/NumberVV
            end
        end
    end
        else LAV1 := 0
    end
    if IVConnect[2,1] = true and ProbabilityOfSucces[3,2] = false then
    If IVAndLAVFix = false
        LAV2 := LAVI
    end
    If IVAndLAVFix = true then
        If eventcontroller.simTime = IVFixTime + LAVTime +0:05 then
            IVAndLAVFix := false
            If SSandSU[3,1] = true then
                LAV2 := IVFacilitySS.xdim/NumberIV
            end
            If SSandSU[3,1] = true then
                LAV2 := IVFacilitySU.xdim/NumberIV
            end
        end
    end
        else LAV2 := 0
    end
    if SPConnect[2,2] = true and ProbabilityOfSucces[3,3] = false then
    If SPAndLAVFix = false
        LAV3 := LAVS
    end
    If SPAndLAVFix = true then
        If eventcontroller.simTime = SPFixTime + LAVTime +0:05 then
            SPAndLAVFix := false
            If SSandSU[3,1] = true then
                LAV3 := SPFacilitySS.xdim/NumberVV
            end
            If SSandSU[3,2] = true then
                LAV3 := SPFacilitySU.xdim/NumberVV
            end
        end
    end
        else LAV3 := 0
    end
    if DNAConnect[2,4] = true and ProbabilityOfSucces[3,5] = false then
    If DNAAndLAVFix = false
        LAV4 := LAVD
    end
    If DNAAndLAVFix = true then
        If eventcontroller.simTime = DNAFixTime + LAVTime +0:05 then
            DNAAndLAVFix := false
            If SSandSU[3,1] = true then
                LAV4 := DNAFacilitySS.xdim/NumberDNA
            end
            If SSandSU[3,2] = true then
                LAV4 := DNAFacilitySU.xdim/NumberDNA
            end
        end
    end
        else LAV4 := 0
    end
```

Figure C.34: Code used in *LAVMethod* to control the shift of capacity for the *LAVFacility* part A

```
    if RNAConnect[2,5] = true and ProbabilityOfSucces[3,6] = false then
    If RNAAndLAVFix = false
        LAV4 := LAVR
    end
    If RNAAndLAVFix = true then
        If eventcontroller.simTime = RNAFixTime + LAVTime +0:05 then
            RNAAndLAVFix := false
            If SSandSU[3,1] = true then
                LAV4 := RNAFacilitySS.xdim/NumberRNA
            end
            If SSandSU[3,2] = true then
                LAV4 := RNAFacilitySU.xdim/NumberRNA
            end
        end
    end
        else LAV5 := 0
        end
        LAVEntranceLock := false

        LAVLines := Lines[2,1] + LAV1 + LAV2 + LAV3 + LAV4 + LAV5

        If SSandSU[3,1] = true then
            If LAVLines > Lines[2,1] then
            LAVFacilitySS.entrancelocked := true
            LAVFacilitySS.xdim := LAVLines
            LAVFacilitySS.entrancelocked := false
            else LAVFacilitySS.entrancelocked := LAVEntranceLock
            end
        end
        If SSandSU[3,2] = true then
            If LAVLines > Lines[2,1] then
            LAVFacilitySU.entrancelocked := true
            LAVFacilitySU.xdim := LAVLines
            LAVFacilitySU.entrancelocked := false
            else LAVFacilitySU.entrancelocked := LAVEntranceLock
            end
        end
    LAVShift[1,LAVShift.ydim+1] := eventcontroller.simTime
    LAVShift[2,LAVShift.ydim] := LAV1
    LAVShift[3,LAVShift.ydim] := LAV2
    LAVShift[4,LAVShift.ydim] := LAV3
    LAVShift[5,LAVShift.ydim] := LAV4
    LAVShift[6,LAVShift.ydim] := LAV5
end
```

Figure C.35: Code used in *LAVMethod* to control the shift of capacity for the *LAVFacility* part B

C.5 Variables for verification and testing

Two groups of variables are controlled and recorded merely for troubleshooting. The first group of such variables are recorded to verify that vaccine platforms are only approved if the random number U is smaller than its probability of success value and only rejected if the random number *M* is smaller than its probability of failure value. Record is kept of the random number *U*, and *M* values, the probability of success, and the probability of failure values at the start of each period. At the start of a period, the current time, along with all of these values for a platform, are inscribed in a table (e.g. *LTable*, which is the table for the LAV platform's values), and the code used to achieve this is shown in Figure C.5. Figure C.36 presents a section of the *LTable*. The Eventcontroller.SimTime at the start of a period is assigned to the *Time* column (*LTable[1,y]*). This is the random number used in the vaccine approval section (refer to Figure C.5).

For example, *L* (for the LAV platform) is assigned to the *Random L* column (*LTable[2,y]*), the probability of success value is assigned to the *POS* column (*LTable[3,y]*), the random number for the rejection section (*M*) is assigned to the *Random M* column (*LTable[4,y]*), and the probability of failure value is assigned to the *POF* column (*LTable[5,y]*).

The second group of variables, recorded only for the purpose of troubleshooting, is recorded to verify that the shifting of capacity between platforms occurs as expected. Each platform has five variables representing the number of production lines received from the five other platforms. For example, the LAV platform has the variables *LAV1*, *LAV2*, *LAV3*, *LAV4*, and *LAV5*, which represent the number of production lines received from the IV, SP, VV, DNA, and RNA platform, respectively. After the initial time delay for a platform has been enforced, the values for each of the five variables for the platform are recorded at the start of each period and inscribed in a table (e.g. *LAVShift* for the LAV platform). The code used to inscribe the values of the variables for the LAV platform is shown in Figure C.35. In Figure C.17, the variables' values are set to zero since the manufacturing for the platform has been de-activated, and the additional production lines are no longer available to the platform. A section of the *LAVShift* table is shown in Figure C.37.

	time 1	real 2	real 3	integer 4	integer 5
string		Random L	POS	Random M	POF
1	1.0000	1.00	100.00	36	0
2	30:00:00:01.0000	57.00	0.00	20	0
3	60:00:00:01.0000	77.00	0.00	38	0
4	90:00:00:01.0000	97.00	0.00	84	100
5	120:00:00:01.0000	77.00	0.00	25	0
6	150:00:00:01.0000	70.00	0.00	15	0
7	180:00:00:01.0000	98.00	0.00	51	0

Figure C.36: Section of the *LTable*

	time 1	integer 2	integer 3	integer 4	integer 5	integer 6
tring	Time	LAV1	LAV2	LAV3	LAV4	LAV5
1	30:00:00:00.0000	0	0	10	0	0
2	30:00:00:03.0000	0	0	10	0	0
3	60:00:00:03.0000	0	0	10	0	0

Figure C.37: A section of the *LAVShift* table

The Eventcontroller.SimTime at the start of a period is assigned to the *Time* column (*LAVShift[1,y]*), while the values of *LAV1*, *LAV2*, *LAV3*, *LAV4*, and *LAV5* are assigned to the appropriate columns.

Appendix D

Original model description

The description of the original model developed in Tecnomatix Plant Simulation is described in this Appendix. No verification or validation has been performed on this version of the model.

D.1 Introduction

This section describes a dynamic and stochastic discrete-event simulation model developed in Tecnomatix Plant Simulation (TPS). The model aims to evaluate the impact of different manufacturing process flexibility configurations on the manufacturing system of Covid-19 vaccines. The manufacturing system consists of six vaccine platforms, namely: Live attenuated virus (LAV), Inactivated virus (IV), Subunit protein (SP), Viral vector (VV), DNA, and RNA, which are considered. The model is divided into three main sections, namely: the approval of vaccines, the rejection of vaccines, and the manufacturing of vaccines. New paragraph. A brief overview of the model is provided with detail regarding the operations of each section within the model discussed later. The model considers the manufacturing of vaccines over a time horizon (e.g. five years), which is divided into equal periods of 30 days. The time is indicated in the following manner in TPS: A:B:C:D, with A indicating the number of days, B indicating the number of hours, C indicating the number of minutes and D indicating the number of seconds. The first period starts at 00:00:00:00 and ends at 30:00:00:00, while the second period will start at 30:00:00:00 and end at 60:00:00:00. Actions regarding the approval, rejection, and manufacturing of vaccines and the reconfiguration of the manufacturing system can only occur at the start of such a period. Vaccines are approved based on a pre-determined probability of success distribution. Once at least one vaccine product of a platform is approved, the manufacturing of the platform is activated. Manufacturing throughput is measured on a platform level only. Thus, if a second vaccine product of a specific platform is approved, this has no impact, as all available manufacturing capacity for the given platform will already have been activated. Approved vaccines may also be

rejected based on a pre-determined probability of failure distribution. The manufacturing of a specific vaccine platform will only cease if all previously approved vaccine products of the platform have subsequently been rejected. The manufacturing system of the vaccine platforms is represented as six manufacturing facilities, each producing one of the six vaccine platforms mentioned previously, with a set manufacturing capacity (i.e. a set number of production lines) available to each manufacturing facility. Process flexibility configurations can be created by setting the production lines of a specific manufacturing facility to have the capability to manufacture more than one vaccine platform. The capacity of an idle vaccine platform's manufacturing facility can be used to manufacture an approved vaccine platform, given that the process flexibility configuration allows it. Shifting manufacturing capacity from one product to another results in a time delay, which differs for the different manufacturing facilities. The model's output is the throughput of vaccine products and is used to evaluate the performance of a specific process flexibility configuration. Figure D.1 represents a process flexibility configuration in which the LAV platform manufacturing facility's (A) capacity can be shifted to produce the RNA and SP vaccine products, respectively. Each of these

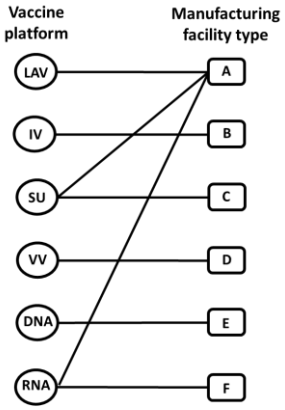

Figure D.1: A flexibility configuration for vaccine platforms

platform's facilities is initially assigned 10 production lines. If, for example, at the start of period 9 of the model run time, the LAV platform has not been approved for manufacturing, but both the RNA and SP platforms are approved, the 10 production lines initially assigned to the RNA platform will immediately start manufacturing RNA vaccine products. The 10 production lines initially assigned to the SP platform will begin manufacturing SP vaccine products immediately. The LAV platform facility's production lines that can be shifted to the RNA and SP facilities will be divided equally between the two platforms. Both the RNA and SP platforms can thus each receive five additional production lines. Due to the time delay associated with the capacity shifts, these additional production lines will only start producing the RNA and SP vaccine products once the respective time delays have been enforced. If, for example, the LAV platform is then approved at the start of period 17, the five additional LAV production lines assigned to

the manufacturing of RNA vaccine products, as well as the five additional LAV production lines assigned to the manufacturing of SP vaccine products will immediately be shifted back to the manufacturing of LAV vaccine products. Manufacturing of the LAV products will only start once the associated time delay for switching the production lines back to the LAV facility has been enforced. The model is not a perfect representation of reality. In deciding whether and how to implement simplifications, the ability to accurately investigate the substantive research questions was the primary consideration. For example, in reality, it is likely that, for various reasons, the manufacturing of a vaccine would not commence at the same time as regulatory approval. However, incorporating a delay for this commencement will not clarify insights on the impact of process flexibility. Especially if this delay is variable, incorporating it may obscure model outputs that can assist in drawing clear conclusions on the impact of process flexibility.

The model aims to consider the impact of process flexibility on the throughput of vaccine products over time, given the relatively high "demand" uncertainty created by the approval of vaccines. (Returning to the example in Figure D.1 to illustrate, if no LAV, SU, or RNA vaccines were approved during a model run time, all 10 production lines of manufacturing facilities A, C, and F would have remained idle throughout.) To ensure that the findings on the throughput performance of various process flexibility configurations under the approval uncertainty are not obscured, unlimited demand for approved vaccines is assumed. Thus, all available manufacturing capacity is utilised to manufacture approved vaccines. The possibility of vaccine rejection is included in the model to represent the reality of the system. As mentioned previously, the model aims to investigate the impact of process manufacturing flexibility on the throughput of vaccine manufacturing. Considering the rejection of vaccine platforms may obscure the results obtained for the flexibility configurations. It is also highly unlikely that a vaccine product will be rejected once approved for manufacturing. The possibility of vaccine product rejection can be ignored in the model by assigning all the platforms a probability of failure value of zero. To further represent the reality of the system, the manufacturing of a system will only be deactivated if a platform has no approved product at the time since the manufacturing for a specific platform will not be terminated if only one of its products becomes rejected.

D.2 Vaccine approval

The graphical representation of the vaccine platform approval subsystem as it has been implemented in TPS is shown in Figure D.2. The vaccine platform approval subsystem operates in a loop structure. The *VaccineApproval* source creates a single object *ApprovedVaccine*, at the start of the model run time and the *ApprovedVaccine* object remains within the loop structure for the remainder of the model run time.

The *BufferDelay* buffer ensures that the *ApprovedVaccine* object remains stationary until the start of a period via the *DelayMethod* method, using the code (SimTalk in TPS) shown in Figure D.3. When the

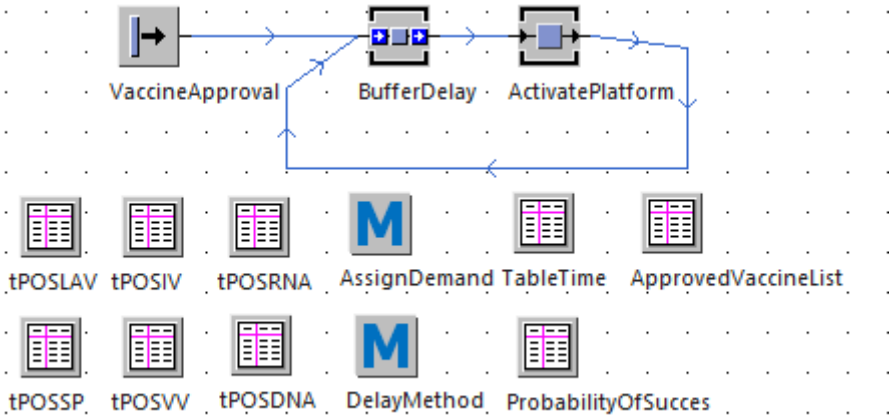

Figure D.2: Graphical representation of the approval of vaccines

object arrives at the *BufferDelay* buffer, the code checks if the current time of the simulation, *eventcontroller.SimTime*, is equal to the start of a period. The time value for the start of each period is given in the *TableTime* table; a section of the *TableTime* table is shown in Figure D.4. If the object arrives at the start of a period, the *BeginPeriod* variable is assigned a true value. Otherwise, the variable is assigned a false value, and a delay time is assigned to the *TimeWait* variable. Suppose the *BeginPeriod* variable has a true value. In that case, the object can proceed to the *ActivatePlatform* station. In contrast, if the *BeginPeriod* variable has a false value, the object is delayed for a time equal to the value of the *TimeWait* variable before it is allowed to proceed to the *ActivatePlatform* station.

```
for var y:= 1 to TableTime.ydim
    if eventController.simtime = TableTime[1,y] then
        BeginPeriod := true
        exitloop
    elseif eventController.simtime < TableTime[1,y] then
        BeginPeriod := false
        TimeWait := TableTime[1,y] - eventController.simTime
            exitloop
         end
next

if BeginPeriod = true then
    @.move
else wait timewait
    @.move
end
```

Figure D.3: Code used in *DelayMethod* to delay the *ApprovedVaccine object*

	time 1
1	0.0000
2	30:00:00:00.0000
3	60:00:00:00.0000
4	90:00:00:00.0000
5	120:00:00:00.0000
6	150:00:00:00.0000
7	180:00:00:00.0000
8	210:00:00:00.0000
9	240:00:00:00.0000
10	270:00:00:00.0000
11	300:00:00:00.0000
12	330:00:00:00.0000
13	360:00:00:00.0000
14	390:00:00:00.0000
15	420:00:00:00.0000
16	450:00:00:00.0000
17	480:00:00:00.0000

Figure D.4: section of the *TableTime* table

The ActivatePlatform has a processing time of one second, and its function is two-fold. It firstly controls which vaccine platform(s) are approved at the start of a period. Secondly, the ActivatePlatform station controls the activation of approved vaccine platforms' manufacturing.

D.2.1 Approval of vaccine platforms

The approval of vaccine platforms at the start of a period is achieved via the *AssignDemand* method. As an example, the code used to control the approval of the LAV platform is shown in Figure D.5. The approval of the other vaccine platforms is achieved via a similar code.

Simulation experiments performed by McDonnell et al. (2020) generated an estimation of the number of vaccine products for each platform that will be approved over a three-year time horizon. These results were utilised to create a probability of success (POS) distribution over time for each vaccine platform using the cumulative exponential function, given in (D.1). The distribution for each platform is recorded in a *POS* table (e.g. *tPOSSP*). As an example, a graphical representation of the probability of success distribution for the SP platform is given in Figure D.7.

```
var L: integer
L := floor(z_uniform(1,1,100))
Ltable[1,Ltable.ydim+1] := eventController.simtime
Ltable[2,Ltable.ydim] := L
LTable[4,LTable.ydim] := MTable[1,1]
LTable[5,LTable.ydim] := ProbabilityOfFailure[2,1]
for local y := 1 to tPOSLAV.ydim
    If eventController.SimTime = tPOSLAV[1,y] + 0:01 then
        Ltable[3,Ltable.ydim] := tPOSLAV[2,y]
        If L < tPOSLAV[2,y] then
            ProbabilityOfSucces[3,1] := true
            LAVApprovedCnt := LAVApprovedCnt +1
            If LAVCreate = false then
            .UserObjects.CapacityDecrease.create(LAVBuffer)
            LAVCreate := true
            end
        end
    end
next
```

Figure D.5: Code used in *AssignDemand* to control the approval of LAV vaccine products.Soms het jy 'n punt en soms nie

$$\mathrm{POS}_{\mathrm{Platform}}(t) = [1 - e^{\frac{-t}{\beta}}] \tag{D.1}$$

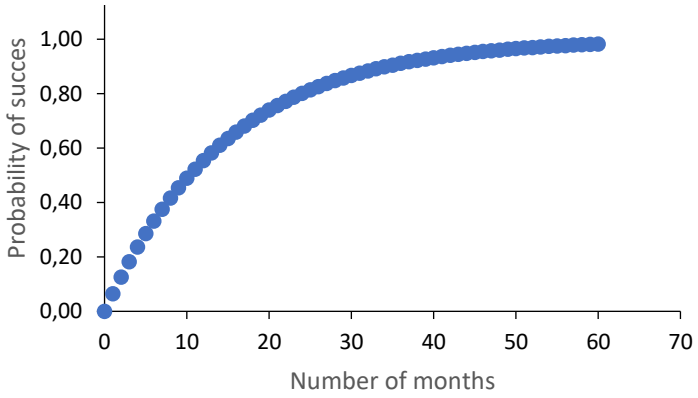

Figure D.6: Graphical representation of the probability of success values for the SP platform over three years.

When the *ApprovedVaccine* object arrives at the *AssignDemand* station, a random number (e.g. *L*) is created. The random number is an integer of any value between 0 and 100. For each period, the random number is compared to the probability of success value for that period in the *tPOSPlatform* table. If the random number is smaller than the probability of success value for that period, the vaccine platform

	time 1	integer 2
1	0.0000	0
2	30:00:00:00.0000	7
3	60:00:00:00.0000	13
4	90:00:00:00.0000	18
5	120:00:00:00.0000	24
6	150:00:00:00.0000	29
7	180:00:00:00.0000	33
8	210:00:00:00.0000	38
9	240:00:00:00.0000	42
10	270:00:00:00.0000	45
11	300:00:00:00.0000	49
12	330:00:00:00.0000	55
13	360:00:00:00.0000	55
14	390:00:00:00.0000	58
15	420:00:00:00.0000	61
16	450:00:00:00.0000	64
17	480:00:00:00.0000	66

Figure D.7: A section of the *tPOSSP* table

becomes approved. A true value is assigned to the Approved status column in the *ProbabilityOfSuccess* table; a section of the *ProbabilityOfSuccess* table is shown in Figure D.8. Record is kept of the number of vaccine products per platform that would have been approved if the approval was considered on a product level by incrementing the *PlatformApprovedCnt* (e.g. *LAVApprovedCnt*) variable by one when a platform's random number is smaller than its probability of success value for a period.

As discussed in the Vaccine Manufacturing section, capacity can be shifted between platforms. Capacity shift loops control this. When a platform is approved, an object is created at the buffer of its capacity shift loop to activate it (e.g. *.UserObjects.CapacityDecrease.create(LAVBuffer)*), as shown in the code in Figure D.5. To ensure that only one object is created per loop, the object is only created if the *PlatformCreate* (e.g. *LAVCreate*) variable has a false value. The *PlatformCreate* variable initially has a false value and is assigned a true value after the object has been created.

D.2.2 Approval of vaccine platforms

The *ActivatePlatforms*tation controls the activation of approved vaccine platforms' manufacturing via the *AssignDemand* method. The activation of all the vaccine platforms' manufacturing is achieved similarly. Only the code used to activate the manufacturing of the LAV platform is shown in Figure D.9.

	string 1	real 2	boolean 3
string	Platform		Approved
1	.UserObjects.LAVPlatform	0.00	false
2	.UserObjects.IVPlatform	0.00	false
3	.UserObjects.SPPlatform	0.00	false
4	.UserObjects.VVPlatform	0.00	false
5	.UserObjects.DNAPlatform	0.00	false
6	.UserObjects.RNAPlatform	0.00	false

Figure D.8: Section of the *ProbabilityOfSuccess* table

The code used to activate the manufacturing of a platform can only be executed if the platform has an approved product (i.e. when the platform has a true value in the Approved status column of the *ProbabilityOfSuccess* table, refer to Figure D.8). Since the model only considers one vaccine product per platform at any given time, the *ApproveFlagPlatform* (e.g. *ApproveFlagLAV*) variable is used to prevent more than one vaccine product of a platform from being approved simultaneously. Thus, for example, a new vaccine product can be recognised as approved only when the *ApproveFlagLAV* variable has a false value. The *ApproveFlagLAV* variable has an initial value of false and is assigned a true value after the approval of the first LAV vaccine product. If the *ApproveFlagLAV* variable has a true value, the approval of the additional vaccine products will not be considered.

As shown in the code in Figure D.8, an approved vaccine platform's manufacturing is activated by assigning a true value to the *ConnectPlatform* (e.g. *ConnectLAV*) variable. The number of approved vaccine products is counted by increasing the value of the *ApprovedVaccineCnt* by one when a vaccine platform is approved. Further, an entry is made in the *ApprovedVaccineList* table, shown in Figure D.10. In the first column of the table, the name of the vaccine platform is entered (*.UserObjects.LAVPlatform*), the status of the vaccine platform is changed to *Approved* in the second column, and the time at which the platform is approved is entered in the third column.

As mentioned previously, the model makes provision for a platform that was once approved to be rejected in future. This is described in more detail in Section D.3. After a vaccine platform has been rejected, a new vaccine product for the platform may be approved.

A section of the *DelayTimes* table referred to in the code in Figure D.8, is shown in Figure D.11. The *DelayTimes* table contains the delay (i.e. switchover time) for each platform's manufacturing facility when capacity is shifted between products. This is discussed in greater detail in Section D.4. Once a vaccine platform has been approved, the code searches for the platform in the *DelayTimes* table and assigns a true value to the *ApprovedStatus* column (*DelayTimes[3,3]*), which represents the same variable

```
If ProbabilityOfSucces[3,1] = true then
    If ApprovedFlagLAV = false then
        ConnectLAV := True
        For local y:= 1 to DelayTimes.ydim
            if DelayTimes[1,y] = "LAV" then
                DelayTimes[3,y] := true
            end
        next
    if LAVApprovedCnt >= 2 and LAVLines = 10 then
        LAVFacility.entrancelocked := false
        LAVFacility.xdim := LAVLines
    end
    ApprovedVaccineList[1, ApprovedVaccineList.ydim+1] := .UserObjects.LAVPlatform
    ApprovedVaccineList[2, ApprovedVaccineList.ydim] := "Approved"
    ApprovedVaccineList[3, ApprovedVaccineList.ydim] := eventController.simTime
    ApprovedVaccineList[6, ApprovedVaccineList.ydim] := false
    ApprovedVaccineCnt := ApprovedVaccineCnt +1;
    ProbabilityOfFailure[2, ProbabilityOfFailure.ydim-5] := POFTable[2,1]
    ApprovedFlagLAV := True
    end
end
```

Figure D.9: Code used in *AssignDemand* to activate the manufacturing of the LAV platform

	object 1	string 2	time 3
string	MU	Approved	Period
1	*.UserObjects.LAVPlatform	Approved	1.0000
2			
3			

Figure D.10: A section of the *ApprovedVaccineList* table

as *ConnectPlatform* (e.g. *ConnectLAV*).

The code includes a section that relates to the approval of a vaccine product for a platform that has previously been both approved and rejected and for which the capacity was not shifted during the rejected state. The code is explained in this section as presented in Figure D.8. However, reference is made to the shifting of capacity and the number of production lines assigned to a manufacturing system which are discussed in Section D.4. If a vaccine platform, which matches the aforementioned criteria, is approved, its manufacturing facility can start manufacturing without delay (*LAVFacility.entrancelocked* := *false*). The manufacturing facility is assigned its initial number of production lines (*LAVFacility.xdim* := *LAVLines*).

	string 1	time 2	boolean 3	boolean 4
string	Platform	Delay Time	ApprovedStatus	ApprovedFlag
1	RNA	29:23:59:56.0000	false	false
2	SP	29:23:59:56.0000	false	false
3	LAV	29:23:59:56.0000	false	false
4	IV	59:23:59:56.0000	false	false
5	DNA	59:23:59:56.0000	false	false
6	VV	59:23:59:56.0000	false	false

Figure D.11: A section of the *DelayTimes* table

D.3 Vaccine Rejection

A graphical representation of vaccine platform rejection as implemented in TPS is shown in Figure D.12. The vaccine platform rejection subsystem operates in a loop structure. The *VaccineRejection* source creates a single object *RejectedVaccine* at the start of the model run time. The *RejectedVaccine* object remains within the loop structure for the remainder of the model run time.

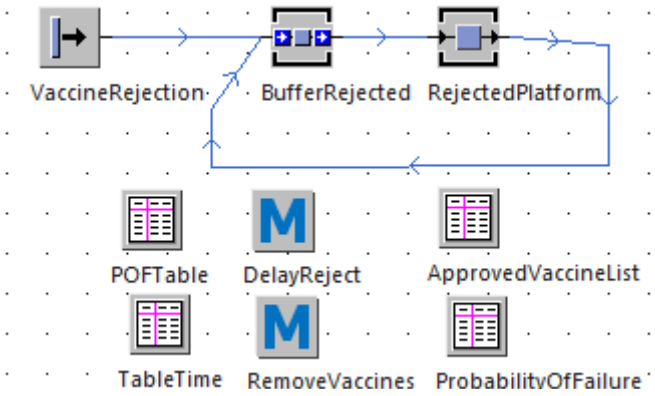

Figure D.12: Representation of the rejection of vaccines

The *BufferRejected* buffer ensures that the *RejectedVaccine* object remains stationary until the start of a period via the *DelayReject* method, using the code shown in Figure D.13. When the object arrives at the *BufferRejected* buffer, the code checks whether the current time of the simulation, *eventcontroller.SimTime*, is equal to the start of a period. If the object arrives at the start of a period, the *BeginPeriodR* variable is assigned a *true* value. Otherwise, the variable is assigned a false value, and a delay time is assigned to the *TimeWaitR* variable. Suppose the *BeginPeriodR* variable has a true value. In that case, the object can proceed to the *RejectedPlatform* station. In contrast, if the *BeginPeriodR* variable has a *false* value, the

object is delayed for a time equal to the value of the *TimeWaitR* variable before it is allowed to proceed to the *RejectedPlatform* station.

```
for var y:= 1 to TableTime.ydim
    if eventController.simtime = TableTime[1,y] then
        BeginPeriodR := true
        exitloop
    elseif eventController.simtime < TableTime[1,y] then
        BeginPeriodR := false
        TimeWaitR := TableTime[1,y] - eventController.simTime
            exitloop
         end
    next

if BeginPeriodR = true then
    @.move
else wait timewaitR
    @.move
    end
```

Figure D.13: Code used in *DelayRejected* to delay the *RejectedVaccine* object

The *RejectedPlatform* station has a processing time of one second, and its function is two-fold. It firstly controls which vaccine platform(s) is rejected at the start of a period, and secondly controls the de-activation of a vaccine platform's manufacturing.

D.3.1 Rejection of vaccine platforms

The likelihood of a vaccine being rejected is managed using a unique probability of failure (POF) value for each vaccine platform. The *POFLAV* value is assigned to the LAV platform in the *ProbabilityOfFailure* table, depicted in Figure D.14.

The *RejectedPlatform* station controls the rejection of platforms via the *RemoveVaccine* method. When the *RejectedVaccine* object arrives at the *RejectedPlatform* station, a random number is generated for each vaccine platform and compared to its pre-determined probability of failure, given in the *ProbabilityOfFailure* table. The code used to achieve this is shown in Figure D.15, while the content of the *ProbabilityOfFailure* table is shown in Figure D.14. Suppose a vaccine platform's random number is smaller than its probability of success value. In that case, the vaccine platform becomes rejected, and it is assigned a *true* value in the *Rejected* status column in the *ProbabilityOfFailure* table.

D.3.2 De-activation of vaccine manufacturing

The *RejectedPlatform* station controls the de-activation of a vaccine platform's manufacturing via the *RemoveVaccine*method. As mentioned in Section D.2, a record is kept of the number of vaccine products

	object 1	integer 2	boolean 3
string	MU	POF	Rejected
1	.UserObjects.LAVPlatform	10	false
2	.UserObjects.IVPlatform	0	false
3	.UserObjects.SPPlatform	0	false
4	.UserObjects.VVPlatform	0	false
5	.UserObjects.DNAPlatform	0	false
6	.UserObjects.RNAPlatform	0	false

Figure D.14: Content of the *ProbabilityOfFailure* table

```
var M: integer
for local y:= 1 to ProbabilityOfFailure.ydim
    M := floor(z_uniform(1,1,100))
    MTable[1,y] := M
    if M <  ProbabilityOfFailure[2,y] then
ProbabilityOfFailure[3,y] := true
end
next
```

Figure D.15: Code used in *RejectedPlatform* for the rejection of vaccine platforms

that would be approved per platform if the approval were considered on a product-level rather than on a platform level. This is used to limit the de-activation of a platform's manufacturing to instances where no approved vaccine product of a platform remains.

The de-activation of all the vaccine platforms' manufacturing is achieved similarly. Only the code used to de-activate the manufacturing of the LAV platform is shown in Figure D.16 as an example. When a vaccine platform is rejected, the *PlatformApprovedCnt* is reduced by one. The rejection of the vaccine is indicated in the *ApprovedVaccineList* by adding to the platform's inscription, as shown in Figure D.17. The platform is assigned a *true* value in the *Rejected* status column in the *ApprovedVaccineList* table, and the time of rejection is recorded. If the platform is approved again later in the model run time, a completely new inscription will be made in the *ApprovedVaccineList* for the platform's approval.

The de-activation of a vaccine platform's manufacturing will only occur when the *PlatformApprovedCnt* (e.g. *LAVApprovedCnt*) is zero. The manufacturing of the vaccine platform is de-activated by assigning a *false* value to the *ConnectDNA* variable. The code searches for the platform (e.g. "LAV") in the *DelayTimes* table and assigns a *false* value to the *Connect* column (*DelayTimes[3,1]*). The platform is assigned a *false* value in the *Approved* status column of the *ProbabilityOfSuccess* table. The platform can no longer be rejected and is assigned a zero probability of failure value in the *ProbabilityOfFailure* table. The number

```
if  ProbabilityOfFailure[3,1] = true then
    LAVApprovedCnt := LAVApprovedCnt -1
    for var y:= 1 to ApprovedVaccineList.yDim
        if ApprovedVaccineList[1, y] = .UserObjects.LAVPlatform and ApprovedVaccineList[6,
            ApprovedVaccineList[4, y] := "Rejected"
            ApprovedVaccineList[5, y] := eventController.simTime
            ApprovedVaccineList[6, y] := true
        end
    next
    IF LAVApprovedCnt = 0 then
    ChangeOverLAVTime := false
    RejectedFlagLAV := true
    ConnectLAV := false
    ProbabilityOfSucces[3,1] := false
    ProbabilityOfFailure[2,1] := 0
    For local y := 1 to DelayTimes.ydim
        if DelayTimes[1,y] = "LAV" then
            DelayTimes[3,y] := false
        end
        exitloop
    next
    ApprovedVaccineCnt := ApprovedVaccineCnt -1;
    LAVFacility.entrancelocked := true
    ApprovedFlagLAV := False
    LAVShift[1,LAVShift.ydim+1] := eventcontroller.simTime
    LAVShift[2,LAVShift.ydim] := 0
    LAVShift[3,LAVShift.ydim] := 0
    LAVShift[4,LAVShift.ydim] := 0
    LAVShift[5,LAVShift.ydim] := 0
    LAVShift[6,LAVShift.ydim] := 0
    If LAVFacility.NumMu = 0 then
    LAVLines := Lines[2,1]
    LAVFacility.xdim := LAVLines
    end
    end
    ProbabilityOfFailure[3,1] := false
end
```

Figure D.16: Code used in *RemoveVaccine* to de-activate the manufacturing of the LAV platform

of approved vaccine platforms is adjusted by reducing the value of the *ApprovedVaccineCnt* by one. To prevent the rejected platform's manufacturing facility (e.g. *LAVFacility*) from manufacturing any further vaccines (i.e. from creating any new *LAVPlatform* objects, for example, as explained in Section D.4), the manufacturing facility's entrance is locked by assigning a *true* value to the *PlatfromFacility.entrancelocked* (e.g. *LAVFacility.entrancelocked*) variable. To allow a new vaccine product of the platform to be approved, a *false* value is assigned to the *AssignedFlagPlatform* (e.g. *ApprovedFlagLAV*) variable.

As previously mentioned, the shifting of capacity is discussed in the Section D.4. However, the code in Figure D.16 contains a section that relates to capacity shifting and the associated time delay. A facility's number of production lines is set to the initial value assigned to the facility before the start of the model run time, which is stored in the *Lines* table. A section of the *Lines* table is shown in Figure D.18. This is performed for the case where the facility had received capacity from another facility. The *ChangeOverPlatformTime* (e.g. *ChangeOverLAVTime*) variable controls the initial time delay for a platform after it has

	object 1	string 2	time 3	string 4	time 5	boolean 6
string	MU	Approved	Period	Rejected	Period	Removed
1	*.UserObjects.LAVPlatform	Approved	1.0000	Rejected	30:00:00:01.0000	true
2						
3						

Figure D.17: Section of the *ApprovedVaccineList* table

been approved. When a platform's manufacturing is de-activated, the time delay that has previously been enforced becomes irrelevant, and a *false* value is thus assigned to the *ChangeOverPlatformTime* variable. To ensure that the removal of a rejected vaccine platform only occurs once, the platform is assigned a *false* value in the *Rejected* status column in the *ProbabilityOfFailure* table, as shown in Figure D.15.

	string 1	integer 2
string	Platform	Production lines
1	LAV	10
2	IV	10
3	SP	10
4	VV	10
5	DNA	10
6	RNA	10

Figure D.18: Section of the *Lines* table

D.4 Vaccine manufacturing

A graphical representation of the vaccine platform manufacturing as implemented in TPS is shown in Figure D.19. Each vaccine platform has a separate manufacturing subsystem with a source (e.g. *LAVDemand*) which continuously creates an object (e.g. *LAVPlatform*), given that the platform's manufacturing is activated, as discussed in the Section D.2. Each manufacturing subsystem has a method (e.g. *MethodLAV*) which delays the creation of objects at a source until the platform's manufacturing is activated. As an example, the code used to achieve this for the LAV platform's manufacturing subsystem is shown in Figure D.20.

The buffer (e.g. *BufferLAV*) stores the objects (*LAVPlatform*) until the manufacturing facility (*LAVFacility*) can process the objects. The manufacturing facility has a pre-determined capacity for the number of production lines (e.g. $LAVLines = 10$), stored in the *Lines* table, as shown in Figure D.18. The number of production lines can be adjusted as capacity shifts between products; this is discussed in more detail later.

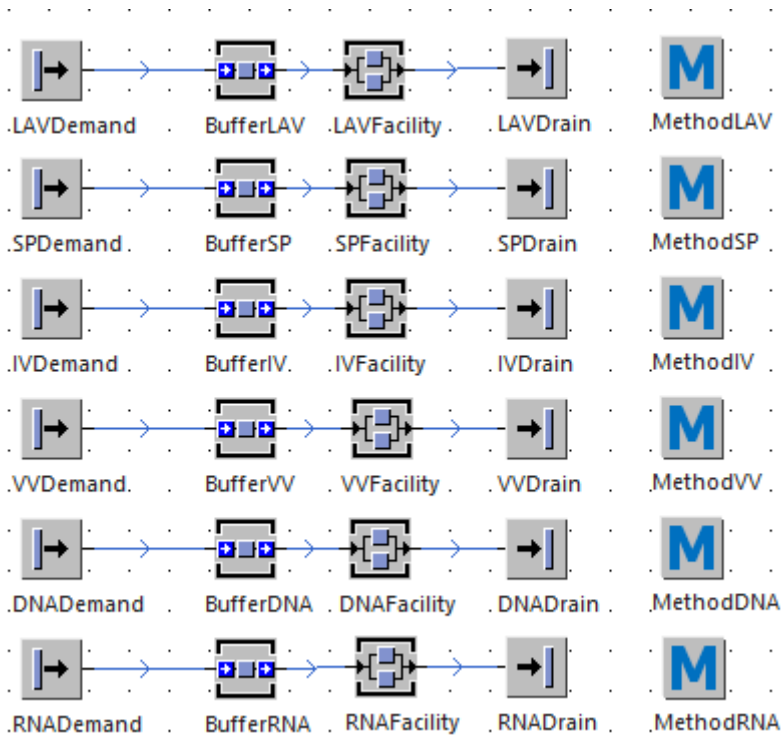

Figure D.19: Representation of the manufacturing of vaccine platforms

```
waituntil ConnectLAV = true
@.move(BufferLAV);
```

Figure D.20: Code used to delay the creation of *LAVPlatform* objects at the *LAVDemand source*

When an object has been processed by the manufacturing facility (*LAVFacility*), the object proceeds to a drain (e.g. *LAVDrain*), which removes the object from the model. The system's throughput is recorded by counting the number of objects that enter each drain and incrementing the *ThroughputVaccines* variable by 10 000, as shown in Figure D.21. Each object that enters the drain (e.g. *LAVDrain*) represents 10 000 manufactured vaccine products. The throughput of each vaccine platform is also recorded separately, as shown in Figure D.21, by incrementing the appropriate *ThroughputPlatformVaccines* (e.g *Throughput-LAVVaccines*) variable with 10 000.

When a vaccine becomes rejected (*ConnectLAV* = *false*), its manufacturing subsystem will still have objects in the manufacturing facility (*LAVFacility*) station, which the manufacturing facility will still process even though the manufacturing for the subsystem has been de-activated. To correct the number of objects

that are considered to enter the platform's drain (e.g. *LAVDrain*) and consequently the throughput for the system, the ThroughputVaccines variable is reduced by 10 000 for each object that enters a de-activated manufacturing subsystem's drain.

D.4.1 Process flexibility

Different process flexibility configurations are created by connecting different plant and manufacturing facilities. Each platform has a *PlatformConnect* table (e.g. *LAVConnect*) in which the connections with its manufacturing facility for a specific configuration are indicated. A section of the *LAVConnect* table is shown in Figure D.22. If the *LAVFacility* can manufacture another platform, a true value is assigned to that platform in the *Configuration* column of the *LAVConnect* table. These values can either be adjusted manually before the start of the model run time or via the TPS ExperimentManager. The example in Figure D.22 indicates that the *LAVFacility*'s production lines can be reassigned to manufacture IV-, SP-, and RNA vaccines. The *Connect* column in the *PlatformConnect* table indicates whether each of the platforms in the *Platform* column has been approved. In the example in Figure D.22, the IV platform has at least one approved vaccine product, but the SP, VV, DNA, and RNA platforms do not have an approved vaccine product. The *LAVFacility*'s capacity can thus be reassigned to the IV platform but not to the SP- or RNA platforms. However, this will only be done if the *LAVFacility* is idle (i.e., there is no approved LAV vaccine). The assignment of values to the Connect column, as shown in Figure D.22, is discussed in the capacity control subsystem Subsection D.4.2.

The shifting of capacity from one product to another results in a time delay, which may differ for each manufacturing facility. The capacity shift and the accompanying time delay are controlled via seven subsystems, as shown in Figure D.23. One of the subsystems is the capacity control subsystem, while the remaining six are platform control capacity subsystems.

D.4.2 Capacity control subsystem

The capacity control subsystem operates in a loop structure. The *CapacitySource* source creates a single object *Capacity* at the start of the model run time. The *Capacity* object remains within the loop structure for the remainder of the model run time.

The *BufferCapacity* buffer ensures that the *Capacity* object remains stationary until the start of a period via the *CapacityDelay* method, using the code (SimTalk) shown in Figure D.24. When the object arrives at the *BufferCapacity* buffer, the code checks whether the current time of the simulation, event-controller.SimTime, is equal to the start of a period. The time value for the start of each period is given in the *TableTime* table. If the object arrives at the start of a period, the *BeginPeriodC* variable is assigned a true value, otherwise, the variable is assigned a false value, and a delay time is assigned to the *TimeWaitC*

variable. Suppose the *BeginPeriodC* variable has a true value. In that case, the object is allowed to proceed to the *CapacityControl* station. In contrast, if the *BeginPeriodC* variable has a false value, the object is delayed for a time equal to the value of the *TimeWaitC* variable before it is allowed to proceed to the *CapacityControl* station.

The function of the capacity subsystem is three-fold and achieves these functions via the *CapacityMethod* method. The *CapacityControl* source has a processing time of two seconds to allow the approval and rejection of vaccine platforms to be completed before the code in the *CapacityMethod* method is executed.

The first function of the *CapacityControl* source is to consider the number of connections between an idle platform's manufacturing facility and approved platform products. The number of approved platform products which are connected to an idle manufacturing system is recorded and used to divide the capacity of the idle manufacturing facility between the connected products. The code used to achieve this for the LAV platform is shown in Figure D.25. Suppose a manufacturing facility is idle (e.g. *LAVFacility*). In that case, the code considers two aspects for each vaccine platform, namely: whether the vaccine platform has been approved (e.g. *ProbabilityOfSucces[3,1]* = *true*, refer to Figure D.8); and whether the vaccine platform is connected with the idle manufacturing facility (e.g. *LAVConnect[2,1]* = *true*, refer to Figure D.22). If both these aspects are true, the number of connections (*NumberLAV*) to the idle manufacturing facility is increased by one. As indicated in Figure D.22, a true value is assigned for the platform in the Connect column of the *PlatformConnect* table of the platform's facility with which it is connected. Suppose an idle manufacturing facility is connected to an approved vaccine platform and its capacity will consequently be shifted. In that case, its number of production lines (e.g. *LAVLines*) is reduced to zero, and the entrance of the manufacturing facility is locked (*LAVFacility.entrancelocked* = *true*) to prevent any objects from entering the manufacturing facility.

When the manufacturing of one of the approved and connected vaccine platforms become de-activated, it is required that a delay occurs before the capacity can be shifted to the remaining approved and connected platforms. The second function of the capacity subsystem is to consider whether any previously approved and connected vaccine platforms have been terminated to activate the process of enforcing additional time delays for the remaining manufacturing facilities. Suppose a vaccine platform has been terminated (*RejectedFlagIV* = *true*, refer to Figure D.16) and the vaccine platform is connected with an idle manufacturing facility (*LAVConnect[2,1]* = *true*, refer to Figure D.22). In that case, the process of time delay is activated by assigning a *true* value to the *FacilityFixVariable* (e.g. *LAVFixVariable*). The *RejectedFlagPlatform* variable is assigned a *false* value to prevent the code from activating the process of additional time delay again.

Due to different lengths of time delays for the different manufacturing facilities, it is necessary to record the time of vaccine platform termination to ensure that the appropriate time delay length can be enforced

for each manufacturing facility. This is thus the third function of the capacity subsystem. The code used to achieve this for the LAV platform is shown in Figure D.26. Suppose the *FacilityFixVariable* variable for a platform's manufacturing system has a true value, the current time, Eventcontroller.SimTime, is recorded. Furthermore, the code considers whether any other vaccine platform(s) is connected with the manufacturing facility (*LAVConnect[2,y]* = *true*, refer to Figure D.22) and has been approved (e.g. *LAVConnect[3,y]* = *true*, refer to Figure D.22). If both these conditions are satisfactory for a vaccine platform, a true value is assigned to the platform in the Delay column of the *LAVConnect* table, shown in Figure D.22.

D.4.3 Shifting capacity between platforms

The shifting of capacity to each platform's manufacturing facility is achieved via its subsystem, comprising of a buffer (e.g. *LAVBuffer*) and a station (e.g. *LAVStation*), which operates in a loop structure. As seen in Figure **??**, an object is created at a platform's buffer once approved. After the object has been created at the buffer, the object remains within the loop structure for the remainder of the model run time.

The buffer (e.g. *LAVBuffer*) ensures that the object remains stationary until the start of a period via the *CapacityDelayPlatform* (e.g. *CapacityDelayL*) method, using the code (SimTalk) shown in Figure D.27. When the object arrives at the *PlatformBuffer* (e.g. *LAVBuffer*) buffer, the code checks whether the current time of the simulation, eventcontroller.SimTime, is equal to the start of a period. The time value for the start of each period is given in the *TableTime table*. If the object arrives at the start of a period, the *BeginPeriodCPlatform* (e.g. *BeginPeriodCL*) variable is assigned a *true* value, otherwise, the variable is assigned a *false* value, and a delay time is assigned to the *TimeWaitCPlatform* (e.g. *TimeWaitCL*) variable. Suppose the *BeginPeriodCPlatform* (e.g. *BeginPeriodCL*) variable has a *true* value. In that case, the object is allowed to proceed to the *PlatformStation* (e.g. *LAVStation*) station. In contrast, if the *BeginPeriodCPlatform* (e.g. *BeginPeriodCL*) variable has a *false* value, the object is delayed for a time equal to the value of the *TimeWaitCPlatform* (e.g. *TimeWaitCL*) variable before it is allowed to proceed to the *PlatformStation* (e.g. *LAVStation*) station. When the object is first created, an additional second is added to the entire processing time of the object, and the *CapacityDelayPlatform* (e.g. *CapacityDelayL*) method thus also allows the object to proceed if the eventcontroller.SimTime is equal to the start of a period plus one second.

The code used to control the shift of capacity to a platform's manufacturing facility is comprised of three different sections. The second section is explained first since it controls the initial time delay that is enforced for a manufacturing facility once its vaccine platform has been approved. As an example, the code for the LAV platform is shown in Figure D.28. When a vaccine platform is approved, a time delay, as specified for the platform's manufacturing system in the *DelayTimes* table, is enforced before the manufacturing facility can receive additional capacity from idle manufacturing facilities with which it

is connected. The code searches within the *DelayTimes* table for the appropriate vaccine platform (e.g. "LAV") and ensures that the vaccine platform is both approved (*DelayTimes[3,y]* = true, refer to Figure D.16) and that it has not yet been delayed (*ChangeOverLAVTime* = *false*, refer to Figure D.28). If both the conditions are satisfactory, the delay time is enforced for the platform (e.g. *Wait DelayTimes[2,1]*, refer to Figure D.11). After the delay time has elapsed, the *ChangeOverPlatformTime* (e.g. *ChangeOverLAVTime*) variable is assigned a *true* value to prevent the code from enforcing another time delay for the platform, and the shifting of capacity can proceed.

Capacity can be shifted to a manufacturing facility after the initial time delay has been enforced (e.g. *ChangeOverLAVTime* = *true*, refer to Figure D.28). As previously mentioned, when an idle manufacturing facility is connected with more than one approved vaccine platform, and one or/more of these vaccine platforms become terminated, the appropriate time delay must be enforced for each of the remaining manufacturing facilities before their capacities can be increased. When the object enters the *PlatformStation* (e.g. *LAVStation*) station, the first section of the code in the *PlatformMethod*, shown in Figure D.29, considers whether the platform's manufacturing facility requires a time delay due to the rejection of another vaccine platform. For each platform's manufacturing facility, the code checks whether the facility is idle (e.g. *ProbabilityOfSucces[3,4]* = *false*, refer to Figure D.8) and whether the facility is connected with the considered platform (e.g. *VVConnect[2,3]* = *true*, a section of the *VVConnect* table is shown in Figure D.30). Suppose both the conditions are satisfactory for a platform's manufacturing facility. In that case, the code considers whether a time delay is required to shift the manufacturing facility's capacity from a previously approved and connected platform to the considered platform. If no time delay is required for the shift of a manufacturing facility's capacity to the considered platform (e.g. *VVConnect[4,3]* = *false*, refer to Figure D.30), the number of production lines available to the platform is assigned to the *PlatformFacility* (e.g. *LAVV*) variable. This is further explained when the third section of the code is discussed. If a time delay is required for the shift of a manufacturing facility's capacity to the considered platform (e.g. *VVConnect[4,3]* = *true*, refer to Figure D.30), the *FacilityAndPlatformFix* (e.g. *VVAndLAVFix*) is assigned a *true* value, and the shifting of the capacity is dealt with in the third section of the code.

The third section of the code controls capacity shifting after the required time delays have been enforced and are shown in Figure D.31. The code considers whether the platform has been approved (*ConnectLAV* = *true*, refer to Figure **??**) and whether the initial time delay has been enforced (*ChangeOverLAVTime* = *true*, refer to Figure D.29). If both these conditions are satisfactory, the code considers whether capacity can be shifted to the platform for each manufacturing facility. It is again ensured that the manufacturing facility is idle (e.g. *ProbabilityOfSucces[3,4]* = *false* refer to Figure D.8) and that the manufacturing facility and the considered platform are connected (e.g. *VVConnect[2,3]* = *true*, refer to Figure D.31). If both these conditions are satisfied, the code then considers whether the platform requires a time delay due to the rejection of another platform. If no time delay is required (e.g. *VVAndLAVFix* = *false*, refer

to Figure D.29), the considered platform receives the additional capacity as determined before the initial time delay. If a time delay is required (e.g. *VVAndLAVFix* = *true*, refer to Figure D.29), the code waits until the delay time passes before the additional capacity can be shifted. When the time delay has been enforced, the *FacilityAndPlatformFix* (e.g. *VVAndLAVFix*) is assigned a *false* value to prevent the code from enforcing the delay again. The additional capacity is shifted to the considered platform (e.g. *LAV1* := *VVFacility.xdim/NumberVV*, refer to Figure D.31). The capacity shift is controlled using the different sections of code since the initial time delay and additional time delay, due to the termination of another vaccine platform, may not necessarily start at the same time, and the additional capacity shift may have to occur at a later stage than the initial time delay. If the capacity shifts are not controlled separately, all required capacity shifts will occur once the first delay has been enforced.

For example: Consider a configuration in which both the LAV platform and the IV platform are connected with the RNA platform's facility, and both the LAV platform and the IV platform are approved at the start of period 1, while the facility for the RNA platform remains idle. The LAV platform has a delay of two periods for the shifting of capacity and can thus only receive additional RNA production lines at the start of period three, while the IV platform has a delay of one period for the shifting of capacity and can thus only receive the additional RNA production lines at the start of period two. If, for example, the IV platform's manufacturing becomes de-activated at the start of period two, the LAV platform can receive the additional RNA production lines originally assigned to the IV platform after a delay of two periods for the shifting of capacity has occurred. The LAV platform can thus only receive the additional RNA production lines at the start of period four. If the two different types of capacity shifts are not dealt with independently, all the RNA production lines will be shifted to the LAV platform at the start of period three, when then the initially assigned RNA capacity is shifted to the LAV platform.

```
If @.name = "LAVPlatform" then
    ThroughputLAVVaccines := ThroughputLAVVaccines + 10000
end
If @.name = "IVPlatform" then
    ThroughputIVVaccines := ThroughputIVVaccines + 10000
end
If @.name = "SPPlatform" then
    ThroughputSPVaccines := ThroughputSPVaccines + 10000
end
If @.name = "VVPlatform" then
    ThroughputVVVaccines := ThroughputVVVaccines + 10000
end
If @.name = "DNAPlatform" then
    ThroughputDNAVaccines := ThroughputDNAVaccines + 10000
    end
If @.name = "RNAPlatform" then
    ThroughputRNAVaccines := ThroughputRNAVaccines + 10000
    end

If ConnectLAV = false and @.name = "LAVPlatform" then
    ThroughputVaccines := Throughputvaccines - UnitCount
end
If ConnectIV = false and @.name = "IVPlatform" then
    ThroughputVaccines := Throughputvaccines - UnitCount
end
If ConnectSP = false and @.name = "SPPlatform" then
    ThroughputVaccines := Throughputvaccines - UnitCount
end
If ConnectVV = false and @.name = "VVPlatform" then
    ThroughputVaccines := Throughputvaccines - UnitCount
end
If ConnectDNA = false and @.name = "DNAPlatform" then
    ThroughputVaccines := Throughputvaccines - UnitCount
    end
If ConnectRNA = false and @.name = "RNAPlatform" then
    ThroughputVaccines := Throughputvaccines - UnitCount
    end
```

Figure D.21: Code used to count the throughput of vaccine products

	string 1	boolean 2	boolean 3	boolean 4
string	Platform	Configuration	Connect	Delay
1	IV	true	true	true
2	SP	true	false	false
3	VV	false	false	false
4	DNA	false	false	false
5	RNA	true	false	false

Figure D.22: A section of the *LAVConnect* table

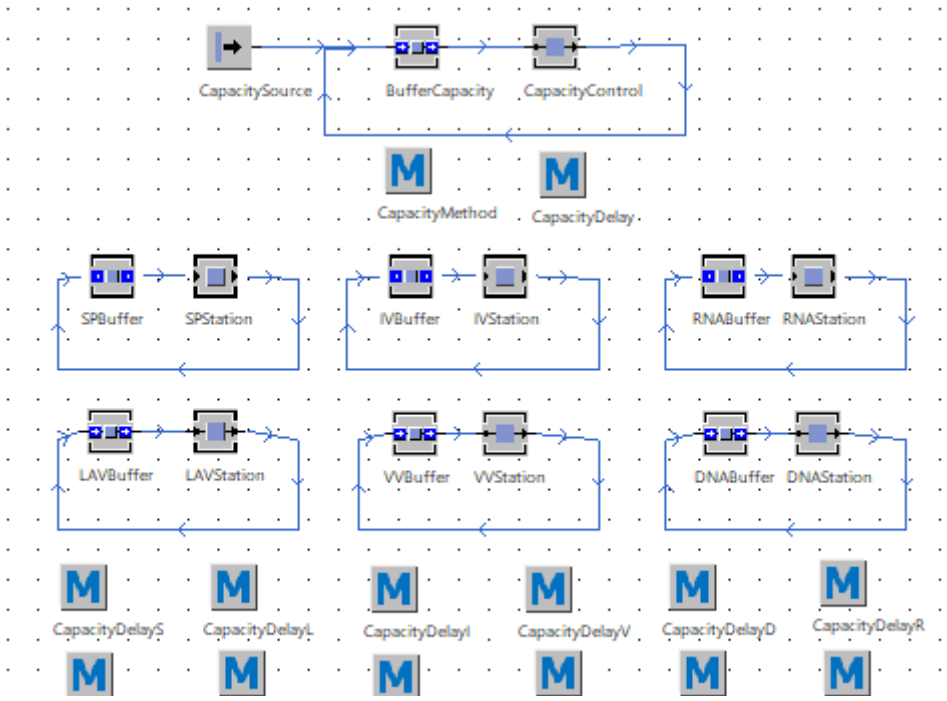

Figure D.23: Representation of the shifting of manufacturing facilities' capacity

```
for var y:= 1 to TableTime.ydim
    if eventController.simtime = TableTime[1,y] then
        BeginPeriodC := true
        exitloop
    elseif eventController.simtime < TableTime[1,y] then
        BeginPeriodC := false
        TimeWaitC := TableTime[1,y] - eventController.simTime
            exitloop
         end
    next

if BeginPeriodC = true then
    @.move
else wait timewaitC
    @.move
    end
```

Figure D.24: Code used in *CapacityDelay* to delay the Capacity object

```
If ProbabilityOfSucces[3,1] = false then
    If LAVConnect[2,1] = true and ProbabilityOfSucces[3,2] = true then
        NumberLAV := NumberLAV + 1
        LAVEntranceLock := True
        LAVLines := 0
        LAVConnect[3,1] := true
    end
    If LAVConnect[2,1] = true and RejectedFlagIV = true then
        LAVFixVariable := true
        LAVConnect[3,1] := false
    end
    If LAVConnect[2,5] = true and ProbabilityOfSucces[3,6] = true then
        NumberLAV := NumberLAV + 1
        LAVEntranceLock := True
        LAVLines := 0
        LAVConnect[3,5] := true
    end
    If LAVConnect[2,5] = true and RejectedFlagRNA = true then
        LAVFixVariable := true
        LAVConnect[3,5] := false
    end
    If LAVConnect[2,3] = true and ProbabilityOfSucces[3,4] = true then
        NumberLAV := NumberLAV + 1
        LAVEntranceLock := True
        LAVLines := 0
        LAVConnect[3,3] := true
    end
    If LAVConnect[2,3] = true and RejectedFlagVV = true then
        LAVFixVariable := true
        LAVConnect[3,3] := false
    end
    If LAVConnect[2,4] = true and ProbabilityOfSucces[3,5] = true then
        NumberLAV := NumberLAV + 1
        LAVEntranceLock := True
        LAVLines := 0
        LAVConnect[3,4] := true
    end
    If LAVConnect[2,4] = true and RejectedFlagDNA = true then
        LAVFixVariable := true
        LAVConnect[3,4] := false
    end
    If LAVConnect[2,2] = true and ProbabilityOfSucces[3,3] = true then
        NumberLAV := NumberLAV +1
        LAVEntranceLock := True
        LAVLines := 0
        LAVConnect[3,2] := true
    end
    If LAVConnect[2,2] = true and RejectedFlagSP = true then
        LAVFixVariable := true
        LAVConnect[3,2] := false
    end
    else NumberLAV:= 0
end
If LAVEntranceLock = true then
    LAVFacility.entrancelocked := true
end
```

Figure D.25: Code used to count the number of connections for an idle LAV manufacturing facility

```
If LAVFixVariable = true then
    for local y:= 1 to LAVConnect.ydim
        If LAVConnect[2, y] = true and LAVConnect[3, y] = true then
            LAVConnect[4, y] := true
            LAVFixTime := eventController.simTime
        end
    next
end
```

Figure D.26: Code used to record the time when a platform, previously connected to the LAV manufacturing facility, is rejected

```
for var y:= 1 to TableTime.ydim
    if eventController.simtime = TableTime[1,y] then
        BeginPeriodCL := true
        exitloop
    elseif eventcontroller.simTime = TableTime[1,y] +0:01 then
        BeginPeriodCL := true
        exitloop
    elseif eventController.simtime < TableTime[1,y] then
        BeginPeriodCL := false
        TimeWaitCL := TableTime[1,y] - eventController.simTime
            exitloop
         end
    next

if BeginPeriodCL = true then
    @.move
else wait timewaitCL
    @.move
    end
```

Figure D.27: Code used in *CapacityDelayL* to delay the object

```
For local y:= 1 to DelayTimes.ydim
    If DelayTimes[1,y] = "LAV" then
        If DelayTimes[3,y] = true then
            If DelayTimes[4,y] = false then
                If ChangeOverLAVTime = false then
                    wait DelayTimes[2,y]
                    LAVEntranceLock := false
                    ChangeOverLAVTime := true
                end
            end
        end
        exitloop
    end
next
```

Figure D.28: Code used in *LAVMethod* to control the initial time delay for the *LAVFacility*

```
if VVConnect[2,3] = true and ProbabilityOfSucces[3,4] = false then
    If VVConnect[4,3] = false and VVAndLAVFix = false then
        LAVV := VVFacility.xdim/NumberVV
    end
    If VVConnect[4,3] = true then
            VVAndLAVFix := true
            VVConnect[4,3] := false
    end
end

if IVConnect[2,1] = true and ProbabilityOfSucces[3,2] = false then
    If IVConnect[4,1] = false and IVAndLAVFix = false then
        LAVI := IVFacility.xdim/NumberIV
    end
    If IVConnect[4,1] = true then
            IVAndLAVFix := true
            IVConnect[4,1] := false
    end
end

if RNAConnect[2,5] = true and ProbabilityOfSucces[3,6] = false then
    If RNAConnect[4,5] = false and RNAAndLAVFix = false then
        LAVR := RNAFacility.xdim/NumberRNA
    end
    If RNAConnect[4,5] = true then
            RNAAndLAVFix := true
            RNAConnect[4,5] := false
    end
end

if SPConnect[2,2] = true and ProbabilityOfSucces[3,3] = false then
    If SPConnect[4,2] = false and SPAndLAVFix = false then
        LAVS := SPFacility.xdim/NumberSP
    end
    If SPConnect[4,2] = true then
            SPAndLAVFix := true
            SPConnect[4,2] := false
    end
end

if DNAConnect[2,2] = true and ProbabilityOfSucces[3,5] = false then
    If DNAConnect[4,2] = false and DNAAndLAVFix = false then
        LAVD := DNAFacility.xdim/NumberDNA
    end
    If DNAConnect[4,2] = true then
            DNAAndLAVFix := true
            DNAConnect[4,2] := false
    end
end
```

Figure D.29: Code used in *LAVMethod* to determine whether time delays are required due to platform termination

string 1	boolean 2	boolean 3	boolean 4
Platform	Configuration	Connect	Delay
IV	false	false	false
SP	false	false	false
LAV	true	false	false
DNA	false	false	false
RNA	false	false	false

Figure D.30: Section of the *VVConnect* table

```
If ChangeOverLAVTime = true and ConnectLAV = true then
    if VVConnect[2,3] = true and ProbabilityOfSucces[3,4] = false then
    If VVAndLAVFix = false
        LAV1 := LAVV
    end
    If VVAndLAVFix = true then
        If eventcontroller.simTime = VVFixTime + LAVTime +0:05 then
            VVAndLAVFix := false
            LAV1 := VVFacility.xdim/NumberVV
        end
    end
        else LAV1 := 0
    end
    if IVConnect[2,1] = true and ProbabilityOfSucces[3,2] = false then
    If IVAndLAVFix = false
        LAV2 := LAVI
    end
    If IVAndLAVFix = true then
        If eventcontroller.simTime = IVFixTime + LAVTime +0:05 then
            IVAndLAVFix := false
            LAV2 := IVFacility.xdim/NumberIV
        end
    end
        else LAV2 := 0
    end
    if SPConnect[2,2] = true and ProbabilityOfSucces[3,3] = false then
    If SPAndLAVFix = false
        LAV3 := LAVS
    end
    If SPAndLAVFix = true then
        If eventcontroller.simTime = SPFixTime + LAVTime +0:05 then
            SPAndLAVFix := false
            LAV3 := SPFacility.xdim/NumberVV
        end
    end
        else LAV3 := 0
    end
    if DNAConnect[2,4] = true and ProbabilityOfSucces[3,5] = false then
    If DNAAndLAVFix = false
        LAV4 := LAVD
    end
    If DNAAndLAVFix = true then
        If eventcontroller.simTime = DNAFixTime + LAVTime +0:05 then
            DNAAndLAVFix := false
            LAV4 := DNAFacility.xdim/NumberDNA
        end
    end
        else LAV4 := 0
    end
    if RNAConnect[2,5] = true and ProbabilityOfSucces[3,6] = false then
    If RNAAndLAVFix = false
        LAV5 := LAVR
    end
    If RNAAndLAVFix = true then
        If eventcontroller.simTime = RNAFixTime + LAVTime + 0:05 then
            RNAAndLAVFix := false
            LAV5 := RNAFacility.xdim/NumberRNA
        end
    end
        else LAV5 := 0
        end
        LAVEntranceLock := false
        LAVLines := Lines[2,1] + LAV1 + LAV2 + LAV3 + LAV4 + LAV5
        If LAVLines > Lines[2,1] then
            LAVFacility.entrancelocked := true
            If LAVFacility.NumMu = 0 then
    LAVFacility.xdim := LAVLines
    LAVFacility.entrancelocked := LAVEntranceLock
            end
            else LAVFacility.entrancelocked := LAVEntranceLock
            end
    LAVShift[1,LAVShift.ydim+1] := eventcontroller.simTime
    LAVShift[2,LAVShift.ydim] := LAV1
    LAVShift[3,LAVShift.ydim] := LAV2
    LAVShift[4,LAVShift.ydim] := LAV3
    LAVShift[5,LAVShift.ydim] := LAV4
    LAVShift[6,LAVShift.ydim] := LAV5
end
@.move
```

Figure D.31: Code used in *LAVMethod* to control the shift of capacity for the *LAVFacility*

D.5 Variables for troubleshooting

Two groups of variables are controlled and recorded merely for troubleshooting. The first group of such variables are recorded to verify that vaccine platforms are only approved if the random number U is smaller than its probability of success value and only rejected if the random number *M* is smaller than its probability of failure value. Record is kept of the random number *U*, and *M* values, the probability of success, and the probability of failure values at the start of each period. At the start of a period, the current time, along with all of these values for a platform, are inscribed in a table (e.g. *LTable*, which is the table for the LAV platform's values), and the code used to achieve this is shown in Figure D.5. Figure D.32 presents a section of the *LTable*. The Eventcontroller.SimTime at the start of a period is assigned to the *Time* column (*LTable[1,y]*). This is the random number used in the vaccine approval subsystem (refer to Figure D.5).

	time 1	real 2	real 3	integer 4	integer 5
string		Random L	POS	Random M	POF
1	1.0000	1.00	100.00	36	0
2	30:00:00:01.0000	57.00	0.00	20	0
3	60:00:00:01.0000	77.00	0.00	38	0
4	90:00:00:01.0000	97.00	0.00	84	100
5	120:00:00:01.0000	77.00	0.00	25	0
6	150:00:00:01.0000	70.00	0.00	15	0
7	180:00:00:01.0000	98.00	0.00	51	0

Figure D.32: Section of the *LTable*

For example, *L* (for the LAV platform) is assigned to the *Random L* column (*LTable[2,y]*), the probability of success value is assigned to the *POS* column (*LTable[3,y]*), the random number for the rejection subsystem (*M*) is assigned to the *Random M* column (*LTable[4,y]*), and the probability of failure value is assigned to the *POF* column (*LTable[5,y]*)

The second group of variables, recorded only for the purpose of troubleshooting, are recorded to verify that the shifting of capacity between platforms occurs as expected. Each platform has five variables representing the number of production lines received from the five other platforms. For example, the LAV platform has the variables *LAV1*, *LAV2*, *LAV3*, *LAV4*, and *LAV5*, which represent the number of production lines received from the IV, SP, VV, DNA, and RNA platform, respectively. After the initial time delay for a platform has been enforced, the values for each of the five variables for the platform are recorded at the start of each period and inscribed in a table (e.g. *LAVShift* for the LAV platform). The code used to inscribe the values of the variables for the LAV platform is shown in Figure D.31. In Figure D.16, the variables' values are set to zero since the manufacturing for the platform has been de-activated, and the

additional production lines are no longer available to the platform. A section of the *LAVShift* table is shown in Figure D.33.

	time 1	integer 2	integer 3	integer 4	integer 5	integer 6
string	Time	LAV1	LAV2	LAV3	LAV4	LAV5
1	30:00:00:00.0000	0	0	10	0	0
2	30:00:00:03.0000	0	0	10	0	0
3	60:00:00:03.0000	0	0	10	0	0

Figure D.33: A section of the *LAVShift* table

The Eventcontroller.SimTime at the start of a period is assigned to the *Time* column (*LAVShift[1,y]*), while the values of *LAV1*, *LAV2*, *LAV3*, *LAV4*, and *LAV5* are assigned to the appropriate columns.

Appendix E

Verification tests

The description and results for the verification tests performed for the rejection section, manufacturing system, capacity shift and time delay, and the types of equipment facilities are provided in this Appendix.

E.1 Rejection section

The rejection section makes use of pre-determined probability of failure values to control the rejection of previously approved vaccine platforms. At the start of a period, a random number is generated for each vaccine platform and compared to its probability of failure value.

If a platform is rejected, the rejection section adds to the inscription in the *ApprovedVaccineList* table by indicating its status as Rejected and the time at which it was rejected. Record is kept of the number of vaccine products per platform that would have been approved if the model considered the approval of vaccines at the individual product level. When a platform is rejected, the *PlatformApprovedCnt* variable is reduced by one. The manufacturing of a platform is only de-activated if the *PlatformApprovedCnt* is zero after the variable has been reduced by one. The rejection section controls the following variables: *ProbabilityOfFailure[3,y]*, *PlatformApprovedCnt*, *ApprovedVaccineCnt*, *ConnectPlatform*, and *ProbabilityOfFailure[3,y]*. When a platform is rejected, and the *PlatformApprovedCnt* is zero, the following variables are assigned a false value: *ProbabilityOfFailure[3,y]*, *ConnectPlatform*, and *ApprovedFlagPlatform*. The *ApprovedVaccineCnt* variable is reduced by one, and since the platform is no longer approved, the platform's probability of failure value is reduced to zero.

The rejection section was verified via two approaches. The first approach involved manipulating both the random number, referred to as *M* in the results, and the probability of failure values for a platform. The second approach involved the manipulation of only the probability of failure value for the platform, while the random number was allowed to be generated by the simulation software.

E.1.1 Approach one

The random number *M* and probability of failure values for a platform were manipulated to create different scenarios for which the outcome can be predicted and verified. The results obtained for the different scenarios for the RNA platform are shown in Table E.1.

Table E.1: Results for RNA platform for manual verification of rejection section

Case 1		
Conditions	**Expected Results**	**Results**
RNA approved	*ConnectRNA* = *false*	✓
Plan A: *POFRNA* = 100%	*ApprovedVaccineList*: *RNAPlatform* Rejected	✓
M = 45	*ApprovedVaccineCnt* = 0	✓
Plan B: *POFRNA* = 75%	*ApprovedFlagRNA* = *false*	✓
M = 45	*RNAApprovedCnt* = 1	✓
Plan C: *POFRNA* = 50%	*POFRNA* = 0	✓
M = 45		
Case 2		
Conditions	**Expected Results**	**Results**
RNA approved	*ConnectRNA* = *true*	✓
Plan A: *POFRNA* = 50%	*ApprovedVaccineList*: *RNAPlatform* Approved	✓
M = 50	*ApprovedVaccineCnt* = 1	✓
Plan B: *POFRNA* = 25%	*ApprovedFlagRNA* = *true*	✓
M = 45	*RNAApprovedCnt* = 1	✓
Plan C: *POFRNA* = 0%	*POFRNA* = 50 (Plan A)	✓
M = 45	*POFRNA* = 45 (Plan B & C)	✓

Case one represents the scenario where the RNA platform, which is already approved, has a random number *M* smaller than its probability of failure value, and it is thus expected to be rejected. The probability of success values were also manipulated to ensure that the *PlatformApprovedCnt* does not exceed one to allow the de-activation of a platform's manufacturing. The platform rejection should result in assigning a *false* value to the following variables: *ApprovedFlagRNA* and *ConnectRNA*. Both the *RNAApprovedCn* and *ApprovedVaccineCnt* variables should be reduced by one, and the platform should receive a probability of failure value of zero.

Case two represents where the RNA platform, which is already approved, has a random number *M* larger than its probability of failure value, and it is thus expected to remain approved. No changes to any variables are expected.

E.1.2 Approach two

In this approach, the random number was not manipulated, and the results are shown in Table E.2. For case one, the probability of failure value was set to 100% for all the platforms, and it is expected that

Table E.2: Results for verification of rejection section with no manipulation

Case 1				
Platform	**POF**	**U**	**Status**	**Action**
LAV	100	57	Rejected	No longer approved
IV	100	42	Rejected	No longer approved
SP	100	24	Rejected	No longer approved
VV	100	10	Rejected	No longer approved
DNA	100	22	Rejected	No longer approved
RNA	100	23	Rejected	No longer approved
Case 2				
Period 1				
Platform	**POF**	**M**	**Status**	**Action**
LAV	25	1	Rejected	No longer approved
IV	25	55	Not rejected	Remains approved
SP	25	33	Not rejected	Remains approved
VV	25	99	Not rejected	Remains approved
DNA	25	93	Not rejected	Remains approved
RNA	25	14	Rejected	No longer approved
Period 2				
Platform	**POF**	**M**	**Status**	**Action**
LAV	0	20	Already rejected	Remains rejected
IV	25	51	Not rejected	Remains approved
SP	25	33	Not rejected	Remains approved
VV	25	61	Not rejected	Remains approved
DNA	25	8	Rejected	No longer approved
RNA	0	74	Already rejected	Remains rejected
Period 3				
Platform	**POF**	**M**	**Status**	**Action**
LAV	0	57	Already rejected	Remains rejected
IV	25	42	Not rejected	Remains approved
SP	25	24	Rejected	No longer approved
VV	25	10	Rejected	No longer approved
DNA	0	22	Already rejected	Remains rejected
RNA	0	23	Already rejected	Remains rejected

all the platforms will be rejected, given that the random number is smaller than 100. For case two, the simulation was allowed to run over three consecutive periods with the probability of failure value initially set at 25%. All platforms with a random number smaller than their probability of failure value are expected to be rejected at the start of a period. A rejected platform is assigned a probability of failure value of zero and cannot be rejected in the following periods regardless of the value of the random number. If a platform is rejected, the platform will be added no longer be approved, while the vaccine will remain approved if it is not rejected. After a platform has been rejected, the platform will remain rejected for the remainder of the run.

E.2 Manufacturing system

The manufacturing system of the vaccine platforms is represented by six manufacturing facilities, one for each vaccine platform. The manufacturing subsection for a platform remains idle until the platform is approved, thereafter, the line is in operation until the unlikely case that the vaccine platform is rejected. The manufacturing subsections control the *ThroughputCnt* variable. Once a platform's manufacturing has been activated, the platform's source is expected to start creating objects, and the facility should process these objects. For each object exiting the manufacturing system, the *ThroughputCnt* is incremented by 10 000.

The manufacturing system was verified via five approaches. The first approach involved the manipulation of the *ConnectPlatform* variable for a platform to verify that manufacturing occurs as expected after the approval of a platform. The second approach involved manipulating the random number *U* and probability of success values for a platform to verify that the approval section, in conjunction with the manufacturing system, performs as expected. The third approach involved the manipulation of the random number *M* and probability of failure values for a platform to verify that the rejection section, in conjunction with the manufacturing system, performs as expected. The fourth approach involved considering the number of products per platform that would have been approved and verifying that the manufacturing of a platform is only de-activated when the *PlatformApprovedCnt* is zero. The final approach involved verifying the manufacturing system in conjunction with the approval and rejection section with no manipulation of any values or variables.

E.2.1 Approach one

The results for approach one are given in Table E.3. The manufacturing of a platform was activated by assigning a true value to the *ConnectPlatform* variable for a platform. Case one, three, five, seven, nine, and eleven represent the scenario where the platform is approved at the start of a period, and it is expected that the source will start creating objects, the facility will process the objects and that for each object the

ThroughputCnt will be incremented by 10 000. Cases two, four, six, eight, ten, and twelve represent the case where the platform, which is already approved, is rejected at the start of a period. It is expected that the source will stop creating objects, the facility's entrance will become locked, and the *ThroughputCnt* variable will remain constant.

Table E.3: Results for manual verification of manufacturing subsections

Case 1		
Conditions	**Expected Results**	**Results**
ConnectLAV = *true*	*LAVDemand* source creates objects	✓
	LAVFacility processes objects	✓
	ThroughputCnt: +10000 for every object	✓
Case 2		
Conditions	**Expected Results**	**Results**
LAV approved	*LAVDemand* source stops creating objects	✓
ConnectLAV = *false*	LAVFacility stops processing objects	✓
	ThroughputCnt: remains constant	✓
Case 3		
Conditions	**Expected Results**	**Results**
ConnectIV = *true*	*IVDemand* source creates objects	✓
	IVFacility processes objects	✓
	ThroughputCnt: +10000 for every object	✓
Case 4		
Conditions	**Expected Results**	**Results**
IV approved	*IVDemand* source stops creating objects	✓
ConnectIV = *false*	*IVFacility* stops processing objects	✓
	ThroughputCnt: remains constant	✓
Case 5		
Conditions	**Expected Results**	**Results**
ConnectVV = *true*	*VVDemand* source creates objects	✓
	VVFacility processes objects	✓
	ThroughputCnt: +10000 for every object	✓
Case 6		
Conditions	**Expected Results**	**Results**
VV approved	*VVDemand* source stops creating objects	✓
ConnectVV = *false*	*VVFacility* stops processing objects	✓
	ThroughputCnt: remains constant	✓
Case 7		
Conditions	**Expected Results**	**Results**
ConnectSP = *true*	*SPDemand* source creates objects	✓
	SPFacility processes objects	✓
	ThroughputCnt: +10000 for every object	✓
Case 8		
Conditions	**Expected Results**	**Results**

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Conditions	**Expected Results**	**Results**
SP approved	*SPDemand* source stops creating objects	✓
ConnectSP = *false*	*SPFacility* stops processing objects	✓
	ThroughputCnt: remains constant	✓
Case 9		
Conditions	**Expected Results**	**Results**
ConnectDNA = *true*	*DNADemand* source creates objects	✓
	DNAFacility processes objects	✓
	ThroughputCnt: +10000 for every object	✓
Case 10		
Conditions	**Expected Results**	**Results**
DNA approved	*DNADemand* source stops creating objects	✓
ConnectDNA = *false*	*DNAFacility* stops processing objects	✓
	ThroughputCnt: remains constant	✓
Case 11		
Conditions	**Expected Results**	**Results**
ConnectRNA = *true*	*RNADemand* source creates objects	✓
	RNAFacility processes objects	✓
	ThroughputCnt: +10000 for every object	✓
Case 12		
Conditions	**Expected Results**	**Results**
RNA approved	*RNADemand* source stops creating objects	✓
ConnectRNA = *false*	*RNAFacility* stops processing objects	✓
	ThroughputCnt: remains constant	✓

E.2.2 Approach two

The manufacturing system was verified with the approval section incorporated. The random number U and the probability of success values were manipulated to create different scenarios for which the outcome can be predicted and verified. The results obtained for the different scenarios for the LAV platform are shown in Table E.4.

Case one represents the scenario where the LAV platform's random number U is smaller than its probability of success value, and it is thus expected that the LAV platform will be approved and its manufacturing will begin. A *true* value should be assigned to the *ConnectLAV* variable, and the name and time of approval should be inscribed in the *ApprovedVaccineList* table. Both the *ApprovedVaccineCnt* and *LAVApprovedCnt* should be incremented by one. It is expected that the source should start creating objects, the facility should process the objects, and the throughput should be incremented by 10 000 for each object that exits the manufacturing system.

Case two represents the scenario where the LAV platform's random number U is larger than its probability of success value, and it is thus expected that the LAV platform will not be approved and its manufacturing

Table E.4: Results for LAV platform for manual verification of manufacturing subsection in conjunction with approval section

Case 1		
Conditions	**Expected Results**	**Results**
Plan A: *POSLAV* = 100%	*ConnectLAV* = *true*	✓
U = 45	*ApprovedVaccineCnt* = 1	✓
Plan B: *POSLAV* = 75%	*ApprovedVaccineList*: *LAVPlatform* Approved	✓
U = 45	*LAVApprovedCnt* = 1	✓
Plan C: *POSLAV* = 50%	*LAVDemand* source creates objects	✓
U = 45	*LAVFacility* processes objects	✓
	ThroughputCnt: +10000 for every object	✓
Case 2		
Conditions	**Expected Results**	**Results**
Plan A: *POSLAV* = 50%	*ConnectLAV* = *false*	✓
U = 50	*ApprovedVaccineCnt* = 0	✓
Plan B: *POSLAV* = 25%	No new entry in *ApprovedVaccineList*	✓
U = 45	*LAVApprovedCnt* = 0	
Plan C: *POSLAV* = 0%	*LAVDemand* source does not create objects	✓
U = 45	*LAVFacility* does not process objects	✓
	ThroughputCnt: remains constant	✓

will remain idle. No changes are expected to occur to any variables

E.2.3 Approach three

The manufacturing system was verified with the rejection section incorporated. The random number *M* and the probability of failure values were manipulated to create different scenarios for which the outcome can be predicted and verified. The results obtained for the different scenarios for the LAV platform are shown in Table E.5.

Case one represents the scenario where the LAV platform, which is already approved, has a random number *M* that is smaller than its probability of failure value, and it is thus expected to be rejected and its manufacturing de-activated. A *false* value should be assigned to the *ConnectLAV* variable, and the name and time of rejection should be inscribed in the *ApprovedVaccineList* table. Both the *ApprovedVaccineCnt* and *LAVApprovedCnt* should be reduced by one. It is expected that the source should stop creating objects, the facility's entrance should be locked, and the throughput should remain constant.

Case two represents the scenario where the LAV platform, which is already approved, has a random number *M* that is larger than its probability of failure value and is expected to remain approved. No changes to any variables are expected.

Table E.5: Results for LAV platform for manual verification of manufacturing subsection in conjunction with rejection section

Case 1		
Conditions	**Expected Results**	**Results**
LAV approved	ConnectLAV = false	✓
Plan A: POFLAV = 100%	ApprovedVaccineCnt = 0	✓
M = 45	ApprovedVaccineList: LAVPlatform Rejected	✓
Plan B: POFLAV = 75%	LAVApprovedCnt = 0	✓
M = 45	LAVDemand source stops creating objects	✓
Plan C: POFLAV = 50%	LAVFacility is entrancelocked	✓
M = 45	ThroughputCnt: remains constant	
Case 2		
Conditions	**Expected Results**	**Results**
LAV approved	ConnectLAV = true	✓
Plan A: POFLAV = 50%	ApprovedVaccineCnt = 1	✓
M = 50	ApprovedVaccineList: LAVPlatform Approved	✓
Plan B: POFLAV = 25%	LAVApprovedCnt = 1	✓
M = 45	LAVDemand source continues creating objects	✓
Plan C: POFLAV = 0%	LAVFacility continues processing objects	✓
M = 45	ThroughputCnt: +10000 for every object	

E.2.4 Approach four

For this approach, both the approval and rejection systems are considered in conjunction with the manufacturing system. The random numbers U and M and the probability of success and probability of failure values are manipulated. The number of products per platform that could be approved when considering the approval of vaccines on the product level is recorded. Different scenarios are created to verify that the manufacturing of a platform only occurs when no product for the platform is approved.

Case one, presented in Table E.7, considers the approval, rejection, and manufacturing of the LAV platform over three consecutive periods.

Table E.6: Case 1 for LAV platform for manual verification of manufacturing subsection in conjunction with both approval and rejection section

Period 1		
Conditions	**Expected Results**	**Results**
POSLAV = 100%	*ConnectLAV* = *true*	✓
POFLAV = 0%	*ApprovedVaccineCnt* = 1	✓
U = 45	*LAVApprovedCnt* = 1	✓
M = 45	*ApprovedVaccineList*: *LAVPlatform* Approved	✓
	LAVDemand source creates objects	✓
	LAVFacility processes objects	✓
Period 2		
Conditions	**Expected Results**	**Results**
POSLAV = 0%	*ConnectLAV* = *false*	✓
POFLAV = 100%	*ApprovedVaccineCnt* = 0	✓
U = 45	*LAVApprovedCnt* = 0	✓
M = 45	*ApprovedVaccineList*: *LAVPlatform* Rejected	✓
	LAVDemand stops creating objects	✓
	LAVFacility: entrancelocked	✓
Period 3		
Conditions	**Expected Results**	**Results**
POSLAV = 100%	*ConnectLAV* = *true*	✓
POFLAV = 0%	*ApprovedVaccineCnt* = 1	✓
U = 45	*LAVApprovedCnt* = 1	✓
M = 45	*ApprovedVaccineList*: *LAVPlatform* Approved	✓
	LAVDemand source creates objects	✓
	LAVFacility processes objects	✓

At the start of period one, the random number U is smaller than the probability of success value, and the LAV platform is expected to be approved. The *LAVApprovedCnt* should be incremented by one. The LAV platform has a probability of zero since it has not previously been approved. At the start of period two, the random number M is smaller than the probability of failure value, and it is expected that the *LAVApprovedCnt* will be reduced by one. The *LAVApprovedCnt* variable should thus be zero, and it is

expected that the LAV platform will be rejected. At the start of period three, the random number U is smaller than the probability of success value, and the LAV platform is expected to be approved. The same results are expected as that of period one.

Case two, presented in Table **??**, considers the approval, rejection, and manufacturing of the LAV platform over three consecutive periods. At the start of period one, the random number U is smaller than

Table E.7: Case 2 for LAV platform for manual verification of manufacturing subsection in conjunction with both approval and rejection section

Period 1		
Conditions	**Expected Results**	**Results**
POSLAV = 100%	*ConnectLAV* = *true*	✓
POFLAV = 0%	*ApprovedVaccineCnt* = 1	✓
U = 45	*LAVApprovedCnt* = 1	✓
M = 45	*ApprovedVaccineList*: *LAVPlatform* Approved	✓
	LAVDemand source creates objects	✓
	LAVFacility processes objects	✓
Period 2		
Conditions	**Expected Results**	**Results**
POSLAV = 100%	*ConnectLAV* = *true*	✓
POFLAV = 0%	*ApprovedVaccineCnt* = 1	✓
U = 45	*LAVApprovedCnt* = 2	✓
M = 45	No new entry in *ApprovedVaccineList*	✓
	LAVDemand continues creating objects	✓
	LAVFacility continues processing objects	✓
Period 3		
Conditions	**Expected Results**	**Results**
POSLAV = 0%	*ConnectLAV* = *true*	✓
POFLAV = 100%	*ApprovedVaccineCnt* = 1	✓
U = 45	*LAVApprovedCnt* = 1	✓
M = 45	*ApprovedVaccineList*: *LAVPlatform* Rejected	✓
	LAVDemand continues creating objects	✓
	LAVFacility continues processing objects	✓

the probability of success value, and the LAV platform is expected to be approved. The *LAVApprovedCnt* should be incremented by one. The LAV platform has a probability of zero since it has not previously been approved. At the start of period two, the random number U is again smaller than the probability of success value. The platform is not approved again since a LAV platform product has already been approved however, the *LAVApprovedCnt* should still be incremented by one. The probability of failure value is set at zero, although it will have a value in the simulation software. This is done merely to indicate that the vaccine platform will not be rejected during this period. At the start of period three, the random number M is smaller than the probability of failure value, and it is expected that the *LAVApprovedCnt* will be

reduced by one. The *LAVApprovedCnt* variable should thus have a value of one, and it is expected that the LAV platform's manufacturing will not be deactivated.

Case three, presented in Table E.8, considers the approval, rejection, and manufacturing of the LAV platform over two consecutive periods. At the start of period one, the random number *U* is smaller than

Table E.8: Case 3 for LAV platform for manual verification of manufacturing subsection in conjunction with both approval and rejection section

Period 1		
Conditions	**Expected Results**	**Results**
POSLAV = 100%	*ConnectLAV* = *true*	✓
POFLAV = 0%	*ApprovedVaccineCnt* = 1	✓
U = 45	*LAVApprovedCnt* = 1	✓
M = 45	*ApprovedVaccineList*: *LAVPlatform* Approved	✓
	LAVDemand source creates objects	✓
	LAVFacility processes objects	✓
Period 2		
Conditions	**Expected Results**	**Results**
POSLAV = 100%	*ConnectLAV* = *true*	✓
POFLAV = 100%	*ApprovedVaccineCnt* = 0	✓
U = 45	*LAVApprovedCnt* = 1	✓
M = 45	*ApprovedVaccineList*: *LAVPlatform* Rejected	✓
	LAVDemand continues creating objects	✓
	LAVFacility continues processing objects	✓

the probability of success value, and the LAV platform is expected to be approved. The *LAVApprovedCnt* should be incremented by one. The LAV platform has a probability of zero since it has not previously been approved. At the start of period two, both the random number *U* is smaller than the probability of success value and the random number *M* is smaller than the probability of failure value. The *LAVApprovedCnt* variable is expected to have a value of one, and the LAV platform's manufacturing should not be deactivated.

E.2.5 Approach five

Lastly, it was ensured that the production lines, in combination with the approval and rejection section, work when it is allowed to run automatically (no manipulation of values). It was verified that when a platform is approved at the start of a period (random number larger than POS value), the platform's manufacturing subsection is activated and that the manufacturing subsection continues to operate until the vaccine platform is rejected. The results for approach five are given in Table E.9.

Table E.9: Results for LAV platform for verification of manufacturing subsection with no manipulation

Period 5						
Platform	**POS**	**U**	**POF**	**M**	**Status**	**Action**
LAV	0	70	0	15	Not approved	Manufacturing idle
IV	20	80	0	84	Not approved	Manufacturing idle
SP	29	90	0	57	Not approved	Manufacturing idle
VV	8	71	0	12	Not approved	Manufacturing idle
DNA	16	67	0	56	Not approved	Manufacturing idle
RNA	22	28	0	66	Not approved	Manufacturing idle
Period 6						
Platform	**POS**	**U**	**POF**	**M**	**Status**	**Action**
LAV	0	98	0	51	Not approved	Manufacturing idle
IV	24	46	0	71	Not approved	Manufacturing idle
SP	27	9	0	97	Approved - SPApprovedCnt = 1	Manufacturing starts
VV	21	81	0	82	Not approved	Manufacturing idle
DNA	19	51	0	46	Not approved	Manufacturing idle
RNA	25	81	0	89	Not approved	Manufacturing idle
Period 7						
Platform	**POS**	**U**	**POF**	**M**	**Status**	**Action**
LAV	0	44	0	38	Not approved	Manufacturing idle
IV	27	65	0	9	Not approved	Manufacturing idle
SP	33	11	18	21	Already approved – SPApprovedCnt = 2	Manufacturing continues
VV	25	40	0	18	Not approved	Manufacturing idle
DNA	22	46	0	14	Not approved	Manufacturing idle
RNA	29	48	0	25	Not approved	Manufacturing idle
Period 8						
Platform	**POS**	**U**	**POF**	**M**	**Status**	**Action**
LAV	0	66	0	80	Not approved	Manufacturing idle
IV	30	94	0	33	Not approved	Manufacturing idle
SP	38	29	18	25	Already approved – SPApprovedCnt = 3	Manufacturing continues
VV	28	90	0	95	Not approved	Manufacturing idle
DNA	25	38	0	54	Not approved	Manufacturing idle
RNA	32	44	0	29	Not approved	Manufacturing idle
Period 9						
Platform	**POS**	**U**	**POF**	**M**	**Status**	**Action**
LAV	0	43	0	5	Not approved	Manufacturing idle
IV	33	17	0	88	Approved – IVApprovedCnt = 1	Manufacturing starts
SP	42	58	18	14	Product rejected – RNAApprovedCnt = 2	Manufacturing continues – products still approved
VV	30	60	0	46	Not approved	Manufacturing idle

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Platform	POS	U	POF	M	Status	Action
DNA	27	66	0	12	Not approved	Manufacturing idle
RNA	35	66	0	14	Not approved	Manufacturing idle
Period 10						
Platform	**POS**	**U**	**POF**	**M**	**Status**	**Action**
LAV	0	35	0	9	Not approved	Manufacturing idle
IV	36	53	20	28	No action	Manufacturing continues
SP	45	39	18	9	Product rejected – RNAApprovedCnt = 2	Manufacturing continues – products still approved
VV	33	8	0	98	Approved	Manufacturing starts
DNA	30	96	0	69	Not approved	Manufacturing idle
RNA	38	34	0	75	Approved	Manufacturing starts
Period 11						
Platform	**POS**	**U**	**POF**	**M**	**Status**	**Action**
LAV	0	84	0	48	Not approved	Manufacturing idle
IV	39	29	20	8	Product rejected – IVApprovedCnt = 1	Manufacturing continues
SP	49	89	18	35	No action	Manufacturing continues
VV	36	28	0	88	Already approved	Manufacturing continues
DNA	32	39	0	54	Not approved	Manufacturing idle
RNA	41	22	0	26	Already approved	Manufacturing continues

E.3 Capacity shift and time delay

When different flexibility configurations are considered, capacity can be shifted from an idle manufacturing facility to an approved and connected platform's manufacturing facility. The shifting of capacity results in a time delay, which may differ for each platform's manufacturing facility. The connections between platforms and manufacturing facilities are manually controlled for each verification step. The capacity shifts and time delays were verified by combining the manufacturing system and the approval and rejection section by manually adjusting the random numbers, the probability of success and the probability of failure values for a platform. Different scenarios were created for which the outcome can be predicted and verified. The capacity shift between the SP and LAV platforms is firstly considered. The system is then expanded to consider the capacity shift between the SP, RNA, and LAV platforms and the SP, DNA and LAV platforms. Lastly, the capacity shift between the SP, RNA, DNA, and LAV platforms is considered.

The SP, RNA, and LAV platforms each have a delay time of one period, while the DNA platform has a delay time of two periods.

E.3.1 SP and LAV

Case one considers the capacity shift between the SP and LAV platforms over two consecutive periods; the results are given in Table E.10.

Table E.10: Case 1 for the capacity shift between the SP and LAV platform

Conditions	Expected Results	Results
Period 1		
ConnectSP = *true* *SPAndLAV* = *true*	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 1 *LAVFacility* entrancelocked	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 1 ✓
Period 2		
ConnectSP = *true* *SPAndLAV* = *true*	*SPLines* = 20 *LAVLines* = 0 *NumberLAV* = 1 *LAVFacility* entrancelocked	*SPLines* = 20 *LAVLines* = 0 *NumberLAV* = 1 ✓

At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay of one period, the capacity can only be shifted to the SP platform at the start of period two. The number of SP production lines is expected to remain 10 during period one and only become 20 at the start of period two. Since the LAV platform's capacity is shifted, its lines are reduced to zero, and its facility's entrance is locked. The LAV platform's manufacturing facility is only connected to one platform for the course of the two periods, and the number of connections is expected to remain one.

Case two considers the capacity shift between the SP and LAV platforms over four consecutive periods; the results are given in Table E.11. At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. The first two periods are expected to occur the same as that in case one. At the start of period three, the LAV platform is approved, however, due to the time delay for the LAV platform, its Manufacturing can only proceed at the start of period four. The number of production lines for the SP facility is immediately reduced to 10, and the number of connections with the LAV platform's manufacturing facility is reduced to zero. At the start of period four, the entrance to the LAV facility should open, and its number of production lines should be 10.

Table E.11: Case 2 for the capacity shift between the SP and LAV platform

Conditions	Expected Results	Results
Period 1		
ConnectSP = *true* *SPAndLAV* = *true*	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 1 *LAVFacility* entrancelocked	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 1 ✓
Period 2		
ConnectSP = *true* *SPAndLAV* = *true*	*SPLines* = 20 *LAVLines* = 0 *NumberLAV* = 1 *LAVFacility* entrancelocked	*SPLines* = 20 *LAVLines* = 0 *NumberLAV* = 1 ✓
Period 3		
ConnectSP = *true* *ConnectLAV* = *true* *SPAndLAV* = *true*	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 0 *LAVFacility* entrancelocked	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 0 ✓
Period 4		
ConnectSP = *true* *ConnectLAV* = *true* *SPAndLAV* = *true*	*SPLines* = 10 *LAVLines* = 10 *NumberLAV* = 0 *LAVFacility* entrancelocked: *false*	*SPLines* = 10 *LAVLines* = 10 *NumberLAV* = 0 ✓

Case three considers the capacity shift between the SP and LAV platforms over three consecutive periods; the results are given in Table E.12.

At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the SP platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. At the start of period two, the LAV platform is approved, however, due to the time delay for the LAV platform, its Manufacturing can only proceed at the start of period three. The number of production lines for the SP facility is immediately reduced to 10, and the number of connections with the LAV platform's manufacturing facility is reduced to zero. At the start of period three, the entrance to the LAV facility should open, and its number of production lines should be 10.

E.3.2 SP, RNA, and LAV

Case one represents the capacity shifting between the SP, RNA and LAV platforms over three consecutive periods; the results are given in Table E.13. At the start of period one, the SP platform is approved, and

Table E.12: Case 3 for the capacity shift between the SP and LAV platform

Conditions	Expected Results	Results
Period 1		
ConnectSP = *true* *SPAndLAV* = *true*	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 1 *LAVFacility* entrancelocked	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 1 ✓
Period 2		
ConnectSP = *true* *ConnectLAV* = *true* *SPAndLAV* = *true*	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 0 *LAVFacility* entrancelocked	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 0 ✓
Period 3		
ConnectSP = *true* *ConnectLAV* = *true* *SPAndLAV* = *true*	*SPLines* = 10 *LAVLines* = 10 *NumberLAV* = 0 *LAVFacility* entrancelocked: *false*	*SPLines* = 10 *LAVLines* = 10 *NumberLAV* = 0 ✓

Table E.13: Case 1 for the capacity shift between the SP, RNA, and LAV platform

Conditions	Expected Results	Results
Period 1		
ConnectSP = *true* *SPAndLAV* = *true*	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 1 *LAVFacility* entrancelocked	*SPLines* = 10 *LAVLines* = 0 *NumberLAV* = 1 ✓
Period 2		
ConnectSP = *true* *ConnectRNA* = *true* *SPAndLAV* = *true* *RNAAndLAV* = *true*	*SPLines* = 15 *RNALines* = 10 *LAVLines* = 0 *NumberLAV* = 2 *LAVFacility* entrancelocked	*SPLines* = 15 *RNALines* = 10 *LAVLines* = 0 *NumberLAV* = 2 ✓
Period 3		
ConnectSP = *true* *ConnectRNA* = *true* *SPAndLAV* = *true* RNAAndLAV = true	*SPLines* = 15 *RNALines* = 15 *LAVLines* = 0 *NumberLAV* = 2 *LAVFacility* entrancelocked	*SPLines* = 15 *RNALines* = 15 *LAVLines* = 0 *NumberLAV* = 2 ✓

its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the SP platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, the RNA facility is approved, and its manufacturing is expected to start. The RNA platform is also connected to the LAV platform's facility, however, due to the time delay, it can only receive the capacity at the start of period three. Since the number of connections with the LAV platform's facility has increased to two, the SP platform only receives half of the available capacity, and its number of production lines is expected to be 15 at the start of period two. At the start of period three, the number of production lines for the RNA platform should be 15.

Case two represents the capacity shifting between the SP, RNA and LAV platforms over two consecutive periods; the results are given in Table E.14. At the start of period one, both the SP and RNA platform is

Table E.14: Case 2 for the capacity shift between the SP, RNA, and LAV platform

Conditions	**Expected Results**	**Results**
Period 1		
ConnectSP = *true*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 10	*RNALines* = 10
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 2	*NumberLAV* = 2
	LAVFacility entrancelocked	✓
Period 2		
ConnectSP = *true*	*SPLines* = 15	*SPLines* = 15
ConnectRNA = *true*	*RNALines* = 15	*RNALines* = 15
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 2	*NumberLAV* = 2
	LAVFacility entrancelocked	✓

approved, and its manufacturing is expected to start, while the LAV platform's facility remains idle. Both the SP and RNA platforms are connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be two. At the start of period two, the number of production lines for both the RNA and SP platforms should be 15.

Case three represents the capacity shifting between the SP, RNA and LAV platforms over three consecutive periods; the results are given in Table E.15. At the start of period one, both the SP and RNA

Table E.15: Case 3 for the capacity shift between the SP, RNA, and LAV platform

Conditions	Expected Results	Results
Period 1		
ConnectSP = *true*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 10	*RNALines* = 10
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 2	*NumberLAV* = 2
	LAVFacility entrancelocked	✓
Period 2		
ConnectSP = *false*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 15	*RNALines* = 15
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 1	*NumberLAV* = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
Period 3		
ConnectSP = *false*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 20	*RNALines* = 20
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 1	*NumberLAV* = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

platform is approved, and its manufacturing is expected to start, while the LAV platform's facility remains idle. Both the SP and RNA platforms are connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be two. At the start of period two, the SP platform is rejected, its number of production lines remains 10, and the entrance to its facility becomes locked. The number of connections with the LAV platform's manufacturing facility should be reduced to one. The RNA platform can receive the additional capacity previously allocated to the S facility after a time delay, and the number of RNA production lines at the start of period two should still be 15. At the start of period three, the number of production lines for the RNA platform should be 20.

Case four represents the capacity shifting between the SP, RNA and LAV platforms over four consecutive periods; the results are given in Table E.16.

At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing

Table E.16: Case 4 for the capacity shift between the SP, RNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = *true*	*SPLines* = 10	*SPLines* = 10
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
	NumberLAV = 1	*NumberLAV* = 1
	LAVFacility entrancelocked	✓
	Period 2	
ConnectSP = *true*	*SPLines* = 15	*SPLines* = 15
ConnectRNA = *true*	*RNALines* = 10	*RNALines* = 10
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 2	*NumberLAV* = 2
	LAVFacility entrancelocked	✓
	Period 3	
ConnectSP = *false*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 15	*RNALines* = 15
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 1	*NumberLAV* = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 4	
ConnectSP = *false*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 20	*RNALines* = 20
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 1	*NumberLAV* = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, the RNA platform is approved, and its manufacturing is expected to start. The RNA platform is also connected to the LAV platform's facility, however, due to the time delay, it can only receive the capacity at the start of period three. Since the number of connections with the LAV platform's facility has increased to two, the SP platform only receives half of the available capacity, and its number of production lines is expected to be 15 at the start of period two. At the start of period three, the SP platform is rejected, its number of production lines remains 10, and the entrance to its facility becomes locked. The number of connections with the LAV platform's manufacturing facility should be reduced to one. The RNA platform can receive the additional capacity previously allocated to the SP facility after a time delay, and the number of RNA production lines at the start of period three should still be 15. At the start of period four, the number of production lines for the RNA platform should be 20.

Case five represents the capacity shifting between the SP, RNA and LAV platforms over four consecutive periods; the results are shown in Table E.17. At the start of period one, both the SP and RNA platform is approved, and its manufacturing is expected to start, while the LAV platform's facility remains idle. Both the SP and RNA platforms are connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be two. At the start of period two, the production lines for both the SP and RNA platforms are expected to be 15. At the start of period three, the SP platform is rejected, its number of production lines remains 10, and the entrance to its facility becomes locked. The number of connections with the LAV platform's manufacturing facility should be reduced to one. The RNA platform can receive the additional capacity previously allocated to the S facility after a time delay, and the number of RNA production lines at the start of period three should still be 15. At the start of period four, the number of production lines for the RNA platform should be 20.

Case six represents the capacity shifting between the SP, RNA and LAV platforms over four consecutive periods; the results are given in Table E.18. At the start of period one, both the SP and RNA platform is approved, and its manufacturing is expected to start, while the LAV platform's facility remains idle. Both the SP and RNA platforms are connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be two. At the start of period two, the LAV platform is approved however, due to the time delay for the LAV platform, its manufacturing can only proceed at the start of period three. The number of production lines

Table E.17: Case 5 for the capacity shift between the SP, RNA, and LAV platform

Conditions	Expected Results	Results
Period 1		
ConnectSP = *true*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 10	*RNALines* = 10
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 2	*NumberLAV* = 2
	LAVFacility entrancelocked	✓
Period 2		
ConnectSP = *true*	*SPLines* = 15	*SPLines* = 15
ConnectRNA = *true*	*RNALines* = 15	*RNALines* = 15
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 2	*NumberLAV* = 2
	LAVFacility entrancelocked	✓
Period 3		
ConnectSP = *false*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 15	*RNALines* = 15
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 1	*NumberLAV* = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
Period 4		
ConnectSP = *false*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 20	*RNALines* = 20
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 1	*NumberLAV* = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

Table E.18: Case 6 for the capacity shift between the SP, RNA, and LAV platform

Conditions	Expected Results	Results
Period 1		
ConnectSP = *true*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 10	*RNALines* = 10
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 2	*NumberLAV* = 2
	LAVFacility entrancelocked	✓
Period 2		
ConnectSP = *true*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 10	*RNALines* = 10
ConnectLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
SPAndLAV = *true*	*NumberLAV* = 0	*NumberLAV* = 0
RNAAndLAV = *true*	*LAVFacility* entrancelocked	✓
Period 3		
ConnectSP = *false*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 10	*RNALines* = 10
ConnectLAV = *true*	*LAVLines* = 10	*LAVLines* = 10
SPAndLAV = *true*	*NumberLAV* = 0	*NumberLAV* = 0
RNAAndLAV = *true*	*LAVFacility* entrancelocked: *false*	✓
	SPFacility entrancelocked: *false*	✓

for both the SP and RNA facility remains 10, and the number of connections with the LAV platform's manufacturing facility is reduced to zero. At the start of period three, the entrance to the LAV facility should open, and its number of production lines should be 10.

Case seven represents the capacity shifting between the SP, RNA and LAV platforms over three consecutive periods; the results are given in Table E.19.

At the start of period one, both the SP and RNA platform is approved, and its manufacturing is expected to start, while the LAV platform's facility remains idle. Both the SP and RNA platforms are connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platforms, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be two. At the start of period two, the number of production lines for both SP and RNA platforms should be 15. At the start of period three, the LAV platform is approved however, due to the time delay for the LAV platform, its manufacturing can only proceed at the start of period four. The number of production lines for both the SP and RNA facility is immediately reduced to 10, and the number of connections with the LAV platform's manufacturing facility is reduced to zero. At the start of period four, the entrance to the LAV facility should open, and its number of production lines should be 10.

Table E.19: Case 7 for the capacity shift between the SP, RNA, and LAV platform

Conditions	Expected Results	Results
Period 1		
ConnectSP = *true*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 10	*RNALines* = 10
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 2	*NumberLAV* = 2
	LAVFacility entrancelocked	✓
Period 2		
ConnectSP = *true*	*SPLines* = 15	*SPLines* = 15
ConnectRNA = *true*	*RNALines* = 15	*RNALines* = 15
SPAndLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
RNAAndLAV = *true*	*NumberLAV* = 2	*NumberLAV* = 2
	LAVFacility entrancelocked	✓
Period 3		
ConnectSP = *false*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 10	*RNALines* = 10
ConnectLAV = *true*	*LAVLines* = 0	*LAVLines* = 0
SPAndLAV = *true*	*NumberLAV* = 0	*NumberLAV* = 0
RNAAndLAV = *true*	*LAVFacility* entrancelocked	✓
	SPFacility entrancelocked	✓
Period 4		
ConnectSP = *false*	*SPLines* = 10	*SPLines* = 10
ConnectRNA = *true*	*RNALines* = 10	*RNALines* = 10
ConnectLAV = *true*	*LAVLines* = 10	*LAVLines* = 10
SPAndLAV = *true*	*NumberLAV* = 0	*NumberLAV* = 0
RNAAndLAV = *true*	*LAVFacility* entrancelocked: *false*	✓
	SPFacility entrancelocked	✓

Case eight represents the capacity shifting between the SP, RNA and LAV platforms over three consecutive periods; the results are given in Table E.20. At the start of period one, the SP platform is approved,

Table E.20: Case 8 for the capacity shift between the SP, RNA, and LAV platform

Conditions	Expected Results	Results
Period 1		
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
Period 2		
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectRNA = true	RNALines = 10	RNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
Period 3		
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectRNA = true	RNALines = 20	RNALines = 20
SPAndLAV = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be two. At the start of period two, the RNA platform is approved, and its manufacturing is expected to start. The RNA platform is also connected to the LAV platform's facility, however, due to the time delay, it can only receive the capacity at the start of period three. The SP platform is also rejected at the start of period two, its number of production lines should remain 10, and the entrance to its facility should be locked. The number of connections with the LAV platform's manufacturing facility should be one. At the start of period three, the number of production lines for the RNA platform should be 20.

Case nine represents the capacity shifting between the SP, RNA and LAV platforms over four consecutive periods; the results are given in Table E.21. At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to

Table E.21: Case 9 for the capacity shift between the SP, RNA, and LAV platform

Conditions	Expected Results	Results
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	Period 2	
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectRNA = true	RNALines = 10	RNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 3	
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectRNA = true	RNALines = 10	RNALines = 10
ConnectLAV = true	LAVLines = 0	LAVLines = 0
SPAndLAV = true	NumberLAV = 0	NumberLAV = 0
RNAAndLAV = true	LAVFacility entrancelocked: false	✓
	SPFacility entrancelocked: false	✓
	Period 4	
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectRNA = true	RNALines = 10	RNALines = 10
ConnectLAV = true	LAVLines = 10	LAVLines = 10
SPAndLAV = true	NumberLAV = 0	NumberLAV = 0
RNAAndLAV = true	LAVFacility entrancelocked: false	✓
	SPFacility entrancelocked: false	✓

the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, the RNA platform is approved, and its manufacturing is expected to start. The RNA platform is also connected to the LAV platform's facility, however, due to the time delay, it can only receive the capacity at the start of period three. Since the number of connections with the LAV platform's facility has increased to two, the SP platform only receives half of the available capacity, and its number of production lines is expected to be 15 at the start of period two. At the start of period three, the SP platform is rejected, and the LAV platform is approved. The number of production lines for both the SP and RNA platforms is expected to be 10, and the entrance to the SP platform's manufacturing facility should be locked. The number of connections with the LAV platform's manufacturing facility should be reduced to zero. The number of production lines for the LAV platform remains 0, and the entrance to its manufacturing facility remains locked. At the start of period four, the entrance to the LAV facility should be opened, and the number of production lines for the LAV platform should be 10.

E.3.3 SP, DNA, and LAV

Case one represents the capacity shifting between the SP, DNA and LAV platforms over three consecutive periods; the results are given in Table E.22.

Table E.22: Case 1 for the capacity shift between the SP, DNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓

At the start of period one, both the SP and DNA platforms are approved, and their manufacturing is expected to start while the LAV platform's facility remains idle. Both the SP and DNA platforms are connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delays, the capacity for the SP platform can only be shifted at the start of period two, while the time delay for the DNA platform can only occur at the start of period three. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be two. At the start of period two, the SP platform is expected to have 15 production lines available to it, while the DNA platform should still only have 10 production lines available. At the start of period three, the DNA platform is expected to also have 15 production lines available.

Case two represents the capacity shifting between the SP, DNA and LAV platforms over four consecutive periods; the results are given in Table E.23.

At the start of period one, both the SP and DNA platforms are approved, and their manufacturing is expected to start while the LAV platform's facility remains idle. Both the SP and DNA platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delays, the capacity for the SP platform can only be shifted at the start of period two, while the time delay for the DNA platform can only occur at the start of period three. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be two. At the start of period two, the SP platform is rejected, and its number of production lines should remain at 10. The DNA platform can receive the additional LAV platform facility's capacity after the required time delay. At the start of period two, the number of production lines for the DNA platform should still be 10 and only increase to 15 at the start of period three. The additional LAV production lines should become available to the DNA platform at the start of period four, and the number of production lines for the DNA platform is expected to be 20.

Case three represents the capacity shifting between the SP, DNA and LAV platforms over five consecutive periods; the results are given in Table E.24. At the start of period one, both the SP and DNA platforms are approved, and their manufacturing is expected to start while the LAV platform's facility remains idle. Both the SP and DNA platform is connected with the LAV platform's manufacturing facility and can thus receive their capacity. Due to the time delays, the capacity for the SP platform can only be shifted at the start of period two, while the time delay for the DNA platform can only occur at the start of period three. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be two. At the start of period two, the SP platform is expected to have 15 production lines available to it, while the DNA platform should still only have 10 production lines available. At the start of period three, the SP platform is rejected, and its number of production lines should be reduced to 10. The DNA platform can receive

Table E.23: Case 2 for the capacity shift between the SP, DNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 4	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 20	DNALines = 20
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

Table E.24: Case 3 for the capacity shift between the SP, DNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 4	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 5	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 20	DNALines = 20
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

the additional LAV platform facility's capacity after the required time delay. At the start of period three, the number of production lines for the DNA platform should be 15 and should remain constant until the start of period five, when the additional LAV production lines become available to the DNA platform. The number of production lines for the DNA platform at the start of period five is expected to be 20.

Case four represents the capacity shifting between the SP, DNA and LAV platforms over five consecutive periods; the results are given in Table E.25.

Table E.25: Case 4 for the capacity shift between the SP, DNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	Period 4	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 5	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1

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Conditions	**Expected Results**	**Results**
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
Period 6		
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 20	DNALines = 20
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

At the start of period one, both the SP and DNA platforms are approved, and their manufacturing is expected to start while the LAV platform's facility remains idle. Both the SP and DNA platform is connected with the LAV platform's manufacturing facility and can thus receive their capacity. Due to the time delays, the capacity for the SP platform can only be shifted at the start of period two, while the time delay for the DNA platform can only occur at the start of period three. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be two. At the start of period two, the SP platform is expected to have 15 production lines available to it, while the DNA platform should still only have 10 production lines available. At the start of period three, the DNA platform should also have 15 production lines available. At the start of period four, the SP platform is rejected, and its number of production lines should be reduced to 10. The DNA platform can receive the additional LAV platform facility's capacity after the required time delay. The number of production lines for the DNA platform remains at 15 until the start of period six, when the additional LAV production lines become available to the DNA platform, and the DNA platform is expected to have 20 production lines available.

Case five represents the capacity shifting between the SP, DNA and LAV platforms over four consecutive periods; the results are given in Table E.26. At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, the DNA platform is approved, and its manufacturing is expected to start. The DNA platform is also connected to the LAV platform's facility, however, due to the time delay, it can only receive the additional capacity at the start of period four. Since the number of connections with the LAV platform's facility has

Table E.26: Case 5 for the capacity shift between the SP, DNA, and LAV platform

Period 1		
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
Period 2		
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
Period 3		
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
Period 4		
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓

increased to two, the SP platform only receives half of the available capacity, and its number of production lines is expected to be 15 at the start of period two, while the number of production lines for the DNA platform is expected to be 10. The number of production lines available to the DNA platform is expected to increase to 15 at the start of period four.

Case six represents the capacity shifting between the SP, DNA and LAV platforms over four consecutive periods; the results are given in Table E.27.

Table E.27: Case 6 for the capacity shift between the SP, DNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndDNA = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndDNA = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 4	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 20	DNALines = 20
SPAndDNA = true	LAVLines = 0	LAVLines = 0
DNAAndLAv = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing

facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, the DNA platform is approved, and its manufacturing is expected to start. The DNA platform is also connected to the LAV platform's facility, however, due to the time delay, it can only receive the capacity at the start of period four. At the start of period two, the SP platform is rejected, its number of production lines should remain at 10, and the entrance to its facility should become locked. The DNA platform can receive the additional LAV platform facility's capacity after the required time delay. At the start of period two, the number of production lines available to the DNA platform should still be 10 and remain constant until the start of period four. At the start of period four, the number of production lines available to the DNA platform should increase to 20.

Case seven represents the capacity shifting between the SP, DNA and LAV platforms over five consecutive periods; the results are given in Table E.28.

At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, the DNA platform is approved, and its manufacturing is expected to start. The DNA platform is also connected to the LAV platform's facility, however, due to the time delay, it can only receive the capacity at the start of period four. Since the number of connections with the LAV platform's facility has increased to two, the SP platform only receives half of the available capacity, and its number of production lines is expected to be 15 at the start of period two, while the number of production lines for the DNA platform is expected to be 10. At the start of period three, the SP platform is rejected, its number of production lines should remain at 10, and the entrance to its facility should become locked. The DNA platform can receive the additional LAV platform facility's capacity after the required time delay. At the start of period four, the number of production lines available to the DNA platform should be 15, and it should increase to 20 at the start of period five.

Case eight represents the capacity shifting between the SP, DNA and LAV platforms over seven consecutive periods; the results are given in Table E.29.

Table E.29: Case 8 for the capacity shift between the SP, DNA, and LAV platform

Conditions	**Expected Results**	**Results**
Period 1		
ConnectSP = true SPAndLAV = true	SPLines = 10 LAVLines = 0 NumberLAV = 1	SPLines = 10 LAVLines = 0 NumberLAV = 1

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Conditions	**Expected Results**	**Results**
	LAVFacility entrancelocked	✓
Period 2		
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
Period 3		
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
Period 4		
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
Period 5		
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
Period 6		
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
Period 7		
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 20	DNALines = 20
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1

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Conditions	Expected Results	Results
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, the DNA platform is approved, and its manufacturing is expected to start. The DNA platform is also connected to the LAV platform's facility, however, due to the time delay, it can only receive the capacity at the start of period four. Since the number of connections with the LAV platform's facility has increased to two, the SP platform only receives half of the available capacity, and its number of production lines is expected to be 15 at the start of period two, while the number of production lines for the DNA platform is expected to be 10 and should remain constant until the start of period four. At the start of period four, the number of production lines available to the DNA platform should increase to 15. At the start of period five, the SP platform is rejected, its number of production lines should remain at 10, and the entrance to its facility should become locked. The DNA platform can receive the additional LAV platform facility's capacity after the required time delay. At the start of period seven, the number of production lines available to the DNA platform should increase to 20.

Case nine represents the capacity shifting between the SP, DNA and LAV platforms over four consecutive periods; the results are given in Table E.31.

At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, the DNA platform is approved, and its manufacturing is expected to start. The DNA platform is also connected to the LAV platform's facility, however, due to the time delay, it can only receive the capacity at the start of period four. At the start of period two, the SP platform is rejected, and the LAV platform is approved. The number of production lines for both the SP and DNA platforms is expected to be 10, and the entrance to the SP platform's manufacturing facility should be locked. The number of connections with the LAV platform's manufacturing facility should be reduced to zero. The number of production lines for the LAV platform

Table E.28: Case 7 for the capacity shift between the SP, DNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndDNA = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndDNA = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 4	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndDNA = true	LAVLines = 0	LAVLines = 0
DNAAndLAv = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 5	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 20	DNALines = 20
SPAndDNA = true	LAVLines = 0	LAVLines = 0
DNAAndLAv = true	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

Table E.30: Case 9 for the capacity shift between the SP, DNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectLAV = true	LAVLines = 0	LAVLines = 0
SPAndLAV = true	NumberLAV = 0	NumberLAV = 0
DNAAndLAV = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectLAV = true	LAVLines = 10	LAVLines = 10
SPAndLAV = true	NumberLAV = 0	NumberLAV = 0
DNAAndLAV = true	LAVFacility entrancelocked: false	✓
	SPFacility entrancelocked: false	✓

remains 0, and the entrance to its manufacturing facility remains locked. At the start of period three, the entrance to the LAV facility should be opened, and the number of production lines for the LAV platform should be 10.

Case ten represents the capacity shifting between the SP, DNA and LAV platforms over four consecutive periods; the results are given in Table E.31. At the start of period one, the SP platform is approved, and

Table E.31: Case 10 for the capacity shift between the SP, DNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectLAV = true	LAVLines = 0	LAVLines = 0
SPAndLAV = true	NumberLAV = 0	NumberLAV = 0
DNAAndLAV = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 4	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectLAV = true	LAVLines = 10	LAVLines = 10
SPAndLAV = true	NumberLAV = 0	NumberLAV = 0
DNAAndLAV = true	LAVFacility entrancelocked: false	✓
	SPFacility entrancelocked: false	✓

its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, the DNA platform is approved, and its manufacturing is expected to start. The DNA platform is also

connected to the LAV platform's facility, however, due to the time delay, it can only receive the capacity at the start of period four. Since the number of connections with the LAV platform's facility has increased to two, the SP platform only receives half of the available capacity, and its number of production lines is expected to be 15 at the start of period two, while the number of production lines for the DNA platform is expected to be 10. At the start of period three, the SP platform is rejected, and the LAV platform is approved. The number of production lines for both the SP and DNA platforms is expected to be 10, and the entrance to the SP platform's manufacturing facility should be locked. The number of connections with the LAV platform's manufacturing facility should be reduced to zero. The number of production lines for the LAV platform remains 0, and the entrance to its manufacturing facility remains locked. At the start of period four, the entrance to the LAV facility should be opened, and the number of production lines for the LAV platform should be 10.

Case eleven represents the capacity shifting between the SP, DNA and LAV platforms over six consecutive periods; the results are given in Table E.32.

Table E.32: Case 11 for the capacity shift between the SP, DNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndDNA = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 10	DNALines = 10
SPAndDNA = true	LAVLines = 0	LAVLines = 0
DNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
	Period 4	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 15	SPLines = 15
ConnectDNA = true	DNALines = 15	DNALines = 15
SPAndDNA = true	LAVLines = 0	LAVLines = 0

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Conditions	**Expected Results**	**Results**
DNAAndLAv = true	NumberLAV = 2	NumberLAV = 2
	LAVFacility entrancelocked	✓
Period 5		
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectLAV = true	LAVLines = 0	LAVLines = 0
SPAndDNA = true	NumberLAV = 0	NumberLAV = 0
DNAAndLAV = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
Period 6		
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectLAV = true	LAVLines = 10	LAVLines = 10
SPAndDNA = true	NumberLAV = 0	NumberLAV = 0
DNAAndLAV = true	LAVFacility entrancelocked: false	✓
	SPFacility entrancelocked	✓

At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, the DNA platform is approved, and its manufacturing is expected to start. The DNA platform is also connected to the LAV platform's facility, however, due to the time delay, it can only receive the capacity at the start of period four. Since the number of connections with the LAV platform's facility has increased to two, the SP platform only receives half of the available capacity, and its number of production lines is expected to be 15 at the start of period two, while the number of production lines for the DNA platform is expected to be 10 and should remain constant until the start of period four. At the start of period four, the number of production lines available to the DNA platform should increase to 15. At the start of period five, the SP platform is rejected, and the LAV platform is approved. The number of production lines for both the SP and DNA platforms is expected to be 10, and the entrance to the SP platform's manufacturing facility should be locked. The number of connections with the LAV platform's manufacturing facility should be reduced to zero. The number of production lines for the LAV platform remains 0, and the entrance to its manufacturing facility remains

locked. At the start of period five, the entrance to the LAV facility should be opened, and the number of production lines for the LAV platform should be 10.

E.3.4 SP, RNA, DNA and LAV

Case one represents the capacity shifting between the SP, RNA, DNA, and LAV platforms over four consecutive periods; the results are given in Table E.33. At the start of period one, the SP platform is

Table E.33: Case 1 for the capacity shift between the SP, DNA, RNA, and LAV platform

Conditions	**Expected Results**	**Results**
Period 1		
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
Period 2		
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 13	SPLines = 13
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectRNA = true	RNALines = 10	RNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 3	NumberLAV = 3
DNAAndLAv = true	LAVFacility entrancelocked	✓
Period 3		
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 13	SPLines = 13
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectRNA = true	RNALines = 13	RNALines = 13
SPAndLAV = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
DNAAndLAV = true	LAVFacility entrancelocked	✓
Period 4		
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 13	SPLines = 13
ConnectDNA = true	DNALines = 13	DNALines = 13
ConnectRNA = true	RNALines = 13	RNALines = 13
SPAndDNA = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 3	NumberLAV = 3
DNAAndLAV = true	LAVFacility entrancelocked	✓

approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines

should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, both the RNA and DNA platforms are approved, and their manufacturing is expected to start. Both the RNA and DNA platforms are also connected to the LAV platform's facility, however, due to the time delay, it can only receive the additional capacity at the start of periods three and four, respectively. Since the number of connections with the LAV platform's facility has increased to three, the SP platform only receives a third of the available capacity, and its number of production lines is expected to be 13 at the start of period two, while the number of production lines for both the RNA and DNA platforms is expected to be 10. The number of production lines available to the RNA platform is expected to increase to 13 at the start of period three, while the number of production lines available to the DNA platform is expected to increase to 13 at the start of period four.

Case two represents the capacity shifting between the SP, RNA, DNA, and LAV platforms over four consecutive periods; the results are given in Table E.34. At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, both the RNA and DNA platforms are approved, and their manufacturing is expected to start. Both the RNA and DNA platforms are also connected to the LAV platform's facility, however, due to the time delay, it can only receive the additional capacity at the start of periods three and four, respectively. The SP platform is also rejected, its number of production lines should remain at 10, and the entrance to its facility should become locked. The number of connections with the LAV platform's facility should be increased to two. The DNA and RNA platforms can receive the additional LAV platform facility's capacity after the required time delay. At the start of period two, both the RNA and DNA platforms should have 10 available production lines. The number of production lines available to the RNA platform should increase to 15 at the start of period three, while the number of production lines available to the DNA platform should still be 10. The number of production lines available to the DNA platform should increase at the start of period four.

Case three represents the capacity shifting between the SP, RNA, DNA, and LAV platforms over five consecutive periods; the results are given in Table E.35. At the start of period one, the SP platform is approved, and its manufacturing is expected to start while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of

Table E.34: Case 2 for the capacity shift between the SP, DNA, RNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectRNA = true	RNALines = 10	RNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
DNAAndLAV = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectRNA = true	RNALines = 15	RNALines = 15
SPAndLAV = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
DNAAndLAV = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 4	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 15
ConnectRNA = true	RNALines = 15	RNALines = 15
SPAndDNA = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
DNAAndLAV = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

Table E.35: Case 3 for the capacity shift between the SP, DNA, RNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 13	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectRNA = true	RNALines = 10	RNALines = 10
SPAndDNA = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 3	NumberLAV = 3
DNAAndLAv = true	LAVFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectRNA = true	RNALines = 13	RNALines = 13
SPAndDNA = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
DNAAndLAV = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 4	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 13	DNALines = 13
ConnectRNA = true	RNALines = 15	RNALines = 15
SPAndDNA = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
DNAAndLAv = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
	Period 5	
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 15
ConnectRNA = true	RNALines = 15	RNALines = 15
SPAndDNA = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
DNAAndLAV = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

period two, both the RNA and DNA platforms are approved, and their manufacturing is expected to start. Both the RNA and DNA platforms are also connected to the LAV platform's facility, however, due to the time delay, it can only receive the additional capacity at the start of periods three and four, respectively. Since the number of connections with the LAV platform's facility has increased to three, the SP platform only receives a third of the available capacity, and its number of production lines is expected to be 13 at the start of period two, while the number of production lines for both the RNA and DNA platforms is expected to be 10. The number of production lines available to the RNA platform is expected to increase to 13 at the start of period three, while the number of production lines available to the DNA platform is expected to increase to 13 at the start of period four. At the start of period three, the SP platform is also rejected, its number of production lines should be reduced to 10, and the entrance to its facility should become locked. The number of connections with the LAV platform's facility should be reduced to two. The DNA and RNA platforms can receive the additional LAV platform facility's capacity after the required time delay. The number of production lines available to the RNA platform should increase to 15 at the start of period four, while the number of production lines available to the DNA platform should still be 13. The number of production lines available to the DNA platform should increase to 15 at the start of period five.

Case four represents the capacity shifting between the SP, RNA, DNA, and LAV platforms over six consecutive periods; the results are given in Table E.36.

Table E.36: Case 4 for the capacity shift between the SP, DNA, RNA, and LAV platform

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectSP = true	SPLines = 10	SPLines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
	NumberLAV = 1	NumberLAV = 1
	LAVFacility entrancelocked	✓
	Period 2	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 13	SPLines = 13
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectRNA = true	RNALines = 10	RNALines = 10
SPAndLAV = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 3	NumberLAV = 3
DNAAndLAV = true	LAVFacility entrancelocked	✓
	Period 3	
Conditions	**Expected Results**	**Results**
ConnectSP = true	SPLines = 13	SPLines = 13
ConnectDNA = true	DNALines = 10	DNALines = 10
ConnectRNA = true	RNALines = 13	RNALines = 13

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Conditions	**Expected Results**	**Results**
SPAndLAV = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 3	NumberLAV = 3
DNAAndLAV = true	LAVFacility entrancelocked	✓
Period 4		
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 13	DNALines = 13
ConnectRNA = true	RNALines = 13	RNALines = 13
SPAndDNA = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
DNAAndLAV = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
Period 5		
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 13	DNALines = 13
ConnectRNA = true	RNALines = 15	RNALines = 15
SPAndDNA = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
DNAAndLAV = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓
Period 6		
Conditions	**Expected Results**	**Results**
ConnectSP = false	SPLines = 10	SPLines = 10
ConnectDNA = true	DNALines = 15	DNALines = 15
ConnectRNA = true	RNALines = 15	RNALines = 15
SPAndDNA = true	LAVLines = 0	LAVLines = 0
RNAAndLAV = true	NumberLAV = 2	NumberLAV = 2
DNAAndLAV = true	LAVFacility entrancelocked	✓
	SPFacility entrancelocked	✓

At the start of period one, the SP platform is approved, and its manufacturing is expected to start, while the LAV platform's facility remains idle. The SP platform is connected with the LAV platform's manufacturing facility and can thus receive its capacity. Due to the time delay for the platform, the capacity can only be shifted at the start of period two. The entrance to the LAV facility's manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the LAV platform's facility should be one. At the start of period two, both the RNA and DNA platforms are approved, and their manufacturing is expected to start. Both the RNA and DNA platforms are also connected to the LAV platform's facility, however, due to the time delay, it can only receive the additional capacity at the start of periods three and four, respectively. Since the number of connections with the LAV

platform's facility has increased to three, the SP platform only receives a third of the available capacity, and its number of production lines is expected to be 13 at the start of period two, while the number of production lines for both the RNA and DNA platforms is expected to be 10. The number of production lines available to the RNA platform is expected to increase to 13 at the start of period three, while the number of production lines available to the DNA platform is expected to increase to 13 at the start of period four. At the start of period four, the SP platform is also rejected, its number of production lines should be reduced to 10, and the entrance to its facility should become locked. The number of connections with the LAV platform's facility should be reduced to two. The DNA and RNA platforms can receive the additional LAV platform facility's capacity after the required time delay. The number of production lines available to the RNA platform should increase to 15 at the start of period five, while the number of production lines available to the DNA platform should still be 13. The number of production lines available to the DNA platform should increase to 15 at the start of period six.

E.4 Types of facilities

As mentioned in Section 5.2, each vaccine platform has two types of equipment facilities, namely: stainless-steel and single-use. These facilities have to be considered separately, and different delay times are enforced for the two types of facilities. Only if an equipment facility type is considered, will that facility type be capable of processing objects. Two approaches were followed to ensure that the equipment facilities function independently.

For approach one, only the stainless-steel equipment facilities were considered and the shifting of capacity for these facilities was permitted. For approach two, both the single-use and stainless-steel equipment were considered, but the shifting of capacity was only permitted for the single-use equipment facilities.

E.4.1 Approach one

Case one represents the capacity shifting between the LAV and VV platforms over three consecutive periods; the results are given in Table E.37. At the start of period one, the LAV platform is approved, and its manufacturing is expected to start. Only the LAV platform's stainless-steel equipment facility is expected to be active, while the single-use equipment facility is expected to be idle. Both the VV platform's facilities are expected to be idle. The LAV platform is connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the LAV platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number

Table E.37: Case 1 for the capacity shift of stainless-steel equipment facilities

Conditions	Expected Results	Results
Period 1		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 2		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 3		
ConnectLAV = true	LAVFacilitySS lines = 20	LAVFacilitySS lines = 20
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓

of connections with the VV platform's facility should be one. At the start of period three, the number of production lines available to the LAV platform's stainless-steel equipment facility should increase to 20.

Case two represents the capacity shifting between the LAV, RNA, and VV platforms over four consecutive periods; the results are given in Table E.38. At the start of period one, the LAV platform is approved, and its manufacturing is expected to start. Only the LAV platform's stainless-steel equipment facility is expected to be active, while the single-use equipment facility is expected to be idle. Both the VV platform's facilities are expected to be idle. The LAV platform is connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the LAV platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be one. At the start of period two, the RNA platform is approved, and its manufacturing is expected to start. Only the RNA platform's stainless-steel equipment facility is expected to be active, while the single-use equipment facility is expected to be idle. The RNA platform is also connected to the VV platform's stainless-steel facility, however, due to the time delay, it can only receive the additional capacity at the start of period four. Since the number of connections with the VV platform's stainless-steel facility has increased to two, the LAV platform only receives half of the available capacity, and its number of production lines for the stainless-steel facility is expected to be 15 at the start of period three, while the number of production lines for the RNA platform's stainless-steel facility is expected to be 10. The number of production lines available to the RNA platform's stainless-steel facility is expected to increase to 15 at the start of period four,

Case three represents the capacity shifting between the LAV, RNA, and VV platforms over five consecutive periods; the results are given in Table E.39.

Table E.39: Case 3 for the capacity shift of stainless-steel equipment facilities

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0

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Conditions	**Expected Results**	**Results**
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 3		
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 4		
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 5		
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 15	RNAFacilitySS lines = 15
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓

At the start of period one, the LAV platform is approved, and its manufacturing is expected to start. Only the LAV platform's stainless-steel equipment facility is expected to be active, while the single-use equipment facility is expected to be idle. Both the VV platform's facilities are expected to be idle. The LAV platform is connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the LAV platform's stainless-steel equipment facility should be 10.

Table E.38: Case 2 for the capacity shift of stainless-steel equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 4	
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 15	RNAFacilitySS lines = 15
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓

The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be one. At the start of period three, the RNA platform is approved, and its manufacturing is expected to start. Only the RNA platform's stainless-steel equipment facility is expected to be active, while the single-use equipment facility is expected to be idle. The RNA platform is also connected to the VV platform's stainless-steel facility, however, due to the time delay, it can only receive the additional capacity at the start of period five. Since the number of connections with the VV platform's stainless-steel facility has increased to two, the LAV platform only receives half of the available capacity, and its number of production lines for the stainless-steel facility is expected to be 15 at the start of period three, while the number of production lines for the RNA platform's stainless-steel facility is expected to be 10. The number of production lines available to the RNA platform's stainless-steel facility is expected to increase to 15 at the start of period five,

Case four represents the capacity shifting between the LAV, RNA, and VV platforms over six consecutive periods; the results are given in Table E.40.

Table E.40: Case 4 for the capacity shift of stainless-steel equipment facilities

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 20	LAVFacilitySS lines = 20
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓

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Conditions	Expected Results	Results
	VVFacilitySU entrancelocked: false	✓
Period 4		
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 5		
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 6		
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 15	RNAFacilitySS lines = 15
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓

At the start of period one, the LAV platform is approved, and its manufacturing is expected to start. Only the LAV platform's stainless-steel equipment facility is expected to be active, while the single-use equipment facility is expected to be idle. Both the VV platform's facilities are expected to be idle. The LAV platform is connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the LAV platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be one. The number of production lines available to the LAV platform's stainless-steel facility

is expected to increase to 20 at the start of period three. At the start of period four, the RNA platform is approved, and its manufacturing is expected to start. Only the RNA platform's stainless-steel equipment facility is expected to be active, while the single-use equipment facility is expected to be idle. The RNA platform is also connected to the VV platform's stainless-steel facility, however, due to the time delay, it can only receive the additional capacity at the start of period six. Since the number of connections with the VV platform's stainless-steel facility has increased to two, the LAV platform only receives half of the available capacity, and its number of production lines for the stainless-steel facility is expected to be 15 at the start of period four, while the number of production lines for the RNA platform's stainless-steel facility is expected to be 10. The number of production lines available to the RNA platform's stainless-steel facility is expected to increase to 15 at the start of period five,

Case five represents the capacity shifting between the LAV, RNA, and VV platforms over three consecutive periods; the results are given in Table E.41. At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Only the LAV and RNA platforms' stainless-steel equipment facilities are expected to be active, while the single-use equipment facilities are expected to be idle. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the both the LAV and the RNA platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be two. The number of production lines available to both the LAV and RNA platforms' stainless-steel facilities is expected to increase to 15 at the start of period three.

Case six represents the capacity shifting between the LAV, RNA, and VV platforms over five consecutive periods; the results are given in Table E.42

Table E.42: Case 6 for the capacity shift of stainless-steel equipment facilities

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓

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Conditions	Expected Results	Results
	VVFacilitySU entrancelocked: false	✓
Period 2		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	ü
	VVFacilitySU entrancelocked: false	ü
Period 3		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 4		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 10	VVFacilitySS lines = 10
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelockedfalse	✓
	VVFacilitySU entrancelocked: false	✓
Period 5		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓

At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is

Table E.41: Case 5 for the capacity shift of stainless-steel equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 15	RNAFacilitySS lines = 15
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓

expected to start. Only the LAV and RNA platforms' stainless-steel equipment facilities are expected to be active, while the single-use equipment facilities are expected to be idle. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the both the LAV and the RNA platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be two. At the start of period three, the VV platform is approved. The number of production lines for both the LAV and RNA platforms is expected to be 10, The number of connections with the VV platform's stainless-steel manufacturing facility should be reduced to zero. The number of production lines for the VV platform remains 0, and the entrance to its stainless-steel equipment manufacturing facility remains locked. At the start of period six, the entrance to the stainless-steel VV facility should be opened, and the number of production lines available to the VV platform's stainless-steel facility is expected to be 10.

Case seven represents the capacity shifting between the LAV, RNA, and VV platforms over six consecutive periods; the results are given in Table E.43.

Table E.43: Case 7 for the capacity shift of stainless-steel equipment facilities

Conditions	**Expected Results**	**Results**
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	ü
	VVFacilitySU entrancelocked: false	ü
Period 2		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 3		

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Conditions	Expected Results	Results
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 15	RNAFacilitySS lines = 15
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 4		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 5		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 6		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 10	VVFacilitySS lines = 10
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked: false	✓

At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Only the LAV and RNA platforms' stainless-steel equipment facilities are expected to be active, while the single-use equipment facilities are expected to be idle. Both the VV platform's facilities are

expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the both the LAV and the RNA platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be two. The number of production lines available to both the LAV and RNA platforms' stainless-steel facilities is expected to increase to 15 at the start of period three. At the start of period four, the VV platform is approved. The number of production lines for both the LAV and RNA platforms is expected to be 10, The number of connections with the VV platform's stainless-steel manufacturing facility should be reduced to zero. The number of production lines for the VV platform remains 0, and the entrance to its stainless-steel equipment manufacturing facility remains locked. At the start of period six, the entrance to the stainless-steel VV facility should be opened, and the number of production lines available to the VV platform's stainless-steel facility is expected to be 10.

Case eight represents the capacity shifting between the LAV, RNA, and VV platforms over five consecutive periods; the results are given in Table E.44.

Table E.44: Case 8 for the capacity shift of stainless-steel equipment facilities

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 3	

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Conditions	Expected Results	Results
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 4		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 5		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 10	VVFacilitySS lines = 10
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked: false	✓

At the start of period one, the LAV platform is approved, and its manufacturing is expected to start. Only the LAV platform's stainless-steel equipment facility is expected to be active, while the single-use equipment facility is expected to be idle. Both the VV platform's facilities are expected to be idle. The LAV platform is connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the LAV platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be one. At the start of period two, the RNA platform is approved, and its manufacturing is expected to start. Only the RNA platform's stainless-steel equipment facility is expected to be active, while

the single-use equipment facility is expected to be idle. The RNA platform is also connected to the VV platform's stainless-steel facility, however, due to the time delay, it can only receive the additional capacity at the start of period four. Since the number of connections with the VV platform's stainless-steel facility has increased to two, and the LAV platform only receives half of the available capacity, and its number of production lines for the stainless-steel facility is expected to be 15 at the start of period three, while the number of production lines for the RNA platform's stainless-steel facility is expected to be 10. At the start of period three, the VV platform is approved. The number of production lines for both the LAV and RNA platforms is expected to be 10, The number of connections with the VV platform's stainless-steel manufacturing facility should be reduced to zero. The number of production lines for the VV platform remains 0, and the entrance to its stainless-steel equipment manufacturing facility remains locked. At the start of period five, the entrance to the stainless-steel VV facility should be opened, and the number of production lines available to the VV platform's stainless-steel facility is expected to be 10.

Case nine represents the capacity shifting between the LAV, RNA, and VV platforms over three consecutive periods; the results are given in Table E.45. At the start of period one, the LAV, RNA, and VV

Table E.45: Case 9 for the capacity shift of stainless-steel equipment facilities

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 10	VVFacilitySS lines = 10
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 10	VVFacilitySS lines = 10
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 10	VVFacilitySS lines = 10
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0

platforms are approved, and their manufacturing is expected to start. Only the stainless-steel equipment facilities of these platforms are expected to be active, while the single-use equipment facilities are expected to be idle. Both the LAV and RNA platforms are connected with the VV platform's stainless-steel manufacturing facility, however, it cannot receive its capacity. The number of production lines available to all three platforms is 10, and is expected to remain as such.

Case ten represents the capacity shifting between the LAV, RNA, and VV platforms over six consecutive periods; the results are given in Table E.46.

Table E.46: Case 10 for the capacity shift of stainless-steel equipment facilities

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
SS flexibility = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SS flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 4	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0

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Conditions	**Expected Results**	**Results**
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 5		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
Period 6		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SS flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 10	VVFacilitySS lines = 10
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked: false	✓

At the start of period one, the LAV platform is approved, and its manufacturing is expected to start. Only the LAV platform's stainless-steel equipment facility is expected to be active, while the single-use equipment facility is expected to be idle. Both the VV platform's facilities are expected to be idle. The LAV platform is connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the LAV platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be one. At the start of period three, the RNA platform is approved, and its manufacturing is expected to start. Only the RNA platform's stainless-steel equipment facility is expected to be active, while the single-use equipment facility is expected to be idle. The RNA platform is also connected to the VV platform's stainless-steel facility, however, due to the time delay, it can only receive the additional capacity at the start of period five. Since the number of connections with the VV platform's stainless-steel facility has increased to two, and the LAV platform only receives half of the available capacity, and its number of production

lines for the stainless-steel facility is expected to be 15 at the start of period three, while the number of production lines for the RNA platform's stainless-steel facility is expected to be 10. At the start of period four, the VV platform is approved. The number of production lines for both the LAV and RNA platforms is expected to be 10, The number of connections with the VV platform's stainless-steel manufacturing facility should be reduced to zero. The number of production lines for the VV platform remains 0, and the entrance to its stainless-steel equipment manufacturing facility remains locked. At the start of period six, the entrance to the stainless-steel VV facility should be opened, and the number of production lines available to the VV platform's stainless-steel facility is expected to be 10.

Case eleven represents the capacity shifting between the LAV, RNA, and VV platforms over five consecutive periods; the results are given in Table E.47.

Table E.47: Case 11 for the capacity shift of stainless-steel equipment facilities

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓

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Conditions	Expected Results	Results
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
Period 4		
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
Period 5		
ConnectLAV = true	LAVFacilitySS lines = 20	LAVFacilitySS lines = 20
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓

At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Only the LAV and RNA platforms' stainless-steel equipment facilities are expected to be active, while the single-use equipment facilities are expected to be idle. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the both the LAV and the RNA platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be two. At the start of period three, the RNA platform is rejected. The number of production lines for the RNA platform should be reduced to 10, The number of connections with the VV platform's stainless-steel manufacturing facility should be reduced to one. The number of production lines available to the LAV platform is expected to

be 15. The LAV platform can receive the additional capacity initially assigned to the RNA platform, but a time delay has to be enforced. At the start of period five, the number of production lines available to the LAV platform's stainless-steel equipment facility should increase to 20.

Case twelve represents the capacity shifting between the LAV, RNA, and VV platforms over six consecutive periods; the results are given in Table E.48.

Table E.48: Case 12 for the capacity shift of stainless-steel equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 15	RNAFacilitySS lines = 15
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 4	
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0

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Conditions	**Expected Results**	**Results**
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
Period 5		
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
Period 6		
ConnectLAV = true	LAVFacilitySS lines = 20	LAVFacilitySS lines = 20
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓

At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Only the LAV and RNA platforms' stainless-steel equipment facilities are expected to be active, while the single-use equipment facilities are expected to be idle. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the both the LAV and the RNA platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be two.

The number of production lines available to both the LAV and RNA platforms' stainless steel facilities is expected to increase to 15 at the start of period three. At the start of period four, the RNA platform is rejected. The number of production lines for the RNA platform should be reduced to 10, The number of connections with the VV platform's stainless-steel manufacturing facility should be reduced to one. The number of production lines available to the LAV platform is expected to be 15. The LAV platform can receive the additional capacity initially assigned to the RNA platform, but a time delay has to be enforced. At the start of period six, the number of production lines available to the LAV platform's stainless-steel equipment facility should increase to 20.

Case thirteen represents the capacity shifting between the LAV, RNA, and VV platforms over four consecutive periods; the results are given in Table E.49.

Table E.49: Case 13 for the capacity shift of stainless-steel equipment facilities

Conditions	**Expected Results**	**Results**
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0

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Conditions	Expected Results	Results
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
Period 4		
ConnectLAV = true	LAVFacilitySS lines = 20	LAVFacilitySS lines = 20
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓

At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Only the LAV and RNA platforms' stainless-steel equipment facilities are expected to be active, while the single-use equipment facilities are expected to be idle. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the both the LAV and the RNA platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be two. At the start of period two, the RNA platform is rejected. The number of production lines for the RNA platform should be reduced to 10, The number of connections with the VV platform's stainless-steel manufacturing facility should be reduced to one. The number of production lines available to the LAV platform is expected to be 10. The LAV platform can receive the additional capacity initially assigned to the RNA platform, but a time delay has to be enforced. At the start of period three, production lines available to the LAV platform's stainless-steel equipment facility should increase to 15, while it should increase to 20 at the start of period four.

Case fourteen represents the capacity shifting between the LAV, RNA, and VV platforms over five consecutive periods; the results are given in Table E.50.

Table E.50: Case 14 for the capacity shift of stainless-steel equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SU flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
	Period 4	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SU flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓

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Conditions	Expected Results	Results
	RNAFacilitySU entrancelocked	✓
Period 5		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SU flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 10	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓

At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Only the LAV and RNA platforms' stainless-steel equipment facilities are expected to be active, while the single-use equipment facilities are expected to be idle. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the both the LAV and the RNA platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be two. At the start of period three, the RNA platform is rejected, while the VV platform is approved. The number of production lines for both the LAV and RNA platforms is expected to be 10, The number of connections with the VV platform's stainless-steel manufacturing facility should be reduced to zero. The number of production lines for the VV platform remains 0, and the entrance to its stainless-steel equipment manufacturing facility remains locked. At the start of period five, the entrance to the stainless-steel VV facility should be opened, and the number of production lines available to the VV platform's stainless-steel facility is expected to be 10.

Case fifteen represents the capacity shifting between the LAV, RNA, and VV platforms over six consecutive periods; the results are given in Table E.51.

Table E.51: Case 15 for the capacity shift of stainless-steel equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 15	LAVFacilitySS lines = 15
ConnectRNA = true	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
SU flexibility = true	RNAFacilitySS lines = 15	RNAFacilitySS lines = 15
LAVAndVV = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
RNAAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	Period 4	
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SU flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
	Period 5	

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Conditions	Expected Results	Results
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SU flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 0	VVFacilitySS lines = 0
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
Period 6		
ConnectLAV = true	LAVFacilitySS lines = 10	LAVFacilitySS lines = 10
ConnectRNA = false	LAVFacilitySU lines = 0	LAVFacilitySU lines = 0
ConnectVV = true	RNAFacilitySS lines = 10	RNAFacilitySS lines = 10
SU flexibility = true	RNAFacilitySU lines = 0	RNAFacilitySU lines = 0
LAVAndVV = true	VVFacilitySS lines = 10	VVFacilitySS lines = 10
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓

At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Only the LAV and RNA platforms' stainless-steel equipment facilities are expected to be active, while the single-use equipment facilities are expected to be idle. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's stainless-steel manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period three, and the number of production lines available to the both the LAV and the RNA platform's stainless-steel equipment facility should be 10. The entrance to the VV platform's stainless-steel manufacturing facility should be locked, and its number of production lines should be zero. The number of connections with the VV platform's facility should be two. The number of production lines available to both the LAV and RNA platforms' stainless-steel facilities is expected to be 15 at the start of period three. At the start of period four, the RNA platform is rejected, while the VV platform is approved. The number of production lines for both the LAV and RNA platforms is expected to be 10, The number of connections with the VV platform's stainless-steel manufacturing facility should be reduced to zero. The number of production lines for the VV platform remains 0, and the entrance to its

stainless-steel equipment manufacturing facility remains locked. At the start of period six, the entrance to the stainless-steel VV facility should be opened, and the number of production lines available to the VV platform's stainless-steel facility is expected to be 10.

E.4.2 Approach two

Case one represents the capacity shifting between the LAV and VV platforms over two consecutive periods; the results are given in Table E.52. At the start of period one, the LAV platform is approved, and its

Table E.52: Case 1 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
SU flexibility = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
SU flexibility = true	LAVFacilitySU lines = 10	LAVFacilitySU lines = 10
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓

manufacturing is expected to start. Both the stainless-steel equipment facility and the single-use equipment facilities for the LAV platform are expected to be active. Both the VV platform's facilities are expected to be idle. The LAV platform is connected with the VV platform's single-use manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period two, and the number of production lines available to both the single-use and stainless-steel equipment facilities for the LAV platform should be 5. The entrance to the VV platform's single-use and stainless-steel manufacturing facilities should be locked, and the number of production lines should be zero. The number of connections with the VV platform's facility should be one. At the start of period two, the number of production lines available to the LAV platform's single-use equipment facility should increase to 10.

Case two represents the capacity shifting between the LAV and VV platforms over three consecutive periods; the results are given in Table E.53. At the start of period one, the LAV platform is approved,

Table E.53: Case 2 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
Period 1		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
SU flexibility = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
Period 2		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 7	LAVFacilitySU lines = 7
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
Period 3		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 7	LAVFacilitySU lines = 7
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 7	RNAFacilitySU lines = 7
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓

and its manufacturing is expected to start. Both the stainless-steel equipment facility and the single-use equipment facilities for the LAV platform are expected to be active. Both the VV platform's facilities are expected to be idle. The LAV platform is connected with the VV platform's single-use manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period two, and the number of production lines available to both the single-use and stainless-steel equipment facilities for the LAV platform should be 5. The entrance to the VV platform's single-use manufacturing facilities should be locked, and the number of production lines should be zero. The number of production lines available to the VV platform's stainless-steel facility should be five. The number of connections with the VV platform's single-use facility should be one. At the start of period two, the RNA platform is approved, and its manufacturing is expected to start. Both the RNA platform's stainless-steel and single-use equipment facilities are expected to be active. The RNA platform is also connected to the VV platform's single-use facility, however, due to the time delay, it can only receive the additional capacity at the start of period three. Since the number of connections with the VV platform's single-use facility has increased to two, the LAV platform only receives half of the available capacity, and its number of production lines for the single-use facility should be 7 at the start of period three, while the number of production lines for the RNA platform's single-use facility is expected to be 5. The number of production lines available to the RNA platform's single-use facility is expected to increase to 7 at the start of period three.

Case three represents the capacity shifting between the LAV, RNA and VV platforms over two consecutive periods; the results are given in Table E.54. At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms are expected to be active. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's single-use manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period two, and the number of production lines available to the both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms should be 5. The entrance to the VV platform's single-use manufacturing facility should be locked, and its number of production lines should be zero. The number of production lines available to the VV platform's stainless-steel facility should be five. The number of connections with the VV platform's facility should be two. The number of production lines available to both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms is expected to increase to 7 at the start of period three.

Case four represents the capacity shifting between the LAV, RNA and VV platforms over four consecutive periods; the results are given in Table **??**. At the start of period one, the LAV platform is approved, and its manufacturing is expected to start. Both the stainless-steel equipment facility and the single-use equipment facilities for the LAV platform are expected to be active. Both the VV platform's facilities are expected

Table E.54: Case 3 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 7	LAVFacilitySU lines = 7
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 7	RNAFacilitySU lines = 7
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓

to be idle. The LAV platform is connected with the VV platform's single-use manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period two, and the number of production lines available to both the single-use and stainless-steel equipment facilities for the LAV platform should be five. The entrance to the VV platform's single-use manufacturing facilities should be locked, and the number of production lines should be zero. The number of production lines available to the VV platform's stainless-steel facility should be five. The number of connections with the VV platform's single-use facility should be one. The number of production lines available to the LAV platform's single-use equipment should increase to 10 at the start of period two. At the start of period three, the RNA platform is approved, and its manufacturing is expected to start. Both the RNA platform's stainless-steel and single-use equipment facilities are expected to be active. The RNA platform is also connected to the VV platform's single-use facility, however, due to the time delay, it can only receive the additional capacity at the start of period four. Since the number of connections with the VV platform's single-use facility has increased to two, the LAV platform only receives half of the available capacity, and its number of production lines for the single-use facility should be 7 at the start of period three, while the number of production lines for the RNA platform's single-use facility is expected to be 5. The number of production lines available to the RNA platform's single-use facility is expected to increase to 7 at the start of period four.

Table E.55: Case 4 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
SU flexibility = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
SU flexibility = true	LAVFacilitySU lines = 10	LAVFacilitySU lines = 10
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 7	LAVFacilitySU lines = 7
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 4	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 7	LAVFacilitySU lines = 7
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 7	RNAFacilitySU lines = 7
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓

Case five represents the capacity shifting between the LAV, RNA and VV platforms over two consecutive periods; the results are given in Table E.56. At the start of period one, the LAV, RNA, and VV platforms are

Table E.56: Case 5 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
Period 1		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
ConnectVV = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
SU flexibility = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
RNAAndVV = true	VVFacilitySU lines = 5	VVFacilitySU lines = 5
	NumberVV = 0	NumberVV = 0
Period 2		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
ConnectVV = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
SU flexibility = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
RNAAndVV = true	VVFacilitySU lines = 5	VVFacilitySU lines = 5
	NumberVV = 0	NumberVV = 0

approved, and their manufacturing is expected to start. Both these platforms' stainless-steel and single-use equipment facilities are expected to be active. Both the LAV and RNA platforms are connected with the VV platform's single-use manufacturing facility, however, it cannot receive its capacity. The number of production lines available to all three of the platforms' stainless-steel and single-use equipment facilities is 5, and is expected to remain as such.

Case six represents the capacity shifting between the LAV, RNA and VV platforms over three consecutive periods; the results are given in Table E.57. At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms are expected to be active. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's single-use manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period two, and the number of production lines available to the both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms should be 5. The entrance to the VV platform's single-use manufacturing facility should be locked, and its number of production lines should be zero. The number of production lines available to the VV platform's stainless-steel facility should be five. The number of connections with the VV platform's facility should be two. At the start of period two, the VV platform is approved, and its manufacturing is expected to

Table E.57: Case 6 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
ConnectVV = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
SU flexibility = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
ConnectVV = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
SU flexibility = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
RNAAndVV = true	VVFacilitySU lines = 5	VVFacilitySU lines = 5
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked: false	✓

start at the stainless-steel equipment facility. The number of production lines for both the stainless-steel and the single-use equipment facilities for the LAV and RNA platforms is expected to be 5. The number of connections with the VV platform's single-use manufacturing facility should be reduced to zero. The number of production lines for the VV platform's single-use facility remains 0, and the entrance to its manufacturing facility remains locked. At the start of period three, the entrance to the single-use VV facility should be opened, and the number of production lines available to the VV platform's single-use facility is expected to be 5.

Case seven represents the capacity shifting between the LAV, RNA and VV platforms over four consecutive periods; the results are given in Table E.58. At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms are expected to be active. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's single-use manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period two, and the number of production lines available to the both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms should be 5. The entrance to the VV platform's single-use manufacturing facility should be locked, and its number of production lines should be zero. The number of production lines available to the VV platform's stainless-steel facility should be five. The number of connections with the VV platform's facility should be two. The number of production lines available to the single-use equipment facilities for the LAV and RNA platforms should increase to 7 at the start of period two. At the start of period three, the VV platform is approved, and its manufacturing is expected to start at the stainless-steel equipment facility. The number of production lines for both the stainless-steel and the single-use equipment facilities for the LAV and RNA platforms is expected to be 5. The number of connections with the VV platform's single-use manufacturing facility should be reduced to zero. The number of production lines for the VV platform's single-use facility remains 0, and the entrance to its manufacturing facility remains locked. At the start of period four, the entrance to the single-use VV facility should be opened, and the number of production lines available to the VV platform's single-use facility is expected to be 5.

Case eight represents the capacity shifting between the LAV, RNA and VV platforms over four consecutive periods; the results are given in Table E.59. At the start of period one, the LAV platform is approved, and its manufacturing is expected to start. Both the stainless-steel equipment facility and the single-use equipment facilities for the LAV platform are expected to be active. Both the VV platform's facilities are expected to be idle. The LAV platform is connected with the VV platform's single-use manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period two, and the number of production lines available to both the single-use and stainless-steel equipment facilities for the LAV platform should be 5. The entrance to the VV platform's

Table E.58: Case 7 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
Period 1		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
Period 2		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 7	LAVFacilitySU lines = 7
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 7	RNAFacilitySU lines = 7
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
Period 3		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
ConnectVV = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
SU flexibility = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked	✓
Period 4		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
ConnectVV = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
SU flexibility = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
RNAAndVV = true	VVFacilitySU lines = 5	VVFacilitySU lines = 5
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked: false	✓

Table E.59: Case 8 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
SU flexibility = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 7	LAVFacilitySU lines = 7
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
ConnectVV = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
SU flexibility = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked	✓
	Period 4	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
ConnectVV = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
SU flexibility = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
RNAAndVV = true	VVFacilitySU lines = 5	VVFacilitySU lines = 5
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked: false	✓

single-use and stainless-steel manufacturing facilities should be locked, and the number of production lines should be zero. The number of connections with the VV platform's facility should be one. At the start of period two, the RNA platform is approved, and its manufacturing is expected to start. Both the RNA platform's stainless-steel and single-use equipment facilities are expected to be active. The RNA platform is also connected to the VV platform's single-use facility, however, due to the time delay, it can only receive the additional capacity at the start of period three. Since the number of connections with the VV platform's single-use facility has increased to two, the LAV platform only receives half of the available capacity, and its number of production lines for the single-use facility should be 7 at the start of period two, while the number of production lines for the RNA platform's single-use facility is expected to be five. At the start of period three, the VV platform is approved, and its manufacturing is expected to start at the stainless-steel equipment facility. The number of production lines for both the stainless-steel and the single-use equipment facilities for the LAV and RNA platforms is expected to be 5. The number of connections with the VV platform's single-use manufacturing facility should be reduced to zero. The number of production lines for the VV platform's single-use facility remains 0, and the entrance to its manufacturing facility remains locked. At the start of period four, the entrance to the single-use VV facility should be opened, and the number of production lines available to the VV platform's single-use facility is expected to be five.

Case nine represents the capacity shifting between the LAV, RNA and VV platforms over three consecutive periods; the results are given in Table E.60. At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms are expected to be active. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's single-use manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period two, and the number of production lines available to the both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms should be 5. The entrance to the VV platform's single-use manufacturing facility should be locked, and its number of production lines should be zero. The number of production lines available to the VV platform's stainless-steel facility should be five. The number of connections with the VV platform's facility should be two. At the start of period two, the RNA platforms are rejected, and the number of production lines for both the single-use and stainless-steel equipment should be 5. The number of production lines available to single-use equipment facility for the LAV platforms is expected to increase to 7 at the start of period two. The LAV platform can receive the additional capacity initially assigned to the RNA platform, but a time delay has to be enforced. At the start of period three, production lines available to the LAV platform's single-use equipment facility should increase to 10.

Case ten represents the capacity shifting between the LAV, RNA and VV platforms over four consecutive periods; the results are given in Table E.61.

Table E.60: Case 9 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
Period 1		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
Period 2		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = false	LAVFacilitySU lines = 7	LAVFacilitySU lines = 7
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
Period 3		
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = false	LAVFacilitySU lines = 10	LAVFacilitySU lines = 10
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓

Table E.61: Case 10 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 7	LAVFacilitySU lines = 7
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 7	RNAFacilitySU lines = 7
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = false	LAVFacilitySU lines = 7	LAVFacilitySU lines = 7
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
	Period 4	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = false	LAVFacilitySU lines = 10	LAVFacilitySU lines = 10
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 1	NumberVV = 1
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	RNAFacilitySS entrancelocked	✓

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Conditions	Expected Results	Results
	RNAFacilitySU entrancelocked	✓

At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms are expected to be active. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's single-use manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period two, and the number of production lines available to the both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms should be 5. The entrance to the VV platform's single-use manufacturing facility should be locked, and its number of production lines should be zero. The number of production lines available to the VV platform's stainless-steel facility should be five. The number of connections with the VV platform's facility should be two. The number of production lines for the single-use equipment facilities for the LAV and RNA platforms should increase to 7 at the start of period two. At the start of period three, the RNA platforms are rejected, and the number of production lines for both the single-use and stainless-steel equipment should be 5. The LAV platform can receive the additional capacity initially assigned to the RNA platform, but a time delay has to be enforced. At the start of period four, production lines available to the LAV platform's single-use equipment facility should increase to 10.

Case eleven represents the capacity shifting between the LAV, RNA and VV platforms over four consecutive periods; the results are given in Table E.62. At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms are expected to be active. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's single-use manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period two, and the number of production lines available to the both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms should be 5. The entrance to the VV platform's single-use manufacturing facility should be locked, and its number of production lines should be zero. The number of production lines available to the VV platform's stainless-steel facility should be five. The number of connections with the VV platform's facility should be two. At the start of period two, the RNA platform is rejected, and the number of production lines for both the single-use and stainless-steel equipment should be 5. The VV platform is also approved, and its manufacturing is expected to start at the stainless-steel equipment facility. The number of production lines for both the stainless-steel and the single-use equipment facilities for the LAV and RNA platforms is

Table E.62: Case 11 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = false	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
ConnectVV = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
SU flexibility = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = false	LAVFacilitySU lines = 10	LAVFacilitySU lines = 10
ConnectVV = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
SU flexibility = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
RNAAndVV = true	VVFacilitySU lines = 5	VVFacilitySU lines = 5
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓

expected to be 5. The number of connections with the VV platform's single-use manufacturing facility should be reduced to zero. The number of production lines for the VV platform's single-use facility remains 0, and the entrance to its manufacturing facility remains locked. At the start of period three, the entrance to the single-use VV facility should be opened, and the number of production lines available to the VV platform's single-use facility is expected to be five.

Case twelve represents the capacity shifting between the LAV, RNA and VV platforms over four consecutive periods; the results are given in Table E.63.

Table E.63: Case 12 for the capacity shift of single-use equipment facilities

Conditions	Expected Results	Results
	Period 1	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 2	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = true	LAVFacilitySU lines = 7	LAVFacilitySU lines = 7
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 7	RNAFacilitySU lines = 7
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 2	NumberVV = 2
	VVFacilitySS entrancelocked	✓
	VVFacilitySU entrancelocked	✓
	Period 3	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = false	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
ConnectVV = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
SU flexibility = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
LAVAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
RNAAndVV = true	VVFacilitySU lines = 0	VVFacilitySU lines = 0
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓

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Conditions	Expected Results	Results
	Period 4	
ConnectLAV = true	LAVFacilitySS lines = 5	LAVFacilitySS lines = 5
ConnectRNA = false	LAVFacilitySU lines = 5	LAVFacilitySU lines = 5
SU flexibility = true	RNAFacilitySS lines = 5	RNAFacilitySS lines = 5
LAVAndVV = true	RNAFacilitySU lines = 5	RNAFacilitySU lines = 5
RNAAndVV = true	VVFacilitySS lines = 5	VVFacilitySS lines = 5
	VVFacilitySU lines = 5	VVFacilitySU lines = 5
	NumberVV = 0	NumberVV = 0
	VVFacilitySS entrancelocked: false	✓
	VVFacilitySU entrancelocked: false	✓
	RNAFacilitySS entrancelocked	✓
	RNAFacilitySU entrancelocked	✓

At the start of period one, both the LAV and the RNA platforms are approved, and their manufacturing is expected to start. Both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms are expected to be active. Both the VV platform's facilities are expected to be idle. Both the LAV and the RNA platforms are connected with the VV platform's single-use manufacturing facility and can thus receive its capacity. Due to the time delay for the facility, the capacity can only be shifted at the start of period two, and the number of production lines available to the both the stainless-steel and single-use equipment facilities for the LAV and RNA platforms should be 5. The entrance to the VV platform's single-use manufacturing facility should be locked, and its number of production lines should be zero. The number of production lines available to the VV platform's stainless-steel facility should be five. The number of connections with the VV platform's facility should be two. The number of production lines available to the single-use equipment facilities for the LAV and RNA platforms should increase to seven at the start of period two. At the start of period three, the RNA platform is rejected, and the number of production lines for both the single-use and stainless-steel equipment should be 5. The VV platform is also approved, and its manufacturing is expected to start at the stainless-steel equipment facility. The number of production lines for both the stainless-steel and the single-use equipment facilities for the LAV and RNA platforms is expected to be 5. The number of connections with the VV platform's single-use manufacturing facility should be reduced to zero. The number of production lines for the VV platform's single-use facility remains 0, and the entrance to its manufacturing facility remains locked. At the start of period four, the entrance to the single-use VV facility should be opened, and the number of production lines available to the VV platform's single-use facility is expected to be five.

Appendix F

Interview guide

The interview guide used for the SME interviews as part of the validation process are provided in this Appendix. The interview guide is divided into different sections, namely: Background on participant, Introduction, Contextual perspective, Manufacturing of vaccines, Process flexibility, Shifting of capacity, Measurement of flexibility, Approval of vaccines, and Rejection of vaccines.

F.1 Background on participant

Q: Do you have any relevant expertise in vaccine manufacturing, and could you elaborate on the expertise if applicable?

Q: Do you have any relevant expertise on process flexibility in manufacturing, and could you elaborate on the expertise if applicable?

Q: How many years of relevant work experience do you have?

Q: What is your affiliation with the relevant fields (academic, industry, etc.)?

Q: What are your academic qualifications?

F.2 Introduction

The study aims to investigate the impact of process flexibility on the manufacturing system of Covid-19 vaccines. This is achieved by representing the manufacturing system as a discrete-event simulation model. The manufacturing considered in the model refers to the manufacturing of the active drug substance (i.e., formulation, manufacturing, harvesting, and purification of the antigen) but does not consider the fill and finishing steps for the final vaccine product. The manufacturing of the following vaccine platforms, over five years, are considered: live attenuated virus, inactivated virus, subunit, viral vector, DNA, and RNA. The manufacturing capacity for each vaccine platform is represented by a number of production lines for

a single facility manufacturing each vaccine platform. Each production line for a manufacturing facility is assumed to have the same processing time (e.g., the processing time for all live attenuated virus vaccines is identical). The model incorporates process flexibility in the manufacturing system to evaluate the impact on the system. Process flexibility is defined as a system's ability to shift manufacturing capacity between the products in the system. The capacity is generally shifted from a product with low demand to a product with high demand to increase the system's overall effectiveness. Process flexibility is incorporated into a system by constructing flexible manufacturing systems, in which the manufacturing process, structured for the manufacturing of a specific product, can be adjusted to produce other products. A few examples of process flexibility configurations for the manufacturing system of Covid-19 vaccines are shown in Figures F.1 (a) – (c). Figure F.1 (a) represents a manufacturing system with no process flexibility, i.e., each facility can only produce one type of product, while Figure F.1 (c) represents a system with total flexibility, i.e., all the facilities can produce all the products in the system. Figure F.1 (b) represents a system with limited process flexibility, in which a facility can only manufacture certain products. This interview aims to gain insights

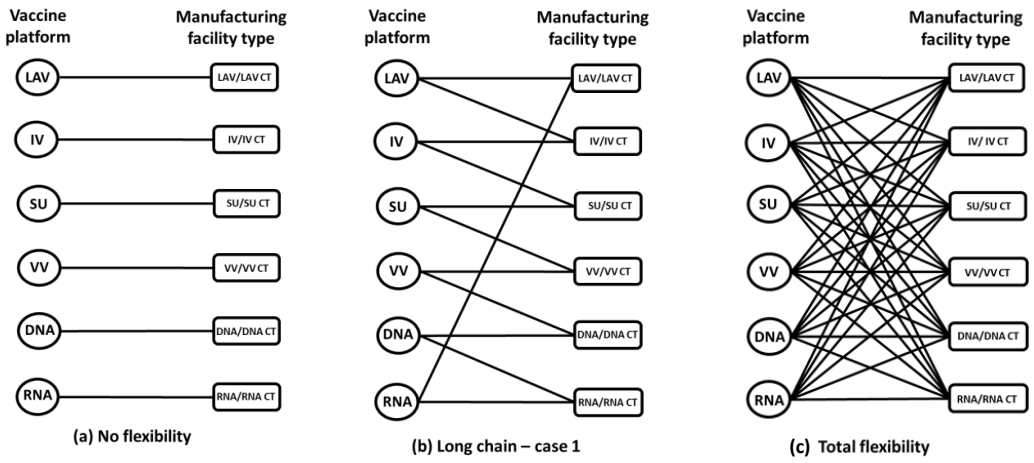

Figure F.1: Different process flexibility configurations

regarding certain aspects of vaccine manufacturing, such as processing times and available capacity, adding process flexibility to the vaccine manufacturing system, and approving and rejecting vaccine products for the Covid-19 vaccine manufacturing system.

F.3 Contextual perspective

Q: If you consider vaccine manufacturing from a system's perspective, and you think back to the period before any Covid-19 vaccines had been authorised for use, can you provide insights on challenges that

potential manufacturers of Covid-19 vaccines may have faced in ensuring that they would be ready to start producing a vaccine as soon as possible after it had received regulatory approval?

Q: Do you know to what extent did uncertainty regarding the vaccine platform(s) that would receive regulatory approval contribute to difficulty in terms of preparing manufacturing capacity?

Q: Are you aware of any vaccine manufacturing facilities worldwide that have been designed to enable process flexibility in terms of being adjusted from producing vaccines of one platform to producing vaccines of another platform?

Q: If you think about vaccine manufacturing facilities worldwide, are these generally constructed to produce a specific vaccine product (e.g. the BCG) or is it unremarkable for facilities to switch between the manufacturing of different vaccine products (even if all of these products are of the same platform)?

Q: Could you provide some insight into how manufacturers were able to meet the demand for Covid-19 vaccines?

- Were these generally produced in new manufacturing facilities that had been constructed specifically to accommodate the demand for Covid-19 vaccines?
- Furthermore, do you have insight into decision-making regarding the construction of these facilities – for example, did pharmaceutical organisations typically wait until a candidate vaccine had passed a specific milestone in the RD process before deciding to construct/modify/prepare a facility that would be able to produce that vaccine?
- Do you have any insight on whether pharmaceutical organisations shared information on promising vaccine candidates with potential contract manufacturers to enable them to make informed decisions on the construction of new manufacturing capacity for specific platforms?

F.4 Manufacturing of vaccines

Q: What do you consider to be the typical unit of measurement used to quantify the output of the active vaccine substance (that would typically be produced via bulk manufacturing rather than in a fill and finish facility)?

Q: Would you expect to see a difference in the processing times for contractor vaccine manufacturers and licensed vaccine manufacturers?

Q: In your opinion, would it be typical to expect bulk manufacturing times for different vaccines of the same platform (e.g. Pfizer-BioNTech and Moderna, which are both RNA vaccines) to differ significantly, or would it be reasonable to assume that bulk manufacturing times for various vaccines of the same platform are relatively similar?

Q: Focusing only on bulk manufacturing (i.e. excluding fill and finish activities), can you provide an indication of the typical, worst, and best processing times for vaccine products for each of these platforms in terms of the unit of measurement given in Q2? (Table F.1 gives an example of how this data may be captured.)

Table F.1: Processing time per measurement unit for each vaccine platform

	Processing time/measurement unit	
Vaccine platform facility (private/contractor)	**Contractor vaccine manufacturer**	**In-house manufacturer**
LAV		
IV		
SP		
VV		
DNA		
RNA		

Q: Are you aware of a publication or database that can give insight on global vaccine manufacturing capacity per platform? (I.e. not for Covid-19 vaccines specifically, but in general.)

Q: Do you have any insight into how the available global vaccine manufacturing capacity (for bulk manufacturing and fill and finish) is split between contract and in-house manufacturers?

Q: Do you have any insight into the proportion of global vaccine manufacturing capacity currently dedicated to producing Covid-19 vaccines?

Q: Do you know how the available capacity, mentioned in Q7, is divided between the contractor and licensed vaccine manufacturers?

F.5 Process flexibility

Q: Do you know whether process flexibility, as defined in the introduction, has been implemented in the manufacturing system of vaccine products?

Q: In your opinion, is it more likely that contract manufacturers will be interested in a flexible manufacturing system than established in-house manufacturers, or would it be equally appealing for both manufacturers?

Q: In your opinion, would it be reasonable to assume that if a contractor vaccine manufacturer can implement a specific process flexibility configuration (e.g. that a contract manufacturer's bulk manufacturing facility can be set up to switch between producing RNA and DNA vaccines), that an in-house vaccine manufacturer could have the same capability, and vice versa?

Q: Process flow diagrams have been drawn up for the manufacturing processes of each vaccine platform. Would you be able to validate the processes by answering the following questions?

- What information do you consider to still be lacking/insufficient on the process flow diagrams of each vaccine platform? Or are there inaccuracies?
- Can you provide the missing information/supplement to the insufficient information?
- Can you recommend any sources that provide detailed information on the manufacturing process for the vaccine platforms?

F.6 Shifting of capacity

The process flexibility incorporated into the system allows the capacity, which is intended to manufacture a specific vaccine platform's products, to be shifted to the manufacturing of other platforms' products. When the capacity is shifted from one platform to another, the manufacturing facility must be adjusted to allow for the new platform's manufacturing, resulting in a delay before the capacity is available. For the model, it is assumed that a facility will experience a set delay when receiving capacity, regardless of the source of the capacity (e.g. the RNA platform's facility will experience the same delay for capacity received from the LAV platform and capacity received from the DNA platform). Creating a process flexible system requires an initial investment. Process flexible manufacturing systems are associated with two types of costs, namely: initial investment costs and switch-over costs. The initial investment costs are utilised to construct a system with flexible production lines, which can produce more than one product. The switch-over cost is incurred each time a production line and/or manufacturing facility must be adjusted to produce a new product. A requirement for the model is to have the change-over time and change-over costs for the possible flexible configurations, as indicated in Table F.2. Q: Which vaccine platforms do you think could feasibly be combined so that a manufacturing facility could be designed with the capability to switch between the production of different platforms?

Q: Can you give an indication of typical expected change-over times for such flexible manufacturing facilities?

Q: Do you expect that there would be any difference in the change-over times for contractor vaccine manufacturers and licensed vaccine manufacturers?

Q: Can you give an indication of the change-over times that will occur for the shifting of capacity between each of the vaccine platforms?

- If YES, then ask if the interviewee can specify separate change-over times for different platform combinations.

Q: Can you estimate an order of magnitude cost for constructing a manufacturing facility with process flexibility versus one with no flexibility?

Q: Can you provide an indication of the construction costs that may be required to construct each of the flexible configurations?

- If monetary values cannot be given, estimated rankings of relative costs would also be valuable.

Q: Do you envision that there would be any difference in the change-over costs for contractor vaccine manufacturers and in-house vaccine manufacturers?

Q: Can you provide an indication of typical change-over costs that are experienced when shifting capacity in a process flexible manufacturing system?

- If monetary values cannot be given, estimated rankings would also be valuable.
- If YES, then ask the interviewee if they can specify separate change-over costs.

Q: Can you provide an indication of the switch-over costs that may be incurred for shifting capacity between each of the vaccine platforms?

- If monetary values cannot be given, estimated rankings would also be valuable
- If YES, then ask the interviewee if they can specify separate change-over costs for each platform-combination

Table F.2: Switch-over time and costs for different vaccine platforms

		Vaccine platform											
		LAV		IV		SP		VV		DNA		RNA	
Type of platform facility		Time[1]	Cost[2]	Time[1]	Cost[2]	Time[1]	Cost[2]	Time[1]	Cost[2]	Time[1]	Cost[2]	Time[1]	Cost[2]
	LAV	N/A	N/A										
	LAV CT	N/A											
	IV			N/A	N/A								
	IV CT			N/A									
	SP					N/A	N/A						
	SP CT					N/A							
	VV							N/A	N/A				
	VV CT							N/A					
	DNA									N/A	N/A		
	DNA CT									N/A			
	RNA											N/A	N/A
	RNA CT											N/A	

Notes: [1] Change-over time is measured in months. The change-over time is N/A if it is judged infeasible to link a platform and facility.
[2] The change-over cost is either an estimated value or a ranking (Low, medium, high).

F.7 Measurement of flexibility

As mentioned in the introduction, the main goal of the model is to evaluate the impact of process flexibility on the manufacturing system of Covid-19 vaccines. Process flexibility is associated with costs, including the initial construction costs and the switch-over costs incurred each time the facility is adjusted to manufacture a vaccine on a different platform. It is proposed that different process flexibility configurations will be distinguished by considering the construction costs associated with a configuration and that the performance of the system will be measured by the overall throughput of vaccine products for the system. It is assumed that the switch-over costs will be much smaller in order of magnitude compared to the construction costs and can thus be ignored when considering different process flexibility configurations. It is further proposed that a trade-off between the cost of a process flexibility configuration and the throughput for the system can be considered, as shown in Figure F.2. The cost is presented as an estimated rating.

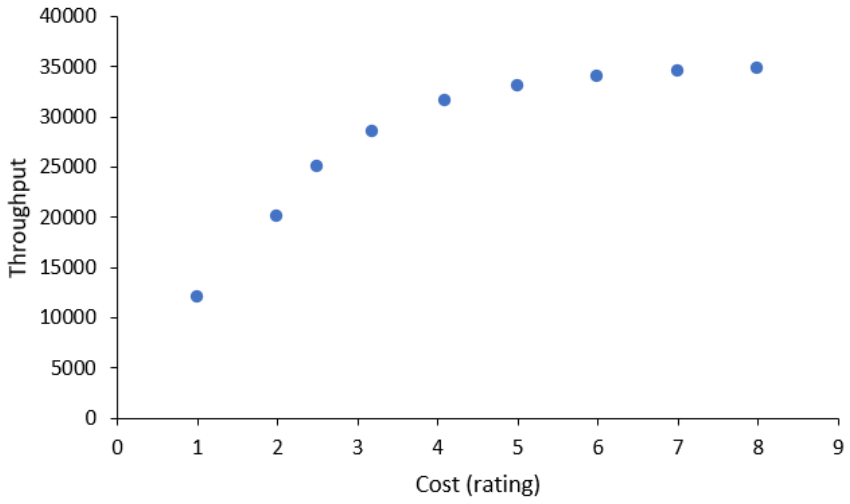

Figure F.2: Graphical representation of an example of process flexibility configuration evaluation

Q: In your opinion, is it reasonable to assume that the switch-over costs for a flexible configuration can be deemed negligible compared to its construction costs?

Q: What measurements are typically used to quantify the performance of a vaccine manufacturing system?

Q: Do you consider the throughput of the vaccine products as a valuable measurement for the performance of the manufacturing system of Covid-19 vaccines, or would you propose an alternative approach?

Q: What metrics are typically considered to evaluate the performance of alternative scenarios when constructing a new flexible facility?

Q: Do you deem evaluating the cost associated with a process flexibility configuration as an appropriate approach for the manufacturing system of Covid-19 vaccines, or would you propose an alternative approach?

F.8 Approval of vaccines

The approval of vaccines is considered at the platform level, and individual products for each platform are ignored. The manufacturing of a platform starts when the first product becomes approved and remains active until the platform becomes terminated (no product is approved for the platform at the time). The approval of vaccine platforms occurs stochastically based on each platform's probability of success distribution. The distribution is created via the following function, using the number of approvals for a platform over a three-year time-span in Table 3, as obtained from simulations performed by McDonnell et al. (2020):

$$POS_{Platform(t)} = (1 - e^{(-t)/\beta})$$

With: t = start of each period;

β = average time between approvals for a platform.

The average time between approvals is calculated as 36 months divided by the number of successes for the platform, indicated in Table F.3. The intention is to run the simulation over a five-year timespan and create the distribution by extending the results of McDonnell et al. (2020)'s work from 36 months to 60 months.

Table F.3: Results from simulation runs of McDonnell et al. (2020) for each vaccine platform

	Months to first success	Number of successes
Live attenuated virus	-	-
Subunit protein	20,9	2,42
Inactivated virus	11,6	1,63
RNA	12,8	1,75
Non-replicating viral vector	14,6	1,76
Replicating viral vector	27,9	1,14
DNA	30,4	1,06

Q: Do you deem the research performed by McDonnell et al. (2020) as a credible source? Does information on actual vaccine approvals that has become available after McDonnell et al. (2020) projections were published play a role in your assessment of the credibility of the source?

Q: Do you agree with the predictions for each platform obtained from the study?

- If NO: Can you provide any source(s) that provide more recent and accurate predictions for the approval of vaccine platforms over this time period?

F.9 Rejection of vaccines

Rejection of vaccine products is included in the model to represent the possibility that a vaccine product may be removed from the market after it has been approved for manufacturing, for example, due to safety concerns or because it may not offer sufficient protection against a new variant. However, the likelihood of a vaccine being rejected is deemed negligible in the model at present. It is also expected that incorporating the rejection of vaccine platforms in the model may obscure the results on the impact of process flexibility on the manufacturing system, which is the model's primary goal. The rejection of vaccine platforms can be ignored in the model by assigning zero probability of failure values for each platform. Even though the approval of vaccines is considered on the platform level, the process of rejecting vaccines can be adjusted to consider the number of products that would have been approved for a platform, if approval was considered on the product level, and only rejecting a single product for the platform. Consequently, the termination of a vaccine platform (de-activation of manufacturing) can be limited to the case where the platform would have no other approved products after the rejection of a product. Q: Does incorporating the possibility of vaccine rejection add to representing the reality of the system, or should it be ignored for the manufacturing system?

Q: Are you aware of any literature that provides insight on the probability that approved Covid-19 vaccine platforms may become rejected?

Q: If no literature is available on the probability of failure values for the Covid-19 vaccine platforms, are you willing to make an estimation of the likelihood of such rejection for vaccines of different platforms?

Appendix G

Box and whisker plots for vaccine platform approval time

The box and whisker plots for the approval times for the cell-based and bacterial platforms, refer to Chapter 7, are presented in this Appendix.

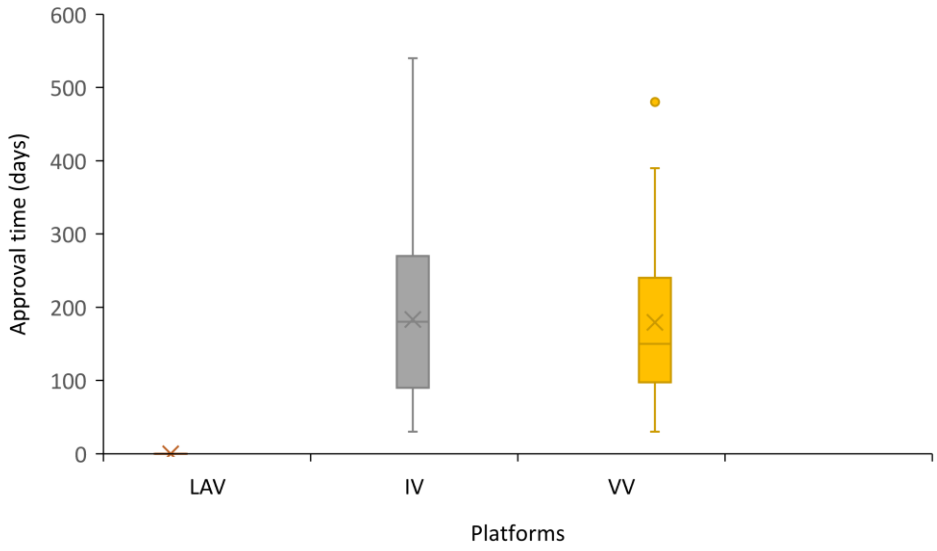

Figure G.1: Box and whisker plot for the approval of cell-based platforms

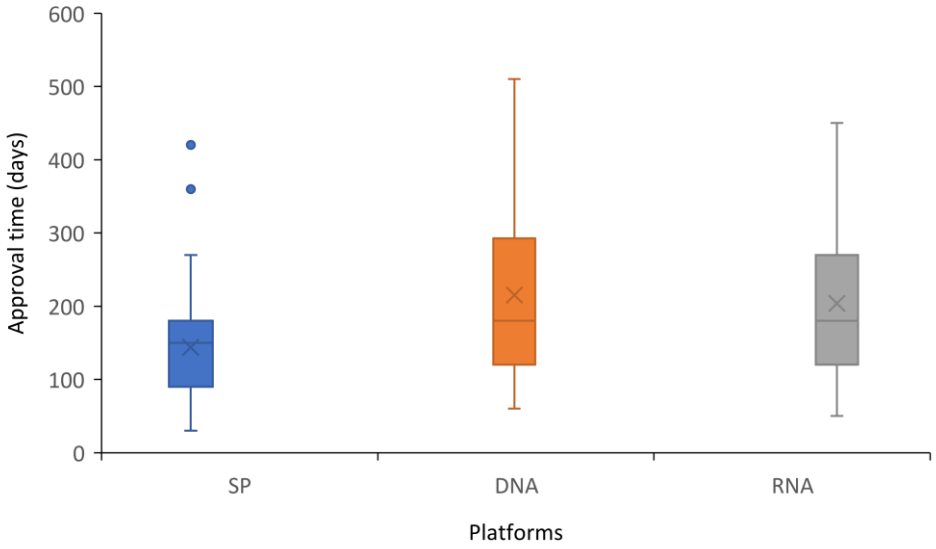

Figure G.2: Box and whisker plot for the approval of bacterial platforms