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Flexible manufacturing – utilizing disposable-based technology for Mab manufacturing in a multi-product facility

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Abstract

A fictive future monoclonal antibody production facility was modelled for manufacturing of several products. This was done to evaluate potential flexibility benefits and the economic feasibility of novel disposable-based manufacturing technology. A range of scenarios were identified were disposable-based technology was economic favourable compared to traditional stainless steel technology.

Keywords

Disposables, single-use technology, monoclonal antibodies, biopharmaceutical manufacturing, production simulation, scheduling, multi-product manufacturing

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Populärvetenskaplig sammanfattning

Användningen av engångsutrustning ökar inom produktionen av bioteknologiska molekyler, som antikroppar och proteinläkemedel. Idag finns engångsutrustning som alternativ för alla procedurer i produktionsprocessen; allt ifrån bioreaktorer upp till hundratals liter till engångskolonner upp till 20 L. Grundtanken är att allt material som kommer i kontakt med processvätskan ska bytas ut kontinuerligt. Istället för att använda dyr stålutrustning används istället material av plast. Implementering av den nya teknologin medför ökade kostnader för förbrukningsvaror, men teknologin har även en rad fördelar, däribland minskad risk för kontamination, ökad flexibilitet, minskade kapitalinvesteringar och ledtider, och färre rengöringsprocedurer.

I detta projekt utvärderades några utav flexibilitetsfördelarna med engångsutrustning vid produktion av monoklonala antikroppar i en fiktiv fabrik designad för produktion av flera produkter. Den nya engångsteknologin jämfördes också med traditionell stationär stålutrustning när det gäller produktionskostnaden per gram antikropp. Modeller för produktionsprocessen, schemaläggning och kostnadsberäkning utvecklades för en fabrik som antingen baserades på engångsutrustning eller traditionell teknologi.

Fabriken designades med en total reaktorvolym på 10 000 L och tillverkning för 10 produkter planerades. Fabriken som baserades på engångsutrustning fick en produktionskapacitet som var 34 procent högre än för den traditionella fabriken. Ett resultat som berodde på snabbare omställning mellan produkter och körningar inom samma produktkampanj. Engångsteknologin möjliggör en annan design av fabriken, vilket ledde till minskat behov av arbetskraft och bättre utnyttjning av utrustning. Trots fördelarna var, i basfallet, tillverkningskostnaden per gram antikropp högre i den nya fabriken, vilket framförallt berodde på höga kostnader för ett väldigt dyrt material (Protein A) som kan återanvändas många gånger i den traditionella processen. Om materialet kunde återanvändas 3 gånger i den nya processen var produktionskostnaderna lika. Vidare visade resultaten att engångsutrustning var att föredra vid låg kapacitetsutnyttjning och mindre skala. Resultaten visade en rad scenarios när fabriken baserad engångsutrustning gav en lägre tillverkningskostnad.

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Abbreviations

BNE	Bottleneck Equipment
COG	Cost of Goods
conv	Conventional
CIP	Cleaning in Place
DSP	Downstream processing
DISP	Disposable-based
MAb	monoclonal Antibody
RtP	Ready-to-process
SIP	Steam in Place
SP	Schedule Pro
SPD	Super Pro Designer
SS	Stainless Steel

1 Introduction

1.1 Problem

The number of biologics, like antibodies and vaccines, in the pipelines of biopharmaceutical companies is increasing [1]. Among several factors related profitability for biologics, time-to-market, manufacturing flexibility and cost-effectiveness has been identified to be among the key ones [2]. A fast market penetration can mean the difference between a block-buster drug and a drug that is just covering research and development expenditures [3]. To cope with the need for a quick introduction of a new drug to the market after drug approval, the manufacturing facilities must be more flexible in terms of fast changeover between products and fast startup times. Furthermore, to maximize profitability and productivity, biopharmaceutical companies try to reduce process maintenance costs and minimizing system downtime, two of the most price-sensitive aspects of manufacturing [4]. All of these improvements must be done without sacrificing product quality, safety and compliance with regulations.

Issues liked those described above have led to the development of flexible manufacturing concepts that enable design and operation of multiproduct facilities. The concept of flexible manufacturing is often closely related to disposable technologies and/or single use technologies. Contract manufacturing organizations (CMOs) have taken the lead in implementing the new disposable technology because of the intrinsic multi-product character of their production [5]. For pharmaceutical companies to adopt the technology, quantitative measures of the advantages of disposables are welcomed. To achieve this, computer simulation tools can be used to model different production scenarios and compare different production technologies.

1.2 Scope of the study

The aim of the study is to examine aspects on the use of disposable technologies in manufacturing of monoclonal antibodies. The aspects in focus are the potential flexibility that can come with an implementation of disposables when producing several products and the economic viability of disposables at a larger scale.

To achieve this objective, a comparison of two future multi-product manufacturing facilities producing monoclonal antibodies using either new disposable technologies or conventional stainless steel equipment will be done using process and scheduling simulations.

2 Background

2.1 Biopharmaceuticals

2.1.1 Definition

Biopharmaceuticals can be defined as "medical drugs that are produced using biotechnology. Biopharmaceuticals are proteins (including antibodies), nuclide acids (DNA, RNA and antisense oligonucleotides) used for therapeutic or in vivo diagnostics purposes, and are produced by means other than direct extraction from a native (non-engineered) biological source." [6].

2.1.2 Market environment

The biopharmaceutical market is growing faster than the traditional small molecules market and biopharmaceuticals has become a multi-billion dollar industry [1, 7].

The biopharmaceutical market has been dominated by recombinant protein products. Many of these product segments have become mature and instead technology advances have open for rapid growth of monoclonal antibodies products.

The main therapeutic areas for new biopharmaceuticals in the next few years are oncology, central nervous system diseases, cardiovascular, autoimmune diseases, inflammatory diseases, diabetes, hormone/enzyme replacement, respiratory and infectious diseases [1]. Oncology is considered to be the major driving force for market growth in the coming years.

Advances in diagnostics and biotechnology in general could lead to realization of the personalized medicine concept, in which an increase in the number of products in the market, but with lower demand, is anticipated. The usually high doses in therapeutics with biopharmaceuticals have the opposite effect giving high production demand. Today, biopharmaceutical products are very expensive due to high development and production costs. Drug expenditures of governments and other healthcare providers are rapidly increasing, making the providers implement a cost-to-benefit view when choosing drug treatment subsidizes. The cost containment policies practiced in most developed countries are a major barrier to market growth for biopharmaceuticals. To get a wide use of biopharmaceuticals, manufacturing companies must be able to produce many products with varying demand to an acceptable cost per dose. This has led to an increased attention on effective production and new production technologies.

Biogenerics, generic biopharmaceuticals launched by a competitor after patent expiration, poses a threat to the biopharmaceutical market. For every month of delayed production, companies lose time on their patent life-time. In addition, a later market entry significantly increases the risk of competitors being first in the market introducing a substitute drug. Thus, fast time-to-market is crucial for the success of biopharmaceuticals.

2.2 Monoclonal antibody production

In this report the production of the monoclonal antibodies (MAbs) will be studied. MAbs are used in diagnostic tests as well as in therapeutic treatments. The market for MAbs is growing in relative importance. Platform procedures both upstream and downstream have been developed. Therefore, a facility producing MAbs is suitable for examining advantages of new production technologies like disposable systems. The production is demanding both in terms of capacity requirements and technology. Therapeutic MAbs require doses of several milligrams up to grams for the whole course of therapy [8]. This kind of product can have a world demand of hundreds of kilograms per year.

The most commonly used expression system of recombinant antibodies is mammalian cells like Chinese hamster ovary (CHO) and murine lymphoid cell lines [9]. Major improvements in the productivity of these mammalian cell cultures have been made in the last decades. Today, new antibody products can have titers (product concentration in harvest) of 5 g/L [8], as compared to under 1 g/L ten years ago [10]. This improvement of in the upstream processes has led to a pressure to increase performance of the downstream purification.

2.3 Disposable versus Stainless steel technology

The value of disposable technologies is getting more and more accepted within the industry. Even though disposable alternatives exist for every procedure in the production process, fully disposable systems have not yet been widely implemented, but incremental increases in integration of disposables in manufacturing processes have been seen [11].

The conventional stainless steel technology is associated with a fixed design. Stainless steel tubing and other components for mixing and storage require much space whether they are in use or not. Single-use containers can use space more efficiently as they can be moved

around the facility on portable holders. Only equipment that are to be used take up space in the expensive production area, other equipment can be stored in cheap storage areas. The support holders are often collapsible when not in use. The single-use components are not stored after use, instead they are discarded.

The number of stainless steel equipment is fixed and requires large capital investment. Disposable bags are just-in-time consumables shifting the cost later in time, from capital investment to operating costs. As operating cost they become variable and only appear when the facility needs them. The steel vessels, which once installed will remain in place, experience more idle time.

The extensive costs and time consumption for the cleaning required in with stainless steel technology have been one of the main arguments for developing disposable systems [12]. Components in contact with processing fluids must be cleaned and sterilized before use. Operations called SIP (steam-in-place) and CIP (clean-in-place) must be used between every batch in reused equipment which has been in contact with process fluids to minimize risk of contamination. Portable SIP stations and CIP skids are often used but the operation can also be integrated as a part of the equipment to be cleaned. Apart from just increasing the procedure turnaround time (with 1.5-3 hours), cleaning requires large amounts of WFI (water for injection), chemicals, steam and labor which all cost money [11]. In addition the waste must be treated. It is commonplace that disposable components are presterilized by the supplier and are "ready-to-use". As a consequence, the number of cleaning utility systems can be reduced which have impact on the capital investment when constructing a new facility and reduces the commissioning and validation of their operations.

In a survey, biopharmaceutical manufacturers were asked for the reasons to implement disposables in their production process [13]. The most important characteristic was the elimination of cleaning requirements, followed by a decreased risk of cross-contamination, a reduced time to get the facility up and running, a lower capital investment, reduced

production cycle times and the flexibility of a ´modular´ approach. These advantages of disposables have to be weighed against the increased cost of single-use consumables.

2.4 Bioprocess simulation modeling

The aim of every production process operation is to maximize profit. As global competition in the pharmaceutical industry and the demands for affordable medicines are increasing, the industry focus their attention on manufacturing efficiencies. To design efficient processes companies use process simulation tools, which are a wide range of computer software analyzing whole processes and not just single operations. Process engineers and scientists model the process in silico and analyze the outcome.

2.4.1 Capabilities of today's simulators

Simulation tools can perform a range of tasks including creating process flow diagrams, generating material and energy balances, determining equipment sizing, and estimating capital and operating costs. Some can also do scheduling, estimate cycle times and estimate other resource demands like labor. The amount of detail needed depends on what questions are to be answered. Some simulators model only single unit operations (individual tasks) in detail when accurate mathematical representations are available. Others model whole processes creating flowsheets consisting of several unit procedures, each containing a set of operations that comprises a processing step. Gosling 2005 [14] presents an overview of tools and techniques for bioprocess simulation.

2.4.2 The role of process simulation

Process simulation can be used in all stages of commercialization. The role of simulators has previously been reviewed [14,15,16]. Here a model presented by Petrides *et al.* 2002 is used to describe the main usages of bioprocess simulation.

Idea generation

Preliminary economic analyzes can be used when products and production concepts are considered in an early stage of development. It allows for project screening and selection and strategic planning.

Process development

When a product has reached preclinical and clinical studies the process development is accelerating. During this process several options for manufacturing, purifying, characterizing and formulating the drug is considered. At this stage, a lot of changes are being made to the process. Different expression systems are explored, new recovery and purification strategies are tested. Process simulation can help evaluate the effect of procedure changes on the overall process. A good model can pinpoint the most cost-sensitive areas of the process: that is parameters that have the most impact on the economic performance of the process. In turn, this can guide R&D to focus on those portions of the process. Process models can also be used in risk assessment when trying to answer "what-if" questions.

Facility design and selection

When the clinical studies are promising and process development is near completion at a pilot scale level it is time to scale up the process for commercial manufacturing. The computer model can have different uses at this stage. It can facilitate the process technology transfer and the design of the facility. Also when deciding whether to produce in-house in an existing plant, build a new facility or outsource the production a good model provides the foundation for a sound decision. If the company decides to build a new plant, process simulators can be used for equipment and supporting utility sizing and estimate the required capital investment. Costs estimates from simulations can also be used in negotiations with contract manufacturers.

Manufacturing

Once the facility selection/design is done and large-scale manufacturing begins simulators are primarily used for scheduling, debottlenecking and process optimization. When adjusting throughput for example, the capacities in the facility can be evaluated with simulators.

3 Methodology

To be able to address the objectives of the present study several tools was needed. Figure 3.1 presents an overview over the software used.

As basis for analysis, a production process of monoclonal antibodies was modeled using the discrete-event simulation tool Super Pro Designer (SPD, Intelligen Inc.). Three base case batch models (recipes) were created; one for a process using stainless steel (SS) technology and two for a process using only disposable-based (DISP) equipment. SPD is able to generate a detailed batch schedule, material balances, equipment sizes, resource consumption and certain operation times.

The production recipes were incorporated in three future facilities and production campaigns of several products were scheduled. Since SPD can only deal with one recipe and product at a time, the scheduling of the facilities was done using Schedule Pro (SP, Intelligen Inc.). The tools are compatible and the batch recipes from SPD can be imported to SP through an intermediate database. SP was used to estimate total equipment and labor requirements, explore scheduling effects in detail and verify the annual productivity.

In turn, SP cannot calculate and report economic data for the facilities. A spread-sheet was instead used to develop the cost models. Some of the input values were collected from SPD and SP, and others from vendors. Even though the economic aspect of manufacturing was considered, the study was not intended to give correct absolute values for costs of production. The focus was instead on the relative difference between the two different technologies and in particular on the manufacturing flexibility differences between the technologies.

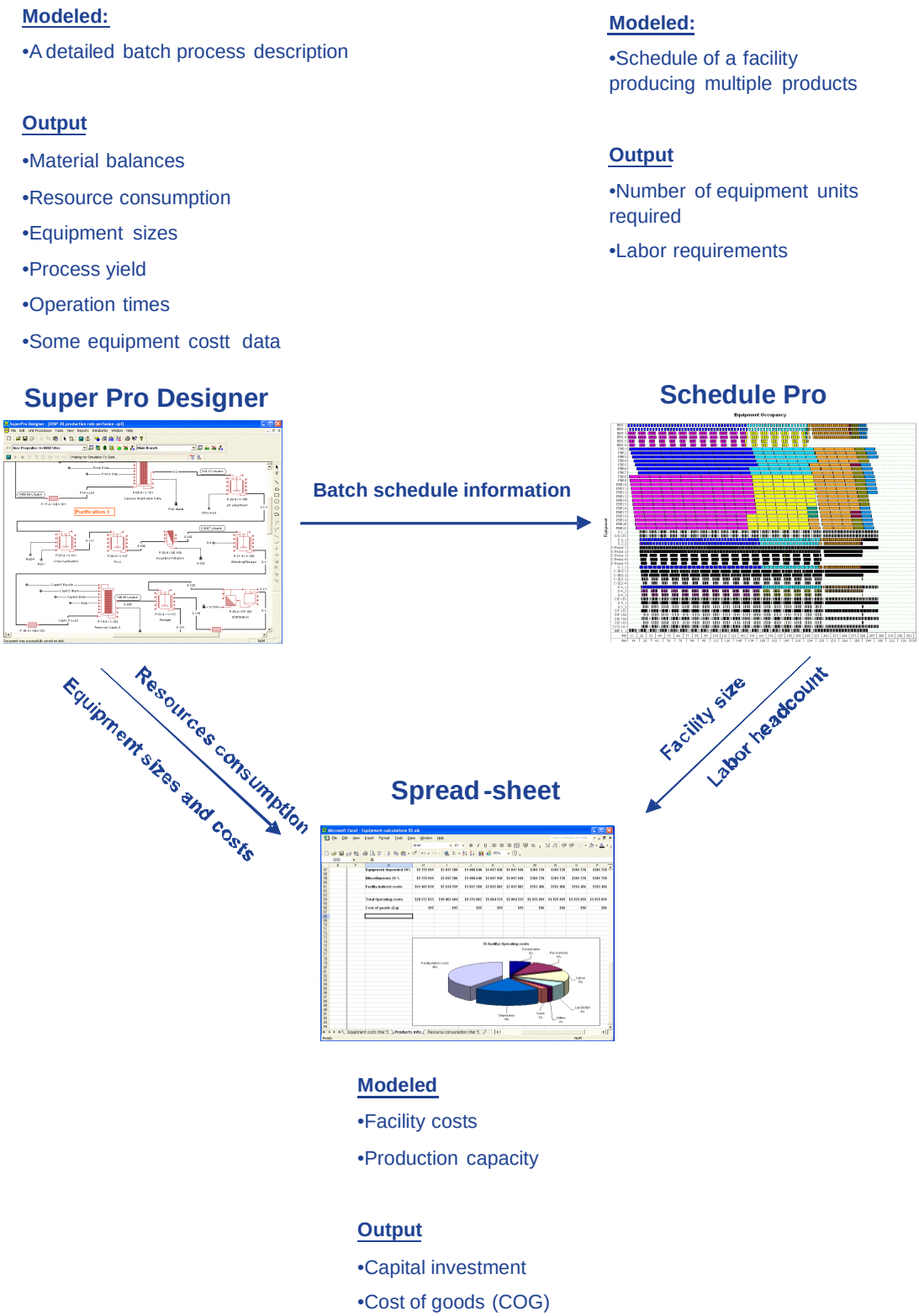

Figure 3.1. Software used, what was modeled with each tool and their output.

4 Base case setup

To evaluate the operational implications of implementing disposables in the production process a case study was set up. The following sections present the key assumptions used for the base case. All results presented in the next chapter were obtained with these assumptions unless noted otherwise.

4.1 Process description

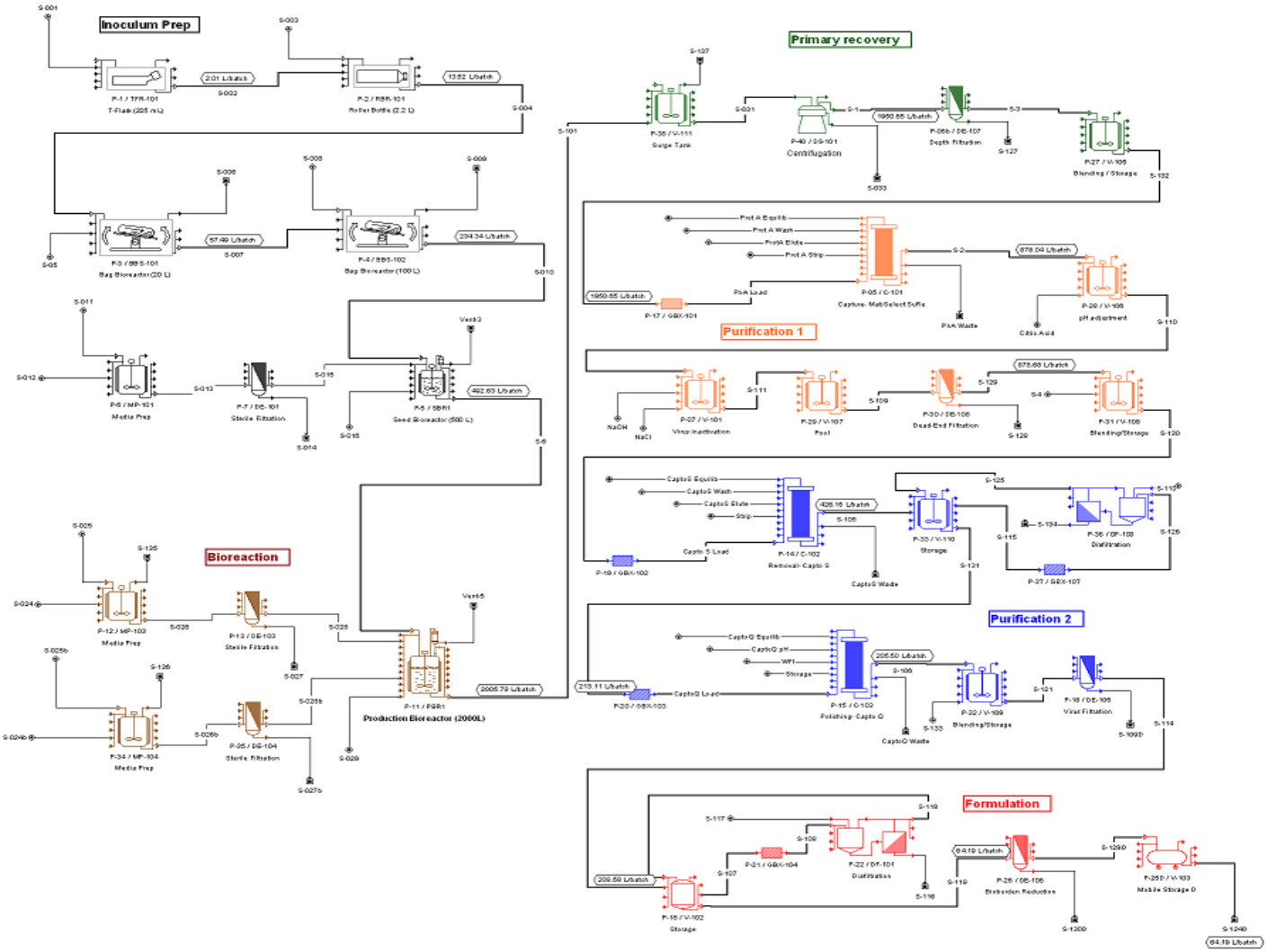

Figure 4.1. Process description. This figure shows a detailed flowsheet of the production process in the stainless steel facility. The same process was used in the disposable-based facilities, but all equipment was exchanged for single-use alternatives. The scale was adjusted to comply with size restrictions on disposable equipment.

The process for the MAb production modeled in the present study uses established procedures that can be found in the literature [17]. The individual steps are updated to match the performance of novel technologies (GE internal communication). The SS fed-batch recipe is described in the section below, followed by a description of what differs in the DISP fed-batch recipe. Finally, a disposable-based perfusion option is presented.

The flowsheet for the SS process is shown in Figure 4.1. In this work a batch size based on a working volume (WV) of 2000 L in the bioreactor was considered. This flowsheet was also used as basis for developing the DISP recipes, exchanging the equipment types and sizes specified by the characteristics of the single-use technology. Buffers were assumed to have arrived premade and presterilized. This assumption reduces the process complexity, but does not affect the final conclusions drawn.

4.1.1 Stainless steel process

Upstream section

The batch begins by inoculating a mammalian cell culture in T-flasks (TRF, 225 ml) and then roller bottles (RBR, 2.2 L). The durations are 4 and 6 days, respectively. The inoculums are further grown in two disposable bag bioreactors (BBS-101 and BBS-102, WV 20L and 100L) for 6 days each. A final seeding step is done in a stirred-tank seed reactor (SBR, WV 500L) and this step runs the same time. Finally, the production of MAb occurs in a stirred-tank bioreactor (PBR) which is occupied for 15.5 days of which 14 days are for fermentation. 1.5 days are used for setup and cleaning procedures. The reactor operates in a fed-batch mode. The titer (product concentration in harvest) is assumed to be 5 g/L. All culture media is prepared in SS tanks (MP) and sterile filtrated (DE).

Downstream section

The generated biomass is removed by centrifugation (DS). The yield of this step is assumed to be 98 percent. Primary capture is then done by Protein A affinity chromatography column (C-101, Resin: MabSelect SuRe from GE Healthcare). This step is based on the following assumptions: a resin binding capacity of 28 g/L, a flow rate of 500 cm/h and a MAb yield of 90 percent. This step is cycled 5 times and requires a resin volume of 70 L. The cycle time is 1 h, excluding pre- and post operations. The total occupancy time is 6.5 h per lot. The subsequent DSP steps are: pH adjustment (V-106) through adding citric acid and virus inactivation (V-101) with salt and sodium hydroxide. The purification proceeds in an ion-exchange chromatography column (C-102, Resin: Capto S from GE Healthcare). It is assumed that this step can purify 96 g of MAb per L resin with yield of 90 percent. The bed size is 100 L. The column is run in one cycle mode and the occupancy time is 2.4 h. The product is concentrated two times and the buffer is exchanges in an ultra/diafiltration step (DF-103) before the final polishing chromatography (C-103, Resin: Capto Q from GE Healthcare) working in flow-through mode, meaning that impurities are retained in the matrix whereas the product flows through. This step can purify more MAb per L resin (160 g/L). The resin volume is 50 L and the occupancy time is 2.0 h (one cycle). A virus filtration step (DE-105) is performed assuming a flow rate of 40 L/m^{2}h. Finally, the product is further concentrated 3 times and the buffer is exchanged for final storage in an ultrafiltration/diafiltration step (DF-101). Additionally, there are some pad filters applied between some of the steps described above. The total yield in the downstream processing is 67 percent and the total continuous processing time is approximately 30 hours.

4.1.2 Disposable based fed-batch process

Disposable alternatives exist for all procedures in the production process of MAbs. But there are size limitations of disposable vessels. The wave bioreactor used in the case study is based on wave agitation created from a rocking motion. When the bags are big, the large linear momentum puts stress on the mechanics making it hard to construct large systems.

The plastic material of the bags has also pressure limits, which are challenged by large volumes. Today, the largest working volumes are 500 L and this size was used in the present study. Since this reactor is smaller than for the SS case, one less seeding step was needed. The same final fermentation time (2 weeks) and titer (5 g/L) was assumed. Prepacked, ready-to-process (RtP) columns replaced the conventional chromatography columns in the purification steps. The largest sizes for prepacked columns are 20 L and these sizes were used in the first two chromatography steps. A 10 L column was enough for the last polishing step. The maximum number of cycles is assumed to be 5 and the Protein A column is cycled 5 times. The same resins and performance of the prepacked columns as for the stainless steel columns was assumed. All SS tanks for holding and mixing were replaced with disposable portable alternatives and the size limitation were not an issue in this case. All parts of the filtration systems in contact with the process material were exchange after each use. For each procedure, that in the SS case needed to be sterilized and cleaned, the SIP and CIP operations and equipment were removed.

4.1.3 Disposable-based perfusion process

As an alternative production mode, a perfusion process was also considered. The same equipment and procedures are used as in the fed-batch mode except for the primary recovery procedure which is exchanged. The product is continuously harvested via an external hollow fiber filtration loop. The cells are returned to the reactor for further production, keeping a high cell density. Half of the reactor volume is exchanged each day. This mode of operation enables a higher volumetric productivity, which is assumed to be twice the productivity in the fed-batch reactor. As much as 10 times increase in volumetric productivity has been achieved with perfusion, but only when compared to a lower fed-batch expression level of 1 g/L in the fed-batch (GE internal). Harvests from 7 days production are pooled and then purified. This gives approximately the equivalent size of the DSP equipment as for the fed-batch process. The maximum duration of a perfusion process is assumed to be 49 days, after which a new culture is started.

4.2 Facility design

A size of manufacturing facility was assumed to match a commercial facility designed for several products. A total of 10 000 L of reactor volume was assumed for the fed-batch facilities. This may seem small compared to today´s capacities where reactors can reach up to 25 000 L [8], but one should have in mind the high titer of 5 g/L assumed, which lower the requirements of large reactor volumes, and that the facilities have multiple product purposes. The SS facility with reactor volumes of 2 000 L have a total of 5 reactors. For the case of the disposable facility the number of bioreactors had to be increased as compared to the stainless steel case because of size limitations on disposable equipment. A total of twenty 500 L disposable production reactors were needed to achieve the specified total volume. This approach of adding several disposable reactors instead of larger stirred tank reactors has been suggested in the literature [18].Ten reactors are assumed in the perfusion case to achieve the same productivity. The bioreactors are the most capital intensive and have the highest occupancy time. Therefore, debottlenecking was performed until the bioreactors constituted the main time and size bottleneck.

Traditional multi-product facilities are designed with several separated production lines. Each line has all the equipment needed for the whole process. According to current good manufacturing practice (cGMP), no transfers and equipment sharing are allowed between the lines [19]. There are also strict restrictions on personnel movement within the facility. In this work, three lines were assumed for the SS facility. The first two have 2 bioreactors and the third has a single reactor. After construction, sizes of all production lines are fixed and it is a comprehensive task to redesign the facility. Each of the lines is in turn divided in contained sections to prevent cross-contamination [24]. These sections are separated by air-locks and have their own air handling systems. Transfers in and out of the sections are regulated, and therefore two products cannot be processed at the same time in the same section. Highest cleanroom classification is needed for sections defined as critical areas. The further downstream in the process, the higher classification is required. Higher classification means lower allowed particle count per air volume, faster air cycling and a

positive air pressure differential to the surrounding areas. For the SS facility, the following sections are assumed: inoculum preparation, bioproduction, previral downstream processing, postviral downstream processing and formulation. All sections are assumed to have a containment restriction except for the inoculum section.

The implementation of disposables in manufacturing processes has consequences for the facility design considerations [20]. For the disposable-based concept facilities it is assumed a manufacturing platform similar to the FlexMax design presented by Xcellerex [23]. The FlexMax platform uses single-use components, aseptic connectors and a cleanroom module technology (isolators) enabling totally closed systems. Compared with traditional multiproduct facilities the area of cleanroom around the equipment is less and different products do not have to be separated in different facility suites. It has also been suggested that, even without the isolator technology, the sterility of the fluid path can be maintained with complete single-use bioprocess systems [21] lowering the requirements of high cleanroom classification and section segregation. As a consequence the number of parallel products is not restricted by the initial design of the facility. The modules can be moved around the facility and production is not conducted in traditional lines with dedicated equipment. Instead, one can imagine stations with sets of procedures at different sizes and with different characteristics defining the processes possible to be executed at the station. The chromatography systems, for example, can use columns of different sizes packed with different resins. In principal this means that one system can be used for all three chromatography steps in a single batch. The same system, but different columns of the same type, can also be used by several products. The process material is transferred between stations in mobile storage units instead of fixed hard piping. The stations and flows are not fixed by facility design. The number of units in production can vary and unused equipment can be hold in cheap storage areas. Pools of storage tank holders with different sizes can be used and the holders can be moved into the production area when needed.

4.3 Scheduling

The facilities are assumed to have 340 days available for manufacturing each year. The rest of time is dedicated for plant and equipment maintenance. The upstream section runs 24/7 with 4 labor shifts. For the downstream section it is assumed facility downtimes on nights and Sundays. The available operation time is 14 hours per day, 6 days a week with 2 labor shifts.

The company has, in the base case, a portfolio of ten mAbs and all are to be manufactured the first year. One of the products have considerably lower selling price because of competition of equivalent drugs and has the lowest priority (Product 1). When production has met the demand of the other nine products the rest of the facility's capacity is used for this product. The demands are displayed in table 4.1.

Table 4.1. Product portfolio

Product number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Total**
Demand (kg/year)	300	200	100	50	50	20	20	20	20	20	800

The scheduling of batches is somewhat different between the SS and DISP facilities. The batch cycle time for a production line is given by

$$\text{Cycle time} = \frac{\text{Occupancy time of bottleneck equipment}}{\text{Number of bottleneck equipment}}$$

The cycle time is the time between the start of two consecutive batches. The production bioreactors (PBRs) constitute the bottleneck in all facilities. When the batches are scheduled in this way, the PBRs experience no idle time (except for cleaning and setup). In line 3 in the SS facility, which has only one PBR, the cycle time equals the PBR occupancy time (15.4 days). Production line 1 and 2 have a cycle time of 7.7 days, since each line has 2

PBRs. The SS facility produces the products on campaign basis, i.e. one product at the time in each line.

The DISP facility enables another scheduling approach, because it does not have traditional equipment lines. A scheduled batch can produce any product in the portfolio. This gives more flexibility, since the production of the products can be distributed over the year. To optimize the downstream processing, it is best to view the DISP facility design as one line with 20 staggered PBRs. This gives a cycle time of 17 hours, which means that a lot is ready to be purified downstream every 17 hours. If a reactor is finished during downstream downtime, the purification starts next morning.

4.4 Cost assumptions

4.4.1 Capital investment

Estimating the capital investment is often done by employing a factorial method [8]. Detailed calculations are done for certain cost items, such as equipment purchases, and associated items are estimated by multiplying these costs by factorial estimates. The factorial estimates, often called Lang-factors [22], are derived from previous projects.

Novais *et al.* have developed a method for estimating the capital investment for a disposable-based facility based on the equipment cost in a conventional equivalent facility [2]. The conventional factors are converted based on differences of the technologies as described below. This approach will be used in the present study.

The fixed capital investment in the conventional facility (FCI_{conv}) is given by

$$FCI_{conv} = L_{conv} E_{conv} = c\left(\sum_{i=1}^{10} f_i\right) E_{conv} \tag{4.1}$$

where L_{conv} is the total Lang factor for the conventional stainless steel plants and E_{conv} is cost for conventional process and utility equipment. The factors f_i are the factorials relating the facility cost items to the equipment purchase cost. A contingency factor c is also applied to cover unexpected events.

The fixed capital investment in the disposable-based (FCI_{disp}) facility is estimated by

$$FCI_{disp} = L_{disp} E_{conv} = c' \left(\sum_{i=1}^{10} f_i f_i' \right) E_{conv} \qquad (4.2)$$

where L_{disp} is the Lang factor for disposable-based facilities based on the conventional equipment cost, f_i' are factors to translate the conventional cost of individual items into a costs viable for the disposable option. c' is the relevant contingency factor. The values of conventional and disposable factors are summarized in table 4.2. The values were taken from Novais *et al.* except for the factors for equipment, building, engineering and construction (f_1', f_2', f_6', f_7' and f_8'). These values were altered because they where derived for a single-product facility working at the same scale. Equipment conversion factor f_1' was calculated explicitly from the model, based on equipment requirements determined in SP. For cost items 2, 6, 7 and 8 the difference is likely larger in multiproduct facilities because the disposable option do not have several production suits. Changing the factors reduces the disposable Lang factor from 4.73 to 4.31.

E_{conv} was calculated by explicitly summarizing the costs of equipment in the three production lines. Prices and sizes were retrieved from the Super Pro Designer database adjusted to 2008 prices.

Table 4.2 Capital investment factors for conventional (f_i) and disposable-based ($f_i f_i'$) bioprocessing facilities.

i	Description	Conventional fed-batch f_i	Disposable fed-batch f_i'
1	Equipment (inc. Utilities)	1	0.51 (0.2)
2	Pipework and installation	0.9	0.2 (0.33)
3	Process control	0.37	1
4	Instrumentation	0.6	0.66
5	Electrical power	0.24	1
6	Building works	1.66	0.6 (0.8)
7	Detail engineering	0.77	0.3 (0.5)
8	Construction and site management	0.4	0.55 (0.75)
9	Commissioning	0.07	1
10	Validation	1.06	0.5
	Contingency factor (c)	1.15	1.15
	Lang factor	L_{conv} = 8.13	L_{disp} = 4.31 (4.73)

Source: Novais *et al.* [2] and estimates. Where values are altered the benchmark values are shown within parenthesis.

The perfusion processes uses half of the reactors as the fed-batch option resulting in lower fixed capital. This is accounted for by subtracting the purchase cost of the additional reactors and their supporting equipment multiplied by a factor of 2 to compensate for equipment depended costs.

4.4.2 Cost of goods

The cost of goods per gram (COG/g) is an important measure of production performance. It is defined as the running costs plus a capital charge divided by the amount of product produced. How the running costs and capital charge were calculated is described in this section.

Labor: In Schedule Pro one can specify the number of operators needed for each operation. The software can also report the total operator requirements over time for the

whole facility or a section. This was done assuming one workforce for upstream processing working 4 shifts and one for downstream processing working 2 shifts. Multiplying the number of operators needed in each shift with the number of shifts gave the operation personnel headcount. For the SS facility it was assumed that a suite had its own personnel pool and that operator could not work at two suits the same day.

Other labor resources were estimated by benchmark factors similar to Lang factors, defined as a percentage of the SS operation workforce. Such benchmark factors have been developed by Sinclair *et al.* [12] for both conventional and disposable-based facilities and are presented in table 4.3. These factors were used for a total headcount estimate.

Table 4.3. Labor benchmark factors. Percentage of conventional operations headcount.

	Conventional	Disposable
Operations	From model	From model
Planning and material management	22%	15%
Others	22%	18%
Engineering	10%	5%
Quality	63%	41%

Source: Sinclair *et al.* [12]

Consumables: A list of the consumables needed for a batch was constructed. The sizes were retrieved from SPD and prices from vendors. The consumables include all disposable process components such as filter membranes, resins, pre-packed columns, plastic bags and some tubing cartridges. The annual consumable cost was calculated by multiplying the batch cost by the number of annual batches.

Materials: This cost category includes raw materials and high-quality utilities used in the process. These are cell culture media, presterilized buffers, cleaning chemicals, process water and water-for-injection. Volumes and masses needed per batch were calculated by SPD.

Indirect costs: The cost for indirect materials was assumed to be 18 percent of the production personnel costs. Equipment maintenance, including vendor support and spare parts, was assumed to generate an annual cost of 10 percent of the equipment purchase cost.

Capital charge: The cost of capital allocated to each year's running costs was calculated as an annuity charge based on the total capital investment, a plant lifetime of 8 years and 15 percent cost of capital. When including the cost of capital in the calculation, the capital charge includes compensation for the fact that the capital investment generates a cash flow upfront, unlike running costs that are paid when they appear.

Neglected: Taxes, royalties and waste treatment costs are not included in the COG calculation. These costs were neglected because waste management costs are very small compared to other running costs [12] and taxes and royalties are not associated with the production technology in any clear way.

5 Results and discussion

5.1 Changeover and capacity analysis

When producing many products in a single facility, the time to change over the production between products may have major impact on the facility productivity. This is especially important in the SS case. Even though the SS facility has 3 production lines, changeover will become an issue when producing more than 3 products. The changeover in the SS facility will be evaluated first, followed by a discussion on how the changeover is affected by the implementation of disposable-based production designs.

The time for cleaning and cleaning validation varies with equipment type. The question is how much the changeover actually delays production. Changing over equipment that has low time utilization may not delay production at all, compared to changing over the bottleneck equipment which will inflict a direct delay. The production bioreactors (PBRs) were the time bottleneck in the present model and their changeover time is therefore most important at first glance. Furthermore, to comply with cGMP and minimize risk of cross-contamination the SS production is organized in contained sections, in which two products cannot be processed at the same time (see chapter 4). It was assumed that each section has to be cleaned and qualified for a new campaign before the next product enters the section. In practice, after cleaning and sterilization the equipment is rinsed and swabbed to test for residues and analyzed for organic carbon, nucleic acids and microbial contaminants such as bioburden and endotoxins [24]. The total changeover delay is the time shift from the end of the first available PBR for the previous product to the start of setting up the first PBR in the next product. Between batches of the same product this time shift is zero. When changing over, the first available reactor must wait for the other staggered reactors to finish. It must also wait for the cleaning and validation of the last reactor. Finally it can not start again until other equipment in the same section has processed the new batch. For the purpose of this work, it was assumed that the last seed reactor was in the same section as the production bioreactor.

Figure 5.1 shows an equipment occupancy chart for the SS facility. This figure represent an example of section depended changeover when 2 products with 6 batches each are scheduled in production line 1. The equipment names are shown in the left margin. Each bar represents the time an equipment unit uses for a particular procedure in a batch. The pink line shows that the seed reactor (SBR-1) do not start until the last production reactor in the previous campaign has been cleaned, since they are in the same section. The green arrow shows the total delay due to the changeover, which is longer than the time for cleaning and assurance assays (semi-white bars).

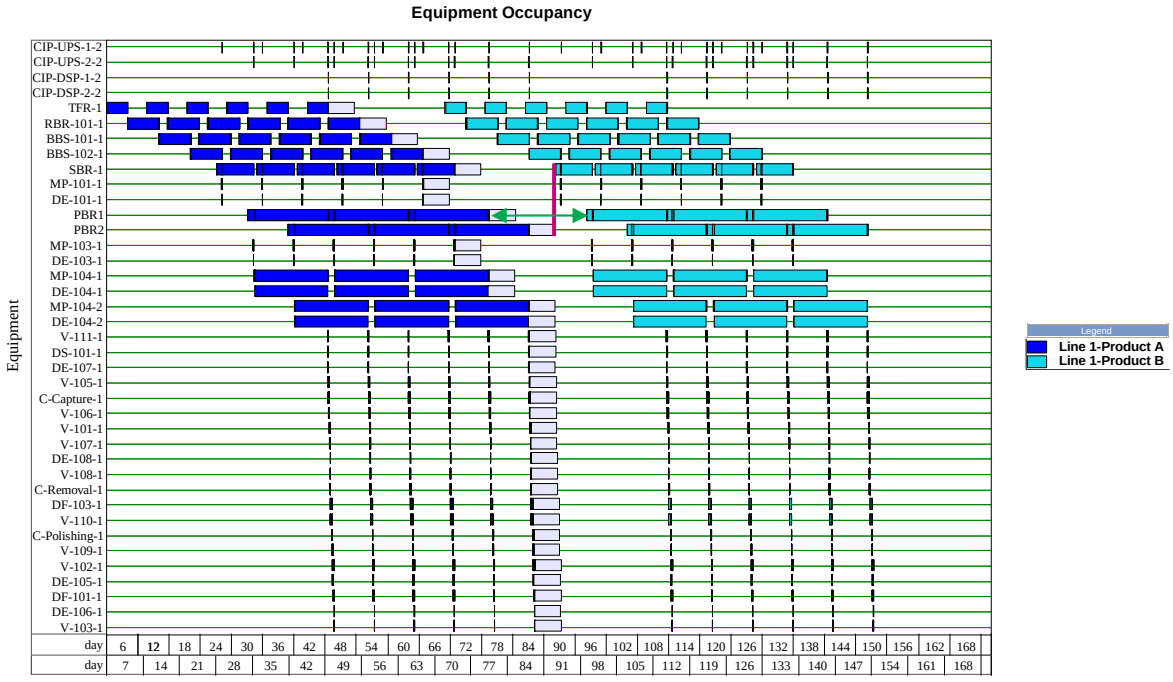

Figure 5.1. Changeover. An example of the delay inflicted by changing over the production to a new product in the SS facility (production line 1). The pink line shows that the seed reactor (SBR) does not start until the production bioreactor (PBR) is cleaned, because they are in the same section. The green arrow shows the actual delay due to the changeover.

The actual delay due to a changeover is rather complex to appreciate and depends on how the process is set up, regulatory compliance and facility design. A detailed mathematical

derivation of the changeover delay with contained sections can be found in Appendix A1. For the purpose of this work these equations can be simplified as follows.

The total delay in production due to changing product, D_{CO}, is given by

$$D_{CO} = D_{Clean} + D_{Stagg} + D_{Section} \tag{5.1}$$

where D_{Clean} is the delay due to cleaning and cleaning validation of equipment, D_{Stagg} is the delay due to waiting for staggered bottleneck equipment and $D_{Section}$ is the delay due to waiting for other section equipment to finish their processes.

D_{Stagg} depends on number of staggered equipment and number of changeover bottleneck equipment (BNE) according to

$$D_{Stagg} = \left(1 - \frac{1}{N_{BNE}}\right) T_{BNE} \tag{5.2}$$

N_{BNE} is the number of BNE and T_{BNE} is the batch occupancy time of the BNE.

$D_{Section}$ is the process time of all equipment in the changeover bottleneck section except the BNE process time. In this case $D_{Section}$ equals the occupancy time of the seed bioreactor until the setup of the PBR is initiated.

Here it is assumed that D_{Clean} is 5 days. Given the assumed SS facility design, $D_{Section}$ equals 6.2 days. For production lines 1 and 2, with two PBRs each (occupancy time 15.4 days), D_{Stagg} equals 7.7 days. This gives a total changeover delay of 19 days. Note that the cleaning time only constitute less then a third of the total time for changing to a new product in these production lines. The amount of staggered equipment and whether or not the bottleneck equipment is in an isolated section (regulation dependent) is just as important.

For the third production line with only one PBR there is no staggered effect and the total changeover delay is 11.2 days.

Are these changeover delays reasonable? In the literature, there is a wide range of turnaround times assumed in similar models, ranging from 4 days (clinical manufacturing) to over 2 months (very large scale manufacturing) [Farid must add, 10]. No detailed discussions on the regulation and specific changeover issues were done in these studies. For the scale used in this study, changeovers between 1 and 3 weeks seem reasonable in this context.

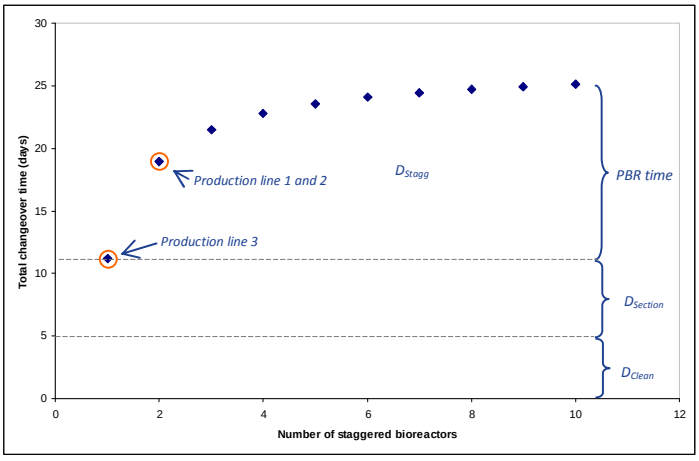

Figure 5.2. Changeover delay. Effects of the number of staggered reactors in a contained production suit on the changeover delay. Production lines 1, 2 and 3 in the modeled SS facility are noted by red circles with 2 and 1 staggered reactors, respectively.

Figure 5.2 describes how the changeover time for one changeover depends on the number of staggered bioreactors, all other parameters unchanged. It shows that the changeover time increases with the number of staggered bioreactors but the incremental effect diminishes when the number of reactors increases. However, the time addition resulting from staggered equipment will not exceed the time usage of the production bioreactor (PBR time). The $T_{Section}$ contribution to the changeover time can be eliminated if the seed reactor gets its own section. But this would require additional utility systems and would lead to a more complex personnel and material flow management. Moving it to the

inoculation section will not improve things much, since this section will then be the changeover bottleneck (See Appendix A1) if the same containment regulation is also valid for this section. But if the whole inoculum section is based on disposable equipment, and two products therefore can be processed in the section, a disposable seed reactor moved to the inoculum section will eliminate this problem and the changeover delay would be reduced from 19 days to 12.8 days in line 1 and 2 and from 11.2 days to 5 days in line 3.

If there are very large variations in changing-over times for different equipment types, another section can become the bottleneck during the changeover. For example, if a production line uses many staggered bioreactors and only one downstream processing (DSP) line and the changeover time for DSP equipment is much larger, one of the chromatography sections may become the bottleneck during the changeover.

When producing several products per year the changeover will occupy a larger portion of the available manufacturing time, lowering plant productivity. How the number of batches was calculated is derived in Appendix A2. Figure 5.3 shows how the SS facility's annual production capacity decreases with the number of products, when assuming that all products have titer of 5 g/L and a cleaning and validation time is 5 days. Furthermore, the calculations assumed that the same number of products is manufactured in each line. When going from manufacturing three products to fifteen (4 changeovers per line), the capacity decreases with 24 percent. If the restriction of contained sections is lifted, the terms D_{Stagg} and $D_{Section}$ is zero and the decrease in productivity is3 times lower.

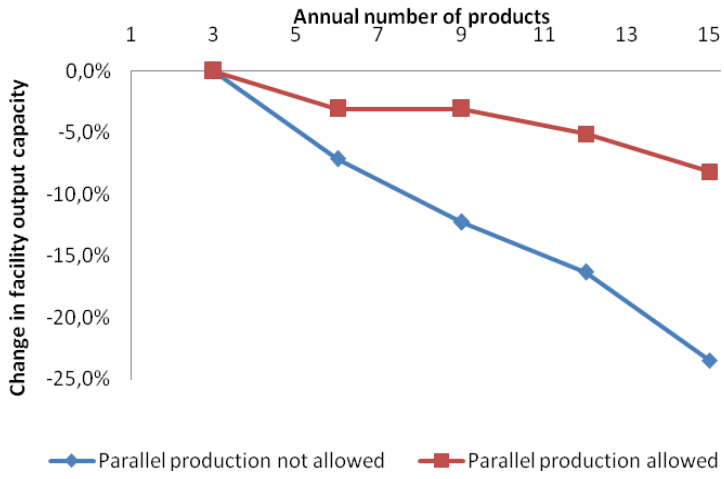

Figure 5.3. Productivity and changeover. Effects of the number of annual products on the production capacity in the SS multiproduct facility with 3 production lines. The 2 curves represent the capacity decrease both when the sections are contained (parallel production is not allowed) and when the sections are not contained (parallel production allowed).

The assumed T_{Clean} of 5 days is based on that each cleaning validation result is satisfactory. In practice, there is always a risk of failure or deviations during cleaning and control assays. Considerable time may be spent on following up on errors. In the worst case some procedures have to be repeated. Additionally, if changes are made in the platform process when a new product is introduced, the whole process may have to be revalidated on site which can take weeks.

Now, let's look at the changeover implications for the disposable-based module design. First, there is no cleaning and cleaning validation required since all equipment in contact with in-process material is discarded after use. This means that T_{Clean} is practically zero. Regarding equipment qualification and process validation, this can mostly be done off-site because of the fact that the modules are portable, resulting in that these procedures do not intrinsically delay production. No additional scale-up studies is needed since a 500 L line can easily be put together in a pilot plant earlier in the development process, which speed up time to commercial manufacturing. Scale-up is done by adding more reactors. Secondly, the isolator technology entails that, in principal, all processing equipment units are in their own contained section. Thus, regardless the degree of containment regulation, $T_{Section}$ and

T_{Stagg} are zero. This is the same as saying that parallel production is allowed in the main production area. Altogether, changeover is not an issue for the facility with the proposed design. As a consequence the advantages of disposables increase with number of products manufactured. Of course, if the new product uses a process that deviates from the platform process, equipment and procedures may have to be qualified and validated under on-site conditions.

The annual output capacities for the facilities are summarized in table 5.1. In the case study with 10 products, the DISP fed-batch facility produces 734 kg of product per annum. The SS facility can only manage to produce 549 kg with the same total reactor volume and 7 changeovers. Thus, the disposable-based design increases productivity with 34 percent. Not wasting value-adding time when changing over contributes to 16 percent. The residual increase of 18 percent is also disposable derived and comes from a lower batch occupancy time of the bottleneck bioreactors and from a reduced seed train. The lower occupancy time allows for faster batch cycling, which means that more batches can be produced per year. The fermentation time is the same but the total occupancy time is lower since no SIP/CIP-operations are needed and the setup is faster. The DISP perfusion facility has the highest output capacity because fewer setups of reactors are needed compared to the fed-batch option. The total maximum output for the perfusion facility is 754 kg per annum.

Table 5.1. Annual output capacity in case study with 10 products and a titer of 5 g/L

	Maximum output (kg)
SS fed-batch	549
DISP fed-batch	734
DISP perfusion	754

5.2 Equipment requirements and utilization

The SS facility has 3 production lines to be able to manufacture products in parallel. However, while adding more production lines increases productivity, it also increases capital investment and facility area since each line needs its own set of process equipment and utility systems. Also, sections and equipment with low occupancy time per batch becomes underutilized. For mammalian cell cultures used for MAb manufacturing, the bioreaction is by far the most time consuming procedure reaching around 2 weeks. The downstream processing (DSP) normally occupy 3 to 4 facility days, indicating that DSP equipment often experience long idle time.

The use of single-use portable components allows for a different approach in equipment usage as discussed briefly in chapter 4.2. Instead of a dedicated equipment unit for each procedure, pools of equipment systems are bought that can be used for several procedures and products. It is the systems and skids that are shared, not the single-use components in contact with the process fluid. The single-use components are as dedicated as they can be since they are discarded after each lot, which means that this production design complies with cGMP specifications [19].

To appreciate the equipment requirement for the DISP facility a detailed downstream schedule was modeled. In the upstream section there are low potential equipment sharing benefits and the equipment requirement estimation is straightforward. The downstream section is somewhat more complicated in the DISP facility because one lot is ready to be purified every 17 hours. Some restrictions on when the processing could be interrupted for facility downtime were applied. This was done because interrupting between certain operations is not desirable, for example within a chromatography cycle. Defining blocks of operations to be executed consecutively also makes it easier for operating personnel and cGMP compliance. Figure 5.5 shows a summary Gantt-chart of the downstream process. The deep blue bars represent the operations blocks which cannot be interrupted. A total

of 5 interrupts are allowed for each batch and the blocks are ranging from 0.73 to 4.65 hours. The total continuous DSP time is 18 hours.

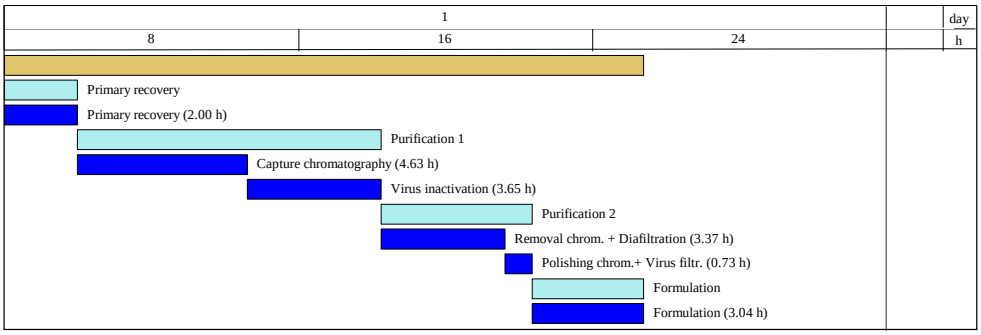

Figure 5.5. A summary Gantt chart of the disposable-based downstream processes. Blue bars represent operation blocks that cannot be interrupted for facility downtime.

The actual facility schedule is shown in figure 5.6. Here, the downstream downtime is considered and the downstream processing takes between 1.5 and 2.5 facility days per batch. The figure gives the support rig (systems) requirements, which are summarized in table 5.2. Each support rig used is displayed in the left margin of the equipment schedule in figure 5.6. Three sizes of storage bag holders are needed: 100/200L, 500L and 1000L. At most, 13 holders are in use in the production area at the same time with a total volume of 7 100 L. This can be compared with the SS facility always having vessels with a total volume of 43 500 L installed in the DSP production areas. Only three chromatography systems and one filter rig per procedure (except DF-103) are utilized at the same time. The total system pools are comparable to one traditional DSP line, which in this case is able to process the flow from as many as 20 reactors.

Table 5.2. Downstream equipment requirements in production area

	SS		DISP	
	# of units	Total size	# of units	Total size
Storage/mixing vessels	27	43 500 L	13	7 100 L
Chromatography columns/systems	9	660 L	3	50 L
Filter rigs	18	-	7	-

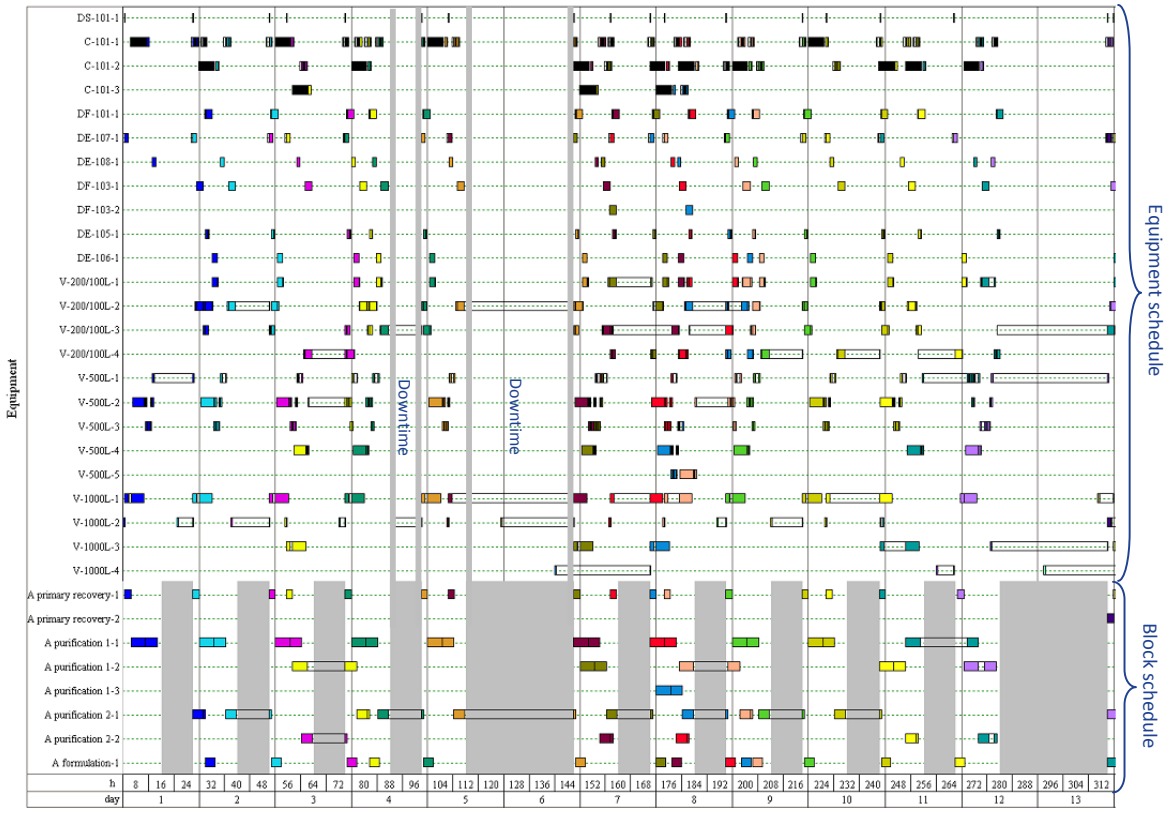

Figure 5.6. Downstream schedule for the DISP fed-batch facility. The 20 reactors generate one lot every 17 hours and the figure shows the DSP equipment rig requirements needed to process this flow. Different colors represent different batches, which can contain any product in the portfolio. In the bottom are the fixed operation blocks displayed, where the grey area represent facility downtime. The equipment is linked to the schedule of the blocks assuring no usage during downtime (white corridors). The only operation allowed during downtime is the transfer in to the bioreactor receiver tank (in a 1000L bag).

The difference in equipment requirements is a good indication of that the disposable-based design leads to smaller production area and lower capital investment. The same process fluid volume is processed but the facility equipment is better utilized than in the SS case. Two flexibility characteristics are the contributing factors: the ability to share equipment between procedures and the possibility to conduct parallel production.

5.3 Different production scales

In the base case, all products have the exact same production process parameter values. A more likely scenario is that some values differ, for example the expression level of MAb. The expression level of product is an increasing function of process development time. The optimization effort of the expression system and the fermentation is normally balanced against the anticipated market potential and benefits of early market entry [9]. Therefore, the expected achieved titer should be lower for low-demand products and materials for clinical trials compared to potential full-scale blockbusters. The downstream performance (mass throughput per size) is less likely to be largely affected by product specific optimization. This means that the required column sizes may vary with product. Also, a change in titer can alter the degree of concentration desired in the diafiltration steps and consequently the downstream volume flow. Thus, the optimum vessel volumes and filter areas can also differ between products.

The flexibility of disposable components is very beneficial regarding these issues. The support systems can often handle varying sizes of equipment. The bags, columns and filters in the process can quickly and easily be exchanged to smaller or larger variants if needed. If the new size challenges the upper size limit, two parallel equipment units can be used.

In a stainless steel facility with fixed equipment and piping, varying scales poses a major obstacle for multi-product manufacturing. The process scale dictates the design of the facility. Once the facility is built, changing scale is not easily done. New equipment may have to be bought and the engineering, installation and qualification may take weeks to conduct. These production equipment changes are also associated with considerable additional capital investments. The utility systems can also become a facility bottleneck when changing scale of production.

5.4 Labor

The production personnel headcount requirements for the facilities are shown in figure 5.7, which gives the maximum number of operators needed in each facility. A summary of the total labor headcount, when all operations shifts are summed and benchmarking factors have been applied, is presented in table 5.3.

Table 5.3. Estimated headcount	**Conventional**	**Disposable**	
	Fed-batch	Fed-batch	Perfusion
Operations	122	96	76
Planning and material management	22	19	19
Others	22	22	22
Engineering	10	7	7
Quality	61	51	51
TOTAL	**237**	**195**	**175**
Savings		18%	26%

The estimated size of the labor workforce in the disposable-based facilities is less than in the conventional stainless steel facility; 195 and 175 employees in the DISP facilities compared to 237 employees in the conventional facility. The number of operation personnel is lower mainly because all processing occurs in one area, allowing for more effective use of the operators. Further savings comes from reduced cleaning and setup operations, and reduced maintenance of the smaller process and utility system infrastructure. Total savings are made even though the DISP facilities process many more batches at smaller scale. The facility based on perfusion processes has fewer operators because it has 10 less bioreactors than the fed-batch option.

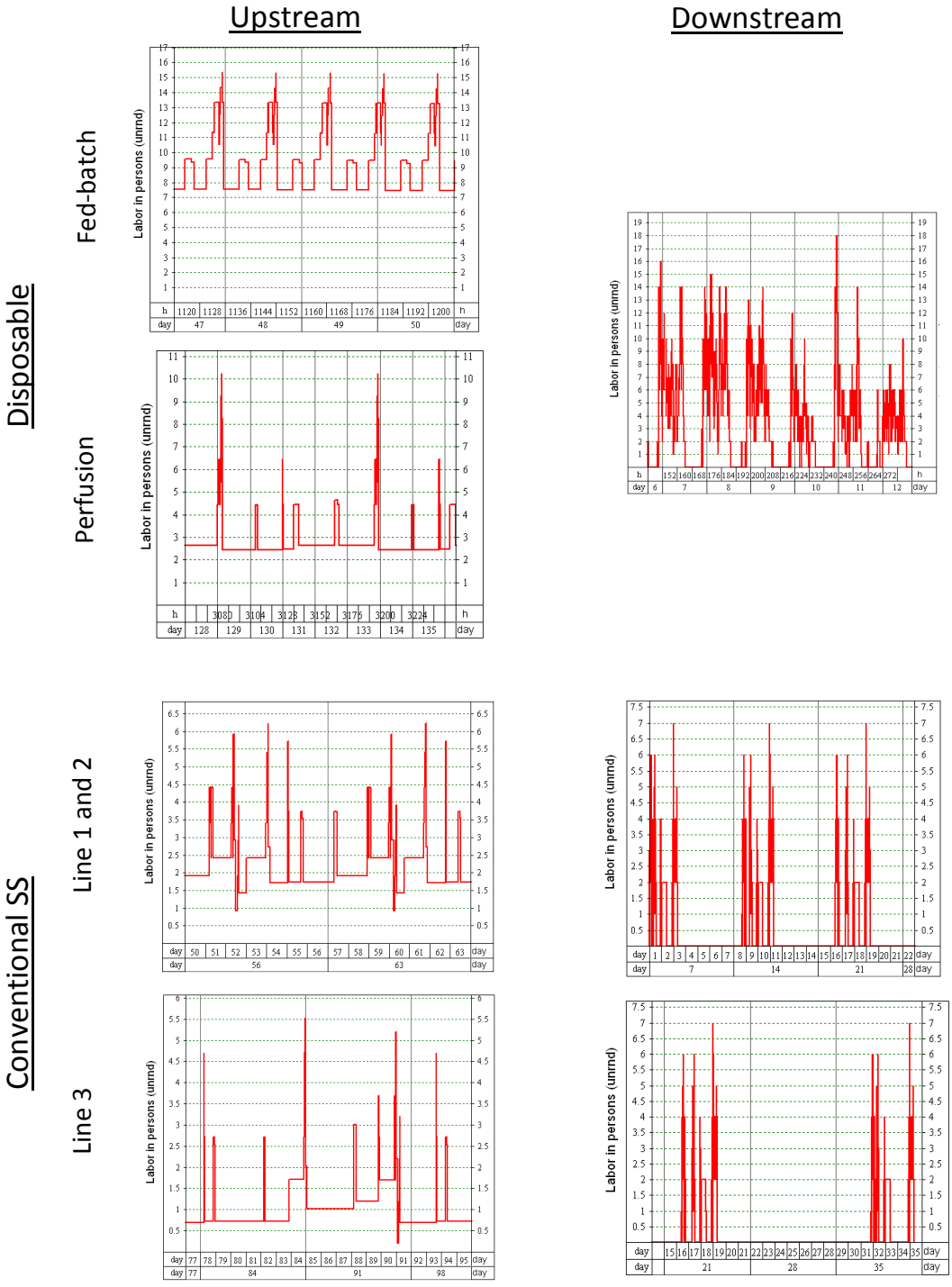

Figure 5.7. Labor requirements per shift for the upstream and downstream areas. The highest peaks represent the maximum headcounts needed and these are assumed to be the numbers of operation employees that are hired. The disposable fed-batch and perfusion facilities purify batches with the same frequency and size and have therefore similar downstream schedules leading to the same size of the downstream workforce.

5.5 Capital investment comparison

Table 5.4 shows a breakdown of the capital investment into each cost category based on the assumed Lang-factors and a calculated conventional equipment cost close to $19M. No capital breakdown is made for the perfusion-based facility because its investment cost is based on the total cost of the fed-batch facility. Savings of 47 percent and 52 percent made for the disposable fed-batch and perfusion facilities, respectively.

Table 5.4. Capital investment

	SS Conventional	**Disposable**	
	Fed-batch	Fed-batch	Perfusion
Equipment (inc. Utilities)	$18 867 000	$9 658 000	-
Pipework and installation	$16 980 000	$3 396 000	-
Process control	$6 980 000	$6 980 000	-
Instrumentation	$11 320 000	$7 471 000	-
Electrical power	$4 528 000	$4 528 000	-
Building works	$31 319 000	$18 791 000	-
Detail engineering	$14 527 000	$4 358 000	-
Construction and site management	$7 546 000	$4 151 000	-
Commissioning	$1 320 000	$1 320 000	-
Validation	$19 999 000	$9 999 000	-
Contingency	$20 008 000	$10 598 000	-
TOTAL	**$153 388 000**	**$81 253 000**	**$74 171 000**
Savings		47%	52%

Note: No capital breakdown is made for the perfusion-based facility because its capital investment cost is based on the total cost of the DISP fed-batch facility.

5.6 Cost of goods comparison

To explore the actual production costs differences, a cost of goods per gram (COG/g) comparison was made. All COG/g numbers were calculated as averages for the 10 products manufactured. Table 5.5 and figure 5.8 show the contribution of the running costs and capital investment to the COG/g. Even though a higher productivity is achieved and large capital and labor savings are made in the disposable options, all savings are offset by an increase in consumable costs and in particular the cost of prepacked disposable columns. The productivity difference only affects the COG/g contributions of items that

are not proportional to number of batches, i.e. capital charge and labor. No such economic benefits arise for consumables and materials when the productivity increases.

Table 5.5. Cost of goods (COG) in USD/g

	SS Conventional	**Disposable**	
	Fed-batch	Fed-batch	Perfusion
Capital charge	$62	$25	$22
Indirect costs	$8	$3	$2
Materials	$13	$12	$14
Labor	$52	$32	$28
Other consumables	$6	$29	$25
Protein A columns	$15	$208	$208
Total	**$157**	**$310**	**$300**

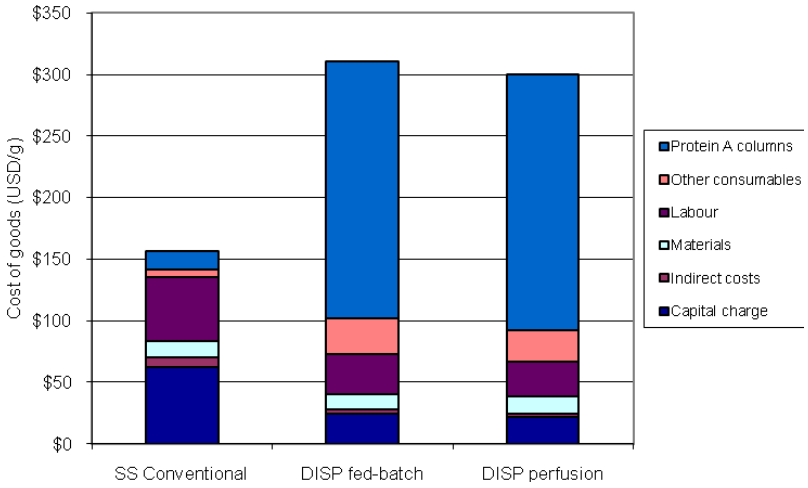

Figure 5.8. Running costs. The contribution of each cost category to the total COG/g for all production technologies in the base case. Disposable Protein A columns are the main cost driver contributing to more than half of the costs in the disposable-based facilities.

Protein A resin is very expensive (~$10 000/L) and is normally a large cost contributor in MAb production. The results presented here show a higher relative cost contribution of the Protein A step, especially for the DISP facilities. One reason for the relative high cost of Protein A in the disposable facilities comes from the prepacked columns are discarded after each batch (5 cycles) whereas the Protein A columns in the conventional facility can be reused (max 150 cycles) for batches of the same product. Another reason is that a high titer was assumed, which increases the downstream portion of the total operating costs. This is because the upstream section can be scaled down when a higher titer is achieved.

Furthermore, the calculations are based on an optimized schedule with high capacity utilization every year. A more normal situation is an average annual capacity utilization of between 50 and 80 percent [13], depending on the purpose of the manufacturing, the number of products produced and the flexibility of the facility. Having lower capacity utilization will increase the portion of the fixed annual costs of the facility which is higher for the conventional design. The effects discussed are further explored in the next sections.

In must also be noted that the COGs have to be put in a larger context, where other performance measures are considered. Even though the conventional facility can, in the base case, produce the MAbs $150/g cheaper, the high performance of the bioproduction and chromatography columns enables COGs in order of magnitude of a few hundreds of USDs for all technologies. This is achieved producing several products at a scale of 20-200 kg per product. Under these circumstances the achieved COGs are low for both the SS and DISP facilities [8]. The $150/g cost increase for the disposable-based facilities must also be compared to proposed economic benefits from a lower contamination rate, a faster time-to-market and faster production modifications, which are performance measures not quantitavily considered in this study.

5.7 Sensitivity analysis

Because the cost of pre-packed disposable columns constitutes such a large portion of the COG in the base case, the impact of the maximum number of chromatography cycles (column life length) on COG was studied (figure 5.9). When the number of cycles can be increased from the 5 cycles used in the base case to 10 cycles, the COG drops considerably for the disposable-based facilities and is only about $40 per gram more than the conventional COG. At 15 cycles the COGs are pretty much the same at 150 USD/g. This means that if the disposable-like ready-to-process (RtP) columns can be run 15 cycles there is no economic disadvantages with the disposable setups. If the columns have longer life lengths than 15 cycles, the MAbs can be produced at a lower cost in the disposable-based facilities.

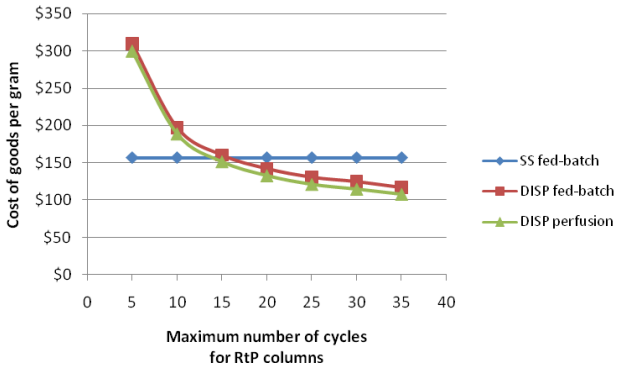

Figure 5.9. Effects on COG/g if the life length of the RtP columns can be increased from the 5 cycles assumed in the base case. At 15 cycles the COG/g are approximately the same for disposable and conventional options.

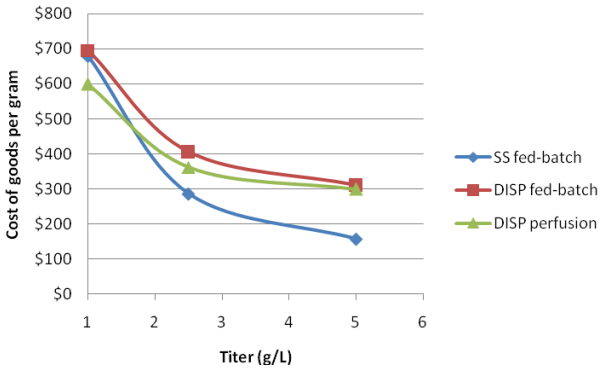

Figure 5.10. Effects on COG/g if the titer is changed from the assumed 5 g/L in the base case. Smaller columns can be used with a lower titer, and the consumables cost constitute a smaller portion of the total COG/g. This makes the disposable options more feasible in terms of COG/g, even though all options have a higher COG/g with low titer because of a reduced output.

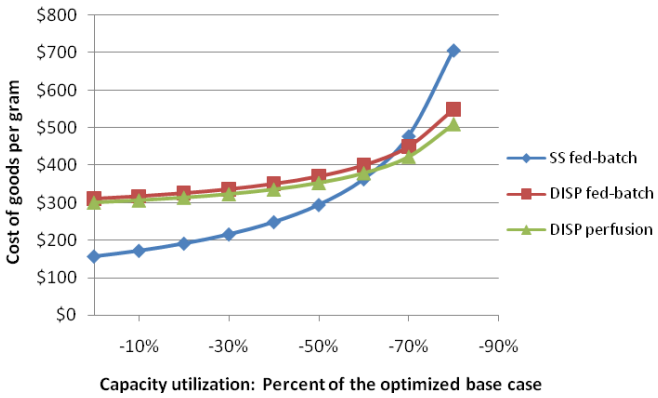

Figure 5.11. Effects on COG/g if the capacities' of the facilities are not fully utilized. The variable costs will be lower but not the fixed costs of capital and labor. Since the SS facility has higher fixed operating costs the COG/g will increase faster when the facility experience more idle time.

Figure 5.10 and 5.11 illustrate the effect of the higher fixed costs in the conventional facility. In Figure 5.10 the effect of titer level on COG/g is shown. With a lower titer than the base case, smaller columns can be used whereas capital investment and labor is not affected to any significant degree. At a titer of 1 g/L, which is reasonable for clinical trials manufacturing, the gap has been reduced and the COGs are very similar between the different production technologies; the perfusion-based facility can even be produced to a lower cost. In Figure 5.11 the effect of capacity utilization on COG/g is shown with a similar dependacy as for titer level change. When the facilities capacity utilization (number of annual batches) is reduced, which is very likely in a multiproduct facility, the disposable option become a more reasonable alternative. For example, demands may vary, a scheduled product can get the market approval withdrawn or delays are encountered in process development or commissoning. All these issues may lead to facility idle time. Keeping all other parameters fixed, a 65 percent decrease in capacity utilization makes the options equivanlent in terms of COG/g.

5.8 Scenario analysis

In the previous section, important parameters were altered one at the time to study the impact on cost of goods. In this section, two parameters are varied at the same time to evaluate the COG/g differences at a spectrum of scenarios.

The first parameters to be explored are titer and facility capacity utilization, displayed in figure 5.12. The curve that separates the green and red area describes the scenarios for which the COG/g is the same for the two fed-batch facilities. The green area describes all scenarios when the disposable design leads to a lower COG/g. When the titer is 2.5 g/L, the capacity utilizations must be more than 50 percent lower than possible for the DISP fed-batch facility to have a lower COG/g. If the titer is 1 g/L, only a 6 percent capacity usage reduction is enough for a lower disposable COG/g. The results support disposable use when the demand for product is low and when there are uncertainties in the production planning.

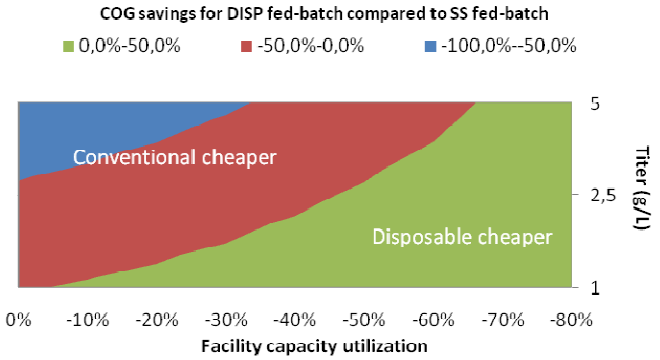

Figure 5.12. Scenarios of at which titer and facility capacity utilization the DISP fed-batch facility can produce MAbs to a lower cost. A maximum of 5 cycles for the disposable columns was assumed.

Next, the maximum number of RtP column cycles were varied together with titer (figure 5.13). When the titer is 2.5 g/L and lower, only a maximum life time of 10 chromatography cycles are needed for the disposable option to be cheaper.

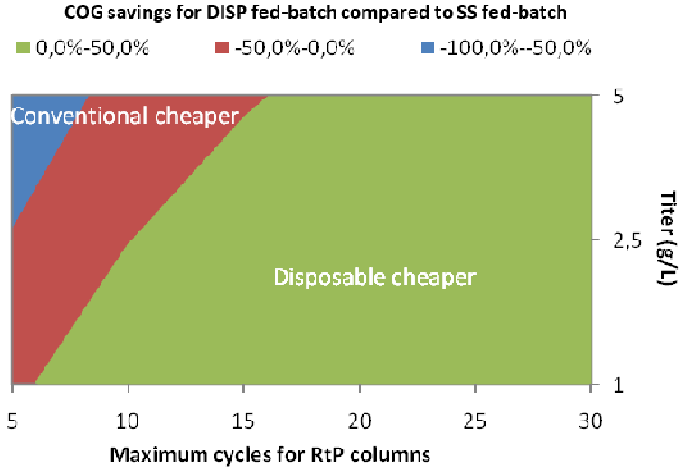

Figure 5.13. Scenarios of at what titer and RtP column life time the DISP fed-batch facility can produce MAbs to a lower cost. Full capacity utilization was assumed.

Finally, the parameters tested were chromatography cycles and capacity utilization (figure 5.14). The results underline that life time of the RtP columns is the most important factor

for disposable-based COG/g advantage. With normal facility utilization, between 10 and 15 cycles give a lower COG/g with the disposable design.

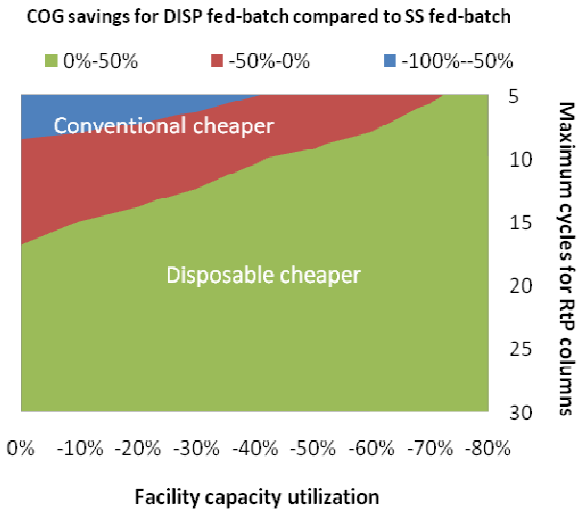

Figure 5.14. Scenarios of at what facility capacity utilization and RtP column life time the DISP fed-batch facility can produce MAbs to a lower cost. A titer of 5 g/L was assumed.

6 Conclusions

In this study, a multiproduct facility producing monoclonal antibodies was modeled. A facility using only disposable-based production technology was compared to a conventional facility using traditional stainless steel equipment.

Utilizing disposables in the production increased flexibility in several ways. The following flexibility benefits were identified for a facility using a closed process with only single-use technology:

- Reduced cleaning and changeover times, which minimized production downtime, increased productivity and could lead to a lower time-to-market.
- More effective use of processing equipment, which led to lower capital investment and could lead to a smaller production area.
- The cleanroom classification requirements and process segregation design was simplified, leading to easier material transfers and better equipment and operator utilization, and reducing issues with utility sizing and maintenance.
- Allowed for faster and easier adoption to products manufactured at different scales and capacity changes.

The economic impact of using disposables was examined with a cost of goods analysis. The disposable-based facility had lower capital investment and labor requirements, but increased consumable costs. The COG analysis showed that, in the base case, the conventional design could produce the products at a cost of $150 per gram lower than with the disposable-based setup. The reason for this was increased consumable cost when using prepacked columns which offset the cost savings for capital and labor. However, when some of the assumptions in the base case were changed, scenarios when the disposable design led to a decreased COG/g were identified. Disposables were shown to be economically favorable when the titer or facility capacity utilization was lower, or when the life time of the prepacked columns could be increased.

The results showed that disposables may in many cases be preferable, both financially and operationally. However, for products with high demand that will be produced within a long time frame, i.e. blockbusters, conventional technology still outperforms the disposables in terms of COG. Completely disposable-based facilities are ideal for products with demand up to 10's of kg per year and when lead times, flexibility and low risk are of most importance. This covers manufacturing of material for clinical trials, initial stock build-up for a quick market launches and commercial manufacturing of products with smaller patient groups or low doses. If the concept of personalized medicine is realized or the potency of antibodies increases, more commercial therapeutic antibody products will have demands suitable for disposable manufacturing.

7 Future research

In this study several commercial tools was used to model a multiproduct facility. They were only partially compatible, meaning that some manual transfers of information had to be made. Changes of parameters in one tool could not automatically be transferred to other tools. This led to restrictions in the sensitivity and scenario analyses. An integrated tool, able to model detailed batch recipes, scheduling of multiple products and performing cost calculations would have been beneficial. Such a tool is not commercially available, but it would be interesting if it could be developed. Furthermore, optimization models for multi-product batch production planning would facilitate similar research projects.

The risk of contamination when implementing disposables has been suggested to be reduced. The results from a study on the batch failure rate with disposables compared to stainless steel production could be incorporated in the COG model, quantifying the financial benefit of this characteristic of disposables.

8 Acknowledgements

I would like to thank my supervisor Karol Lacki for encouraging me during the work and for his expertise. I would also send my regards to other colleagues in the R&D department at GE Healthcare, Uppsala, for their warm welcome and interesting lunch meetings and coffee breaks.

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10 Appendix

A1. Changeover delay

This section presents a mathematic description of the total delay due to changing over a manufacturing facility to a new product in a conventional production line. The production is divided into p number of contained sections. Contained means that more than one product cannot be processed in one section at the same time. The sections have to be cleaned before a new product enters the production area. For a graphical example to refer to during the derivation, please go to figure A1 in the end of Appendix A2.

First, the sections are looked at upon as independent and scheduling is optimized for each section i, $i = 1, 2, ..., p$. The lowest batch cycle time for each section (time between two consecutive batches), T_{cycle}^{i}, is defined as

$$T_{cycle}^{i} = \frac{T_{BNE}^{i}}{N_{BNE}^{i}} \tag{A1}$$

T_{BNE}^{i}: Time occupancy of bottleneck equipment (BNE). The bottleneck equipment is the equipment that does not experience idle time in a fully optimized schedule.
N_{BNE}^{i}: Number of staggered BNE equipment units.

The total delay due to the changeover is the time between the start of the first batch of the new product compared to when the same batch would have started if no changeover was necessary. This time is the same as the time between the completion of the BNE in the last batch of the previous product and the start of the BNE in the first batch of the new product. Within a production campaign this timeshift is zero. Three components

contribute to the delay. With staggered BNEs and no changeover, the next BNE would start before the other staggered BNEs have finished the processing. For the new product on the other hand, the BNE must wait until the other BNEs have finished their processing before it can enter the section. This delay is called D^i_{stagg}. Furthermore, it has to wait for additional processing in equipment downstream of the BNE in the last batch and the processing upstream of the BNE in the new batch before the BNE can start again. This delay is called $D^i_{\sec}$. Finally it has to wait for the cleaning and cleaning validation, T^i_{clean}, which is assumed to be the same for all equipment in one section. The total delay because of the changeover in independent sections, T^i_{CO}, is then given by

$$T^i_{CO} = T^i_{clean} + D^i_{stagg} + D^i_{\sec} \tag{A2}$$

where T^i_{clean} is given by the equipment type and its associated cleaning protocols and

$$D^i_{stagg} = \left(1 - \frac{1}{N^i_{BNE}}\right) T^i_{BNE} \tag{A3}$$

$$D^i_{\sec} = T^i_{\sec tion} - T^i_{BNE} \tag{A4}$$

where $T^i_{\sec tion}$ is the total time required from start to finish of a batch in the section.

The above analysis applies to each section assuming a possibility for independent optimization by identifying the bottleneck, minimum cycle time and the changeover delay for each section. However, when all sections are scheduled together the section with the largest cycle time will define the cycle time of the entire batch. This means that the other sections will be cycled slower than optimum and the section BNE will experience idle time. This idle time can be used for cleaning of the equipment (T^i_{clean}) and waiting ($D^i_{\sec}$ and

D^i_{stagg}), meaning that the other sections can have a higher T^i_{CO} than the bottleneck section without delaying production. The idle time for the BNE in section i is given by

$$T^i_{idle} = \left(\max_j\left(T^j_{cycle}\right) - T^i_{cycle}\right)N^i_{BNE} = N^i_{BNE}\max_j\left(\frac{T^j_{BNE}}{N^j_{BNE}}\right) - \frac{T^i_{BNE}N^i_{BNE}}{N^i_{BNE}} =$$
$$= N^i_{BNE}\max_j\left(\frac{T^j_{BNE}}{N^j_{BNE}}\right) - T^i_{BNE} \qquad \text{(A5)}$$

The total idle time should be subtracted from the independent section changeover time defined in A2 when considering the actual inflicted delay of a section. The delay of a section (D^i) becomes

$$D^i = T^i_{clean} + D^i_{stagg} + D^i_{\sec} - T^i_{idle} \qquad \text{(A6)}$$

The delay of the whole batch comes from the section that has the longest delay. That is, the batch delay due to the changeover, D_{CO} is

$$D_{CO} = \max_i D^i = \max_i\left(T^i_{clean} + D^i_{stagg} + D^i_{\sec} - T^i_{idle}\right) =$$
$$= \max_i\left(T^i_{clean} + \left(1 - \frac{1}{N^i_{BNE}}\right)T^i_{BNE} + \left(T^i_{\sec tion} - T^i_{BNE}\right) - \left(N^i_{BNE}\max_j\left(\frac{T^j_{BNE}}{N^j_{BNE}}\right) - T^i_{BNE}\right)\right) =$$
$$= \max_i\left(T^i_{clean} + \left(1 - \frac{1}{N^i_{BNE}}\right)T^i_{BNE} + T^i_{\sec tion} - N^i_{BNE}\max_j\left(\frac{T^j_{BNE}}{N^j_{BNE}}\right)\right) \qquad \text{(A7)}$$

Normally in bioproduction, staggered equipment is only used in the section with the batch BNE (often bioreactor) and therefore $N_{BNE}^{i} = 1$ for all i except $i = h$, where h is the section with the batch BNE. If this is assumed then equation A7 becomes

$$D_{CO} = T_{clean}^{k} + T_{section}^{k} - T_{batchcycle} \quad \text{(A8)}$$

where section k is the section with the longest delay.

To summarize, the delay due to changeover depends on the cleaning and section processing time in the changeover bottleneck section and the batch cycle time. Reducing cleaning time or having more sections ($T_{section}^{i}$ lower) or reducing the number of bottleneck equipment will reduce the production delay due to the changeover.

A2. Annual number of batches

The campaign time (T_{camp}) for one product is given by

$$T_{camp} = T_{batch} + T_{batchcycle}\left(N_B - 1\right) \tag{A9}$$

where $T_{batchcycle}$ is the cycle time in the suit, N_B is the number of batches manufactured and T_{batch} is the time for a whole batch from inoculum start until formulation is completed. To calculate the number of batches that can be produced within a given year, equation A8 is solved for N_B and T_{camp} is set to the annual available manufacturing time. The total changeover time between products can be seen as a reduction in the available manufacturing time. When this is done the annual available manufacturing time is

$$T_{camp} = T_{facility} - N_{CO}D_{CO} \tag{A10}$$

where $T_{facility}$ is the number of facility days open for production, N_{CO} is the number of changeovers in the suite and D_{CO} is the changeover delay as defined in equation A7.

Solving equation A9 for N_B and using A10 gives the number of annual batches that can be produced in a production line

$$N_B = \frac{T_{facility} - N_{CO}D_{CO} - T_{batch}}{T_{batchcycle}} + 1 \overset{\text{[Equation A8]}}{=} \frac{T_{facility} - N_{CO}\left(T_{clean}^{bioreaction} + T_{section}^{bioreaction} - T_{batchcycle}\right) - T_{batch}}{T_{batchcycle}} + 1 \tag{A11}$$

The bioreaction section was the changeover bottleneck in the case study (determined using A7), when assuming that the inoculum section did not need to be contained. The integer solution of equation A10 gave the number of batches produced in the suits of the SS facility.

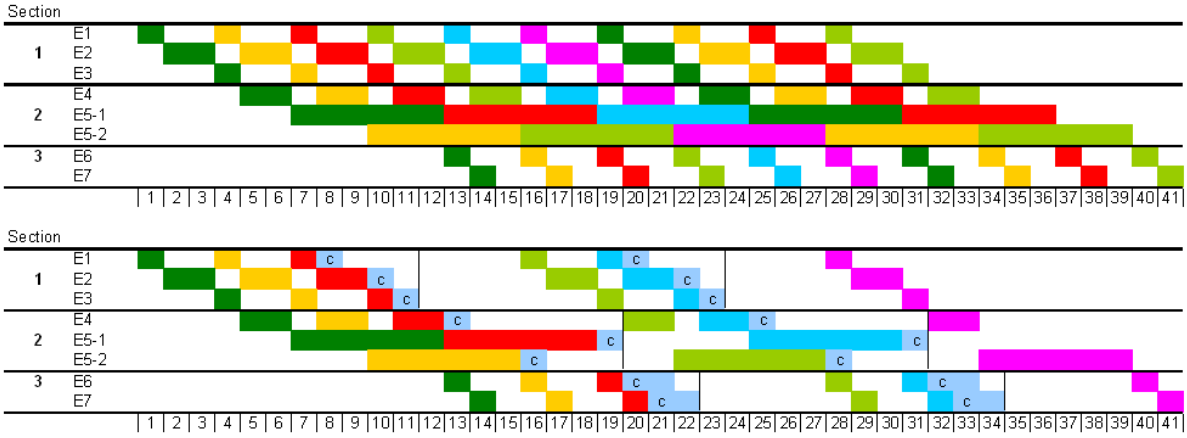

Figure A1. Scheduling example. This example can be used to verify the equations derived. The horizontal axis is in time units. E1 to E7 is different equipment types used in the process. Different colors represent different batches. The schedule on the top is a schedule without changeovers. The schedule in the bottom shows what happens when 2 changeovers are introduced (c stands for cleaning and cleaning validation). Vertical lines show when the section is available for a new product. The delay due to one changeover is 6 time units (for example: the light green batch is finished at time 23 without changeover and at time 29 with one changeover). Section 2 is the changeover bottleneck and the 2 changeovers reduce the total number of batches produced from 10 to 6 within the specified time frame.

Figure A1 shows an example of a production line either producing one product or three within a specified time. Table A1 presents the example results of calculations using equations A1, A6, A7 and A11. The calculations are consistent with figure A1.

Table A1	Section		
	1	2	3
Given			
Bottleneck equipment	E2	E5	E6 and E7
T_{BNE}	2	6	1
N_{BNE}	1	2	1
$T_{section}$	4	8	2
T_{clean}	1	1	2
Calculated			
T_{cycle} (min)	2	3	1
$D_{i,CO}$	2	6	1

		Equation used
$T_{facility}$	41	Given
D_{CO}	6	A7
N_B (one product)	10	A11
N_B (three products)	6	A11