TACTICAL PLANNING OPTIMIZATION FOR CAMPAIGN SCHEDULING OF ACTIVE PHARMACEUTICAL INGREDIENT PRODUCTION BASED ON MONOCLONAL ANTIBODIES

by

Shai Assia

B.Sc. Bio-Medical Engineering, Tel-Aviv University, Tel-Aviv, Israel 2010

Submitted to the MIT Sloan School of Management and the Department of Mechanical Engineering in Partial Fulfillment of the Requirements for the Degrees of Master of Business Administration, and Master of Science in Mechanical Engineering In conjunction with the Leaders for Global Operations Program at the Massachusetts Institute of Technology

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Abstract

Monoclonal Antibodies (mAb’s) are the fastest growing segment in the biopharmaceutical industry. They are used today as therapeutics and diagnostics for several medical applications, including various types of cancer, rheumatoid arthritis, psoriasis, severe asthma macular degeneration, multiple sclerosis and more. In recent years, industry trends and market pressure have driven pharmaceutical companies to focus efforts on increasing operational efficiency in order to reduce the financial burden associated with drug manufacturing. Consequently, Novartis Pharma Technical Operations' is currently engaging in efforts to obtain Class “A” Manufacturing Resource Planning (MRP II). This project was chosen to analyze and address the current Integrated Business Planning (IBP) technically and financially by analyzing critical processes, their bottlenecks, and prioritizing improvement opportunities. We focus on tactical planning at the Multiproduct Process Unit at BioPharm Ops.

This paper describe the development of a Tactical Planning optimization tool, which implements SuperPro Designer© and SchedulePro© (Intelligen Inc., NJ, USA) for campaign scheduling of active pharmaceutical ingredient production based on mammalian monoclonal antibodies (mAb’s). Results have shown great potential benefits for Novartis, including but not limited to: Creating and modifying campaign schedules in hours (not days); increased operational efficiency; Max Run Rate Optimization, cycle time reduction and significant production cost savings; analytic tool to support long-term strategic decisions with the flexibility to address real-time adversity and automated conflict resolving.

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<th>Definition</th>
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<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>BioPharmOps</td>
<td>Biological Pharmaceutical Operations</td>
</tr>
<tr>
<td>BOM</td>
<td>Bill of Materials</td>
</tr>
<tr>
<td>BPR</td>
<td>Batch Production Record</td>
</tr>
<tr>
<td>CAGR</td>
<td>Compound Annual Growth Rate</td>
</tr>
<tr>
<td>CAPA</td>
<td>Corrective Action Preventive Action</td>
</tr>
<tr>
<td>c/GMP</td>
<td>current /Good Manufacturing Process</td>
</tr>
<tr>
<td>CHO</td>
<td>Chinese Hamster Ovarian</td>
</tr>
<tr>
<td>CIP</td>
<td>Cleaning In Place</td>
</tr>
<tr>
<td>COGS</td>
<td>Cost of Goods Sold</td>
</tr>
<tr>
<td>DP</td>
<td>Drug Product</td>
</tr>
<tr>
<td>DS</td>
<td>Drug Substance</td>
</tr>
<tr>
<td>DSP</td>
<td>Down Stream Process</td>
</tr>
<tr>
<td>ERP</td>
<td>Enterprise Resources Planning</td>
</tr>
<tr>
<td>FMEA</td>
<td>Failure Mode &amp; Effect Analysis</td>
</tr>
<tr>
<td>FCS</td>
<td>Finite Capacity Scheduling</td>
</tr>
<tr>
<td>HVAC</td>
<td>Heat, Ventilation and Air-Conditioning</td>
</tr>
<tr>
<td>IBP</td>
<td>Integrated Business Planning</td>
</tr>
<tr>
<td>IQP</td>
<td>Innovation, Quality and Productivity</td>
</tr>
<tr>
<td>IT</td>
<td>Information Technology</td>
</tr>
<tr>
<td>KPI</td>
<td>Key Performance Indicator</td>
</tr>
<tr>
<td>MES</td>
<td>Manufacturing Execution System</td>
</tr>
<tr>
<td>MPS</td>
<td>Master Production Schedule</td>
</tr>
<tr>
<td>MRP</td>
<td>Material Requirements Planning</td>
</tr>
<tr>
<td>MRP II</td>
<td>Manufacturing Resources Planning</td>
</tr>
<tr>
<td>MS&amp;T</td>
<td>Manufacturing Science and Technology</td>
</tr>
<tr>
<td>NBE</td>
<td>New Biological Entities</td>
</tr>
<tr>
<td>NPV</td>
<td>Net Present Value</td>
</tr>
<tr>
<td>OTC</td>
<td>Over The Counter</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>QC</td>
<td>Quality Control</td>
</tr>
<tr>
<td>RA</td>
<td>Regulatory Affairs</td>
</tr>
<tr>
<td>S&amp;OP</td>
<td>Sales &amp; Operations Planning</td>
</tr>
<tr>
<td>SCM</td>
<td>Supply Chain Management</td>
</tr>
<tr>
<td>SIP</td>
<td>Steaming/Sterilizing In Place</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>TPL</td>
<td>Technical Project Leader</td>
</tr>
<tr>
<td>TRD</td>
<td>Technical Research and Development</td>
</tr>
<tr>
<td>UF/DF</td>
<td>Ultrafiltration / Diafiltration</td>
</tr>
<tr>
<td>USP</td>
<td>Up Stream Process</td>
</tr>
<tr>
<td>WCB</td>
<td>Working Cell Bank</td>
</tr>
<tr>
<td>WFI</td>
<td>Water For Injection</td>
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</tbody>
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1 Introduction

"The significant problems we face cannot be solved at the same level of thinking we were at when we created them" (Albert Einstein)

1.1 Motivation

While the healthcare industry has been consistently growing for several decades, both positive and negative trends continue to impact the way in which pharmaceutical companies operate. Greater access to healthcare in emerging markets, scientific and technological advancements and the demographic shift towards an aging population create both challenges as well as opportunities to enhance the lives of patients. At the same time, economic uncertainty, regulatory and litigation manners, patent expiration, pressure to reduce costs, and manufacturing competition issues exert downward pressure. As healthcare spending outpaces the economic growth, tensions increase and manufacturers are faced with the demand to optimize operational efficacy.

Meeting summary with Dirk Boehm, Head of BioPharm Ops PLANT X:

At the beginning of the year, the new Head of Novartis' Global TechOps, Juan Andres, presented his vision for TechOps, under the theme "Making quality medicine, on time, every time". To support this vision, which builds on the foundations laid in the past, Juan also introduced the "Manufacturing Manual" which summarizes the general approach that will follow TechOps in the form of seven manufacturing principles and a group of practices to implement these principles. Key issues dealt in this initiative:

• To achieve this vision, we must primarily focus on materials safety, quality and reliability
• The process-oriented organization (POO) is a key enabler, empowering partners and limiting hierarchical levels to the minimum required
• Ensuring a reliable supply of goods and adhering to schedule is essential to our business – on time, every time
• We must strengthen our working methods to achieve this goal. TPM and MRP II class A are some of the aspects related to this point
• Priority should be given to the prevention of problems rather than "fire-fighting" as it is often the case today
• Employees and organizational capabilities must continue to be developed and this should be an important part of our business
• Make up problems or issues and propose or develop solutions together

Continuous Improvement of Novartis' processes, Manufacturing Science & Technology (MS&T), systems and core competencies aim at increasing the stability and predictability of the company's technical operations and ensure a reliable supply of product quality at competitive costs:

• Supply Reliability - to minimize risk of shortage and stock outs
• Quality - safety and robustness of products and processes across the company, including compliance with cGMP and RA
• Competitive Costs - achieving business advantage related to the industry

These principals and practices are valid for all divisions and should be applied to all. How they are applied depends on the divisional business model and external environment in which the specific division operates.

1.2 Primary Goals for the Internship

The primary objective of this project is to analyze and address from both a technical and financial point of view the integrated business planning (IBP) of the current manufacturing processes for the production of mammalian monoclonal antibodies used in biopharmaceuticals. We look to optimize Campaign Scheduling for batch Production of Biological API in order to increase the overall operational efficiency.

Novartis Pharma TechOps would like to obtain a Class A certification for its Manufacturing Resources Planning (MRP II) by: Securing supply chain management (SCM); Improving productivity, efficiency and transparency; Creating flexibility to address real-time adversity and reduce variation and deviation.

1.3 Scope

As part of Novartis Pharma Technical Operations' vision - Making Quality Medicine: On Time, Every Time - the division is currently engaging in efforts to obtain Class ‘A’ Manufacturing Resource Planning (MRP II). In the scope of this project, we focus on the Multiproduct Process Unit at the BioPharm Ops site in PLANT X. The primary work takes place within tactical planning, aimed at aligning long run strategic planning and short-run operational planning and execution. The facility is divided into two process units (PU): First is a perfusion process unit for the production of a single product, PROTEIN E; Second is a fed-batch process unit for the production of multiproduct: PROTEIN A, PROTEIN B, PROTEIN C and PROTEIN D (real names and product configurations have been omitted from this paper due to confidentiality restrictions). Currently, the internship project applies for the multiproduct facility, but is likely to apply to the perfusion PU as well.

1.4 Problem Statement

1.4.1 General

At the current state, demands for Drug Substance (DS) and for Drug Product (DP) are communicated separately to the BioPharm Ops and the Pharm Ops production sites, respectfully. Demands are also sent separately per product by the Supply Chain Management (SCM) for commercial use, and by the Technical Research and Development (TRD) for clinical use. In order to meet demand, Active Pharmaceutical Ingredients (API) are produced in a fed-batch manner, in which
campaigns are allocated for each product. This requires frequent communication with the direct customer downstream (Pharm Ops) to verify the production process alignment and capacity compliance.

1.4.2 Specific

From the Tactical Planning point of view, Campaign Scheduling is currently done manually, resulting in a time-consuming process with little flexibility to address real-time deviations. There is little automation in the connection with other planning levels (strategic and operational). This also hinders informational outputs to other functions in the organization with clear interests in the production process (such as Finance, HR, SCM, etc.).

The common planning tool is Excel-based. While this tool is easy to use and broadly familiar, assumptions tend to get lost in the formulation of the cells and treated as given data, making the production system vulnerable to inaccuracies, resulting in delivery-time errors and under utilization of capacity.

1.5 Approach

This project has a Process Improvement and Lean approach, and includes activities such as:

- Technical and costs analysis of current production operations and their planning
- Proposal of process improvements (and business cases associated) to increase the number of drug substance batches per week and better forecast long term capacity for number of campaigns per year
- Priority assessment for potential solutions (investment, benefits, estimated work duration, etc.)
- Piloting one possible solution, and setting the ground for a division-wide Implementation

In practice, this project takes a 2-part approach: specific product recipe modeling, and multiproduct campaign scheduling and simulation.

1.6 Research Methodology

The framework draws upon Novartis' biological products' manufacturing processes, the current resource capacity, and mid-term (1-2 years) product demand projections from Supply Chain Management and Technical Research & Development.
1.6.1 Process for API Production Recipe Model Development

Data Collection

Data regarding mAb production were collected via broad scientific literature review. Value Stream Mapping (VSM) of product-specific manufacturing steps was done through interviews with process and quality experts from the production facility, in conjunction with the existing planning tools currently implemented at the PU: mostly SAP, MS Excel and MS Project. To verify data accuracy, all quantitative values were compared to those mentioned in the latest revision of the controlled internal documentation (standard operating procedures, or SOP).

Hypothesis Development

The first phase implements SuperPro Designer© (Intelligen Inc., NJ, USA) to model specific API production recipes. The model describes the production process flow, the required resources (main and auxiliary equipment, material preparations and labor) and specifies the time durations and sequencing of each unit-procedure and operation.

Hypothesis Testing

Once completing the product recipe, the model produces several outputs, including an operational Gantt chart describing the sequence of operations needed to produce the modeled mAb substance, and an equipment occupancy chart. In addition, a production schedule summary is available, specifying the batch time, overall and minimum cycle time, and the cycle slack time, as well as other useful information such as the longest unit procedure and the scheduling bottleneck [full definitions of these parameters are discussed in this paper].

The output feasibility was verified against the available data from the SAP and Excel files, considered as the gold standard.

Application

While SuperPro Designer© models may be used for various process engineering applications, the product-specific recipe modeled in this part was primarily used as the building stones of the multiproduct campaign scheduling in the second part of the project.

The visual representation of the recipe may also be used as a VSM that presents the production equipment layout and procedure sequencing for both USP and DSP simultaneously.
1.6.2 Process for Multiproduct Campaign Schedule Development

Data Collection

Data regarding tactical planning and campaign scheduling were collected via broad scientific and business literature review. Planning practices at Novartis BioPharm Ops were collected through interviews across a wide range of stakeholders at different organizational functions, including Production, IQP, SCM, Finance, TRD, TPL, IT and more. To verify data accuracy, all quantitative values were compared to those mentioned in the latest revision of the controlled internal documentation (standard operating procedures, or SOP). Product demand projections were taken from current production orders and from historical data (commercial and clinical from SCM and TRD, respectively).

Hypothesis Development

The second phase implements SchedulePro© (Intelligen Inc., NJ, USA) to determine the optimal fed-batch campaign schedule to minimize cycle-time, and simulate What-If scenarios. The multiproduct facility model builds on the specific recipes modeled in the first phase of the project and considers additional plant-wide information, such as maintenance downtimes and work area constraints.

Hypothesis Testing

The model uses the consolidated product demands as input parameters and yields a recommended production schedule, given the existing capacity and resources availability. Feasibility of schedules, scenarios and simulations outcomes were verified by the qualified production personal at the PU against the gold standard. Prior to the pilot launch, key stakeholders were gathered to collect a well-defined set of acceptance criteria to meet the proof-of-concept. The criteria were selected such that the new tool, if found appropriate, will not only perform equally as good as the gold standard, but also offer an added value in terms of convenience of use, robustness of results and quality of analyses it provides.

Application

This pilot project functions primarily as a proof-of-concept to the implementation of a planning tool at the specific BioPharm Ops production site and across other TechOps sites. For the pilot stage, the software was installed on a single computer within the local (PLANT X) IT, and the model developed off-line to not interfere with the operational network system.

A relating pilot was executed in parallel at a ChemOps manufacturing site.

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1 Note: SchedulePro© was not selected to completely replace SAP as the ERP tool, but rather to compliment it as a method for tactical planning of campaign schedules
2 Christopher Wilson, "Application of Simulation for Planning in Multi Product Pharmaceutical Manufacturing."
1.7 Thesis Outline

This thesis is structured according to the following chapters:

Background

The next chapter provides an overview on Novartis Pharma and the biopharmaceutical industry in order to lay out the business context in which the work takes place. We focus on the unique features of monoclonal antibodies (mAb’s) and their relevancy in the production process, as well as planning for the manufacturing procedures in the multiproduct plant. This chapter introduces the BioPharm Ops site in PLANT X, and ends by connecting the production tactical planning with the greater Supply Chain Management (SCM).

Literature Review

Chapter 3 further explores the topics of production and production planning and scheduling, found in the academic literature. Relevant case studies are presented to extract best practices that were tested and applied in the industry.

Pilot Setup

In Chapter 4 we review potential methods for scheduling optimization and discuss the rational of selecting SchedulePro© for our application. This chapter sets the ground for the practical part of the thesis described in the next chapter, by defining the functional requirements of the model and its design considerations.

Methodology

Chapter 5 goes into the fine details of the model development, building on the functional requirements that were previously described. It explains how the parameters of interest are defined to accommodate for manufacturing resources' capacity and other practical scheduling constraints. This chapter is divided into three sub-sections: Part I – Modeling Specific Product Recipe using SuperPro Designer©; Transition; and Part II – Production Campaign Scheduling and Simulation using SchedulePro©

Results

The model outcomes are discussed in Chapter 6 in accordance to the proof-of-concept criteria, established earlier on. Capacity and Sensitivity analyses are performed through scenario testing, and the financial implications evaluated.

Conclusions

The final chapter summarizes the benefits that the model, described in the preceding chapters, offers Novartis as well as specific recommendations and additional potential applications in this industry and others. Model limitations and risk mitigation are discussed and future work to be done is suggested along with an implementation strategy.
2 Background

“Novartis aims to become the world’s best pharmaceutical manufacturer by improving operational excellence in manufacturing and supply. Our goal is to enhance the stability and predictability of our technical operations and thereby the quality of our products” (Joseph Jimenez, CEO, Novartis)

2.1 Industry Context

2.1.1 Biopharmaceuticals Overview

Despite the decreased growth rate in North America and Europe, global spending on prescription drugs was over $954 billion in 2011. With $340 billion in annual sales, the USA accounts for over a third of the entire global pharmaceutical market, followed by the EU and Japan. A significant growth (81%) was noticed in emerging markets such as China, Russia, South Korea and Mexico. According to IMS the current (2014) global pharmaceutical industry reaches an estimated US$1.1 trillion.

Factors differentiating the pharmaceutical industry from other industries include very long product development times, large capital investments, extensive regulations and high level of business uncertainty. Unlike other industries that constantly come out with new designs or improved models for their products, the pharmaceutical industry may seem very conservative when it comes to change. For example, a retail company’s product portfolio will include many different designs and new items would launch every season. Items from last season will be considered out of fashion and obsolete. Pharmaceuticals on the other hand take a long time to develop and even longer to approve by the regulatory authorities.

Furthermore, every country (or market) has its own notified body that must approve the product before it could be commercially distributed within that market, making the total time-to-market process longer and delaying the return on capitalization. A typical product takes 10-15 years and a capital investment of $800M-$1B to develop from early stage to a commercially available product. Less than 15% of the products that enter Phase I clinical trials will become FDA approved. Therefore, a product that was released for sale will remain in production as long as no other competitor proved better results and the intellectual-property protection is still valid.

While industry regulations help ensure the safety and efficacy of medical products, it requires constant auditing and is heavily cost and time consuming. Consequently, regulations indirectly inhibit continuous improvement once a product is approved and/or a manufacturing facility is quality certified, and make it particularly challenging to implement new initiatives in existing processes. The industry’s openness (or lack of it) to changes in existing products is in contrast to extensive investments that are made in research and development for new products. In recent years this trend seems to be changing.

---

1 Gary Gatyas and Clive Savage, “Biopharma Forecasts & Trends.”
2 Suresh and Basu, “Improving Pharmaceutical Product Development and Manufacturing.”
due to several developments, such as increasing market demand for cost reductions to compensate for financial losses following patent expirations.

In addition to being On-Patent or Off-Patent (generic and biosimilar), Pharmaceutical products are often distinguished by categorizing them as Small-Molecule or Large-Molecule; the first, typically created by chemical synthesis, whereas the later, typically complex proteins created through biological proliferation of genetically-modified living organisms. Biopharmaceuticals are projected to be the prime drivers of growth in the pharmaceutical market.

2.1.2 Biologics and Therapeutic Proteins

As highly target-specific and potent medicines, therapeutic proteins offer real hope for many unmet patient needs, particularly in complex diseases, including autoimmune diseases and cancer.

Therapeutic antibodies have long half-life and activity can remain effective for 2 to 4 weeks, so less frequent administration is required. Other advantages include a lower tendency for side effects than traditional chemical drugs. From a business perspective, biopharmaceutical companies face a higher likelihood of reaching the market and generally sell at higher prices. In addition, they are better protected from competition since biologics are more difficult to copy than small molecule drugs. However, regulatory burden is higher than for small chemical drugs, the main reasons being inherent variability of biological production systems and the greater complexity of the product.

To minimize major regulatory challenges (mainly cost and bureaucratic delays), Phase III clinical trial materials for biopharmaceuticals should be produced with the final process in mind and at the final commercial production site. It is, therefore, common that Phase III production site selection determines the commercial production site. Final manufacturing process is transferred to the launch site before the start of phase III campaigns.

The drug substance production facility's utilization and occupancy are the largest potential cost drivers. A production facility, for example, that runs at a very high titer yield for a single product will have the capability to produce a great amount of product per year. But if the demand for that product does not reach the productivity potential, the facility's cost structure will not be able to take advantage of its high performance process. This fact drives companies to design and operate facilities for multiple products, benefiting from standardized processes. In addition, as a result of excess capacity, recent trends aim to distribute plant overhead among several products and bring new products to currently operating facilities.

2.1.3 Monoclonal Antibodies (mAb)

Monoclonal Antibodies (mAb) are large and complex protein molecules produced from immune cells that are all clones of a unique parent cell. mAb's consist of two regions, Fragment Antigen Binding (FAB) and Fragment Crystallizable (Fc), and have monovalent affinity (i.e. specifically bind to the same epitope of a target substance). This characteristic has proven very useful for targeting specific biological conditions and, therefore, mAb's are used as therapeutics and diagnostics for several medical
applications, including various types of cancer, rheumatoid arthritis, psoriasis, severe asthma macular degeneration, multiple sclerosis and more.

mAb are produced from mammalian cells (e.g. human, CHO, Rabbit, etc.) or microbial fermentation. Through recombinant technologies, the genes can be carefully inserted into the genome (DNA or genetic material) of the host cells so that the cells express the protein of interest. While the host cells may come from a variety of sources, Chinese hamster ovary (CHO) cells are considered attractive for mAb production due to their process performance attributes allowing productive growth, like robustness and high adaptability to the chemical media, rapid amplification a high expression of the protein. Today, CHO cells are the most commonly used mammalian hosts for industrial production of recombinant protein therapeutics. Most mAb's are produced in a fed-batch manner, followed by purification and viral clarification.

Different classes and sub-classes of mAb's vary in the exact structure of product separation and purification, yet the general structure is typically the same. Therefore, manufacturing processes for different applications often share the same practices, allowing multiple products to be produced in a single factory – as is the case for BioPharm Ops PLANT X's PU multiproduct. However, running several products simultaneously is highly complicated and holds a risk for cross-contamination. Therefore, different substances are produced in product-specific campaigns, separated by strict changeover procedures that significantly limit the allowed overlap between consecutive campaigns.

2.2 Company overview

2.2.1 Novartis AG

Novartis AG is one of the leading pharmaceutical companies in the world in size and revenues with strong presence in diverse biopharmaceutical segments. It is engaged in research, development, manufacturing and marketing of branded drugs, generic pharmaceuticals, medical devices, preventative vaccines, diagnostic tools and consumer health products. The company operates in more than 140 countries and employs 123,686 people across the world5. Novartis' global headquarters is located in Basel, Switzerland.

Last year, Novartis reported net sales of $56.7B, down 3% from 2011 (unchanged in constant currencies, or cc). The company is an industry leader in product pipeline, with more than 200 projects in clinical development, including 138 in the Pharmaceutical division. The company operates through five business segments:

- **Pharmaceuticals** (or, Pharma) – researches, develops, manufactures and distributes patented prescription medicine in a range of therapeutic sectors, including cardiovascular and metabolism; oncology; neuroscience and ophthalmics; respiratory and integrated hospital care. Marketing of the various pharmaceutical products is done by global business franchises.

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• **Alcon** – Novartis' ophthalmic division is the global leader in eye care products, offering surgical equipment, instruments, intraocular implants and disposables, as well as therapeutics for acute and chronic diseases, OTC medicine and contact lenses.

• **Sandoz** – Novartis' generic pharmaceuticals division operates in three verticals: retail generics, anti-infective and biopharmaceuticals. Sandoz develops, produces, and markets off-patent API and biosimilars.

• **Consumer Health** – operates as two sub-divisions: OTC (over-the-counter) provides for in-home self-used products; and Animal Health for pets and farm animals.

• **Vaccines & Diagnostics (NVD)** - researches, develops, manufactures and markets preventative vaccine treatments for viral and bacterial diseases, and diagnostic tools for blood detection of infectious diseases.

### 2.2.2 Novartis Pharmaceuticals

Novartis Pharma is the biggest division of the Novartis Group, with net sales over $32B (56.7% of total group) and core operating income over $10B (66% of total group). The division's product portfolio includes more than 50 key marketed products in addition to a pipeline of 141 products in various development stages. Novartis' pharmaceutical products are categorized into one of the following groups:

- Oncology
- Primary Care
  - Primary Care Medicines
  - Established Medicines
- Specialty Care
  - Ophthalmology
  - Neuroscience
  - Integrated Hospital Care
  - Critical Care

The group within Novartis Pharma, responsible for manufacturing the pharmaceutical products, is the TechOps (technical operations), consisting of:

- ChemOps – produces active pharmaceutical ingredient (API, or Drug Substance) through chemical synthesis
- BioPharmOps - produces active pharmaceutical ingredient (API, or Drug Substance) based on complex proteins from genetically modified cells
- PharmOps – formulates the Drug Substance (DS) into Drug Product (DP) and Final Product (FP)

For a comparison between ChemOps and BioPharmOps, see Appendix 1. Biological Vs. Chemical Pharmaceuticals
2.2.2.1 Novartis BioPharm Ops

In 2005, Novartis Pharma established its biopharmaceutical operations for the purpose of 'late phase clinical and commercial manufacturing of biopharmaceutical drug substances'. Since then, biologics have expanded in a significant rate, with approximately one new launch per year from 2014 onwards. Novartis' biologic portfolio is expected to grow significantly in the next few years and become a significant share of the Pharma pipeline. As a result, a growth is also expected in the biologic therapeutics based on mammalian cell culture. This triggers the need to expand Manufacturing Capacity in Cell Culture and improve performances.

2.2.3 PLANT X Center for Biotechnology

2.2.3.1 Site Overview

The biotechnology manufacturing center of PLANT X is dedicated to the manufacturing of biopharmaceutical drug substance (DS) based on mammalian monoclonal antibodies (mAb's).

BioPharm Ops PLANT X is divided into two Process Units (PU's):

- **PU Perfusion:** semi-continuous production of PROTEIN E, operating on 5 days/week basis by 2 shifts
- **PU Multiproduct:** fed-batch production of PROTEIN A, PROTEIN B, PROTEIN C and PROTEIN D, operating on 24/7 continuous shift work basis

In addition to the mentioned PUs, the site includes QC laboratories, Manufacturing Technology laboratories and warehouses.

2.3 Production Planning: Strategic, Tactical and Operational

Manufacturing companies usually take a "top-down" approach to production planning: begin with their objectives and then develop strategies for how to carry out these objectives. The **strategic planning** refers to the process by which management establishes and attempts to accomplish long-term objectives, providing the general vision for the company. Strategies are road maps or particular approaches the company takes in an effort to reach its objectives. On the other hand, the **operational planning** is the critical final stage, in which specific actions are assigned to departments and qualified employees. Operational plans are short-term action plans that break down high level goals and strategies into narrower, actionable tasks. The key to a well-developed operational plan is specificity in stating actions assigned to particular employees (and resources) with specific deadlines.

Linking between the long-term (5-10 years) strategic planning and the short-term operational planning (daily, for 1-2 weeks) and execution, is the **Tactical Planning**. Tactical plans should focus on a handful
of core company goals; otherwise, activities become too fragmented and it is hard for employees to understand how their actions ultimately tie into the big picture goal. Some best practices in management consulting advise corporations to develop tactical plans with three to five strong goals in mind. A goal is strong if it is feasible, specific and measurable.

The "Top-Down" Planning Pyramid

- **Objective**: Define a roadmap for business decisions and create a common set of goals
  - Long Run 5-10 years

- **Objective**: Breakdown high-level goals and strategies into a tangible, measurable action plan
  - Extension of strategy, 1-2 years

- **Objective**: Define specific tasks to comply with overall vision in accordance with existing capacity
  - Short Run 1-2 Weeks

Note: In some industries these definitions of Tactical and Operational Planning are replaced

Figure 1. Production planning hierarchy according to the "Top-Down" planning pyramid

One of the biggest challenges in tactical planning is separating strategy from tactic. A strategy is essentially a framework or plan, but it provides no tangible results on its own. Tactics are steps for implementing your strategies and are actionable and have a purpose and a measurable result. Tactical planning is an extension of strategic planning, and tactical plans are created for all levels of an organization. A firm's tactical plan can include the input of many of its departments.

Tactical planning focuses on the production, equipment, personnel, inventory and processes of a business. It uses the organization's financials in order to analyze profitability. Once operational shortcomings are discovered, management can take the necessary steps to make corrections. Effective tactical plans must include the input of individuals involved in the day-to-day operations of a firm.

In the context of this work, strategic plans span over 5-10 years, tactical plans span over 1-2 years (typically 18 months), and operational plans span over 1-2 weeks in an hourly resolution.

2.3.1 Campaign Scheduling
Different drug substances are produced in product-specific campaigns, separated by strict changeover procedures that significantly limit the allowed overlap between consecutive campaigns. The changeover operations are not only equipment-specific, but also product-specific, meaning that switching from product A to product B may take longer/shorter than from product B to product A (changeovers will be discussed in more details later in this paper). One of the tactical planner's most important jobs is finding the optimal sequence of production campaigns that satisfies individual product demands in a timely manner. Value occurs not only when products are sold and services used, but also when resources are wisely conserved.

Delivery due dates are critical to consider, since DS has an expiration date, but more so because the pharmaceutical industry cannot afford stock-outs. This may mean that in order to satisfy all production due dates, big campaigns (>15 batches) may be split to two or more (smaller) campaigns, as is usually the case with the most popular products.

In order to plan a campaign schedule over a period of 12-24 months, we first need to know how long will each campaign take? Let's say for example that we need to plan for 10 batches of PROTEIN A. From Error! Reference source not found., we see that the total time for a single batch is 40 days. Does this mean that a 10-batches campaign will last 400 days? No. Waiting to finish a full batch before proceeding to the next batch is a waste of time and resources. Instead, we can start the next batch on the equipment that finished the previous batch and is now idle, after only a short cleaning operation. In a way, batches of the same product in a single campaign may be viewed as mini-campaigns with zero changeover times. There is, however, a minimum time that is required between batches of the same product, depending on the run rate at which the production facility is operating (Run Rate will be discussed in further details in Chapter 0 This chapter further explored the topics of production and production planning / scheduling, as described in the academic literature for different levels and functions of the organization. Next we will apply these best practices (particularly, those relevant to MRP II) for the specific case of Novartis BioPharm Ops PLANT X.
Pilot Setup). Again, from Error! Reference source not found., we see that the time between consecutive batches for PROTEIN A is 3.5 days.

We can now declare that a 10-batch campaign for PROTEIN A will take:

\[
\text{40 days} + \left[ 3.5 \text{ days} \times (10 - 1) \right] = 71.5 \text{ days}
\]

For this example, the BioPharm Ops tactical planner will allocate 72 days in the production calendar, dedicated for the manufacturing of 10 batches of PROTEIN A (that is: at least 72; downtimes and other constraints might require extending this time). But would this period be used exclusively for PROTEIN A? Not necessarily. Other campaigns might and should start before the PROTEIN A campaign fully ends – as long as a sufficient changeover has been executed. The degree of overlap allowed can also be extracted from Error! Reference source not found.. In this table the major production steps for mAb are listed in order on the left-hand side of the table. The columns for each product state the number of days that each major procedure lasts. This is, of course, not specific enough for operational planning purposes – but provides a general breakdown of operations for tactical planning. Notice that procedures are color-coded according to sections (in bold) and production zones. The production zone is the plant’s bottleneck in terms of switching from one product to another: Regulatory restrictions on biologic substance manufacturing prevent having 2 products simultaneously in the same room for the Final Purification procedure (zone D). In other words, we can overlap different products’ campaign only to the extent that the first batch of the later product does not start its final purification before the last batch of the previous has finished its final purification.

Once establishing all campaigns in the desired sequence, the plan is revised in finer details to allow for other production constraints.

Note: The data presented in the table and figure below – product/equipment/zones names and numeric values – have been modified due to confidentiality considerations, and should only be viewed as representative examples.

<table>
<thead>
<tr>
<th>Product</th>
<th>PROTEIN A</th>
<th>PROTEIN B</th>
<th>PROTEIN C</th>
<th>PROTEIN D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inoculum Seed Lab (zone Z1)</td>
<td>18</td>
<td>16</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Seed</td>
<td>15</td>
<td>13</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Seed Bioreactor</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Large Scale Cell Culture (zone Z2)</td>
<td>15</td>
<td>14</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>BR1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>BR 2</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>BR 3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>BR 4</td>
<td>7</td>
<td>9</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Initial Purification (zone Z2)</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Chromatography I</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Chromatography II</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Final Purification (zone Z8)</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Chromatography III</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>UF/DF (zone Z1)</td>
<td>0.5</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Filling (zone Z1)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Freezing</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
### Table 1. Time durations of production unit procedures for each drug substance

<table>
<thead>
<tr>
<th>Material Preparation (zone Z1)</th>
<th>27</th>
<th>29</th>
<th>33</th>
<th>39</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaOH Media preparation</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General Media preparation</td>
<td>17</td>
<td>15</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Buffer Preparation</td>
<td>10</td>
<td>12</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Total Time (Single Batch)</td>
<td>40</td>
<td>39</td>
<td>41</td>
<td>45</td>
</tr>
</tbody>
</table>

| Run Rate                     | 2  | 1.5| 2.5| 1  |
| Time Between Batches         | 3.5| 4.67|2.8| 7  |

The figure below is a visual representation of the table above:

![Visual representation of unit procedures durations per drug substance](image)

**2.3.2 New Product Introduction**

Implementing new products and/or transferring the production to a new plant require a heavy investment in both time and capital. According to the BioPharm Ops’ TRD, it takes approximately 6 months and 1.5M euros to implement a new product line, update documentation, train operators, prepare raw materials and adjust equipment. Once implemented, every week of production costs the plant an additional 1M euros in material consumption and overhead (approximately; costs and time vary according to product). Since the production is transferred to the manufacturing plant while still in process of obtaining clinical regulatory approvals, this adds to the already-long Time-To-Market. Thus there is a financial incentive for Right-The-First-Time and the BioPharm Ops production plant strives to never having to do technical runs (trial & error) - only cGMP (current Good Manufacturing Practice) runs, since the later could be easily upgraded to commercial production runs. To achieve this the Manufacturing Science & Technology (MS&T) is highly integrated in the BioPharm Ops production plant and is involved in the production transfer process.

**2.3.2.1 Regulatory effects on New Product strategy:**

The same biopharmaceuticals can often be used to treat several medical conditions. But while having a broad indication-for-use definition may be an appealing business benefit in terms of market size, biopharmaceutical companies put many efforts in avoiding the misuse of their products for inappropriate
and potentially dangerous indications. Each indication for use must be tested and approved, adding to this highly cost and time consuming process. Biopharmaceutical companies are left with a trade-off:

*Broad indication and large potential market, or first-mover advantage and rapid time-to-market?*

As a result, pharmaceuticals companies revised their launching strategies: submit approval applications for the most severe and/or rare indication. A drug that may treat a life-threatening condition or one that affects only a small portion of the population is likely to be expedited by regulatory authorities and reach the market sooner. Then, once approved for one indication it is usually easier to approve it for other indications as well, even if just for clinical trials.

Obviously, this strategy has its drawbacks as well. Expediting the process may sometimes be achieved at the price of rushing (or even skipping) phase II clinical trials. Less knowledge is available and higher risks for unexpected side effects must be taken into account.

Rare and severe diseases have low demand in the market, but the product may still be high in demand for clinical research of other indications, which if approved, will increase the commercial demand as well. In the context of this project, production of the DS is similar regardless of whether the order came from SCM or TRD. However this type of strategy should be taken into consideration as it also affects the ratio between commercial/clinical demands, which might have different tolerance to adhering to schedule.

### 2.3.3 New Product Development – Pipeline Glossary

*Source: Novartis Group, Annual Report 2012*

**Phase I** - First clinical trials of a new compound, generally performed in a small number of healthy human volunteers, to assess the clinical safety, tolerability, as well as metabolic and pharmacologic properties of the compound.

**Phase II** - Clinical studies that are performed on patients with the targeted disease, with the aim of continuing Phase I safety assessment in a larger group, assessing the efficacy of the drug in the patient population and determining the appropriate doses for further testing.

**Phase III** - Large-scale clinical studies with several hundred to several thousand patients to establish the safety and effectiveness of the drug for regulatory approval for indicated uses. Phase III trials also may be used to compare a new drug against a current standard of care in order to evaluate the overall benefit/risk relationship of the new drug.

**Confirmatory Development** - Projects for which a positive proof-of-concept has been established and are currently in either post proof-of-concept clinical trials (Phase I/II/III) or under review by the regulatory agencies for the purpose of granting marketing authorization (submission).

**Submission** - An application for marketing approval has already been filed with one or both of the following regulatory agencies: FDA (United States), EmA (European Union). Novartis has not yet received marketing authorization from both regulatory agencies for pipeline products. The application contains comprehensive data and information gathered during the animal studies and human clinical trials conducted through the various phases of development of the drug.
### 2.3.4 Planning for new product integration

To account for a new product in an existing facility, several techniques are considered in the tactical planning:

- Increasing Run Rate when applicable to allow more released product per year. Production plants do not always operate at maximum Run Rate in order to avoid excess inventory and idle capacity.
- Pre-plan a time slot in the production schedule at the tactical horizon for new products. This creates some flexibility but will most likely have to be revised as time gets closer or once there are concrete plans for a new product to be manufactured there.
- Platform Process (strategic horizon) - developing an infrastructure to feed other facilities in the future so production of different products will be allocated according to core-competencies and product similarity.

The last strategy involves a technology transfer, typically done in parallel to Phase II clinical trials, allowing production for Phase III to take place at the commercial site. At this point, BioPharm Ops will take over the production process from TRD-BPRD. A schematic of the New Product Development timeline is shown below:

![New Product Development Timeline](image)

Figure 3. New Product Development Timeline

Once technology is transferred, production of a new product is usually done in three successive runs. The first vial would take on average 57 days for the USP (cell culture) plus an additional 21 days for the DSP (purification) - total of 58 days. The second and third vials will start production in gaps of 14 days from the start of the previous vial, in order to allow some time for updates and adjustments if needed. Overall the 3 runs will take around 3 months.
Another point to consider when planning for a new product implementation is the adjustments and reorganization of the manufacturing facility. Arguments in favor of applying new technologies to meet growing mAb demands are often overoptimistic or neglect to consider competition from other therapeutics, which would most likely cap the demand below 2-4 tons per year for all but the most successful blockbusters².

2.4 Supply Chain Management (SCM)

SCM spans all storage and movement of raw materials, work-in-process (WIP) inventory and finished goods along the supply chain from manufacturer to consumer. APICS, the Association for Operations Management, defines the role of SCM as "design, planning, execution, control, and monitoring of supply chain activities with the objective of creating net value, building an competitive infrastructure, leveraging worldwide logistics, synchronizing supply with demand and measuring performance globally". It is clear from this definition that SCM strives for an integrated approach.

2.4.1 Manufacturing Planning and the Supply Chain Management (SCM)

Biopharmaceutical companies chose to retain control over the drug substance manufacturing and outsource the drug product manufacturing. Since many quality attributes of mAb-based drug substance are set by the manufacturing processes, in companies that chose to retain control over both the drug substance and drug product manufacturing, there is a natural tendency to control critical steps in the supply chain level⁷.

SCM constantly deals with Trade-Offs: minimal excess inventory vs. sufficient safety stock, quality vs. cost, information sharing vs. intellectual property protection, etc. Trade-offs may increase the total cost if only one activity is optimized, thus it is imperative to apply a system approach for logistical and operational planning. Improving the trust and collaboration among supply chain partners, may reduce this negative effect, leading to better visibility and higher velocity of inventory movement. The concept of business relationships extends beyond traditional enterprise boundaries and seeks to organize entire business processes throughout a value chain of multiple companies. In recent decades, globalization, outsourcing trends and advancements in Information Technology have enabled organizations to operate successful collaborative supply networks focusing on the core competencies of each member⁸.

Today, SCM deals with a higher necessity for specification, due to market forces that may shift demands from any of the supply network components with no early notice. Variability has a significant effect on the supply chain infrastructure, from the foundation layer of establishing and managing the electronic communication between the trading partners to more complex requirements including the configuration of the processes and work flows, essential to the management of the network.

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⁶ Kelley, "Industrialization of mAb Production Technology The Bioprocessing Industry at."
⁷ Hilliard, "Achieving and Sustaining an Optimal Product Portfolio in the Healthcare Industry through SKU Rationalization, Complexity Costing and Dashboards."
⁸ Zachariev, "Peter Drucker's Conception of the New Management Paradigm."
2.4.2 Supply Chain at BioPharm Ops PLANT X

SCM in Novartis Pharma is organized by products in 3 different categories:

a. Specialty and Critical Care
b. Primary Care
c. Oncology

SCM deals with commercial products or pipeline products in advanced phase III / submission status. For other products - that are in clinical trials and/or for R&D purposes - demand is communicated to the production plant by TRD (Technical Research and Development) or TPL (Tactical Planning Leader). Products in early phase III still do not have a fixed submission date, and therefore are not assigned to a brand leader within SCM - even though they shares the manufacturing resources with all other products, made in the multiproduct PU.

Currently, the main tool for communicating product demand between BioPharm Ops PLANT X and SCM (and Pharm Ops) is an Excel spreadsheet, which among other factors specifies:

- Forecast for PharmOps demand (FP) per month
- Capacity from PharmOps
- Forecast for PLANT X demand (DS) per month
- Capacity from PLANT X
- Inventory Projection (difference between the two) + Safety Stock

---

\[^9\] Novartis AG
The output is a graph and is used to evaluate Business Continuity depending on the parameters above. Inventory projections (to be sold + safety stock) should always be above a certain line. This is used to calculate cash flow from that product. The file is shared between a few manufacturing stakeholders but is controlled by the SCM.

* * * * *

In this chapter we explored Novartis Pharma and the biopharmaceutical industry in order to provide the business context for the remaining of the thesis. We were also introduced to the unique features of monoclonal antibodies (mAb's) that are relevant in the production process, as well as the production planning process itself in the multiproduct plant. Now that we have a general understanding of the BioPharm Ops site in PLANT X, we can further explore the knowledge and best practices that exist in professional literature.
3 Literature Review

"The world is full of obvious things which nobody by any chance ever observes" (Sir Arthur Conan Doyle, author of the Sherlock Holmes books)

3.1.1 Economic aspects of mAb production

Monoclonal Antibodies are the fastest growing segment in the biopharmaceutical industry, with a market size of over $35 Billion in 2010. More than 20 mAb have been approved by the FDA and are currently in commercial use and approximately 200 more mAb’s are in clinical trials for a wide range of indications. However, mAb are also among the most expensive forms of medicinal treatment due to their marketing for chronic conditions and their low potency, resulting in large cumulative doses. Consequently, large-scale production capacity is of high demand for this type of biologics. The production titer, the final mAb concentration of the fermentation process and the yields of the chromatography steps contribute most of the economic uncertainty, contributing to the variability of Return on Investment (ROI) and Net Profit Value (NPV) objective functions. If impurities were to be reduced such that only two chromatography steps were necessary then this would lead to a substantially predictable process. This might be achieved if strain requirements allow a change in the medium. Where such a change is not feasible (due to either physical restrictions or reluctance to undergo further regulatory approvals), pharmaceutical companies turn to seeking process improvement through lean and efficient methods.

The pharmaceutical industry differs from other industries in cost structure. Pharma companies typically spend a smaller part of their revenues on costs of goods sold (COGS) and the COGS/sales ratio is only around 15-25%. Total batch cost is calculated by summing three factors: Fixed cost, materials cost (consumables) and other variable costs. For example, overhead can be viewed as either fixed or other variable cost depending on the period in mind and specific requirements and campaign characteristics. Overhead costs are also distributed across all the products that are produced at the PU, proportional to a weight function that considers the amount of product produced. Yet, this distribution may not reflect the actual overhead expenditure, as it will likely change if a certain product is approved for an additional use-indication.

The fixed capital investment traditionally includes the facility building cost along with all infrastructure (piping), equipment and utilities. Reports in the literature estimate mAb production facility investments in a wide range of $40M-$650M, varying not only by site size but also location. Pavlotsky reports that non-USA based facilities cost approximately 28% less than USA based ones.

10 Farid, “Process Economics of Industrial Monoclonal Antibody Manufacture.”
12 Sundaramoorthy et al., “Capacity Planning for Continuous Pharmaceutical Manufacturing Facilities.”
Also regarding fixed cost and utilities of pharmaceutical cGMP plants, monitoring the direct utilities costs should consider infrastructure systems like the Heating, Ventilation and Air Conditioning (HVAC), which are critical for controlling air particulate levels and pressure differentials in different production zones in order to prevent contamination.

A breakdown of facility and process-related construction costs allow process engineers to benchmark investment costs relative to key factors, such as plant capacity, demand forecast, titer yields and overall productivity. Myers14 claims that the production costs for mAb can roughly be divided equally between Cell Culture, Purification and support. One might expect other considerations to affect this ratio, such as change in scale, whether the COGS account for the drug substance manufacture alone or also for the drug product formulation, and whether the production line operates on a single- or multi-product basis. Still, Mayer's statement is not far from reality. The Centrifuge and filters are the most expensive equipment in the plant. But what if there is only one centrifuge and several production bioreactors? This raises a different risk assessment question: what happens if there is a malfunction in the centrifuge? This may lead to a shutdown of the production for an entire year and scrap all work in process that have not yet been clarified through this step, resulting in a significant financial loss.

In recent years, a common trend in the biopharmaceutical industry associates the increasing demand for therapeutic mAb with a need for new and more advanced technologies. While this statement is mostly true, argues B. Kelley15, the forces of competition from other substances for common indications, combined with improved mAb characteristics that allow the usage of lower doses and cap the maximum annual demand for all but the most unusual blockbuster products. For most products, there will be little direct relation between DS production COGS and sale prices under the existing economies of scale. Titer is likely to have a bigger effect on the COGS, where the USP costs are in inverse proportion and the DSP is in direct proportion to the mass being processed. As a result, this can also be viewed as a diminishing return of increasing titers.

In an article by Petrides et al.16, the production cost is found to drop exponentially as the annual production rate is increased 10-fold, demonstrating the sensitivity of the first to the second. Furthermore, the annual production rate is shown to affect the ratio between USP costs and DSP costs, in such a way that for a rate of 0.2kg/year and titer of 0.1g/L the ratio is 46:54, whereas for a rate of 100kg/year and titer of 0.5g/L the ratio is 20:80. The meaning of this for a manufacturing plant is that an investment for adding a bioreactor at the USP for example, may cause a slight increase in the unit cost and a shorter lead-time to meet schedule, but if used for manufacturing additional products or a larger amount of one product (that will still go through the DSP) the unit cost may decrease significantly.

Nevertheless, the USP and DSP cost structures cannot be easily separated, as Farid notices in her research17. For an example, a conventional 200L might be associated with a Protein A Chromatography step costing $7,500/L, as the resin for Protein A affinity is known to be the most expensive material in

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15 Kelley, “Industrialization of mAb Production Technology The Bioprocessing Industry at.”
mAb production. A larger scale of 10,000L bioreactor operating on a 1g/L titer may than result in a $4-5M matrix for this step alone. Such expensive costs have led biopharmaceutical companies to revise their purification process so that instead of one large-scale chromatography column or multiple smaller-scale columns, the DSP reuses one small-scale column in several cycles. Of course, operating in cycles increases the processing time for this unit-procedure and the need to clean the resin between batches require additional CIP operations to be added. Consequently, the process economics have a strong influence on its duration and scheduling.

Sommerfeld and Strube add that binding capacity of resins can be increased to optimize costly purification steps, but resins used for ion exchange chromatography are less expensive and, therefore, the increasing their binding properties has a lower impact on the process economics. Thus efforts to optimize these steps should be considered against the trade-off with higher labor costs to meet the improved resin.

Lim et al. investigated production strategies regarding fed-batch versus perfusion techniques. The main trade-off that was presented was whether to invest in small capacity for DSP and pool broth for purification more frequently, or to invest in a large capacity for DSP with less frequent broth pooling. Lim et al. concluded that the perfusion method was favorable when subject to small variations in titer and yield. This poses a greater operational risk but offers a lower upfront investment and higher NPV projection compared to fed-batch processes. However, when accounting for the fluctuations in titer, DSP yields and contaminations risks, Monte Carlo simulations determine that unless these factors are dealt with, fed-batch is still the better option for most cases.

Factors like those mentioned above indicate that the largest potential cost driver is the plant's utilization. A plant with the capacity to produce more than the market demand of a certain product will remain with either excess inventory or with a cost structure that does not take advantage of the higher titer capability. For this reason, manufacturing companies operate facilities that consist of multi-products with similar, standard processes. In the pharmaceutical industry specifically, this is also an important driver for phase III product allocation decisions to existing production sites.

“*When I was young I thought money is the most important thing in life. Now that I’m old, I KNOW it is...*” *(Oscar Wilde)*

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Sommerfeld and Strube, "Challenges in Biotechnology Production—generic Processes and Process Optimization for Monoclonal Antibodies."

3.2 Planning on the Organization Level – Systems and Disciplines

*Integrated Business Planning (IBP)*

Integrated Business Planning (IBP) is a holistic command and control process for all aspects of a business. It drives and directs revenue and overall performance. At its core is Sales & Operations Planning (S&OP), engaging the management team in integrated management of the supply chain. IBP has been long gaining recognition as a best practice approach for bridging the gap between strategic objectives and routine activity, keeping all stakeholders to a common agenda and set of priorities. IBP also provides a long-term visibility, which enables the use of rigorous risk management tools to permit suitable contingency planning.

*Manufacturing Execution Systems (MES)*

Another approach suggests Manufacturing Execution Systems (MES) for the control, optimization and documentation methodology of business practices executed on the shop floor in full compliance with industry standards and regulations. MES's objective is to improve product quality by increasing the manufacturing reliability and its vertical integration in the production supply chain. In order to achieve business-related optimization in practice, IT infrastructure and support must be standardized in logic units and workflows. Typical examples include electronic batch records, equipment management, deviation management, and FMEA and CAPA functions. Measurable and quantifiable advantages in these procedures provide the necessary justification to support economical investments. Nevertheless, decisions for or against the implementation of a MES are often driven by immeasurable factors such as user-friendliness or ease-of-use that instead relies on indirect quantifiable scores that are represented by a learning curve.

While not always the case, MES is meant to reduce administrative work for maintaining production forms and documents. If this is enabled, a better transparency is achieved throughout the process, deviations (caused by unavailability of manufacturing resources) are recognized at an earlier stage and delays are minimized.

*Enterprise Resources Planning (ERP)*

An Enterprise Resources Planning (ERP) system plays the role of an informational highway linking the organization to a decision support system. The "highway" must contain several entry/exit points to different levels in the organization, providing a constant feedback mechanism to control indicators, such as performance, capacity, constraints and time considerations. The ERP provides visibility in real time.

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80 M. Rosenberg, "Proceedings of IBC’s Production and Economics of Biopharmaceuticals – Transcending the Limits of Manufacturing Medicines."
81 Blumenthal, "Manufacturing Execution Systems to Optimize the Pharmaceutical Supply Chain."
82 Linders, "Development of a Risk Management System for Consumables Used in Biopharmaceutical Manufacturing."
to core business processes, kept and managed in a common database. The importance of the ERP is in facilitating error-free transactions of physical resources and financial information in complex organizations. The complexity challenge leads many firms to implement an ERP suite from one IT vendor (as opposed to a single source approach), and incorporate stand-alone point solutions to achieve higher levels of integration and improve customer relations and supply chain efficiency.

Most ERP systems are pre-incorporated with "best-practices", reflecting the vendor's approach for optimal business management. The best practices help reducing time-consuming non-strategic tasks, like configuration, documentation, testing, etc. The setup of the ERP is critical for reducing risk and failure prevention, usually associated with poor understanding of the business needs prior to implementation. To prevent this, the organization must first link the current practices to the long-term strategy and analyze the effectiveness of the processes. The implementation is considerably more politically charged (and hence difficult) in decentralized organizations and may require a greater degree of customization – which also serves the purpose of competitive advantage.

3.3 Manufacturing Resources Planning (MRP II)

3.3.1 MRP Vs. MRP II

Material Requirements Planning (MRP) is a production planning and inventory control system used in manufacturing managements in order to simultaneously ensure materials availability, maintain minimal stored inventory and plan manufacturing-related activities and scheduling. Its basic function is to determine what product/item is required? How much of it is required? And when is it required for? As an output, the MRP will then provide a recommended schedule for two actions: Production and Purchasing of consumed resources.

MRP must consider different data in order to control the production process. For example, the Bill Of Materials (BOM), the End Item (level 0 in the BOM), timeline breakout (required quantity at any given time), shelf life and lead times, safety stock and more. It is therefore not surprising that the greatest concern regarding MRP systems is Data Integrity - the necessity to avoid GIGO (Garbage In, Garbage Out). This concern is often addressed by physically and frequently verification of the BOM against the existing inventory, after taking into account a certain level of depreciation and shrinkage.

Another major drawback of MRP is its disregard of capacity, utilization and actual Run-Rate. These topics and more are largely dealt with by Manufacturing Resources Planning (MRP II) systems, also integrating financials into the system. MRP II takes into account fluctuations in forecasted data through master production schedule simulations and sensitivity analyses. MRP II is a total company management concept that should in theory be able to address operational and financial uncertainties and answer "what if" questions for long term control. It should also provide consistent data to all players in the manufacturing process as the product moves through the production line. Therefore, MRP II is by

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*E. Monk and B. Wagner, Concepts in Enterprise Resources Planning.*
definition a fully integrated system that may provide, in addition to better process control, a productive relationship between suppliers.

Key functions and features of this system include but are not limited to:

- Materials Requirements Planning (MRP)
- Master Production Schedule (MPS)
- Bill of Materials (BOM)
- Inventory Management and Control
- Purchasing Management
- Capacity Requirements Planning (CRP)
- Standard Costing and Cost Reporting

Depending on the environment and the industry, specific characteristics may also apply to these functions. In our case, for example, the highly regulated pharmaceutical industry requires measures such as lot traceability.

### 5.3.2 Class “A” MRP II: Origin & Development

The concept of MRP II was introduced in the early 1970's by Oliver Wight**, who referred to MRP II as the method for "unlocking America's productivity potential". It was heralded as the approach that would enable Western manufacturers to attain and maintain world-class status. In 1977, Wight published a checklist of 20 simple evaluative questions, a manager should answer about her or his business' performance. As the conception of operational excellence evolved over the years to become more and more critical and competitive, the short list grew into an entire book (see summary in

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** Oliver Wight International, *The Oliver Wight Class A Checklist for Business Excellence.*
Appendix 2. A company that is able to answer "YES" to at least 90% of the questions is awarded Class "A" recognition. Class "A" is one of the most sought for, and least frequently achieved, awards available to manufacturing companies. However, the fact that very few companies achieved the full potential of MRPII does not imply that these companies were unsuccessful. The vast majority of companies implementing MRPII demonstrated improvements in all major aspects of their business.

Companies successful with world-class manufacturing techniques are those prepared to make fundamental changes in the way they do business. But does this necessarily require the use of computerized planning methods and control systems? Japanese manufacturing pioneers simplified production processes using innovative - yet manual - methods of control. Such example is the kanban system, introduced by Toyota for Lean and Just-In-Time (JIT) production, and adapted at many other industries, including the pharmaceutical industry. As time has gone by and manufacturing has scaled up, many of these companies have begun to use computerized systems. Nissan, for example, integrated MRPII into their production planning processes but have combined it with the radical changes in management philosophy needed to bring about total quality and continuous improvement. Moreover, these companies have done so without resorting to a Western style MRPII. MRPII and other modern production and distribution techniques were developed in a very different environment from that of world-class manufacturing, although many paradigms are quite similar.

3.4 Scheduling & Simulation

Contrary to many other industries, pharmaceuticals' inventory safety stocks are intentionally kept high, due to both high margins and the risk cost (both financially and in terms of corporate responsibility) of a stock-out is much higher compared to the cost of holding excess inventory of a product that does not require much shelf space. All this and more drives pharmaceutical companies to focus efforts on manufacturing efficiency optimization. Such optimization is greatly facilitated through what-if and sensitivity analyses computed by simulation and scheduling tools, which evaluate the impact that critical parameters have over key performance indicators (KPI) in a feasible range, from plant throughput and manufacturing costs to production cycle time and run rate.

Whether the manufacturing is aimed towards large-scale commercial use or small clinical trials, production planning tools and models are used to generate on-going production schedules that do not conflict with limiting constraints like available capacity. These tools have become critical for the implementation of Lean principles, including Just-in-Time (JIT), low Work-in-Process (WIP) and eliminating waste - all depend on the ability to accurately estimate the existing capacity and its utilization. In other words, they bridge the gap between organizational strategy (through ERP and/or MRPII) and specific plant floor.

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[65] Brian H. Maskell, "Why MRP II Has Not Created World Class Manufacturing and Where Do We Go From Here?".
[66] Petrides et al., "BioProcess Design And Economics."
Another use for dynamic scheduling tools is recalling earlier versions of schedules from the database for multiple purposes, from investigating a quality-failed batch to evaluating performances based on deviations between planned and executed schedules.

3.4.1 The significance of scheduling & simulation tools in pharmaceutical production

Pharmaceuticals are usually produced in a batch or semi-continuous mode (perfusion). Therefore, modeling the unit procedures of the production process is different compared to continuous production lines with larger throughputs. While in continuous manufacturing, a single piece of equipment performs a single operation perpetually, in batch manufacturing an equipment item goes through a set of operations. Batch processing is also associated with a greater variability in resources demand as a function of time.

Production planning and optimization tools are also used for process scheduling and cycle time reduction. For example, an Equipment Occupancy Chart (EOC) may be generated to indicate the status of each machinery in the manufacturing facility. The vertical axis will display all equipment, whereas the horizontal axis will display the time line and often include a real-time indicator. Multiple bars on the same horizontal line represent reuse (sharing) of equipment by multiple procedures. Overlap in shared procedures' cycle time is an infeasible scenario and should be resulted by the optimization model. On the other hand, white space between bars represent idle time, and capacity utilization may be derived from it. Ideally, idle time is minimized to increase utilization, however, this indicator is also used to point the process' bottleneck by identifying the equipment with the least idle time. Identifying bottlenecks is especially important when determining the maximum number of batches that may be produced in a given time frame. Perhaps more importantly, since major process changes in pharmaceutical cGMP require extensive regulatory approvals, in practice, cycle time reduction for an already-approved product/process is usually achieved by equipment debottlenecking (i.e. adding more units of the bottleneck equipment).

By aligning the demand for resources with the EOC and resources utilization reports, we can identify equipment-procedure pairs that constitute size bottlenecks and determine the maximum possible batch size (and eventually, throughput) that the plant can produce. Any effort to exploit the economy of scale through different sized lots, should first concentrate in resolving the size bottleneck.

Dynamic sensitivity analysis assists in understanding the individual impact of various input parameters on the overall process variance of the output, even when insolation of these parameters is unavailable. Process improvements efforts will then be focused at the parameters with the greatest contribution.

Production Planning tools are also used for cost analysis and when preparing for technology transfer. As mentioned before, to reduce the complication of product changeover, the amount of different types of equipment and the level of expertise required by the production staff - manufacturing facilities are organized by type of products and core competencies. When the organization is in need of new or improved manufacturing capabilities to accommodate new products in its pipeline or increasing demands of existing products, decisions are made to modify the facility or build a new one. As this involves major capital expenditure and an extensive time investment, management must make an informed decision based on accurate data and knowledgeable estimations. Costs are based on quotes correlations from a set of vendors, some of which may already be built-in the SW database. Although
there is rarely a one-size-fits-all solution, a high degree of customization may be achieved by deriving information from existing sources, easing the decision making process.

Once a process is transferred to a new PU for large-scale production, the production schedule facilitates its proper execution by specifying operations sequences, labor and equipment allocation and material flow. The general plan begins with defining the production period at hand, starting usually with the long-term strategic plan without going into fine details and specific tasks. This plan is mostly influenced by the market demands and status of new products (under clinical development) and old products (with upcoming patent expiration). With this vision for the manufacturing plant, the planners schedule the necessary operations and material requirements that must be met. This plan is mostly influenced by the available capacity and resources.

As the production schedule is executed, real-life issues create deviations from the plan and adjustments needs to be made. An optimization planning tool should therefore allow a certain degree of flexibility to address such deviations. In addition, campaign scheduling conflicts may be resolved through exploiting alternatives declared in the resources pools or by introducing timing modification. Counter-intuitively, delaying the start date of a campaign may result in a shorter total production duration (if, for example, delayed to a time where more capacity is available and the run rate is greater).

Maintenance downtime constraints may be represented either as an outage of a resource (e.g. periods of specific unavailability). Alternatively, another approach that allows more flexibility is treating preventative maintenance as a schedulable activity that has its own recipe and may be scheduled at the first convenient opportunity.

Different activities of the SCM require an estimation (rough or accurate, depending on the horizon) of the plant’s capacity. With every deviation from the original plan requiring time-consuming adjustments at the next link, an upstream delay will likely follow a bullwhip effect and grow as it progresses down stream, resulting in great loses for the organization.

All this and more demonstrate the importance of having competent planning tools that consider the effective capacity, and adhering to the plan it generates.

Furthermore, pharmaceutical manufacturing facilities are typically multi-product/purpose facilities, which sometime include multiple production lines and zones that may or may not share resources and utilities. Even with a high degree of shared resources, considerable changeover time is required between production campaigns of different products. Considering this fact makes the planning process far from trivial.

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This chapter further explored the topics of production and production planning / scheduling, as described in the academic literature for different levels and functions of the organization. Next we will

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apply these best practices (particularly, those relevant to MRP II) for the specific case of Novartis BioPharm Ops PLANT X.
4 Pilot Setup

"It's better to be roughly right than precisely wrong..." (John Maynard Keynes, economist)

4.1 Monoclonal Anti Bodies Production

To understand the factors that go into biopharmaceutical production planning, we first describe the production process for this type of product.

Note: This section describes a general case for mammalian mAb production in one of two methods: Fed-Batch or Perfusion – actual recipes (including materials, quantities, conditions and operation times) are proprietary and described in the company's SOPs, and therefore omitted from this paper.

4.1.1 Fed-Batch mAb production

While specific steps vary between different mAb's, most mAb's generally follow a similar production process\(^\text{30}\).

A Working Cell Bank (WCB) is delivered frozen to the Production Unit (PU) by the up-stream supplier. Production of mAb's begins once the WCB is thawed and fermented in a seed train (Inoculum train), providing the necessary amount of cells. During this period, the culture is amplified and cells proliferate and produce the protein of interest through transcription in the nucleus and subsequent translation in the cytoplasm. The optimal period is selected to maximize the amount of useable protein.

After the cells have grown in a serum-containing medium, they are transferred to another set of reactors and adapted to serum-free medium. All types of medium are prepared prior in separate tanks and are filter-sterilized. In addition to the medium, nutrients and clean air are supplied to the bioreactors and spent air is properly discharged to control oxygen level, as well as pH and temperature that are constantly monitored. A small percentage of the batches are expected to fail the fermentation process, therefore, success rates are accounted for in the planning process. The cell culture's seed / inoculum trains typically last 14-21 days, depending on the product. During this period the media's components are converted into mAb, Biomass, CO\(_2\), and other impure organic components such as proteins, acids and peptides.

At the end of the cell culture process, the substance's concentration (titer) is measured in order to indicate the amount of product that can be obtained from this specific batch. The process described so far is referred to as the Up Stream Process (USP) and is followed by the Down Stream Process (DSP), starting with the harvest of the cells.

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\(^{30}\) E. Heinzle, A. Biwer, and C. Cooney, Development of Sustainable Bioprocesses: Modeling and Assessment.
The biomass is separated in the primary recovery section using centrifugation and remaining debris is clarified through a set of filters. Purification is then performed in several chromatography steps; each requiring specific levels of ionic strength, pH and salt concentration. The mAb is purified using small resin beads that attach either the mAb itself (as is in most cases) or the impurities. The attached product is then washed in the column before being eluted with a buffer. As a result of these steps, the substance concentration increases. The elution is filtered and possible viral contaminants are inactivated using a low pH treatment (phosphoric acid).

The solution is next processed through an ion-exchange chromatography, targeting different electronic charges of the molecules in two steps: Cation exchange chromatography - the resin contains negative charges that attract positively charged molecules; and Anion exchange chromatography - the resin contains positive charges that attract negatively charged molecules. Immediately after, the product is washed in the column using a buffer solution and the mAb is eluted again. Serum proteins are eluted according to their isoelectric points, typically starting with the basic immunoglobulin. This process is done in cycles and a buffer is added to increase the ionic strength of the solution.

Affinity chromatography takes advantage of the complex interaction of antibodies and antigen or receptors and ligands. Particularly, Protein A chromatography relies on the protein's bond to fragment crystalized portion of the mAb. Hydrophobic Interaction Chromatography (HIC) is used to remove proteins, DNA and other antibody aggregates that might be leached from the column. The mAb is retained in the column, eluted and filtered once again, and the liquid waste is neutralized.

The solution undergoes two more filtration steps to reach its final concentration: Ultrafiltration and Diafiltration (UF/DF). In the first, large impurities are removed by forcing the solution through a semi-permeable membrane. In the second, small impurities are removed by trapping them in a tangential filter.

Finally, the Drug Substance (DS) is packed and frozen - and now ready to be shipped from the API production facility to the pharmaceutical production facility, where it will be transferred into a Drug Product (DP) and from there the finished good are distributed around the world.

**Note:** Proteins used in biopharmaceuticals may also be obtained from microbial cells. The advantages of using bacterial cells for mAb production are their lower cost, robustness in terms of contamination resistance, rapid growth time and higher titers. However, while mAb cell culture methods are quite similar in the cases of mammalian and microbial cells, the downstream purification process is more complicated for cells of microbial origin since the produced protein often require a re-folding processes. Microbial mAb's are not in the scope of this project.

The diagram below is a simplified schematic of the Production Process, where the Cell Culture (USP) steps are shown at the top and the Purification (DSP) steps are shown at the bottom.
4.1.2 Perfusion mAb Production

The manufacturing steps for mAb's in a Perfusion Process Unit are quite similar to those performed in the Fed-Batch Process Unit to a certain extent. Main differences include the time the cell culture spends in the final bioreactor and the division of the culture batch to lots during the initial purification process.

Prior to the Cell Culture phase (USP), stock solutions are prepared independently, to be used as components of the medium. Each solution is homogenized and filtered. The cell culture medium is prepared separately in a single tank, raw materials added, weight and pH are adjusted and the medium is distributed in sterile containers.

Cells thawed from the WCB are amplified to produce the inoculum for the seed bioreactor in several successive passages. Each passage increases the overall number of cells and culture volume, and is followed by a measurement of the cell density and viability (concentration and percentage of live cells) to determine the volume transferred to the next passage.

Although the fragile cell suspension is particularly sensitive to mechanical forces, it has to be agitated during the passage homogenization in order to prevent cell attachment to the vessel that will affect the homogeneity of the culture prior to the Quality Control sampling. The quantity of cells necessary for production in the main bioreactor is obtained in a smaller inoculation bioreactor. Up to this stage, the culture volume is progressively increased by adding fresh culture medium at each passage (similar to the Fed-Batch mode). From here, culture extension will be done in Chemostat mode. Volume is maintained constant by cell elimination of the suspension and simultaneous addition of fresh culture medium at the same flow.

Production in the main bioreactor is done in Perfusion mode and consists of the inoculated mAb from the seed train and continuous cell amplification. The mAb substance is harvested continuously, while fresh culture is added simultaneously to maintain a constant volume.
The first purification stage of the Down-Stream Process (DSP) after the cells are harvested is expended bed absorption chromatography. Cellular debris and other contaminants are eliminated by ion exchange chromatography, resulting in a significant concentration of the substance. The harvest pool is diluted to decrease the ionic force and promote the adsorption of the antibodies on the resin during the load. The resin is then packed instantly. An elution phase returns the mAb by increasing the ionic force and breaking the electrostatic bounds with the resin.

Viruses are inactivated at a low pH, causing denaturation of viral particles. After this process the pH level is restored, typically near neutral to avoid denaturation of the mAb itself. The pH restoration stimulates a turbidity following the denaturation of DNA and lipid residues that will be then be physically separated by nano/filtration.

The majority of the residual contaminates, mainly host cell proteins (HCP), are eliminated through an affinity chromatography. The next purification step includes anion/cation exchange chromatography to eliminate DNA residues. The last step of the purification is ultrafiltration and diafiltration (UF/DF), in which the final substance consecration is achieved and phosphate salts are reduced from the substance. Finally, the DS is frozen before final formulation and conditioning at the pharmaceutical site.

### 4.2 MAb Production Planning - Current State Analysis

At the current state, demands for different products, sometime different indications of the same product, are not consolidated through a single channel, nor are they transparent to all parties through a shared SAP or equivalent ERP system. This may lead to a lack of accountability between different parties operating within the same organization and makes it difficult for anyone, not physically at the manufacturing area, to understand what percentage of the plants capacity is utilized at a given time.

In section 2.3.1 Campaign Scheduling, we introduced a visual representation of the main unit-procedures’ durations for each drug substance. As mentioned, the Final Purification zone is subject to cGMP restrictions, preventing two different substances from being processed at the same room at the same time. On the visual tool, this is the darker red time-blocks. When processing another batch of the same product, we are not subject to the same restriction, but instead to the effective Run Rate – a parameter that is given to the tactical planner as a fixed constant, representing the number of batches that can be harvested per week (discussed furthermore in this chapter). This, in return, translates to the number of days setting apart two consecutive batches of the same DS type. While run rate values are prone to change,

<table>
<thead>
<tr>
<th>Product</th>
<th>PROTEIN A</th>
<th>PROTEIN B</th>
<th>PROTEIN C</th>
<th>PROTEIN D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Time (Single Batch)</td>
<td>40</td>
<td>39</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>Run Rate</td>
<td>9</td>
<td>1.5</td>
<td>2.5</td>
<td>1</td>
</tr>
<tr>
<td>Time Between Batches</td>
<td>3.5</td>
<td>4.7</td>
<td>2.8</td>
<td>7</td>
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</table>

Table 2. presents typical values that are considered by the tactical planner.
The visual tool, discussed earlier, is altered accordingly to account for the next batch consideration in Figure 6. For each product (dark blue background) that is manufactured in the PU Multiproduct, we create a stand-alone figure representing the timeline of a consecutive batch of either the same product (light blue background), OR a new product (white background).

**How to read this figure:** Let's say for example we are currently processing PROTEIN D at the production site. The last block in Figure 6, marked “From PROTEIN D”, starts this batch on day 1. If we wish to manufacture another batch of the same product, PROTEIN D, we can decide when to start it based on the information in

<table>
<thead>
<tr>
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<td>45</td>
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<td>1.5</td>
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<td>4.7</td>
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Table 2. Since the Time Between Batches is 7 days for this product (remember: these are modified values and not the actual ones used in the real plant), this means that the next batch will start 7 days after the current batch — on day 8, as can be seen in the figure. Alternatively, we can also check the diagonal line in Table 3, going from PROTEIN D to PROTEIN D.

Now let’s say we want to switch from the current product (again, PROTEIN D for this example) to another product, PROTEIN C. Since different products are constrained at the purification steps, we “shift” the second product (PROTEIN C) to the right, until the Initial Purification block (light red) is after the end of PROTEIN D’s Final Purification block (dark red) — in our example, this occurs on day 44. Extrapolating back, we see in the figure that to achieve this, we should start the production of PROTEIN C on day 12 of the last batch of PROTEIN D’s campaign (alternatively, see Table 3.).

<table>
<thead>
<tr>
<th>Product</th>
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<th>PROTEIN C</th>
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<td>Run Rate</td>
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<td>1</td>
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<td>Time Between Batches</td>
<td>3.5</td>
<td>4.7</td>
<td>2.8</td>
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Table 2. Product batch-manufacturing times
Based on the figure above, we can also extract at what day of DS A production can we start DS B Production:

<table>
<thead>
<tr>
<th>A \ B</th>
<th>PROTEIN A</th>
<th>PROTEIN B</th>
<th>PROTEIN C</th>
<th>PROTEIN D</th>
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<tbody>
<tr>
<td>PROTEIN A</td>
<td>3</td>
<td>9</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>PROTEIN B</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>PROTEIN C</td>
<td>7</td>
<td>10</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>PROTEIN D</td>
<td>11</td>
<td>16</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 3. Next batch start day

While this tool is relatively straightforward to use, its simplicity neglects real-life constraints that are then treated ad-hoc, one by one. Doing so manually on an Excel-based tool can be quite time-consuming.
consuming. In addition, assumptions may get lost in cell formulation and considered as verified data, making the production system vulnerable to inaccuracies.

The model, described herein aims to address these downsides and provide additional value in the form of informational outputs to other functions in the organization with clear interests in the production process (such as Finance, HR, SCM, etc.).

4.3 Model Considerations

4.3.1 General Considerations:

- The model has to be practical and easy to use, otherwise its intended user will not adapt it, or even worse – it will be used incorrectly
- The model should be intuitive and follow a logical structure. Users should not be confused over its input and output parameters, and should be able to reach them quickly. The organization should be clear enough to allow different users to detect the sections they are responsible for and focus on them, rather than get overwhelmed by irrelevant information. And yet, the way analysis results are displayed must be in a language independent from the person reading it
- Without the right data, the model is useless. Current data must be pooled according to a consistent method and from the controlled database. Allowance to introduction of new products
- In order for a cross-functional model to be implemented, it must address the incentives of each stakeholder

4.3.2 Site-specific Considerations:

- PLANT X might face a multi demand per product (i.e. several due dates for different quantities) - this may be addressed by treating multi demands as separate product campaigns (PROTEIN A1, PROTEIN A2, etc.)
- Run Rate is an input parameter that is frequently changed according to existing resources/capacity
- Rooms constraints: the model should consider the restrictions of each room/production zone in the PU regarding number and type of products being processed. Production areas are spaces that are controlled by a single Heating, Ventilation and Air Conditioning (HVAC) system
- The time per batch is not linear with the number of batches produced because of setup time. There is often an overlap between the last steps of a certain product and the first steps of the following product - one option to deal with this is by a separate database from which the model will pool the time for a given number of batches of each product. Example: 1bt=8wk, 2bt=14wk, 3bt=21wk...
- The model should account for existing inventory and for safety stocks - to be used by SCM for dynamic performance measures
- Additional Time constraints: HETP (Height Equivalent to Theoretical Plate) - verification of symmetry and packing at the beginning and end of a campaign (specified in SOP): every 10
batches of a certain product (specifically for PROTEIN A, every 10 batches for Q and SP ion exchange columns, and every 20 batches for Protein A)

- Cleanliness of all equipment from the main bioreactor on. Done during the changeover. Currently not a bottleneck because there is enough time to do this during the purification (actual bottleneck), but if we find a way to expedite the time spent on final purification this will be the next bottleneck in line
- Periodical maintenance - breaks during the year. If Run Rate is increased, we might not have time for these steps. i.e. - may be used as an upper limit to max run rate

4.3.3 Product-specific Considerations:

Depending on the specific products' commercial nature, several considerations should be taken into account when designing a planning model. These include, but are not limited to:

- Well established and commonly used products have relatively high and steady demand on a monthly basis. Most of the demand is for commercial use. Main consideration (from SCM perspective) is never to go below a 6-month (or other commonly kept) safety stock.
- Products that treat rare conditions have low demand for commercial use (a single batch may be sufficient for more than a year horizon). SCM often remains with excess inventory. However, as the due date for production gets closer there is less flexibility to make changes in quantity in case we need more than originally planned. Most of this product's demand is for clinical and development use for testing new indications-for-use.
- Products that are currently not commercial (so all demand is for TRD), but SCM is preparing for the upcoming launch and wants an initial safety stock of 12 months (would typically drop to 6 months gradually). In case the product is expected to be a blockbuster, commercial/clinical demands ratio will reverse after launch. What remains uncertain in the case of new launches is HOW FAST will demand grow, so the forecast is associated with a larger variance.

4.4 Campaign Schedule Modeling as a Mixed Integer Linear Problem (MILP)

Scheduling has a major impact on the overall productivity of a manufacturing process. The objective is to increase the production efficiency by either minimizing time and costs or maximizing the productivity (amount of valuable product per batch- in our case, the titer). Production scheduling helps the operation in deciding when to produce what and with which resources (materials, equipment, staff). In all levels of the planning pyramid, the company uses forward and backward scheduling for allocating resources to processes and purchasing materials and additional resources. In Forward Scheduling, production tasks are set from the time resources become available, in order to determine the final due date. In Backward Scheduling, production tasks are reverse-planed from the due date, in order to determine the start date and any change required in capacity and/or resources.

Automated production scheduling tools are mathematical programming methods that involve formulating the scheduling problem to minimize or maximize a defined objective function subject to a
series of constraints. Such tools greatly outperform manual methods by optimizing real-time workloads in various stages. It can also be used to visualize different stages of the process.

The benefit of such tools include reduction in process change-overs, inventory levels and scheduling time and effort, and increase in production efficiency, delivery dates and costs quotes accuracy and flexibility to address real-time adversity. It also allows better resource allocation: maximizing outputs for given inputs or minimizing necessary inputs for a target output.

4.4.1 Batch Production Scheduling

While production scheduling may play an important role in any manufacturing industry, its importance is especially apparent in the batch production of pharmaceuticals and other biotechnological products, due to several reasons:

- The sensitivity of the material being processed - one cannot simply stop a biological process at any given stage and store the work-in-process for later
- Substance expiration dates
- Equipment maintenance and sterilization between every stage: Clean-In-Place (CIP) and Steam-In-Place (SIP)
- Long production time. A single batch can take a few weeks; need to prepare more time in advance
- Absolutely no rework! (Biopharmaceuticals only) A batch that has been compromised must be completely scrapped

Scheduling algorithms for pharmaceuticals Production Processes can take a significant computing power due to large number of tasks and materials used. To deal with this issue, dispatching rules are used. These are short-cut algorithms that can be categorized in one of the two following groups:

- Stochastic - economic lot/batch scheduling and production quantity
- Heuristic - modified due dates and shifting bottlenecks

The BioPharm Ops fed-batch processes done in the multiproduct PU can be described as the execution of a recipe. Each DS produced has a different recipe comprising of the BOM and the operating instructions described in the company's Standard Operating Procedures (SOPs). A scheduling algorithm should organize recipes into series of unit-procedures. Unit-procedures should be organized into operation, and operations into phases, specifying time durations. In addition to the individual time duration for a single operation, the process is subject to precedence constraints, describing start and end times of dependent operations in respect to each other. Start and/or end time of successive operations may also be limited by the fact that some of the biological materials are perishable or unstable.

4.4.2 Cycle Time Analysis

Analyzing the production recipe reveals the production rate limiting unit/s. When several batches of a certain product are to be produced, calculating the minimum Cycle-Time (the time between the start
time of two consecutive batches) may be an effective performance measurement as well as useful information for other functions in the company. For example, Finance may be interested to know overhead cost-per-batch (labor and utilities), and Supply-Chain Management may be interested to know shipments due dates.

Since a new batch of a similar product (and in limited cases, of a different product) may start before the production of previous batch ended, the minimum cycle-time can be calculated as:

\[ CT_{\text{min}}(i) = \max_{j=1,K} \{ r_{i,k} \} \]

Equation 1. Minimum Cycle Time

Where \( CT_{\text{min}}(i) \) is the minimum Cycle-Time for Product \( i \), consisting of \( K \) unit-procedures, each with a total duration of \( r_{i,k} \). This equation assumes that each unit-procedure occupies a single dedicated equipment unit, otherwise \( r_{i,k} \) should be divided by the number of redundant equipment units available for unit-procedure \( k \) of product \( i \). In our case, this may apply only in the Up Stream Process (USP) where cell culture is grown in one of several bioreactors.

This information may also be used to identify bottlenecks in the procedure, by searching for the unit-procedure with the maximum duration.

Since the biopharmaceutical production process consists of precedent unit-procedures, the actual cycle-time of product \( i \) is the sum of all unit-procedures

\[ CT(i) = \sum_{j=1}^{K} r_{i,k} \]

Equation 2. Total Cycle Time

However, one major limitation with this equation is that the overall cycle-time is not linear with the number of batches produced. Change over times and material preparation steps for batches of the same product must also be considered, as well as equipment setup and adjustments when switching between different products.

### 4.4.3 Run Rate & Changeover Times

The \( CT \) equation describes the time between two consecutive batches. In practice, there is an overlap between the end of product A and the beginning of product B. How much of an overlap is determined by the systems' bottleneck. In PLANT X, the bottleneck is the last step of the purification process, since this step must take place in a certain area (dedicated production zone) and two batches must never be at the same room at the same time. Therefore, the initial purification of product B cannot start until the final purification of product A ended. The inoculum trains of both products, on the other hand, can take place simultaneously since there are two separated areas for this step.
The true time between batches of the same product, therefore, represent the time between cell-harvest from the production bioreactor (or alternatively, the beginning of the initial purification process). This may be calculated as the reciprocal of the Run Rate for that product, or in terms of days as:

\[ T_{BB}(i) = \frac{7}{\text{Run Rate}(i)} \]

Equation 3. Time Between Batches

Where, TBB is in days per batch (of a similar product, i) and Run Rate is the number of batches per week (of a similar product, i). TBB would usually be rounded up to represent an integer number of days.

From here we can find the duration of an entire campaign consisting of N batches of product i, where production from the second batch on may have a certain overlap with the previous batch.

\[ \text{Duration } (P_i, N) = C_{T_{min}}(P_i) + \sum_{j=1}^{N-1} T_{BB_j} \]

Equation 4. Total Campaign Duration

Note that here, \( C_{T_{min}}(P_i) \) is the duration of the first batch, to which we add \( N-1 \) batches, each adding its own TBB to the overall duration, depending on the current Run Rate that may vary from batch to batch.

Not only batches' production may overlap, but also full campaigns to a certain extent.

Currently, the optimal changeover duration is limited such that it must be at least as long as the minimum purification time (initial plus final). In the future, this constraint may be replaced by other bottlenecks in the system or it may be removed if additional columns become available to process the final purification of a second batch in a separate production zone.

We define \( X_j \) as the day (of the year or other given timeframe) in which we start the production of batch j of product i.

Mathematical Representations of the constraints:

- Minimum Time Between Batches:
\[ X_{i,j} - X_{i,j-1} \geq TBB(i) \quad \forall j \geq 2 \]

Equation 3. Minimum Time Between Batches Constraint

- Due Date:

\[ X_{i,j} + CT(i) - 1 \leq Due\ Day(i,j) \]

Equation 6. Due Date Constraint

- Disjunctive Constraints:

\[ Yb(i,j) > Ye(i',j') \quad OR \quad Ye(i,j) < Yb(i',j') \quad \forall i \neq i' \]

Equation 7. Disjunctive Constraint/s

Where,

\[ Yb(i,j) = X_{i,j} + Beginning\ day\ of\ Initial\ Purification\ for\ Product\ i \]

\[ Ye(i,j) = X_{i,j} + Ending\ day\ of\ Final\ Purification\ for\ Product\ i \]

No Purification Overlap: the final purification step is done in Zone D of the production area. In this zone, there must never be more than one product that is being processed at any given time. This constrain dictates that when switching between two different products, the Final Purification of the previous product must end before the Initial Purification of the next product may start.

Since the different products may be produced in any order, to mathematically express this disjunctive constraint, we define a binary decision variable, \( Y_0(i, i') \), having value 1 if \( i \) precedes \( i' \) and 0 otherwise. The new representation will turn the OR condition to an AND condition and will now be:

\[ Yb(i,j) + M(1 - Y_0(i, i')) > Ye(i',j') \quad \forall i \neq i' \]

\[ Ye(i,j) < Yb(i',j') + M(Y_0(i, i')) \quad \forall i \neq i' \]

Equation 8. Disjunctive Constraint/s (alternative)

Where \( M \) is a value large enough.

This representation of the zone constraint can also be generalized by defining \( K \) zones and considering \( Yb(i,j,k) \) and \( Ye(i,j,k) \) for every \( k=1..K \). However, in our case it was simplified by the fact that there is only one Final Purification zone.
Sequence dependent setup time may also be considered by adding a variable \( S_{jk} \) that represents the setup time when switching between job \( j \) and \( k \). It may be different according to the direction (i.e. \( S_{jk} \neq S_{kj} \)). It may also exist between batches of the same products (i.e. \( S_{kk} \neq 0 \)). Ideally, the scheduling systems should account for equipment malfunctions and process variations, but in any case, it should consider availability constraints due to fixed breakdowns (e.g. plant shutdown on holidays, periodic maintenance activities, etc.).

Blocking is a phenomena that occur when a flow shop has limited buffer in between two successive tasks or stations. It implies that a completed job must remain in the upstream processing equipment and cannot move until the preceding job is complete. This is common when no overlap is allowed between jobs and when the system operates in a FIFO manner. Blocking may have a sever effect on the downstream jobs if there is low tolerance to wait-time of work-in-process.

Finally, Plant shutdown / Periodical Maintenance / Holiday / other No-Production days:

\[
X_{i,j} + CT(i)-1 < NP(i,h) \quad \text{OR} \quad NP(i,h) < X_{i,j}
\]

Equation 9. No Production Day Constraint

Where, \( NP(i,h) = \) No Production Day (of the given timeframe) for product \( i \), for task/reason \( h \).

While this framework allows us to define a model to optimize the number of batches per campaign and their sequence, its functionality is limited compared to existing commercially available production planning tools. Therefore, the next section evaluates potential Manufacturing Resources Planning tools to be used in Novartis’ BioPharm Ops Tactical Planning.
4.5 Planning Tool Selection

The selection of a suitable platform for the model depends on the application requirements of the output, the level of details and the identity of the intended user. For cost modeling, for example, key input factors are resources demand and utilization (materials, labor, and other consumables), equipment depreciation, utilities and an objective measure of overall performance (e.g. annual throughput in kg product). Bioprocesses modeling, on the other hand, typically consist of a combination of design equations and Mass and Energy (M&E) balances referring to the technical and environmental performance of the unit-procedures.

Key choices in tool selection include whether the model is static or dynamic, and whether it is deterministic or stochastic.

4.5.1 Static versus dynamic models

Static models are considered simpler compared to dynamic models, and are typically in the form of spreadsheets that are easy to build and modify. These models are mostly common at an early stage, where low resolutions of costs and time estimation are sufficient for a general impression of the system's performance. Interconnected models, models of multiple products and/or production line and models of facilities that make use of shared manufacturing resources – these are all difficult to manage and update using static models. For example, the model cannot account for a situation in which a real-time delay is caused by the unavailability constraint of a certain resource. Another limitation of static models that implement simple spreadsheets is the layout of model assumptions, which often "get lost" in the cell formulation and are mistakenly treated as facts.

Dynamic models, on the other hand, consider time-dependent operations and discrete-event simulation techniques. What makes discrete-event simulators popular for operation models is their ability to comprise activities that compete for resources. This type of dynamic modeling is more complicated to build and require a high level of data accuracy, but in return will provide the user with a reliable and realistic production schedule and a more accurate estimation of measures like capacity and throughput.

4.5.2 Deterministic versus Stochastic models

As in any industry, biomanufacturing includes decision-making in uncertainty, associated with some degree of risk. Traditional modeling and investment analysis techniques assume the most statistically likely outcome is determined to occur. It is critical to understand that this is true in most cases, not all. In addition to risk factors that are common across all manufacturing industries, such as volatile market demand and batch/equipment failure, biologics are associated with additional uncertainties like fermentation titers and purification yields.

There are various approaches to reduce risks related to process uncertainty. One of the most common approaches is conducting a sensitivity analysis on individual input variables. Sensitivity analyses shows how a unit change in a variable effect on the target (objective function), but it does not tell us what is the likelihood of that change occurring. The later requires a subjective measure of scenario's probability distribution, and may be captured using a Risk Adjustment methodology or a Monte Carlo simulation.
4.5.5 Planning tools comparison

4.5.5.1 Excel Solver / MS-Project

The planning tools that are currently used at the BioPharmOps facility are Microsoft Excel spreadsheets and MS-Project. These tools allow the production staff to develop a plan, assign resources to tasks, track progresses and manage the budget.

The Solver application (currently not used) is an Excel Add-In that can be used for what-if analyses and optimization of a target objective function.

- **Pros**: Simple to use. Excel based tools are already implemented in the plant, so the learning curve is very short, compared to other SW that require specific training. No capital investment is required for SW license.
- **Cons**: Operations and unit-procedures are not optimized, only the objective function. The link between tactical and operational planning is manual and not automated. The capability to process heavy-load data as well as the information that is extracted (i.e. analyses reports) are limited. The model must be built from scratch instead of taking advantage of pre-designed process flow model that has already been extensively tested for similar applications. In addition, while previous experience and familiarity with the software is considered a strong pro for this option, it also holds a higher risk of GIGO (Garbage-In-Garbage-Out) due to misuse of untrained operators.

4.5.5.2 BioSolve

An Excel-based COGS model that provides user configurable process sequences and manufacturing cost calculations, aimed at modeling biotech processes.

- **Pros**: Includes a database for commonly accepted cost values that might be used for benchmarking. As an Excel-based SW it is easier to use, compared to other customized modeling tools, such as SuperPro Designer (Intelligen, Inc.) and Aspen Batch Process Developer (Aspen Technologies, Inc.), with a shorter learning curve. Also, software costs are lower.
- **Cons**: Limited capabilities on the operational level. This tool only models the processes but does not optimize them. Analyses are done per product and the SW is not able to analyze multiple products simultaneously, nor is it appropriate for campaign scheduling - the main focus of this project.

4.5.5.3 SAP Advanced Planner and Optimizer (APO)

The component Production Planning and Detailed Scheduling (PP/DS)\(^1\) enables planning and optimization of multi-site production (notice the difference from multi-product site) while simultaneously taking into account product and capacity availability.

\(^1\) [http://help.sap.com/saphelp_apo/helpdata/en/7e/08347004d9b1ee10000009b388d7c7/frameset.htm](http://help.sap.com/saphelp_apo/helpdata/en/7e/08347004d9b1ee10000009b388d7c7/frameset.htm)
• **Pros:** SAP is already available in the system and planners are more familiar with its various functions.

• **Cons:** This tool was not designed specifically for Biotech, so for an advanced planning tool it still requires large customization. While greatly functional, its core competencies are not within tactical planning.

4.5.3.4  **Bio-G**

Real-Time Modeling System that consolidates supply chain and manufacturing operations data, to provides outcomes like quality by design (QbD), real-time scheduling, debottlenecking and more, across a facility, or a global network of facilities39.

• **Pros:** Operations Research experts fully dedicated to biomanufacturing. Link to multiple data sources already existing at BioPharm Ops (SAP, Delta-V). Feedback mechanism allows real-time control over scheduling.

• **Cons:** External consulting will require Novartis to rely heavily on a third party every time modifications and/or new products are introduced (cost and confidentiality).

4.5.3.5  **SuperPro Designer + Schedule Pro**

SuperPro Designer facilitates modeling, evaluation and simulation of integrated processes in a wide range of industries. In the biotech industry specifically, it includes over 120 modeled unit-procedures built in for comprehensive optimization of batch and continuous processes, cost of goods analysis, cycle time reduction, environmental impact assessment, and other tasks. SuperPro Designer does not account for constraints related to dynamic resource allocation, however SchedulePro gradually deals this.

SchedulePro is a finite capacity scheduling (FCS) tool that facilitates production scheduling and planning, capacity analysis, and debottlenecking of multi-product manufacturing facilities. It considers constraints related to the limited availability of facilities, equipment, resources (e.g., labor, utilities, raw materials, etc.) and work areas. SchedulePro operates seamlessly with SuperPro (through automatic importing of its recipes) but it also functions as a stand-alone application

• **Pros:** Build-in templates for mAb batch & semi-continuous production; automatic link between tactical & operational planning; provides additional analyses (capacity, COGS, Equipment occupancy); Build-in campaign scheduling optimization for multiproduct

• **Cons:** Requires configuration of the operation processes, resulting in occasional resistance from the production people that have spent much time developing the previous model. Highly customized and sophisticated, this SW is also associated with more complications and a greater learning curve.

39  http://www.bio-g.com/
4.5.3.6 *Aspen Tech Inc.*

Integrated SW solutions customized to various industries, including pharmaceuticals, for process optimization and production management. The aspenONE Production Management & Execution module targets end-to-end operational efficiency.

- **Pros:** Along with the Intelligen Suite (SuperPro Designer+ SchedulePro), this is among the most functional customized SW packages available for the pharmaceutical industry
- **Cons:** More complicated (and expensive) than the Intelligen Suite, without offering an additional value, for the needs of this project

4.5.4 Establishing the Proof-of-Concept Criteria

SuperPro Designer and AspenTech have been reported to be most widely in use for bioprocess simulation. Both contain the capability to handle economic evaluations, equipment sizing and M&E balances in one incorporated package. Both also share other advantages like having an intuitive graphical process representation, default commonly-accepted values for unspecified parameters (from the molecular weight of a raw material to standard equipment capital investment) and optimization and simulation capabilities for production scaling.

In order to decide which SW package to use for this pilot, the author of this paper assembled a committee of key stakeholders and potential end users from the production group to establish a set of criteria for the proof of concept stage. Criteria items were further prioritized according to specifically address the needs of BioPharm Ops PLANT X, and compared across all evaluated planning tools mentioned (see Table 4).

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31 Shanklin T et al., "Selection of Bioprocess Simulation Software for Industrial Applications."
Table 4. Planning Tools Comparison

Based on the tool comparison and this set of criteria, the **Intelligen Suite (combination of SuperPro Designer and SchedulePro)** was selected as the platform for this pilot project. The recommendation to use this SW package was presented to a steering committee, made of the BioPharm Ops's board of directors and representatives from Novartis Pharma's global headquarters (including IQP, Finance, and IT) - the pilot received a green light.

* * * * *

SchedulePro has been tested in the past at the BioPharm Ops PLANT X, but the project was discontinued since it seemed too complex for daily use. Nevertheless, the application that this project aims to solve is on a tactical level rather than an operational one. Key take-away can be learned from this in order for the project to have a long-lasting impact:

1. The tool must be intuitive for use and outputs must be straightforward: *What wouldn't be simple -- simply wouldn't be!*
2. The intern should not work alone, but rather be part of (or lead) a team dedicated to this initiative, that would be able to maintain the project's integration in the organization after the internship ends
3. Having the right tool is only good when it is used for the right application!
5 Methodology

"I can't give you a surefire formula for success, but I can give you one for failure: try to satisfy everyone at the same time" (Herbert Bayard Swope, Pulitzer prize-winning journalist)

A Scheduling project consists first and foremost of recipes and resources. Recipes are series of processing steps that describe the required tasks for producing each specific product in the facility or Processing Unit. Recipes provide information about how the steps relate to one another in time and what resources are required (equipment, labor, materials, etc.). They are divided into sections, representing a distinct part of the entire process. Sections are further divided into unit procedures according to a major step that takes place in a primary piece of equipment. Unit procedures are divided into operations, describing specific tasks and other required resources like material, auxiliary equipment and labor allocation.

Resources include equipment, work areas, labor, materials, utilities and inventory capacity. Time-based resource availability is entered in a built-in calendar in order to avoid conflicts. This includes: Equipment downtime and maintenance schedules, Labor shift schedules, Material shipments and more.

Schedules may be generated forward from a start date, backwards from a due date, or manually. Where recipes describe a general (and often, fixed) process, schedules describes a specific execution plan: which recipe to produce, using which resources, and when do what.

Multiple equipment items of the same type may be utilized in a facility in order to reduce the cycle time of a batch process. In BioPharm Ops PLANT X, this is noticeable in the USP, where several Bioreactors of the same size operate in a staggered (i.e. alternating) mode, which is equivalent to creating a pool of similar equipment items.
5.1 Part I – Modeling Specific Product Recipe using SuperPro Designer©

As mentioned in the previous chapter, most mAb's share a similar production process. In this part of the project, the processes for manufacturing the specific Active Pharmaceutical Ingredient were modeled using SuperPro Designer© (Intelligen Inc. NJ, USA). However, the recipe described herein is of a representative example for mAb production, consisting of the following 12 sections (based on the process described in 4.1.1):

- Inoculum Preparation
- Cell Culture
- Primary Recovery
- Protein A Chromatography
- Virus Inactivation
- Ion Exchange (IEX) Chromatography – Cation
- Ion Exchange (IEX) Chromatography - Anion
- Ultrafiltration / Diafiltration
- Pack & Freeze
- Intermediate Filtration
- Media Preparation
- Buffer Preparation

In some mAbs, an additional section of Nanofiltration, is adjacent (before or after) to the last chromatography step. Error! Reference source not found.

Procedures belonging to the main process (critical path) are marked by P-(procedure #) and a bold process line. Those belonging to the Media or Buffer Preparation sections are marked by MP-(procedure #) or BP-(procedure #), respectfully. Intermediate Filtration procedures are marked F-(procedure #) and are spread along the entire process rather than being separated to USP and DSP since they do not affect the production scheduling and are of relatively low interest in the scope of this project (the entire section is hidden from the Production Gantt Chart and Equipment Occupancy Chart).

The model specifies the following information:

For each Unit-Procedure

a. To which Section it belongs
b. The sequence of Operations
c. The main equipment occupied
d. The number of cycles

For each Equipment Unit

e. Whether the equipment operates in staggered mode (and how many additional units)
f. Whether the equipment includes multiple units (and how many units)
g. Whether the equipment is shared by multiple procedures

For each Operation
a. Type
b. Input and/or Output streams (when applicable)
c. The process time – absolute or depending on another operations (Master-Slave relationship)
d. The setup and turnaround times (if applicable), and
e. The scheduling link and time shifts
f. Auxiliary equipment used (in our case, only CIP skids were modeled as auxiliary equipment)

The process (see appendix 4) starts after thawing the frozen Working Cell Bank (WCB) and preparing the inoculum in a seed lab, where cells are grown for an extended period in selective medium in increasing-sized vessels. The last step of the Inoculum Prep takes place over several days in a seed bioreactor (operating in Staggered Mode). During the Cell Culture phase, the suspension amplifies in volume and transferred to larger bioreactors. The media that feeds the bioreactors and provides nutrients for the cells is prepared separately in tanks. All media goes through sterile filtration before being transferred into the bioreactors.

A typical sequence of operations in a bioreactor includes: CLEANING-IN-PLACE (CIP) \(\rightarrow\) STEAM-IN-PLACE \(\rightarrow\) (SIP) \(\rightarrow\) SETUP \(\rightarrow\) TRANSFER-MEDIA-IN \(\rightarrow\) TRANSFER-CELLS-IN \(\rightarrow\) FERMENTATION \(\rightarrow\) TRANSFER-CULTURE-OUT. The operation with the greatest influence on the schedule is the TRANSFER-CELLS-IN. This operation is in a Master-Slave relationship (same duration and starting point) with the TRANSFER-OUT operation of the previous procedure. Within the same procedure, all operations preceding TRANSFER-CELLS-IN are scheduled backwards (i.e. scheduled to finish relative to the beginning of the next step) and all following operations are scheduled Forward (i.e. scheduled to start relative to the end of the previous step). This is generally the case for all procedures along the critical path (production main process).

The cell culture reaches its optimal condition (number and concentration of vital cells) in the main production bioreactor. The Primary Recovery section begins with the cells harvest in a disc-stacked centrifuge and the separated biomass pooled to a tank. Remaining debris is removed through depth filtration while the solution is transferred to a storage tank.

During the entire Down-Stream-Process (DSP), buffers are added to allow the optimal conditions. The solution goes through clarification and purification in three chromatography steps: Protein "A" Affinity, Cation Exchange (CEX) and Multimodal Anion Exchange (MAC). The sequence of the chromatography steps varies between products. A chromatography procedure consists of the following typical sequence of operations: EQUILIBRATE \(\rightarrow\) WASH \(\rightarrow\) LOAD \(\rightarrow\) ELUTE \(\rightarrow\) REGENERATE. Since (some of the) chromatography procedures are cycled several times, the first Chromatography procedure in this example is modeled as 3 unit-procedures sharing a single piece of equipment: P-12a is the pre-processing step and includes the setup and the first cycles; P-12 includes the main chromatography steps and is programmed to repeat for X cycles; P-12b is the post-processing step and includes cleaning and storage of the column. Following the Protein "A" chromatography, a virus inactivation step takes place using low pH buffers.

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35 An operation in the model can belong to one of the following types: Transfer In/Out, Pull In/Out, Charge, Agitate, Ferment, Centrifuge, Hold, Setup, SIP, CIP, Equilibrate, Test, Wash, Load, Elute, Regenerate, Concentrate, Filter, Mix, Store
36 The scheduling link can be absolute or relative to another operation – i.e. operation B start after the finish of operation A, or operation C ends before the start of operation D
The cleaning operation for the chromatography procedures is different than that of bioreactors and other tanks in the plant in that the CIP does not take place in the main equipment but rather in the Transfer Lines (TL) that carry the eluted solution from the chromatography columns to their respective pool tanks. Therefore, these lines were added to the model in order to account for the CIP skid availability.

The last purification step is in fact a 2-part step that is treated as a single procedure: First is Ultrafiltration to intermediate concentration, followed by Diafiltration with formulation buffer to final concentration. At the end of this step we are remained with the final formulation of the drug substance (DS). The DS is now ready to be packed and frozen, and shipped to the PharmOps production site, where it will be formulated to a drug product (DP).

Overall, the recipe in this example consists of 12 Sections, 75 Unit-Procedures and more than 300 Operations.

Once completed, all recipes were exported from SuperPro Designer to a recipe database, and imported from the database to SchedulePro. Additional information that cannot be modeled in SuperPro Designer was added in SchedulePro, and will be discussed furthermore in Part II.
5.2 Transition from Part I to Part II – Separation of Material Preparation operations

The recipe modeled in Part I included all material preparations (media and buffers) as part of the main recipe. The problem is that not all materials are prepared every batch. Instead, some are prepared once per batch while others every 2-4 batches. Consequently, the current model will schedule more buffer preparation steps than necessary, resulting in an inaccurate equipment occupancy and higher utilization of CIP skids than in reality.

To solve this issue, the Material Preparation was separated from the Main Production Process and into its own “bundle” of recipes. The bundle included 2-4 recipes (product dependent) grouped according to the frequency of preparation: all media and buffers that are prepared (at least) once per batch in one recipe, all buffers that are prepared every 2 batches in a second recipe, all buffers that prepared every 3 batches in a third recipe, and so on. Since the original procedures duration for preparing and storing the media and buffers assumed 1 batch, using them for 3 batches requires adjustments. The change does not affect much the preparation time, but it does affect the storage time and therefore also the scheduling of the CIP operations. This requires adding HOLDING times between batches.

A CT “operation” was created in a separate “procedure”, and set its duration to the product’s Cycle Time and its scheduling time to start with the start of the first Media Prep. This “operation” is used as a variable that can be changed easily whenever the real Run Rate is changed without having to modify the entire recipe.

Next, the HOLDING operations were added before the TRANSFER-OUT and their duration set to be equal to the CT “operation”. The meaning of this change is that the storage tank will now be occupied for the duration of X batches before being cleaned.

For example, if we want to schedule the production of 12 batches of PROTEIN A we create the following campaigns:

- one campaign using the PROTEIN A MAIN PROCESS recipe, set for 12 batches at a 3.5-day Cycle time (equivalent to a Run Rate of 2 batches/week)
- one campaign using the PROTEIN A MATERIAL PREP-1 recipe, set to 12 “batches” at a 3.5-day Cycle Time
- one campaign using the PROTEIN A MATERIAL PREP-2 recipe, set to 6 “batches” at a 7-day Cycle Time (≈ 2 x 3.5 days), and
- one campaign using the PROTEIN A MATERIAL PREP-3 recipe, set to 4 “batches” at a 10.5-day Cycle Time (≈ 3 x 3.5 days).

The material preparation campaigns’ scheduling starting time (more on this feature in Part II) is linked to that of the main campaign. This way we can align the main campaign with the material-prep bundle so that every X DS batches of PROTEIN A, the algorithm will schedule another round of material preparation. This approach is just as easy to manage for tactical planning and allows more flexibility than before due to the separation.

Overall, the model includes 5 Main Process recipes (PROTEIN A in 2 configurations, PROTEIN B, PROTEIN C and PROTEIN D), and 12 Material Preparation recipes.
5.3 Part II – Production Campaign Scheduling and Simulation using SchedulePro©

A SchedulePro project consists of 4 components: Recipes, Materials, Facility and Production Schedule. For our purposes, Materials are not within the scope of the project, therefore the next section focuses on the other 3 model components.

5.3.1 Model components on the Recipe level

*Operations Scheduling Flexibility* - allow delaying certain operations up to a predefined period (i.e. "tolerance") for predefined reasons (unavailability of resources, facility downtime, etc.). If a certain operation is flexible and its resource is temporarily unavailable, we do not have to delay the entire batch but can rather set the model to schedule only that operation later or earlier given the specific situation. Only if the delay exceeds the maximum tolerance (for example, if the CIP must take place within 72 hours from the Transfer Out operation) will the algorithm delay the entire batch. For further information, refer to *Effect of Scheduling Flexibility* in chapter 6.

We can also specify whether an operation must run continuously or may be interrupted. If, for example, an operation takes 48 hours and tomorrow the plant is closed for a national holiday – should we still start the operation today? This type of information may interest top management for making the decision between running a facility 24/7 or 16/5. For BioPharm Ops PLANT X specifically, the Multiproduct PU is operated on a 24/7 basis, but the Perfusion PU on a 16/5. If in the future more products will be transferred to this PU, capacity will have to be increased in order to comply with demand. Interruptions of operations is less common in biological processes, which generally run continuously (within the context of the batch cycle), but are quite popular in chemical syntheses operations, which tend to be more modular. Therefore, this feature is more useful for API produced in ChemOps rather than in BioPharm Ops.

5.3.2 Model components on the Facility level

*Resources* – Within the facility, the resources that are considered by the model are Equipment, Labor, and Work Areas.

- Equipment – importing the product recipe from Part I to SchedulePro automatically registers the necessary equipment to the facility. When duplicating the recipe for other products, the recipe may utilize the existing equipment or new equipment that is added to the facility. Here we differ between staggered equipment, used in Part I, and equipment pools: where SuperPro Designer defines the staggered mode as part of the equipment data, SchedulePro assigns a pool of equipment for procedures. In a single-product facility there would have been no difference, however in multi-product facilities the separation is critical. In addition, a changeover matrix can be defined for a certain equipment unit. The matrix specifies the required time necessary to prepare the equipment unit when switching campaigns. This feature of the model will only be used if selected on the Schedule Level (for further elaboration see 5.3.3 Model components on the Production Schedule level).
Based on product type, the matrix entries represent the duration of the changeover operation when transitioning recipes from the row to the column. For example, when switching from a campaign of PROTEIN C to PROTEIN A, a changeover of 7 days is required, but when switching to PROTEIN D, 10 days are required. Notice that when the recipe type remains the same (descending diagonal) or when switching to/from idle state, no changeover time is required (only cleaning).

<table>
<thead>
<tr>
<th>Duration (day)</th>
<th>Idle</th>
<th>Protein A</th>
<th>Protein B</th>
<th>Protein C</th>
<th>Protein D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idle</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Protein A</td>
<td>0.00</td>
<td>0.00</td>
<td>7.00</td>
<td>7.00</td>
<td>7.00</td>
</tr>
<tr>
<td>Protein B</td>
<td>0.00</td>
<td>7.00</td>
<td>0.00</td>
<td>10.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Protein C</td>
<td>0.00</td>
<td>7.00</td>
<td>10.00</td>
<td>0.00</td>
<td>10.00</td>
</tr>
<tr>
<td>Protein D</td>
<td>0.00</td>
<td>7.00</td>
<td>10.00</td>
<td>10.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Table 5. Equipment Changeover Matrix.

*Labor* – As mentioned in Chapter 0, best practices in ERP rely on competency-based management to not only define what will be accomplished, but also with what resources will this be accomplished. Human Resources are arguably the most difficult to manage due to different levels of qualifications and experience, not to mention personal manners arising from individual characteristics. For the purposes of this project – a *proof of concept* for upgrading the existing tactical planning tools – the labor requirement was treated as the number of (general?) operators needed to perform each operation.

Labor requirements are specified on the Operations level (i.e. each task has a required number of operators). However, not all tasks require an operator: intermediate filtrations, mixing, holding/storing and other automatic operations do not occupy labor. TRANSFER-IN operations are often left blank as well, since the labor needed to perform this task was already accounted for under the TRANSFER-OUT operation of the previous procedure, as these occur simultaneously by definition.

The number of operators does not have to be an integer. Many operations require the presence of operators for only a fraction of the processing time. During this time, the same operators can work on other tasks. For example, SIP of a buffer preparation tank typically requires a little less than an hour and 2 operators, but within that hour several tanks can go through SIP – thus the model specifies a labor requirement of 0.5 operators for each task.

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For more information regarding the shortcomings of using general operators (as opposed to function-specific) see 7.3 Model Limitations.
In addition to Labor, there is an option to specify Staff per operation. While Labor refers to a Pool of a specific type of worker, Staff refers to Individuals that may be assigned to an operation. For each staff member, the user can specify the number of parallel tasks that the individual can perform, and for each operation, who is allowed (qualified) to perform this task. The staff option was not implemented in this model due to time limitations, but future implementation of this feature could be very useful for human resource management in the PU.

- *Work Areas* - pharmaceuticals manufacturing facilities are subject to strict regulatory requirements. Depending on the production step, restriction may apply on the number and type of batches that are processed simultaneously in the same room/zone. Areas in the production facility are also separated by Heat Ventilation and Air Conditioning (HVAC) systems. ISO standards and cGMP require certain steps of the production process, like the final purification, to take place in an isolated environment where only one product may be processed at a time to avoid risk of cross contamination. As a result, each Procedure Unit is allocated to a specific room in the facility. This information is relevant for the scheduler to consider in a multi-purpose facility when switching between campaigns of different products - it is the key to defining changeover times.

The BioPharm Ops PLANT X facility that was modeled in SchedulePro contains 19 rooms (work areas) divided to 5 production zones, each with its restrictions.

**Resources Availability and Downtimes** – downtimes are calendar-based and are scheduled as single occasions or periodical reoccurrences. Downtimes can be facility-wide (complete shutdown) or resource-specific (holiday, periodical utility maintenance, equipment calibration, etc.).

### 5.5.3 Model components on the Production Schedule level

Once all recipes are built in the system and the facility and resources defined, we can create and schedule batch production campaigns for the PU. The information in this section is specified for each Campaign:

**DS Demand Projection** - consolidated from SCM and TRD:

- **What?** The API to be produced (and configuration when applicable)
- **How Much?** The amount of DS needed in terms of batches (can also be given in kilogram product, but this was not implemented in the model)
- **When?** Main Process recipes can be produced according to Earliest Release Date (forward scheduling), Due Date (backwards scheduling), or Relative to Previous Campaign (this option is relevant to Material Preparation recipes scheduled in respect to the main process)

---

3 Usage Policy defines whether a work area may be used by any activity or only by activities within the same Campaign/Recipe/Batch

---

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**Cycle Time Based Scheduling** – the user can either set the Cycle Time\(^9\) itself (the time between the beginnings of two consecutive batches) or the Slack Time, where:

- \(\text{Cycle Time} \left[ \frac{\text{days}}{\text{batch}} \right] = \frac{1}{\text{Run Rate} \left[ \frac{\text{batches}}{\text{week}} \right]} \)

- \(\text{CT}_{\text{min}} = \text{Min Cycle Time} = \frac{\text{Longest Procedure Duration}}{\# \text{ of Equipment Units for that Procedure}}\)

- \(\text{Cycle Time} = \text{CT}_{\text{min}} + \text{Slack}\)

**Equipment Changeover Time** - there are two ways to deal with changeover (time added at the end of the last equipment used during the campaign):

1. Based on Changeover Matrix – matrices are defined on the equipment level for specific equipment units. Several matrices can be chosen. This option is more detailed and therefore accurate
2. Fixed Duration – the same changeover time will be added at the end of the last batch of the campaign for all equipment utilized by the recipe. This is done on the campaign level and is much simpler to implement (currently used at the PU)

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\(^9\) In order for the model to consider Cycle Time as a given input, the scheduling mode should be set to Automatic or Layout. If set to ASAP, the system will ignore this input and schedule the campaigns once available – according to the optimal Cycle-Time.
6 Results and Analysis

"However beautiful the strategy, you should occasionally look at the results..." (Winston Churchill)

6.1 Preliminary Results from Part I

Note: Results from Part I lack some of the information considered on the facility level in part II and should, therefore, only be viewed as general principles

With the recipe complete in SuperPro Designer©, we can now explore the single-product production procedures for one or more batches. A good place to start is the operational Gantt chart - specifying each section/procedure/operation with their absolute or relative duration start time and end time. This provides us with a few interesting pieces of information, such as the batch time, the cycle time slack and the equipment bottleneck (see Figure 8 ). Notice that "equipment bottleneck" is not necessarily the equipment with the longest unit procedure, which is the fermentation in the largest production bioreactor. Instead the system identified unrealized bottleneck equipment: a tank used to prepare a buffer during PROTEIN A's DSP. This tank is occupied for 5.4 days during the DSP, so how could it be a bottleneck compared to the production bioreactor? This makes sense, since most buffers prep tanks are used for only one material per recipe, whereas this particular tank is used for 3; on the other hand, there are X production bioreactors working in a staggered mode, so the length of the fermentation is effectively divided by X.

To view the effect of an equipment bottleneck on an entire campaign we turn to the Equipment Occupancy Chart (EOC – see Figure 9 ) of multiple batches. The significance of this control tool goes beyond listing our resources' availability and utilization. This is the best way to visually detect the process bottleneck. The bottleneck equipment is the equipment with the least idle time. For example, it's very clear from a single batch EOC that the Production Bioreactor is the unit-procedure with the single longest duration. However, if we are producing several batches and we have X production bioreactors but only one of each seed bioreactor, than the smaller bioreactors that only process a batch for few days will become the new bottleneck. This leads to the concept of using staggered equipment.

As seen in the scheduling summary on the Gantt chart, the equipment bottleneck is the prep tank mentioned earlier, since it has the least idle time out of the main equipment. Perhaps, the reason that this piece of equipment has been overlooked in the past, is because it does not reach 100% utilization – it is limited by another bottleneck: the CIP skids. These are considered Auxiliary equipment (hence, the model did not mention them as the main bottleneck) but in practice, CIP availability is responsible for many delays. If the plant management decides to invest in more skids and debottleneck this issue – next in line would be the prep tank.

However, this result also points out an error with the first part model: mAb's are produced in batches, and while every batch requires the use of buffers, the buffers themselves can be prepared once every few mAb batches. In other words, some materials are utilized over 2, 3 or even 4 rounds, thereby reducing the relative occupancy of the equipment in which they were prepared. This problem is solved in Part II of this project by separating the main process recipes and the material prep recipes.
Figure 8. Preliminary Results from Part I - Operational Gantt Chart (partial)

<table>
<thead>
<tr>
<th>Task</th>
<th>Duration (hr)</th>
<th>Start Time (hr)</th>
<th>End Time (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Batch Programming</td>
<td>2.00</td>
<td>00.00</td>
<td>02.10</td>
</tr>
<tr>
<td>2. Buffer (CIP)</td>
<td>0.50</td>
<td>02.10</td>
<td>02.30</td>
</tr>
<tr>
<td>3. Cell Line</td>
<td>1.40</td>
<td>00.00</td>
<td>03.00</td>
</tr>
<tr>
<td>4. Transfer Media</td>
<td>1.20</td>
<td>03.00</td>
<td>04.20</td>
</tr>
<tr>
<td>5. Transfer Cell</td>
<td>1.80</td>
<td>04.20</td>
<td>06.00</td>
</tr>
<tr>
<td>6. End Point</td>
<td>0.30</td>
<td>00.00</td>
<td>00.30</td>
</tr>
</tbody>
</table>

Figure 9. Preliminary Results from Part I - Equipment Occupancy Chart
6.2 Proof-of-Concept Results from Part II

6.2.1 Feasible Campaign Scheduling

With all model components in place and after specifying the DS demand for all products, we now have a campaign schedule for the desired period of 2 years. The schedule is presented in Figure 10 in the form of a Gantt chart, similar to that generated by MS-Project (gold standard). For the example below, we used 5 campaigns of 3 batches each. For each DS campaign we also generate a material preparation campaign (for producing the media and buffers). The Gantt chart is organized in layers, so that the user may decide to keep a bird’s eye view of the campaigns layout over the entire period (light green bars, for both main product campaigns and material preparation campaigns). Alternatively, we can also open the next layer and view the specific schedule for each batch, within each campaign (light brown bars).

Technically, the planner can zoom-in further on specific unit procedures (dark green bars) and operations (light blue bars – not presented in this figure). However, for tactical purposes, this resolution is too detailed, and it is most likely that at least some fine details will change over this period.

Figure 10. Operational Gantt Chart

Figure 11. shows the EOC for an example campaign schedule, consisting of: 10 batches of PROTEIN A (configuration 1), 2 batches of PROTEIN C, 6 batches of PROTEIN A (configuration 2), 12 batches of PROTEIN B and 7 batches of PROTEIN D. For each campaign a release date and due date were assigned.

The different colors in the EOC correspond to different campaigns (the EOC may also be color-coded per batch), with darker shades representing main equipment (on the “critical path”) and light shades representing auxiliary equipment (material preparation and storage tanks and CIP skids). Intermediate filters and transfer lines are omitted from the EOC for simplicity.
The blank (or white) boxes at the end of the last batch in every campaign represent the changeover operation on the relevant equipment unit. The grey zone represents a facility-wide downtime for semi-annual utility maintenance.

A filter function may also be used in order to focus on specific sections of the production process (e.g. USP or DSP), or specific type of equipment (only main equipment, only CIP skids, etc.).

Figure 11. Equipment Occupancy Chart
6.2.2 Real-Time control and Conflict Resolving

Tracking the status of production schedules is facilitated by the concept of current time, which separates past from future activities. The red vertical line in Figure 12 represents the current time. The current time line results in the division of activities into three categories: completed (displayed by a crossed hatch pattern), in-progress (diagonal hatch) and not-started (filled pattern). The classification of activities is automatically updated when the current time is changed. The use of the current time facilitates the monitoring of the production progress. The current time value may correspond to the computer clock time or can be set by the user.

A significant value added of this dynamic tool compared to the existing spreadsheets is the ability to control progress in real-time and address deviations as they occur. If a piece of equipment is unexpectedly unavailable, automatic conflict resolving is used to reschedule all other pieces of equipment affected by the change.

Figure 12. Real-Time Control Application
6.2.3 Overall Equipment Effectiveness

The equipment time utilization chart (Figure 13.) displays the percentage of the total schedule time during which each equipment or work area unit is occupied. Utilization is counted as the time that the unit is occupied during the selected time span. This is a common tool at most manufacturing industries. Nevertheless, certain characteristics of the biopharmaceutical industry make this tool even more important as a Key Performance Indicator (KPI) for Overall Equipment Effectiveness (OEE). For example, the rigorous cleaning procedures to avoid cross-contamination require the use of auxiliary equipment. In the case of unavailability of this auxiliary equipment, the main equipment may be sitting idle for a longer time even though it is not being used to process a new batch. Put simply, equipment may be *idle* but considered *occupied* if it is waiting to be cleaned.

![Figure 13. Equipment Time Utilization](image)

% **occupied** – total: The percentage of scheduling horizon during which a unit is occupied by procedures.

% **occupied** – busy: The percentage of scheduling horizon during which a unit is occupied by operations.

% **occupied** – idle: The percentage of scheduling horizon during which a unit is reserved by procedures but not performing operations (i.e. waiting for operations to begin or resume).
6.2.4 Labor Management

Since all operations require a certain number of operators, for every production schedule we can also observe the number of operators necessary for completing the job. The currently used Excel model at the PU uses General Operators. We may also set Labor Types to account for different qualifications (for example: separate USP/DSP operators, QC experts, middle management, etc.). For this model, operators in the BioPharm Ops PLANT X facility were divided to 4 types: USP-Main, DSP-Main, USP-Media Prep, and DSP-Buffer Prep.

Labor - as well as Materials and Utilities, which were not in the scope of this project - can also be set as Soft Constraints: the SW will allow the schedule even if these resources are unavailable, but will send a violation warning.

Figure 14. shows the labor demand for a single campaign of 10 batches of an example product. Figures A-D are labor breakdowns for each of the 4 mentioned stages, and figure E is the total labor requirement at the PU.

Figure 14. Human Resources Management: Labor Utilization
For labor, the user may specify deviations from a base availability. For instance, you may specify that a facility consist of twenty operators during the day shifts and 10 operators during the night shift. If labor constraints are considered in scheduling, this will delay the execution of certain tasks during the night shift.

6.3 Results Analyses

What-if Analyses was done through scenario testing. To maintain consistency in the results, all scenarios were based on a campaign of 10 batches of the same representative product, PROTEIN A. For the next figures, the different colors do not represent different campaigns, but rather different batches of the same campaign.

Key assumptions used for the scenario testing are that PLANT X has the labor capacity to handle a higher Run Rate and that Material Preparation is not a bottleneck.

6.3.1 Capacity Analysis

Capacity analysis is most commonly done by measuring the amount of product that a plant can produce in a given time, or by the time it takes to produce a given amount of product (for this paper, the second method was chosen). The plant’s nominal capacity includes all resources - from utilities and equipment to labor and professional operators - necessary to manufacture the plant’s products. However, the effective capacity is the actual capacity achieved in practice and also depends on the way resources are used (e.g. are resources available but idle due to a system bottleneck? Could this have been resolved by scheduling activities differently?). The effective capacity is, therefore, lower than the nominal capacity. In any case, the plant’s capacity should exceed the demand, at least in the long run and in the pharmaceutical industry specifically in the short run as well, since the tolerance for medicine stock-outs is very low.

Scenario I: Baseline (current situation)

The baseline scenario was tested accordingly to the current run rate (Cycle Time), which was assumed to remain constant throughout the campaign. The result is shown below:
Output: the campaign for 10 batches of PROTEIN A at current Run Rate results in a total duration of **79.05 days**

**Scenario II: Max Run Rate (ASAP mode)**

It should be noted that SchedulePro© is a FCS tool and not an optimizer. Optimization can, however, be achieved for the specific objective function of minimizing the Cycle-Time. This requires us to look at the (potential) Run Rate of the PU as an output and not just an input for tactical planning – and is inherently different from the way this parameter is treated today. With the existing capacity, the maximum run rate is shown below.
Effect of Scheduling Flexibility

Switching from the standard mode (fixed cycle time) to ASAP mode (As Soon As Possible – optimized cycle time) resulted in a reduction of almost 8 days in the total campaign duration. This is due in large to the scheduling flexibility that was defined in the recipe level for the bottleneck equipment. Currently, when a bottleneck equipment (in this case, CIP skid) is unavailable, operations are delayed and a wait-time is inserted in the Excel spreadsheets, however the decision how much to delay them may occasionally be quite arbitrary, relying heavily on the planners' experience. It might be that certain operations are delayed more than is necessary, resulting in a longer batch cycle time.

The scheduling optimization model will maximize the run rate by setting a flexible operation (in our case, the cleaning) to best fit the situation on a case-by-case method. Wait-times will only be added as necessary. Therefore, it is possible to get an optimized schedule, reducing the overall cycle time and saving the plant operating costs.

6.3.2 Sensitivity Analysis

The Sensitivity analysis refers to the manner in which uncertainty in the output of a mathematical model is apportioned to uncertainty in the input. It provides insights on the relationship between input and output variables in the system, and to what extent would a change in the first alter the second. A sensitivity analysis is also a useful method to test the robustness of the model's results.

Scenario III: USP Debottlenecking (At Max Run Rate)

From the Capacity Analysis, we learned that the bottleneck equipment, when operating at Max Run Rate, is the CIP skid that is used for cleaning the Bioreactors (USP). Therefore, the following scenarios focus on the affect of a change in the CIP equipment pool.

The figure below is an extraction of the mentioned CIP equipment from the EOC, demonstrating the utilization given the existing capacity (left) versus the scenario, in which an additional single CIP skid is added and pooled for USP (right).
What if we purchase another skid for the campaign for 10 batches of PROTEIN A at Maximum Run Rate possible with an additional CIP, segregated for USP, results in a total duration of 62.53 days with an average Run Rate: 3.23 (Max RR: 3.29)

Scenario IV: DSP Debottlenecking (*At Max Run Rate*)

What if we purchase another skid for DSP? The next scenario is a demonstration of the importance of wise resource allocation. The figure below demonstrates a situation, similar to that of the previous scenario, with the exception of the extra CIP being allocated for DSP instead.

Output: the campaign for 10 batches of PROTEIN A at Maximum Run Rate possible with an additional CIP, segregated for DSP, results in a total duration of 70.02 days.
This is still an improvement, compared to the scenario II. However, the effect is not as meaningful as it was in scenario III.

**Scenario V: Purchase two more CIP skids (for both USP and DSP)**

![Diagram](image)

Figure 19. Sensitivity Analysis - Scenario V: USP + DSP Debottlenecking (EOC)

- Output: the campaign for 10 batches of PROTEIN A at Maximum Run Rate possible with two additional CIP's, segregated for both USP and DSP, results in a total duration of **69.58 days**.

The output of this scenario is the same as that of scenario III, indicating that the second CIP *does not add value – we should only purchase one!* How come? Debottlenecking the system by purchasing the CIP skid for USP allows us to operate at run rate that is now limited by the production bioreactor and the UF/DF. The decision whether to continue lead-time reduction by expanding capacity at the new bottleneck, will now depend on the opportunity costs of these equipment units. However, adding another production bioreactor is not as straightforward as adding an auxiliary equipment, as it is essentially opening a new production-stream and would require an expansion in labor and overhead as well.

From scenarios IV and V we learn not only to consider the question *"should we invest?"* but instead ask: *"where should we invest?"*
This thesis set to analyze and address the integrated business planning at Novartis' BioPharm Ops from a technical and financial point of view. Specifically, focusing on tactical planning and campaign scheduling optimization as a method to reduce operational costs and improve cross-functional information flow.

The results shown in this chapter demonstrate potential to reduce the batch-production cycle time, and consequently reduce the overall campaign duration by days. What is the financial significance?

*A week in production of a Multiproduct PU costs approximately $1.5M!!!*
7 Conclusions

"Tell me and I will forget; show me and maybe I will remember; involve me and I will understand…"

(Chinese Saying)

Mathematical modeling of complex operational processes is far from being straightforward to understand. Those who read the outcomes often do not fully comprehend the sources of the data or where the numbers came from, often leading operators to either unthinkingly follow the figures or ignore and manually override them. The analysis becomes useless in this situation and the mode of operations remains according to the status quo, rather than following a continuous improvement mindset – “because that is how we always did it…” What is worse is that the higher management may not even be aware that the tactics they agreed upon did not in fact percolate down to the shop-floor.

Best-in-class manufacturing practices stress simplicity of both manual and computerized methods in order for the system to work effectively. Shop-floor personnel should be empowered and involved in the bigger picture, and accordingly, must be trained to use the system properly. As front-line users, their insights on the performance of the system may well be the most accurate indicator for actual continuous improvement towards operational excellence.

Note: SchedulePro was selected for the purpose of this thesis, as its specifications seem to best answer the burning needs of the company, but the outcomes and key take-home message from this project should not be viewed as a sales-pitch for one commercial product. Instead, this thesis aims provide a proof-of-concept for Novartis to strengthen its planning arsenal with a simulation-based scheduling tool.
7.1 Bottom Line: Did we meet the criteria?

We go back to the proof-of-concept criteria that was established earlier on in the project to assess whether this model indeed answers BioPharm Ops' needs:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>SchedulePro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automatic and optimal scheduling</td>
<td>Meets partially – see model limitations</td>
</tr>
<tr>
<td>Output: Equipment Occupancy Chart</td>
<td>ü</td>
</tr>
<tr>
<td>Output: Required Resources &amp; Labor</td>
<td>ü</td>
</tr>
<tr>
<td>Adapted to multi-product scheduling</td>
<td>ü</td>
</tr>
<tr>
<td>Able to consider run rate</td>
<td>ü</td>
</tr>
<tr>
<td>Able to consider Changeover times</td>
<td>ü</td>
</tr>
<tr>
<td>Define equipment redundancy</td>
<td>ü</td>
</tr>
<tr>
<td>Resources availability / unavailability considered automatically</td>
<td>ü</td>
</tr>
<tr>
<td>Able to assign specific equipment to tasks</td>
<td>ü</td>
</tr>
<tr>
<td>Consider main operational constraints (CIP, holding time, etc.)</td>
<td>ü</td>
</tr>
<tr>
<td>Sensitivity Analysis</td>
<td>ü</td>
</tr>
</tbody>
</table>

Complexity: Low

<table>
<thead>
<tr>
<th>Annual License Cost</th>
<th>SchedulePro</th>
<th>Site</th>
<th>Corporate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$3</td>
<td>$5</td>
<td>$8</td>
<td>$10</td>
</tr>
</tbody>
</table>

Table 6. Proof-of-Concept summary

7.2 Recommendations and Potential Benefits

- Regardless of whether PLANT X’s leadership chooses to implement SuperPro Designer (or just SchedulePro, or neither), the process flows created in the first Part of this thesis should be printed as a large poster and used as Value Stream Maps of the entire production process. This will help aligning operators and other production staff to the common language used in the entire PU (without separation of USP/DSP/Material Prep) for better control, and may also function as training tool for new employees

- Using a simulation-based scheduling tool gives us the ability to create and/or modify feasible campaign schedules in hours instead of days due to operations’ time optimization. It also provides the flexibility to address adversity and bottlenecks in real time, as well as resolve conflicts in an automated manner. All this allows increased operational efficiency, saving valuable time

- The planning tool, presented in this thesis should support operational planning efforts to maximize Run Rate, resulting in cycle time reduction and significant production cost savings
• Long-term strategic decisions, mainly Manufacturing Resources Planning, should be supported by sensitivity and capacity analyses for better understanding of potential outcomes of different actions. Before making tactical or strategic decisions to invest, ask: “what will happen if I invest here instead?” Such analyses are addressed in this thesis through production schedules scenario testing.

7.3 Model Limitations and Improvement Opportunities

“We confess our little faults to persuade people that we have no large ones…” (Francois De La Rochefoucauld, 17th century French courtier and aphorist)

• Materials and Utilities availability were not in the scope of this model. One challenge with managing certain resources on separate MRPII/ERP systems is in the definition of fixed versus variable costs. Raw materials, for example, are largely consumed on a daily basis and their periodic expenses are linearly related to the produced quantities, while certain equipment and the facility itself are owned by the company and are reusable. However, even fixed assets have maintenance costs and depreciation rates that depend on production quantities. Raw-Material inventory management may be the subject of a follow-up internship/IQP project.

• The current model uses General Operators. For accurate Human Resource management, we may set Labor Types and/or Specific Staff and account for different qualifications and authorizations. The difference is that Labor is a pool of a specific type of worker, where the user may set the pool size, calendric availability and base hourly rate. Staff, on the other hand, are individuals that may be assigned to an operation, where the user may specify the number of parallel tasks and the allowed operations (qualified for...).

• SchedulePro does not automatically optimize the number of batches per campaign and prioritize their sequence. Optimal solution is done by scenario testing. However, Optimization of the operations start/finish times is possible (Objective Function: minimize Cycle-Time).

• Data accuracy must be consistent with the ERP system. While production recipes are not changed often, they should be periodically reviewed to ensure compliance with SAP.
7.4 Future Outlook

7.4.1 Project Hand-off

The last stage of the internship project consisted of transferring the knowledge and ownership of the developed model to the responsible personnel in the production site for implementation, expansion and improvement of the model. A large group of stakeholders were presented with the outcomes, potential benefits and key learning from the pilot, including Novartis' BioPharm Ops Global IQP, Finance, IT, PLANT X's executive management, MS&T and Production. A training seminar – both general use of the SW and specific features of the PLANT X model – was conducted for the site's tactical planners and two process experts, according to a hand-off roadmap.

7.4.2 Implementation Strategy

Since any planning tool considerably effect the plant's operations and throughput, its integration into the system requires a planning process on its own. The implementation should be carried out gradually in phases. This project focused on the pilot phase in which a proof-of-concept demonstrated the functions that may add value to the existing capacity at the current situation. Functions that were missing or in which the performance was insufficient, as well as functions that were not originally considered and consist further opportunity for improvement are assessed at the end of this phase and adjustments to the strategy are made.

The next phase is a validation phase to ensure data accuracy according to the most recent controlled parameters. The BOM should be revised for all products, organized by common raw materials and product-specific materials, and all departments (internal and external to the production site) aligned to a single source for consistency.

Once verified for accuracy, the system is faced with different scenarios across a wide range to evaluate its credibility. The system outputs are constantly compared to the gold standard, which it aims to replace – in our case, the tactical planning Excel spreadsheets – while the actual operations in the plant still rely on the gold standard. Master Production Scheduling (MPS) attainment is often particularly challenging due to this metric's dependency on many variables, both in terms of objective limitations (such as capacity) and even interpersonal.

Key users should be integrated at an early stage, since this is also an opportunity for the future users to become familiar with the new model. Operators are educated on the importance of their specific role in the value chain and the expectation from them. Trust is established among team members to openly discussing setbacks and improve overall cross-departmental communication.

Only after completing the mentioned above, can the new model proceed to implementation in the system.
8 References:


9 Appendices

Appendix 1. Biological Vs. Chemical Pharmaceuticals ................................................................................. 90
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Appendix 1. Biological Vs. Chemical Pharmaceuticals

(or: BioPharm Ops vs. ChemOps)

The list below specifies the main differences between biological and chemical pharmaceuticals that affect the production and production planning practices.

a. **Manufacturing method**: Chemical Pharmaceuticals are small molecules produced through chemical synthesis, while Biologics are large and complex proteins that are produced by living genetically-modified organisms. Chemicals can be produced in batch mode or in continuous mode. Biologics are produced in batch mode or semi-continuous mode (perfusion).

b. **Raw materials supply lead times**: Chemicals have a typical lead time of up to 9 months for normal products and 6 months for strategic products. In Biologics, the Working Cell Bank (WCB) and other recombinant derived special materials have a longer lead time, exceeding 2 years.

c. **GMP conditions**: Apply to chemicals only as of the DS registered starting material, while it applies to biologics for all manufacturing steps starting from WCB generation, prior to DS production.

d. **Process validation**: is part of the regulatory dossier of biologics only, and is done before finalizing Phase III clinical study, as oppose to before product launch in the case of chemicals.

e. **API storage conditions**: Chemical DS is stored at room temperature, while biologic DS is stored frozen.

f. **Bio-burden Risk**: Up Stream Process (USP) of biologics is done in sterile conditions, while Down Stream Process (DSP) and chemical API production, hold low bio burden.

g. **Manufacturing Economics**: Low to medium COGS for chemical API; Medium to high COGS (relative to industry) for biological API.

h. **Medicine delivery system**: Biologics are subject to parenteral formulations (lyophilize or liquid in vials or ampoules), whereas chemicals may be applied in any dosage form.

i. **Production Process**: Biological API production follows a End-to-End process, DSP follows directly after USP; in chemicals, steps may be separated.

j. **Production duration**: Several weeks per batch of biologic API; Shorter for a single batch of chemical API (however, due to the modularity nature of chemical substances, products are often paused in the intermediate state and end-to-end production might take 6 months).

k. **Equipment and Production areas**: fixed in BioPharm Ops; modular in ChemOps (reactors are moved between production lines).
Manufacturing Method
Chemical synthesis

Produced by living genetically modified organisms, followed by purification without further modification

Raw and starting materials
Supply lead time: av. 6 months for strategic products, up to 9 months for normal products
Supply lead time for WCB and special recombinant derived raw materials: > 2 years

GMP conditions DS
Applied as of registered starting materials (3 chemical modification steps before final structure)
Applied to all manufacturing steps starting from cell bank generation.

Process validation
Not part of regulatory dossier (done before launch)
Part of regulatory dossier (before finalization of Phase III study)

Storage conditions API
Room temperature
Frozen

Sterile production API
Low bio burden
Sterile production for USP, low bio burden for DSP

COGS
Low to medium
Medium to high (relative to industry)

Dosage form
All dosage forms possible
Parenteral formulations (lyophilizate or liquid in vials or ampoules)

Batch production
Higher modularity; Steps may be separated
End-to-End, DSP follows directly after USP

<table>
<thead>
<tr>
<th>Topic</th>
<th>Small molecules</th>
<th>Large molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing Method</td>
<td>Chemical synthesis</td>
<td>Produced by living genetically modified organisms, followed by purification without further modification</td>
</tr>
<tr>
<td>Raw and starting materials</td>
<td>Supply lead time: av. 6 months for strategic products, up to 9 months for normal products</td>
<td>Supply lead time for WCB and special recombinant derived raw materials: &gt; 2 years</td>
</tr>
<tr>
<td>GMP conditions DS</td>
<td>Applied as of registered starting materials (3 chemical modification steps before final structure)</td>
<td>Applied to all manufacturing steps starting from cell bank generation.</td>
</tr>
<tr>
<td>Process validation</td>
<td>Not part of regulatory dossier (done before launch)</td>
<td>Part of regulatory dossier (before finalization of Phase III study)</td>
</tr>
<tr>
<td>Storage conditions API</td>
<td>Room temperature</td>
<td>Frozen</td>
</tr>
<tr>
<td>Sterile production API</td>
<td>Low bio burden</td>
<td>Sterile production for USP, low bio burden for DSP</td>
</tr>
<tr>
<td>COGS</td>
<td>Low to medium</td>
<td>Medium to high (relative to industry)</td>
</tr>
<tr>
<td>Dosage form</td>
<td>All dosage forms possible</td>
<td>Parenteral formulations (lyophilizate or liquid in vials or ampoules)</td>
</tr>
<tr>
<td>Batch production</td>
<td>Higher modularity; Steps may be separated</td>
<td>End-to-End, DSP follows directly after USP</td>
</tr>
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</table>

Table 7: Small Vs. Large Molecule Production Comparison
# Class A Checklist

**MRP II Performance Summary**

<table>
<thead>
<tr>
<th>NO.</th>
<th>Description</th>
<th>YES</th>
<th>NO</th>
<th>Score</th>
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<tbody>
<tr>
<td>1.</td>
<td>Management Commitment to Excellence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Planning and Control Processes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Strategic Planning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Business Planning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Sales and Operations Planning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Single Set of Numbers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>&quot;What if&quot; Simulations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Forecasts That are Measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Integrated Customer Order and Promising</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>10.</td>
<td>Master Production Scheduling</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>11.</td>
<td>Supplier Planning and Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>Material Planning and Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>Capacity Planning and Control</td>
<td></td>
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</tr>
<tr>
<td>14.</td>
<td>New Product Development</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>15.</td>
<td>Engineering Integrated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>Data Management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>Integrated BOM and Routing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>BOM Accuracy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>Inventory Accuracy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td>Routing Accuracy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22.</td>
<td>Product Change Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.</td>
<td>Communication and Involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.</td>
<td>Employee Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25.</td>
<td>Partner Relationships with Customers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partner Relationships with Suppliers</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

92
## Class A Checklist
### MRP II Performance Summary – cont.

<table>
<thead>
<tr>
<th>PERFORMANCE MEASUREMENTS</th>
<th>YES</th>
<th>NO</th>
<th>SCORE</th>
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</thead>
<tbody>
<tr>
<td><strong>Planning and Control Process Measurements</strong></td>
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</tr>
<tr>
<td>26. Sales Plan Performance</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>27. Production Planning Performance +/-2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28. Master Production Schedule Performance 95-100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29. Manufacturing Performance 95-100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30. Supplier Delivery Performance 95-100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Company Performance Measurements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>31. Customer Service Delivery OTIF 99-100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32. Cost Performance Measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33. Velocity Performance Measured</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Benefits Achieved</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34. Inventory reduced substantially</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35. Cost of sales reduced significantly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36. Productivity increased significantly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37. Customer service increased significantly</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Appendix 3. Planning Tools Selection Options – Summary

<table>
<thead>
<tr>
<th>MS Excel (Solver) + MS Project</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently in place at BPO Hunningue are Excel spreadsheets and Project Gantt charts. The Solver application is an Excel Add-in that can be used for what-if analyses and optimization of a target objective function.</td>
</tr>
<tr>
<td><strong>Pros:</strong></td>
</tr>
<tr>
<td>- Simple to use, short learning curve</td>
</tr>
<tr>
<td>- Already implemented in the plant</td>
</tr>
<tr>
<td>- No capital investment required for SW license</td>
</tr>
<tr>
<td><strong>Cons:</strong></td>
</tr>
<tr>
<td>- Operations / unit-procedures are not optimized</td>
</tr>
<tr>
<td>- No link between tactical and operational planning</td>
</tr>
<tr>
<td>- Limited capability / information</td>
</tr>
<tr>
<td>- Model must be built from scratch</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BioSolver</th>
</tr>
</thead>
<tbody>
<tr>
<td>An Excel-based COGS model that provides user configurable process sequences and manufacturing cost calculations, aimed at modeling biotech processes.</td>
</tr>
<tr>
<td><strong>Pros:</strong></td>
</tr>
<tr>
<td>- Commonly accepted cost values for benchmarking</td>
</tr>
<tr>
<td>- Relatively easy to use, compared to customized tools</td>
</tr>
<tr>
<td>- Software costs are lower</td>
</tr>
<tr>
<td><strong>Cons:</strong></td>
</tr>
<tr>
<td>- Limited capabilities on the operational level</td>
</tr>
<tr>
<td>- Analyses are done per product (no multiproduct)</td>
</tr>
<tr>
<td>- Not suited for campaign scheduling</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SAP Advanced Planner &amp; Optimizer (APO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production Planning and Detailed Scheduling (PP/DS component) enables multi-site production optimization while simultaneously taking into account product and capacity availability.</td>
</tr>
<tr>
<td><strong>Pros:</strong></td>
</tr>
<tr>
<td>- SAP is already available in the system</td>
</tr>
<tr>
<td>- Planners are more familiar with its various functions (purchasing, maintenance scheduling)</td>
</tr>
<tr>
<td><strong>Cons:</strong></td>
</tr>
<tr>
<td>- Not designed specifically for Biotech, therefore still requires large customization.</td>
</tr>
<tr>
<td>- Core competencies are not within tactical planning</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bio-G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real-Time Modeling System that consolidates supply chain and manufacturing operations data, providing outcomes like quality by design (QbD), real-time scheduling, debottlenecking etc., across a facility or network.</td>
</tr>
<tr>
<td><strong>Pros:</strong></td>
</tr>
<tr>
<td>- Operations Research experts dedicated to biotech</td>
</tr>
<tr>
<td>- Link to multiple data sources (SAP, Delta-V)</td>
</tr>
<tr>
<td>- Feedback mechanism for real-time schedule control</td>
</tr>
<tr>
<td><strong>Cons:</strong></td>
</tr>
<tr>
<td>- External consulting, requires Novartis to rely on a 3rd party for modifications and/or new products</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SuperPro Designer + SchedulePro</th>
</tr>
</thead>
<tbody>
<tr>
<td>SW suite to facilitates modeling, evaluation and simulation of integrated processes, compatible with biotech batch and semi-continuous production. Cost of Goods analysis, cycle time reduction, environmental impact assessment, and other tasks. Suited for multi-product manufacturing facilities.</td>
</tr>
<tr>
<td><strong>Pros:</strong></td>
</tr>
<tr>
<td>- +120 build-in templates for mAb (batch &amp; semi-cont.)</td>
</tr>
<tr>
<td>- Automatic link between tactical &amp; operational plans</td>
</tr>
<tr>
<td>- Sensitivity analyses: Capacity, COGS, resources, HR</td>
</tr>
<tr>
<td>- Campaign scheduling optimization for multiproduct</td>
</tr>
<tr>
<td><strong>Cons:</strong></td>
</tr>
<tr>
<td>- Highly customized and sophisticated, this SW requires configuration of the operation processes and a learning curve</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aspen Tech Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrated SW solutions, customized to various industries for process optimization and production planning. The aspenONE Production Management &amp; Execution module targets end-to-end operational efficiency.</td>
</tr>
<tr>
<td><strong>Pros:</strong></td>
</tr>
<tr>
<td>- Fully Functional (similar to SuperPro+SchedulePro)</td>
</tr>
<tr>
<td>- Adapted to many industries, including pharmaceutical</td>
</tr>
<tr>
<td><strong>Cons:</strong></td>
</tr>
<tr>
<td>- More complicated and expensive than the Intelligor Suite without an additional value</td>
</tr>
</tbody>
</table>
API Production Process

Example

---

Recipe:
- 12 Sections
- 75 Unit Procedures
- 29 Main Process (P)
- 7 Media Prep (MP)
- 27 Buffer Prep (BP)
- 3 Transfer Lines (TL)
- 12 Intermediate Filtration (F) Operations

---