

**Modeling Drug Substance Purification Manufacturing through
Schedule Optimization and Simulation**

By

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BME, University of Minnesota, 2012

Submitted to the MIT Department of Mechanical Engineering and the MIT Sloan
School of Management in partial fulfillment of these requirements for the degrees of
Master of Science in Mechanical Engineering

and

Master of Business Administration

in conjunction with the Leaders for Global Operations Program at the
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2017

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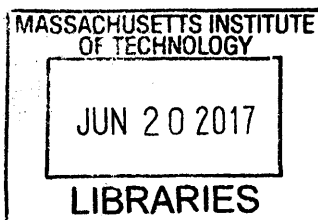
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Abstract

This thesis develops a method by which overtime could be reduced in a highly variable drug substance purification manufacturing environment. Purification production overtime (20%) is a big cost driver at Building XX¹ (BXX). Current production planning and labor resource evaluation methods at BXX Purification are manual, do not capture schedule delays, and do not adequately account for labor availability. Because of this, BXX is unable to accurately evaluate to what extent labor resource contributes to bottlenecking or how to improve overtime. A tool is devised in the Virtually Exhaustive Combinatorial System (VirtECS®) Scheduler software whereby purification production schedules are modeled and optimized. The model simulates production delays and the flow of production. Results lead to a more accurate understanding of how labor resource constrains the lot cycle time and where improvements in shift structure could be made to improve lot cycle time and variability of lot cycle time.

The purification production schedules of two monoclonal antibodies (mAb) were modeled with the use of VirtECS® Scheduler. These two drug substances are selected to reflect the majority of BXX's mAb pipeline. The plant, BXX, produces a high mix of clinical and commercial launch drug substances, and is subject to a number of stochastic scheduling delays. Excel® is used to generate random sets of process times to simulate delays. These process times are fed into VirtECS®, a production schedule optimization tool, which then produces a simulated set of production schedules.

Scheduling decisions of shift labor allocation and when manufacturing should start production during the week are simulated using the model. Results from this evaluation illustrate opportunities for BXX to improve overtime. Lot cycle time is found to be reduced by up to 5.9% based on model results by moving the start of production towards the end of the week and allocating more resources to the third shift from second shift. Additionally, cycle time variability, could be reduced by up to 22%. The model makes a number of assumptions which simplify purification operations whose effect should be further investigated. Future improvements for VirtECS® are proposed to better model BXX processes.

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¹ Building XX is a pseudo-name to preserve confidentiality.

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Acknowledgements

The author wishes to acknowledge the Leaders for Global Operations Program at MIT for its support of this work, including the support of his academic advisors Don Rosenfield and Stan Gershwin.

He would also like to thank the helpful staff at Amgen and especially Building XX. This includes his advisor Josh Jones, LGO alum Cathy Fang, the AMaSE team (Bob Gorski, Kevin Roy, Larry Sun), and many others.

Finally, the author would like to thank his wife Angie and son Max who have been a tremendous source of support for him throughout this journey.

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Glossary of Terms

100% Labor Availability - All labor hours scheduled are assumed to be available and workers are trained to execute all activities. This excludes time needed for breaks, training, or some gaps in staff proficiencies.

BXX - Building XX is one of Amgen's manufacturing locations.

Campaign - A campaign is when more than one batch of the same drug substance are manufactured sequentially.

Cell culture - A portion of the manufacturing process of drug substance whereby a small number of cells is grown into a large target volume, the product protein is expressed by the cell culture, then the culture is harvested, and then sent on to purification.

Cycle time - The time it takes to execute a process from start to finish. For this project, cycle time typically refers to how long it takes to produce one lot. For Purification, this is defined as the time from when the lot's titer results become available until the last task for the lot is complete (excluding holding equipment for cleaning).

Chromatography - Separating a mixture into two or more parts through the use of a medium.

Drug product - The drug in its final form.

Drug substance - This term is used to describe drug solution before it is in its final, patient ready formulation and container.

Harvest - This is a processing step after cells have traveled through cell culture whereby unnecessary material within the solution is discarded.

Product Contact - This refers to a step, activity, or piece of equipment where the drug substance was used and came into contact with.

Production schedule - For this thesis this term generally is referring to the prioritization of tasks and resources within a given day or over the course of a lot's production.

Purification - A manufacturing method that involves multiple filtration, chromatography, and chemical techniques to capture target proteins from a homogeneous mixture to ensure appropriate drug substance quality.

Purification (PUR) - This term is used to encompass the group that works and manages the purification manufacturing portion of BXX.

Lot - A drug substance batch.

Model throughput - A name unique to this thesis and has no bearing on the accepted concept of throughput. In this this, model throughput is the aggregate time needed to complete all tasks as solved by VirtECS® Scheduler model given a set of process inputs. VirtECS® Scheduler's objective is to minimize this quantity. It can also be seen as the entire cycle time of the optimized schedule from start to finish.

Non-product Contact - Equipment that is used in the production process and becomes dirty but does not touch drug substance. This equipment typically has lower

cleaning requirements than product contact equipment because there is no product carryover concern with non-product contact equipment.

Runtime - This term is interchangeable with cycle time.

Stage - A term used in this project to describe the group of tasks that surround a particular purification filtration step.

Titer - A test that determines the number of target monoclonal antibodies in a solution (or the product's starting concentration). This test is taken after Cell Culture and before handoff to Purification.

1 Introduction

The purification manufacturing of a drug substance plant (BXX) currently uses Excel® based tools to schedule production and evaluate their workforce needs. These methods have been kept basic and flexible for easy operation by staff who have to contend with a diverse pipeline of products going in and out of the plant on a weekly basis. While flexible, these tools do not account for 1) possible production schedule delays, 2) the complex linkages between tasks within the production process, or 3) the available labor and staff proficiency required to perform specific unit operations. This leaves management with an incomplete picture that is less data driven and more experience driven when faced with challenges (such as overtime) or arbitrary scheduling decisions.

This project incorporates both production delays and production flow into a scheduling software VirtECS® Scheduler. Purification methods and production vary greatly across different drug substances. A model of two drug substances' production schedules are created to span a significant portion of BXX's pipeline. Aside from weekly variability in the type of products being made, process step delays occur stochastically that affect the schedule. These delays are brought on by equipment malfunctions or simply because this is the first time the drug substance has been manufactured at clinical scale. Clinical drug substance is not yet approved by Federal Food and Drug Administration (FDA) regulators and is undergoing medical testing before approval. Random number generation in Excel® is utilized to simulate these effects on production.

The output analyzed from the VirtECS® model is lot cycle time and corresponding labor statistics. These statistics are compared to actual cycle time data to provide a partial validation of the model. Shift structure decisions are then simulated with the model. The specific decisions tested are when Production's week should start and how many workers to allocate to third shift. Results demonstrate that Purification can reduce their overtime by starting their shift structure later in the week and by increasing labor in their night production shift (3rd shift).

1.1 Problem Statement

BXX Purification manufacturing currently needs to improve labor capacity to better meet demand in a timely fashion or respond effectively to delays. This manifests itself in excessive overtime (20%) and Purification does not currently have a tool to test production improvements.

1.2 Project Objective

The objective of this project is to devise a method to allow BXX's Purification team to accurately evaluate their labor resource utilization and prescribe ways to reduce overtime. The method will provide BXX Purification with a way to make data-based decisions around reducing overtime. Overtime is driven by two factors: lot cycle time and lot cycle time variability. Reducing either of these two will lead to a reduction in overtime.

The method devised will test the hypothesis that weekly production scheduling decisions can be optimized to reduce cycle time and cycle time variability. The "production schedule" is defined as tasks and resource assignments in a given day or over the course of the production of a drug substance lot. Scheduling decisions analyzed in this project are production shift structure and labor allocation to the different shifts.

1.3 Scope Exclusions

This project is scoped to encompass only purification production scheduling in a plant that also executes cell culture operations. The efforts to improve purification production's scheduling methodology will be kept at a high level (shift scheduling) to illustrate the model's usefulness. The actual process of purification (order of major purification steps and procedures) will not be altered. Cross-training of floor workers will also not be considered, as BXX has historically low employee turnover. BXX will be modeled in their current level of resources as of Q1 2017, which includes a floor expansion. Maintenance and training activities are not included in this analysis; only production activities will be scheduled. No analysis will be conducted on improvement of lot cycle time due to learning/experience or changing the schedule of future demand. This is a high product mix facility with very little chance for ramp-up and the schedule of future demand isn't within the facilities ability to change.

1.4 Thesis Overview

This thesis is constructed to provide context for the challenge, examine prior work that relates to the issue, model execution, the analysis methods, results, and conclusions/next steps. Emphasis is given to problem solving methodology since this project conducts operational analysis in a unique manufacturing environment.

2 Background: Problem Context

Building XX's Purification team is challenged with high overtime (20%) and not equipped with the proper tools to analyze this challenge. To understand the context of this issue, industry and company context are given before narrowing down to BXX and purification manufacturing's specific issue.

2.1 Industry Overview: Pharmaceuticals

The biopharmaceutical industry is constantly changing and evolving. Because the plant analyzed in this project produces drug substance for clinical trials as well as commercially available drugs, a brief description of the clinical trial process is provided. The Food and Drug Administration (FDA) regulates the drugs or pharmaceuticals that are available for purchase in the United States. They require potential treatments to go through a development and approval process which typically involves three to four clinical trial phases. At the end of each of these phases, the FDA reviews the clinical data produced by the study and provides guidance for the next step for the drug. Ultimately they are looking for drug safety (Phase I), drug efficacy (Phase II), and statistical significance of the drug versus a placebo (Phase III). Clinical trials last approximately 2 years each, with the total cost of bringing drugs to market estimated at \$802M on average in terms of 2000 USD [1].

2.2 Amgen Inc

Amgen has been an innovator, manufacturer and distributor of therapeutics for over 35 years. Amgen's products focus on oncology/hematology, bone health, nephrology, inflammation, cardiovascular disease and neuroscience. Headquartered in Thousand Oaks, CA, Amgen has operations spanning the globe. Their 2015 revenue was \$21.7B with a net income of \$6.9B, a 35% increase of net income from 2014 [2]. Their product line that is currently available to US customers includes 16 products, the majority of which are therapeutics made up of mammalian cells [3]. They have a diverse pipeline of 33 drug substances.

The majority of Amgen's revenue comes from eight products, many of which were developed before 2000 [2]. Patents for biopharmaceuticals generally have a lifetime of 20 years after filing. As these patents near the end of their life and government regulation opens up the path for biosimilars (a biological product that is demonstrated to be highly similar to an already FDA approved biologic treatment), Amgen will be faced with additional competition. The need to react fast to challenges therefore becomes important.

2.3 Building XX Operations - Monoclonal Antibody Drug Substance Manufacturing

This project is focused on purification production at Building XX (BXX), one of Amgen's clinical and commercial launch manufacturing facilities. BXX historically is a clinical drug substance manufacturing site but recently has added commercial launch capabilities to help with Amgen's strategy to improve speed to market. This has added additional regulation hurdles and product mix to BXX's operations.

The majority of Building XX's capacity is currently devoted to the production of monoclonal antibody (mAbs) therapeutics². A brief review of a generic manufacturing process of mAbs follows. Emphasis is given to the second portion of the manufacturing process, purification.

The manufacturing of drug substance involves three main steps: cell culture, purification, and final fill as seen in Figure 1. Cells go from a cell bank to cell culture, purification, and then final fill where the drug substance becomes drug product after it is placed in the container such as a syringe or vial. Drug substance manufacturing at BXX is broken down into two sections: cell culture and purification. For the purpose of this paper, cell culture will include the initial harvest and titer steps that occur after cell culture. This coincides with how BXX manufacturing personnel are allocated to the two groups.

BXX is a high mix, low volume production environment where ~50% of the lots produced in 2016 were different. BXX is split into two separate groups: Cell Culture (CC) and harvest or "upstream" and Purification (PUR) or "downstream." A master production schedule is sent out weekly that provides the building with expected future demand for each group. Below the director of BXX, upstream and downstream have separate operational, planning and budgeting entities. The manufacturing flow of drug substance goes from CC to PUR.

CC's cycle time on average per lot is 4 weeks or approximately 1 month. CC increased their equipment capacity from 3 to 4 lots per month as of Q1 2017, allowing them a throughput of roughly one drug substance per week (and in some cases a faster theoretical throughput). PUR's equipment capacity is such that they should be able to achieve a one drug substance per week throughput on average. However according to historical data and discussions with PUR staff, PUR struggles to match that one week cycle time. This makes Purification the future potential bottleneck of BXX.

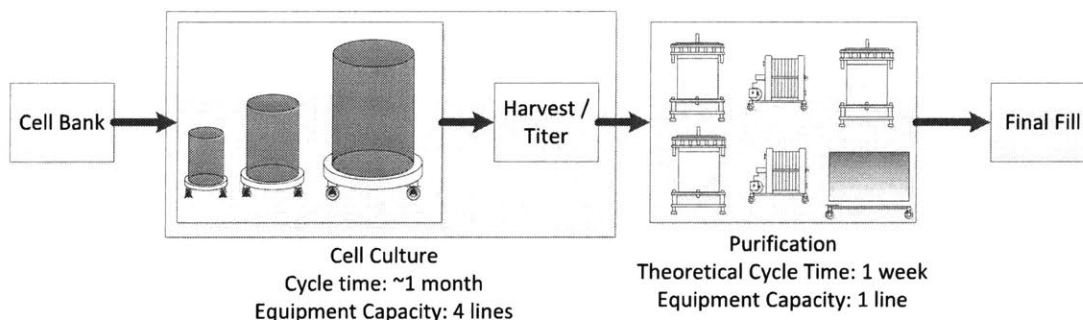


Figure 1 - Drug substance manufacturing flow overview

2.3.1. Cell Culture

² Other therapeutics produced at BXX are excluded from the scope of this project.

Cell Culture (CC) is the first step of drug substance manufacturing. CC takes cells from a cell bank and executes an expansion process. Using various metabolic and chemical reactions, the small volume of cells is expanded into larger volume through a series of larger bioreactors while inducing protein growth. After a target volume is achieved, the CC completes with a harvest operation where the cells are separated from the protein product. This process of CC and harvest takes approximately one month. When harvest is complete, the CC team will take a sample of the solution to undergo a titer test to determine concentration levels of target proteins. Upon receiving test results, CC sends the lot on to PUR. CC is typically on a consistent production schedule that sends the drug substance on to PUR every week. PUR takes the harvest material through various purification and filtration techniques, ultimately getting a substance that has a high concentration of target proteins needed for the biopharmaceutical drug.

2.3.2.Purification at BXX

For the purposes of this report, the purification process can be generalized as a single batch process with six to eight stages that occur in series. All stages have a number of activities to perform that can be described as either preparation, product, or breakdown activities.

- **Preparation activities** include creating subassemblies such as liquid buffer, cleaning equipment, and assembling the filtration equipment. These activities are executed before the drug substance can enter the stage.
- **Product activities** are when the drug substance is at the stage and is being processed by the equipment. The substance undergoes chromatography, filtration, or concentration type activities. Product activities are the "value-added" manufacturing steps from a lean perspective. Target therapeutic proteins are captured within the solution and sent on to following steps.
- **Breakdown activities** happen after the drug substance has moved onto the next stage, and are simply disassembling equipment or cleaning equipment for the next use.

As mentioned previously, purification manufacturing varies from one product to the next. This includes the equipment or subassemblies used, the stages themselves, and how the product flows from stage to stage. In addition, there has been a move in the industry towards using single use bags and equipment. This reduces the amount of cleaning required, but also changes the manufacturing process. These manufacturing methods have been ingrained in the development of the therapeutic. By the time they reach BXX, these methods have already been defined. To illustrate the differences in

manufacturing procedures across products, two methods, discrete batch processing and connected processing, are described in the following sections.

2.3.2.1. Discrete Batch Processing

Discrete batch processing is executed in a stage-by-stage basis. The whole drug substance lot enters a stage and a product activity (filtration, chromatography, or concentration) is executed. As the solution slowly exits the product activity, it is pooled in a pool vessel or storage tank. The pool vessel will wait until all of the drug substance has passed through the purification step before the solution is tested. After testing, the lot is then moved to the next stage in the process. Figure 2 illustrates a general example of the manufacturing flow of product which is purified using discrete batch processing. From a manufacturing standpoint, all of the equipment in a particular stage must be cleaned, assembled, and ready before the drug substance can be placed in the stage. Typically the next stage is ready when the last stage is complete, but sometimes there are delays that require the drug substance to wait for the next stage to be prepared. Drug substances have a hold time limit based on the solution's degradation properties (chemical or metabolic processes). A drug substance that exceeds its designated hold time has compromised quality, which ultimately could lead to the whole lot being thrown out. Moving the drug substance from stage to stage thus presents the opportunity for product quality failures within batch processing if production is behind schedule.

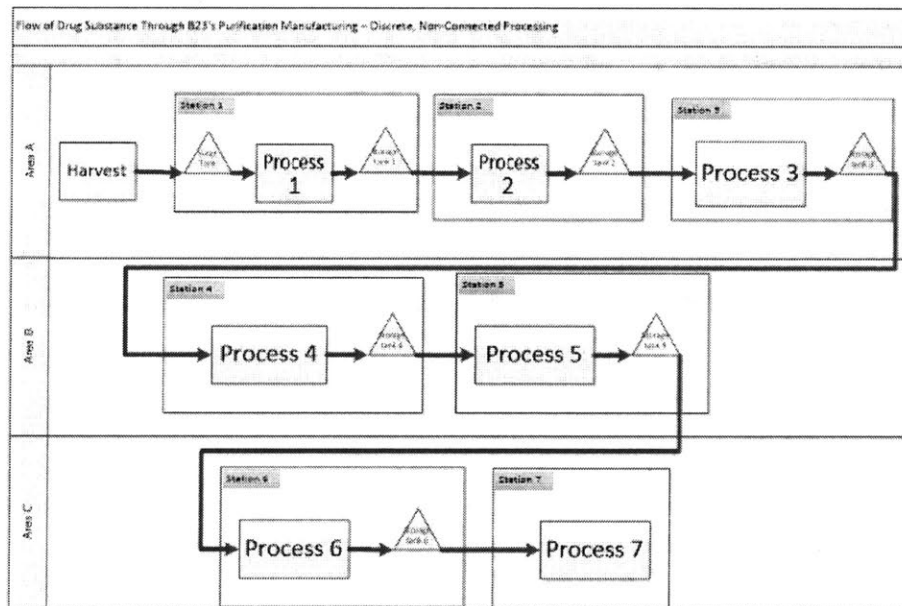


Figure 2 - Purification Manufacturing Flow: Discrete Batch Processing

2.3.2.2. Connected Processing

Connected processing is where a portion of the stages are executed continuously with no pooling. In the connected portion, the solution is automatically sent forward with pumps and control systems. See Figure 3 for an example of a typical production process with connected processing. In this case, stage 4 is a connected process and the rest operate as discrete batch processing. Stages 4-6 from Figure 2 have been combined into stage 4 in Figure 3. Stage 4 now has 3 purification steps inside it. The benefit of connected processing from an operations standpoint is the reduction in stops or intermediate holds that the product needs to take. As mentioned in 2.3.2.1, after each stage the pool is tested and manually transported to the next stage. The connected process removes the need for some of these intermediate steps which hypothetically improves the overall cycle time versus if the same product was processed in a discrete batch.

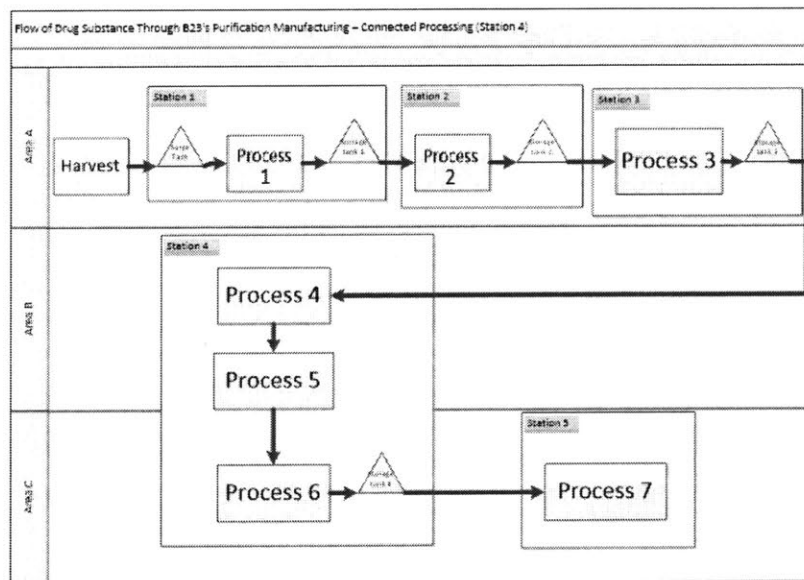


Figure 3 - Purification Manufacturing Flow: Continuous Flow Processing

One challenge connected processes pose to production staff is the importance of managing their schedule. The stage that contains the connected process takes a significant time to set up because of the large amount of equipment needed to run all the purification steps. Logically, production could take the approach of setting up the stage as early as possible. However, before setting up equipment, it must first be cleaned. Equipment have clean hold times that limit how long the equipment remains clean after a cleaning (even when unused). Clean hold times can vary on the order of days depending on equipment type at BXX. Thus, production cannot prepare the connected stage too far in advance without risking equipment violating a clean hold time. Violating a clean hold time would require staff to re-clean the equipment, which would take

approximately the same amount of labor hours as the first cleaning. There is a delicate balance that the scheduler and production must attain: don't prep the connected process too early and risk a clean hold time violation while at the same time ensure there is enough buffer time to be ready. Often these timelines don't match up despite the best efforts of the scheduler and floor staff, leading to delays.

2.4 Production Scheduling of Purification in Building XX

Historically a clinical facility, BXX's systems and processes are rooted in Process Development. Because BXX is often the first plant to make a drug substance at commercial scale, data tracking tools and methods focus on monitoring the properties of the drug substance to ensure product quality and safety for patients. While there is some operational data collection ongoing, operational metrics such as expected cycle time, step process times, or schedule adherence are often not tracked. This makes it challenging for the scheduler to set the next week's production schedule.

Currently PUR sets their production schedule to complete drug substances in one week excluding a handful of drug substances where equipment capacity restricts runtime to 1.5 - 2 weeks. Purification utilizes a 5 day, 24 hour production shift structure with 3 shifts. First and second shift is eight hour days, five days a week, and third shift is split into two shifts that each operate 4 days a week for 10 hours. Half of third shift goes from Monday through Thursday and the other goes from Tuesday to Friday. The two parts of third shift overlap on three days (Tuesday-Thursday). The production stays relatively constant regardless of what drug substance is being processed that week.

BXX produces a mixture of drug substances primarily for clinical use and secondarily for commercial launch. There is significant product variety (50% of lots produced in 2016 were different from each other) and very few opportunities are available for campaigning lots. This leads to a production schedule that changes dramatically week-in-week-out.

Because of the ever-changing nature of the types of drug substances coming into BXX, Purification has kept their operations flexible and simple so they can execute drug substances whose production requirements and methods vary. From a scheduling perspective, this entails manually creation of daily and weekly tasks in Excel® executed by a scheduler. The scheduler uses knowledge and historical process data (if available) to estimate how the weeks' activities will play out. In the instances of repeat demand, the scheduler will apply data gathered from the last run to inform their decisions. Not all production tasks are accounted for in the schedule. The weekly schedule is an overview of the main purification activities and some supporting steps that the scheduler envisions should happen in a given day or shift. Most of the schedule and order of tasks are left up to the floor to determine and execute.

2.5 Current State of BXX PUR: Observed Symptoms

Purification struggles to meet their current schedule target of five days for lot cycle time. Often PUR finds that it needs workers to either stay later, overlapping with other shifts, or to come in on the weekends. This has led to plant overtime in 2016 of approximately 20% and is the primary problem this project tries to help. A number of symptoms were observed as a part of the evaluation of this project and are listed below:

- Manual scheduling methods - Excel® based schedules are published the Friday before the following week. Because of employee time constraints, schedules are often not updated after they are created, and are used more as a prioritized checklist.
- Delays often happen in the production schedule. These delays seem to happen at random and impact productivity at the very least and often impact overall cycle time of production.
- Schedule miscommunication - the floor will sometimes deviate from what the scheduler wanted them to do, leading to communication breakdown at times.
- The complete status of production is unknown or poorly communicated. Updates are emailed after each shift to the full Purification team but these do not contain a sense of overall production progress.
- The critical path is unclear to staff.
- It is unclear to most floor workers if production is “on-time” to be completed by the end of the week. Often management does not have a sense of this until later in the week, and must scramble to put together a weekend shift (overtime) which consists of floor workers from weekday shifts.
- Important metrics are not present - schedule adherence (comparing when the product completes versus when it was planned), risk to schedule (possibility of delays).
- There are over/under-utilized workers due to recently hiring new employees which have yet to be sufficiently cross-trained.
- Rework frequently occurs in the form of re-cleaning of equipment when the equipment’s clean hold time is violated and extra testing for equipment who violated their dirty hold time.

These observations characterize an environment where personnel are constantly reacting to challenges and little is done in the way of predicting when these challenges will occur or devising preventative measures to mitigate them.

2.6 Future State

Building XX and Purification envision having a “connected” digital plant when the status of production is known in real time and can be monitored from a centralized location. Delays to the predicted schedule will be predicted ahead of time and mitigated through smart scheduling techniques. Any delays that do occur will be highly visible and responded to in quick succession. There will be no overtime, and staff focus will be shifted from reacting to being proactive. This project is seen as one step in that direction.

3 Problem Solving Methodology

Due to the complex nature of production, a number of possible approaches are considered for the purpose of analyzing Purification’s capacity and overtime issues. A tool is identified to help aggregate and disseminate available operations data. First, a general methodology is constructed to quantify Purification’s capacity and cycle time challenges - modeling Purification’s production schedule with an over-the-counter modeling tool. Second, a software is selected to execute the analysis. This project adopts the method of modeling Purification production through the use of VirtECS® Scheduler.

3.1 Selection Criteria - General Approach

A number of general methods for approaching the issue of reducing overtime and cycle time are considered. To effectively select from these options, selection criteria are devised based on the needs of BXX and the timeline for this project. The selection criteria are accuracy, ease of use, time to implement, and adaptability. These different selection criteria focus on the ability of the solution to be easily adapted by BXX Purification staff.

Accuracy. Applying any particular framework to BXX Purification will need to provide an acceptable level of complexity to accurately model production. This includes accounting for resource and process constraints.

Ease of use. BXX does not have any dedicated programmers. The knowledge base that the tool/method will rely on lies within the production staff and the scheduler, the likely end user.

Time to implement. As this project is based on a 6 month internship, some consideration was made for the author to be able to execute the methodology in a proof-of-concept form during the time allotted.

Adaptability. This has two separate but intertwined meanings for BXX purification: (1) the framework can apply to a variety of drug substance production methods and (2) the ability to adapt to advances in plant technology. Amgen as a whole has embraced big data, launching a platform that unifies the data across sites. Any tool should have the potential to tap into this new platform.

Ultimately, the specific methodology explored should be able to capture the complexity of the plant operations and identify ways in which BXX can drive improvements in overtime.

3.2 General Approach Options

Four approaches to the problem were explored. They are analyzing only the protein affinity chromatography operation, whole production resource capacity analysis, off-the-shelf production modeling software, and modeling the whole production within a self-coded model.

Analyze first chromatography operation. This project would focus on improving the operational scheduling and task prioritization of the first column chromatography. The first stage in purification production for mAbs is on average one of the longest filtration steps in Purification. Completing this stage on-time is a critical indication whether the lot will be completed within the five day production week. This approach would create a detailed analysis of the chromatography operation and then provide a method to apply the solution to the rest of production.

Resource capacity analysis. This method would analyze the resource usage (labor, equipment, and cleaning resources) and come up with estimated productive time, forced idle time, and idle time. This would take a holistic approach to the production on a weekly basis, and would come up with recommendations about how to use equipment and labor more efficiently.

Off-the-shelf production modeling. Modeling full production using off-the-shelf software would allow the project to take advantage of an already built architecture. Production for select drug substances could readily be modeled that span the spectrum of BXX's demand. Challenges this would face involve making sure BXX's unique capabilities could be properly approximately with the off-the-shelf software.

Modeling production from scratch. This would model full production by generating novel code. Similar to the other modeling option, this option would provide a tailored production model that provides specific operational insights. Due to project time constraints it would apply a limited amount of constraints and model complexity.

3.3 Problem Solving Approach Selection - Off-the-shelf Software

In order to select a general problem solving method, four different general approaches were proposed and compared to the selection criteria. Based on conversations with vendors and Amgen user groups for a variety of off-the-shelf modeling tools, software applications have been applied in numerous cases to pilot plants with variable schedules. There is also considerable published work done using readily available software applications in drug substance manufacturing scheduling [4] [5] [6] [7]. Ease of use was of particular concern for BXX who values tools that are quickly cross-trained when faced with limited staffing. A software with a well-developed user interface would

most likely provide the best ease of use. From this analysis, an off-the-shelf modeling tool fit the needs for BXX and that can adequately fit the production process.

3.4 Simulation of Production Schedule

Production schedules are inherently complex, requiring that a number of constraints be met for a feasible schedule to be obtained. Typical linear programming or deterministic type optimization does not work in the case of BXX Purification because of the added characteristic of stochastic delays. A solution to this is to provide for an iterative sampling approach, whereby a model could be run multiple times with a mix of process times that are delayed or not delayed based on historical data. This is the framework for a stochastic model which could represent Purification's production schedule.

A model alone is insufficient to answering the question of how overtime can be reduced. What is required is a simulation, whereby the stochastic model can be run multiple times to test decisions. The objective of the simulation could be to minimize or maximize the output of the model. Simulation, in its basic form, runs the model multiple times to represent random inputs which vary, interprets the output, makes a new scheduling decision that changes the model, reruns the model, and compares the output to the previous output. If the objective function of the simulation is met, the new decision(s) are recommended and can be explored further. In the case of scheduling production for purification, the decisions that could be tested include shift structure and employee resource allocation.

3.5 Software Selection

To find a tool that best suits BXX Purification, a review and investigation was conducted on six different software packages. The software packages analyzed are Pro-model®, Promodel® Process Simulator, VirtECS® Scheduler, SchedulePro®, and MES Scheduler. A number of other software packages, including Bio-G® were analyzed by Amgen in a separate study. Both projects determined that VirtECS® Scheduler was the best option to pursue given a number of financial and technical selection criteria.

Amgen's analysis of production scheduling software is motivated by a global initiative to make a connective production platform across the Amgen network. Unlike the efforts of this project, Amgen's project took into account the needs across the spectrum of Amgen operations. At the conclusion of the study in Q4 2016, the group within Amgen recommended VirtECS® Scheduler. However this thesis had to make a software decision as of Q3 2016. The knowledge that VirtECS® was one of the finalists in the study, coupled with the fact VirtECS® was easily accessed through Amgen network did influence the selection of VirtECS® as the scheduling software to use.

3.5.1. Software Package Selection Method

The software packages were evaluated based on their computational ability as well as their short term and long term compatibility with BXX's operational goals. Computational ability looked at the software's ability to properly model BXX's processes, which included stochastic delays in schedule, general flow of production, equipment and labor constraints. The short term criteria is based on ease of creating a full test case for BXX as part of this project. Long term goals of BXX for the software included both ease of use, ability to apply the software to its portfolio, and whether it could automatically link to real-time production generated data.

3.5.2. Review of Software

Six different software packages, Promodel® Process Simulator, Promodel®, SchedulePro®, Super Pro Designer®, VirtECS® Scheduler, and a generic MES Scheduler software, were evaluated as part of this project. Published papers and user guides that are readily available online were reviewed. Conversations were initiated with sales representatives for five of the six options, and demonstrations and/or small trials were executed. All packages had drawbacks to modeling purification production at BXX. The MES Scheduler software package was quickly eliminated from consideration because it was not a fully developed application. ProModel® Process Simulator did not demonstrate the ability accurately model BXX's labor resources. ProModel®'s ease of use and ability to adapt to BXX was questionable. SchedulePro® and VirtECS® both did not demonstrate clearly how they could model stochastic delays. Ultimately none of the software packages stood out as being significantly better than VirtECS® which was readily available within the Amgen network and to a lesser degree BXX.

3.5.3. Selection: VirtECS® Scheduler

The two primary candidates that came out of this analysis were VirtECS® Scheduler and SchedulePro®. SchedulePro® offered a number of additional features if SuperPro® Designer was purchased as well. However, it has been demonstrated previously that mass balance / material preparation was a particular challenge to model within the SchedulePro® / SuperPro® Designer suite requiring workarounds [6], something that is an integral part of VirtECS®'s abilities. While both VirtECS® and SchedulePro® appeared to struggle with modeling stochastic delays, VirtECS® offered a slight work-around. A VirtECS® license was also readily available through Amgen's current subscription, making it by far the cheapest option. Based on a number of positives, VirtECS® was selected as the software to create the production schedule model.

3.5.4. VirtECS® Scheduler

VirtECS® Scheduler (Advanced Process Combinatorics® (APC)) has a five year history with Amgen. Over this time, APC has worked with Amgen to develop a customized version of VirtECS® Scheduler to model a variety of production schedules across

the Amgen network. VirtECS® is not new to BXX Purification - a successful pilot study was commissioned in 2014 with APC. At the end of the study BXX decided to not pursue VirtECS®. The project was ultimately shelved, even though the 2014 study yielded an optimized production schedule for a drug substance that BXX Purification was able to consistently follow.

As a part of the initial evaluation, it was unclear how VirtECS® Scheduler could model stochastic events or delays properly in the production schedule. There is a functionality within VirtECS® to randomize inputs based on a known distribution but is limited to uniform, triangle, and normal distributions. The intent of this project was to model stochastic delays as a random draw of delayed or not delayed, a feature currently not available in VirtECS®. A partial workaround is detailed in section 4.3.5.

BXX employees familiar with VirtECS® questioned its ease of use, specifically around the user interface (UI) which in the past provided little feedback when the model was setup incorrectly. However, from the perspective of the author there was little difference between VirtECS® and SchedulePro® in terms of ease of use.

4 Modeling Methods: BXX Purification Production

In order to analyze the challenges facing BXX Purification, a model was created using VirtECS® Scheduler software that consisted of the schedules of two different drug substances. The two drug substances are selected to represent the spectrum of Purification's mAbs product portfolio. A detailed production scheduling model is created in VirtECS® that represents the peak production or worst case scenario for BXX Purification. Tasks within the production schedule that are susceptible to delay are assigned a probability that delay could occur and an average impact of that delay. Both the impact and probability of delay is estimated using historical data from the past two years. A simulation of the delays is created by using a random number generator in Excel®, modeling process times in a binary fashion - average process time or delayed. Samples of the process times are aggregated into multiple trials to be iteratively run in VirtECS® Scheduler. The drawback from this method is primarily that VirtECS® Scheduler will depress the cycle time variability lots because the delays are randomly generated prior to being input into VirtECS®. VirtECS® creates a schedule with full knowledge of what the delayed and non-delayed task times are.

4.1 Selection of Drug Substances to Model

Drug substance AA and drug substance BB (pseudo names to protect proprietary information) were selected as candidates to model and analyze. These two drug substances were picked because they have characteristics that span a number of different monoclonal antibodies that BXX manufacture and were on the 2017 production schedule as of Q3 2016. The major differences between them are summarized in Table 1.

From VirtECS® Scheduler’s standpoint, the largest impact of these differences is in the flow of the manufacturing process.

Property	AA	BB	Impact
Drug type	Monoclonal antibody	Monoclonal antibody	(same)
Flow of process	Discrete	Discrete and Connected	Differences in schedule (see 2.3.2.1 and 0)
Phase of product development	Commercial	Clinical	Cleaning is verified for AA, typically longer clean hold times
Equipment	Stainless steel	Partial single use	Less equipment for BB to clean
Total expected duration of value-added purification steps	65.5 hours	74 hours	BB has slightly longer filtration steps on the whole.

Table 1 - Differences between drug substances AA and BB

4.2 Summary of Data Sources

A variety of sources were used to gather the required data to make a model that represents BXX purification production. As noted previously, the majority of the data collected by BXX is focused on product development and not on operational metrics such as the time it takes to do production tasks or schedule adherence. In some cases, estimates of process times were needed for which there was little or no data. For all data sources, this project analyzed only data that was posted in the past two years, 2015 through 2016.

Historical records were collected from the purification scheduler. The scheduler’s primary concern is recording how long the value-added purification steps are. For both AA and BB, two runs worth of data were available. The averages of these process times were taken for use in the model. Additional records collected included the historical rate at which column packing occurs (a preparation process where special filters are assembled).

BXX Purification Work Force Model is BXX purification management’s current tool for estimating plant capacity. The model provides important information such as the order of preparation, product, and breakdown activities. It also provides the process times for the majority of the preparation and breakdown steps. The process times are estimates provided by line leaders and floor staff of the average time to execute any particular process.

BXX SQDIP Lean Tool is used by BXX management to track the Safety, Quality, Delivery, Inventory, and Productivity of BXX's operations. This was the primary source for the frequency and impact of delays that occur in purification production. This tool is reviewed and updated daily by BXX management. Only delays greater than four hours were tabulated here, and impact (time of delay) was subjectively estimated those attending the meeting that might not always be intimately involved in the issue. In addition, delays' root cause were not always assigned to a specific part of the manufacturing process. This required additional inferences or assumptions to clarify the data.

Shift notes for BXX Purification. Shift notes are created by the production floor after each shift and give a summary of what they did and what is ongoing on the floor. For this project, information was gathered about how often equipment cleaning occurred and the failure rates of the cleaning. Additional information gathered from this source is available but is hard to extract, as they are notes written in a non-standard format.

Master Production Schedule for BXX tracks the drug substance lots that BXX historically produced. This was used to estimate the total number of activities that were executed over the past two years.

MES Generated Data provides a few data points, of which one this project uses. This is the average time it takes to prepare buffer solution, a preparation activity.

Delta V captures data automatically from the manufacturing process on cleaning equipment. Querying this database has given insights into how utilized the various cleaning equipment, clean-in-place (CIP), clean out of place (COP), glassware washer and autoclaves, are on a given week during peak demand.

4.3 Production Schedule Model

VirtECS® Scheduler is the primary tool for modeling purification production. Excel® is only used on a limited basis to randomly generate numbers to create random sets of process times to model delays. These randomized delays are sampled and fed into VirtECS® Scheduler to simulate delays.

4.3.1. VirtECS® Model: Peak Production

The model constructed in VirtECS® Scheduler simulates a month where BXX is at peak production. This is defined as a small ramp-up period of three days where preparation activities can occur before the first lot, followed by four successive drug substance lots. Figure 4 demonstrates both how the model is setup and how BXX would ideally be able to operate production during peak time. Each lot production has Monday through part of Tuesday designated as prep time (blue) for that week's lot where outstanding activities from the last week can also be executed as well as

preparation process steps. Upstream of Purification, Cell Culture (CC) is modeled to consistently deliver a new drug substance every week on Tuesday evening to purification (green lines in Figure 4). This assumes no variability in the handoff time from CC to Purification, which is out of scope for this analysis. In addition, column packing/preparation activities will be ongoing at a rate of one per lot.

Column packing is the preparation of complex filters for the use of chromatography. Data from the past two years indicates that a column packing happens 30-40% of the time in BXX. However, two to three columns are needed per lot. A moderate approximation of this 30-40% column packing rate is one column per lot assuming 3 columns are needed. The model sets due dates for the lots at the end of the week (red lines). This model setup reflects how the weekends contend with and disrupt production flow, given that Purification operates on a 5 days per week 24 hour shift structure.

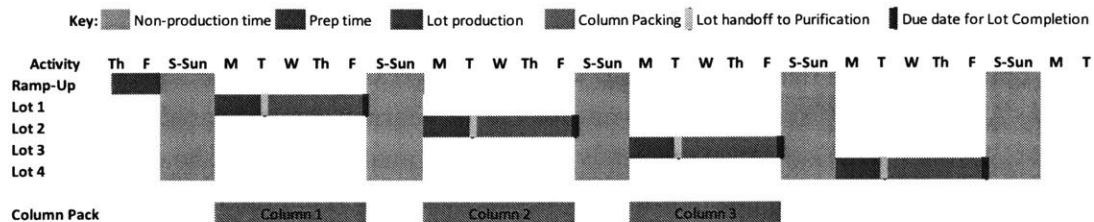


Figure 4 - Illustration of production demand and due dates set for purification lots/columns.

4.3.2. Model Assumptions

In modeling purification production, a number of assumptions were made about BXX's operations. Many of these assumptions came from either the computational limitations of VirtECS®, limited access to data, or project scope challenges. Based on the structure of VirtECS® Scheduler, a few of these assumptions can be readily tested. The major assumptions are listed below, and additional assumptions can be found in Appendix A.

- The normal randomness that occurs when executing any particular process is small when compared to the overall process time of that step. The normal randomness has minimal impact to the overall schedule and can be ignored. Only large delays (one hour or more) have meaningful impact on the schedule.
- Processes can be modeled in a binary “delayed” or “not delayed” fashion based on average impact of similar delays in the past.
- Shifts operate at 100% labor resource available with no lunch break as if in peak production mode.

- Normal operation is to schedule breaks when there are gaps in the production schedule. VirtECS® Scheduler does not have that flexibility.
- All tasks / activities cannot be interrupted and must go to completion once started.
- It takes three days from the time a piece of equipment is cleaned to when it can be released to the floor for use.
 - This assumes a worst case scenario: that the equipment needs bioburden testing, which takes at least three days for results to be made available.
- Except for product activities, no production multitasking is allowed - thus two workers need to be available to execute most tasks.

4.3.3. VirtECS® Optimization

Decision variables, an objective function and constraints that come with constructing an optimization are defined internally within the VirtECS® Scheduler software. Because APC rightfully keeps a significant amount of information associated with VirtECS® Scheduler proprietary, a completely transparent analysis of how the optimization is conducted is not possible. Thus, this section goes over the number of constraints that VirtECS® has observed to adhere to along with other important aspects of how VirtECS® reaches solutions. There are also a number of “soft constraints” that the software provides but were not observed to adhere to in the way that mimics BXX’s operations. This analysis is conducted on a build of VirtECS® Scheduler that has been customized for Amgen.

4.3.3.1. Model Objective Function

The **objective function** of the working version of VirtECS® Scheduler, as defined by the manufacturer, is to “minimize throughput.” Throughput, as defined by the manufacturer, is the aggregate time needed to execute all activities. In terms of Figure 4, this is the entire schedule. This is not the standard use of the term throughput in a manufacturing setting. Typically in operations throughput is defined as a flow rate of material through a process (i.e. one drug substance lot per week). However, in an attempt to stay consistent with the manufacturer and for the purposes of this report, this definition of “throughput” is defined as the **model throughput**. Note that this optimization solves for the fastest way to complete all activities as opposed to optimizing individual lots’ cycle times within the production schedule. Cycle time of lots are defined as the time from when the lot is available (typically Tuesday evening) at Purification to the time it is completed. This objective function is subject to equipment, labor, cleaning, and additional resource constraints.

4.3.3.2. Observed Model Constraints

Constraints in VirtECS® Scheduler that were utilized as part of the optimization model are both observed and published constraints by APC. The primary constraints of importance for this project are listed below:

Equipment can only be occupied by one task at a time. If dirtied, the equipment must be cleaned before additional use. Volume of tanks and equipment groupings are another portion of these constraints.

Sequence of activities within stages are upheld when resources (equipment, product contact) are shared.

Mass-Balance. To keep track of buffer solution recipes and other solutions, VirtECS® imposes mass-balance constraints or physics.

Labor resource. Tasks or activities have a defined number of labor hours needed to execute. The user defines the time and amount of labor resource available at a given time during the week.

Testing hold time. This is a unique user defined constraint created for these models. After equipment is cleaned, it needs to be held until the test results from that cleaning become available.

4.3.3.3. “Soft Constraints” that are not Observed

All so-called “soft constraints” that VirtECS® provides were not observed to act as expected when tested. Thus, these will not be considered as constraints but rather drawbacks in terms of the model’s ability to approximate Purification’s operations.

Due Date - The user can define a “due date” in VirtECS® Scheduler for a lot or a column pack. Due dates as a constraint make little sense and are redundant given the objective function of the software. Soft constraints are ignored for the purpose of this project.

Maximum hold time - Maximum hold time is the amount of time a drug substance can be held between purification steps without having an adverse quality issue occur (degradation of the drug substance from sitting too long between steps). In reality this is a hard constraint that production must meet. In VirtECS®, this constraint was observed to not always be adhered to, and is thus seen as a “soft-constraint.” A work-around that this project takes is to lump multiple activities together so that there is no gap between time dependent steps. Basically, the hold time between steps is effectively zero, and steps must occur right after each other so there is no chance of a maximum hold time being violated. This is a conservative approach where production loses schedule flexibility - all steps that have hold time issues in the model occur in directly after each other, where in reality production has the slack of several hours between steps.

Clean hold - The operation of this constrain as seen by Purification is that if violated, the equipment must be re-cleaned. VirtECS® only publishes a warning when this is violated. The consequence of this is that VirtECS® may schedule cleanings too far in advance of when the equipment is next needed. For general equipment, clean

hold failures are captured in the model by applying a chance that the cleaning itself will fail. In the event that a cleaning fails, the equipment is re-cleaned right away. While this does not properly apply the nature of clean hold constraints, this occupies the equipment, associated labor hours, and cleaning resources. For pieces of equipment that have a high likelihood of a clean hold failure occurring (clean hold times are approximate 1 day), a re-cleaning activity was added to the model with a 75-85% chance of occurrence based on conversations with floor staff.

Dirty hold - Equipment, after it is dirtied, has to be cleaned within a certain dirty hold time. If it waits too long, there is a penalty (extra cleaning and testing). VirtECS® offers a “Dirty hold” option in the software but does not penalize violations or constrict operations to meet the specified dirty hold time. Similar to the clean hold constraint issue above, a chance that cleaning failures occur was applied to all cleaning activities, requiring the equipment be re-cleaned.

In addition, there is no constraint currently for shelf life. Buffer solution on the shop floor has a shelf life of as little as five days. The model can currently schedule a buffer solution too far in advance of what is obtainable in reality. However, in the course of running the model numerous times, only rarely was it observed that a buffer was created too early with respect to its shelf life.

There were also a number of unused constraints such as water for injection (WFI). For WFI it was determined that the plant had excess utility capacity through conversations with BXX maintenance given how Purification is currently running operations.

4.3.4.Shift Structure Modeling

Because labor resource is seen as a primary bottleneck for BXX Purification, this section focuses specifically on the way it is treated in the model and compared to reality. BXX Purification’s shift structure covers Monday through Friday, five days a week, 24 hours each day. There are three shifts. The first two shifts are eight hours, five days a week. The third shift split into two groups that each run ten hours, four days a week - one Monday through Thursday, and the other Tuesday through Friday. For simplicity lunch and breaks will be ignored. Breaks are staggered in an ad-hoc manner to have minimal impact to the flow of production. There is significant overlap between shifts (1-2 hours). However this overlap is spent either filling out paperwork or catching the next shift up on production status. The shift structure of BXX Purification was modeled with 100% labor resource available. While no resource can be fully utilized, this assumption was made with the intention of conducting a sensitivity analysis on the labor to gather trends.

Shift	Start	End	Staffing Level at 100% Capacity				
			Monday	Tuesday	Wednesday	Thursday	Friday
1st Shift	7:15	15:15	12	12	12	12	12
2nd Shift	15:15	22:30	11	11	11	11	11
3rd Shift	22:30	7:15	5	10	10	10	5

Table 2 - Model approximation of Purification’s production shift structure.

4.3.5. Modeling Delays with Iterative Sampling

Based on the data available on delays in Purification, an approximation was made such that individual process steps i each have a random task time T_i that has a probability of being delayed, p_i . Each task time T_i are independent from each other. Process time of tasks can be modeled using a binary delayed or not-delayed variable X . The task time will either have a value of the standard task time t_i or be impacted by a delay and have a time t_i plus an impact due to delay d_i that is unique to that specific task. d_i is assumed to be a constant value or the average impact given a delay of process step i . Each individual process step is considered an independent event and is modeled as a Bernoulli process.

$$P_i (X = 0) = 1 - p_i$$

Equation 1 - Probability of process step i not being delayed

$$P_i (X = 1) = p_i$$

Equation 2 - Probability of process step i being delayed

$$T_i(X) = \begin{cases} t_i, & X = 0 \\ t_i + d_i, & X = 1 \end{cases}$$

Equation 3 - Task time of process step i as a function of X (not delayed/delayed)

The probability of delays occurring, standard times and impact times were estimated by collecting historical data (see Section 4.2) and averaging the values collected across the past two years. The events that are subject to random delays include preparation steps (cleaning failures, buffer preparation failures, column repacking, process specific equipment failures) as well as breakdown activities (re-cleaning due to clean hold expiring). Excel®’s random number generator was used to produce independent events and simulate the delays. The “RAND()” function produces a randomly generated number between 0 and 1. Equation 4 illustrates in general terms the logic used in Excel® to calculate process times.

$$T_i = \text{If}\{\text{Rand} () \leq p_i \text{ then } t_i + d_i, \text{ else } t_i\}$$

Equation 4 - Process time calculation and logic in general syntax for Excel(R)

There are 107 different process steps that are subject to delay or approximately 60 processes for each drug substance. The question then becomes how many times must

these 60 different process times be sampled to create a statistically significant representation of the process? There are two considerations when answering this question: 1) the runtime of the software and 2) what target confidence the sampling will achieve in accurately representing the average aggregate delay impact on the schedule.

Each sample across the 60 process times represents one trial that is submitted to VirtECS® to solve. Thousands of samples cannot be taken simply because it will take the software a significant amount of time to run the same number of trials and the associated post processing of the results.

The aggregate delays themselves are assumed to follow a normal distribution. To test this assumption, 200 samples were taken of the 107 process steps and the distribution of their aggregate process time is shown in Figure 5. From Figure 5, the total labor-hour impact of delays to the production schedule can be seen as normally distributed. Delays are the only source of variation to the production schedule within the VirtECS® Scheduler model.

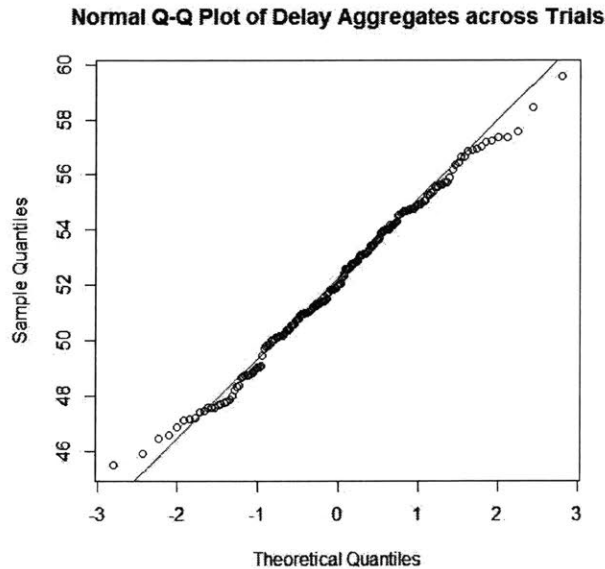


Figure 5 - Distribution of the total weekly impact of delays captured in the model.

Using a 95% confidence and a sample size of 200, the confidence interval can be calculated with Equation 5 [8]. A confidence interval for the distribution of total labor-hours due to delay can be determined assuming no knowledge of the sample mean or variance using a t-test. Variables and their values include: the number of samples, n (200), the sample mean \bar{x} (52.5 hours), the sample variance s is 2.78 hours, and $t_{\alpha/2, n-1}$ was estimated to be 1.96 based on the large number of samples. The confidence interval around the estimated average delay μ impacting the schedule was calculated to be plus or minus 0.38 hours. From this analysis, it can be inferred that delays to the pro-

duction schedule average 25.25 hours (half of the delays are allocated to drug substance AA and half to BB), or 52.5 labor-hours per lot manufactured assuming that two shift workers are required to respond to any particular delay in the schedule.

$$x - \frac{t_{\frac{\alpha}{2}, n-1} s}{\sqrt{n}} \leq \mu \leq x + \frac{t_{\frac{\alpha}{2}, n-1} s}{\sqrt{n}}$$

Equation 5 - Confidence interval for mean of a population, mean and variance unknown.

To model delays occurring in the schedule, 200 independent process times for all activities were randomly generated using the above method. Activity process times were then combined to create 200 unique sets of inputs which were then fed into the model separately. These 200 iterations of the model represent one stochastic model run of VirtECS® Scheduler - the mix of schedules output from this run represent the variety of scheduling outcomes that could occur given delays. The method for how the process times are input into VirtECS® Scheduler to run one trial of the model is shown in Figure 6.

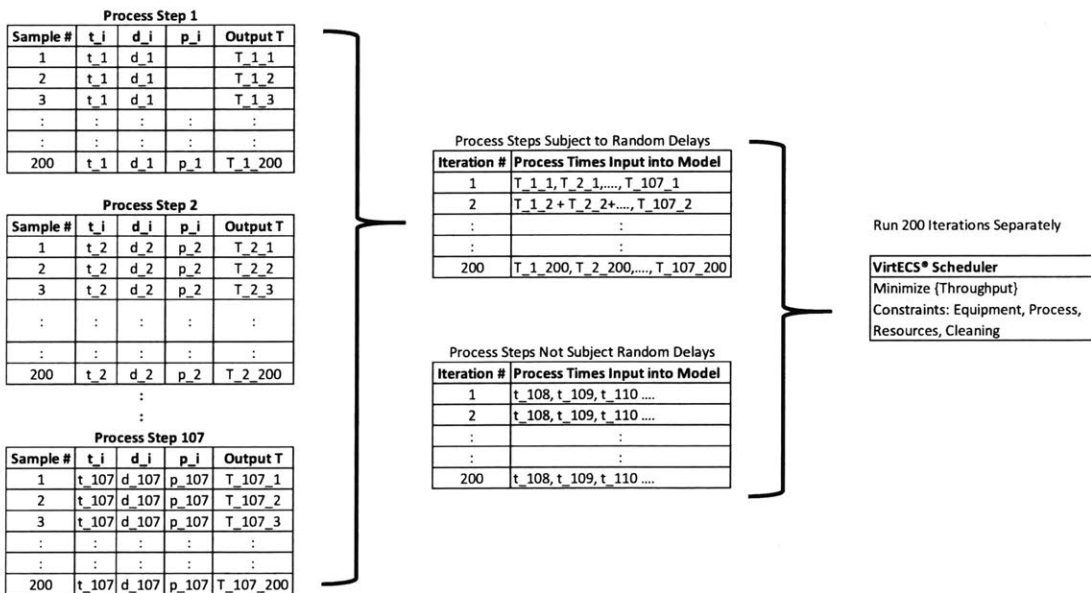


Figure 6 - Method for inputting stochastic process times into VirtECS® for one trial run.

4.3.6. Model Output Interpretation: Cycle Time of Lots

The model output measured for all of the analysis is the cycle time of the lots produced. In the analysis section, trials are run in two different manners: deterministic and stochastic. Stochastic runs are illustrated in section 4.3.5 which require 200 iterations of the model for one run. The deterministic trials run the VirtECS® Scheduler

model only once and without accounting for delays' impact to process times. Deterministic runs simply use the standard process time for all process steps. In effect, these deterministic runs are the fastest Purification can operate.

The output analyzed from either the deterministic or stochastic runs of the model remains the same: the cycle time of lots 1 through 4. The cycle time of each lot is defined as the time after titer is executed (Cell Culture's last step) to the last production process step tied to the specific lot. The cycle time results do not include weekends where labor resource is not scheduled. The standard deviation is also calculated from the different lot times to gather an estimate of variability in the production schedule.

4.4 Model Drawbacks with VirtECS® Scheduler

The model created in VirtECS® Scheduler is an approximation of Purification production during a peak month of production. With any model there are tradeoffs that occur. The main tradeoffs for this project fall under three categories: model constraints, computational, and measured system output. The consequence of these drawbacks is that the model loses scheduling flexibility, underestimates cleaning resource utilization, and underestimates delays' impact to lot cycle time. Additionally, there is a mismatch between the optimization function and the output measured. These disconnects between the model created and reality make it challenging to verify the model's results, especially given the lack of historical data on peak production cycle times. Thus, the model will serve more as a way to analyze trends when decisions are made such as altering the weekly shift structure as opposed to targeted recommendations.

4.4.1. Impact of Model Constraints

A loss of schedule flexibility occurs when trying to fit BXX Purification's processes in VirtECS® Scheduler. This arises from VirtECS® Scheduler not having the Maximum Hold time constraint. In order to avoid impossible production schedules, many scheduled tasks must be combined into one. In the end, this loss of flexibility serves to make VirtECS®'s estimations of weekly cycle time more conservative because the schedule is more likely to be disrupted by the weekend. For example, if a task takes 13 hours to execute and there is only 12 hours left before the weekend, the task gets pushed to after the weekend and the remaining 12 hours of the week are potentially less utilized. Overall, this combination of the inflexibility of the labor resource and artificially long tasks will increase lot cycle time estimates in the model.

Purification constantly struggles with clean hold and dirty hold times. Because these constraints are not enforced means that equipment and cleaning resources will be less occupied in the model as well as the required to clean equipment. Lost complexity means that the model will not reflect actual challenges on the floor, leading to an artificial reduction in variability and potentially cycle time.

4.4.2. Computational Challenges

Despite the intention of modeling delays in VirtECS®, the way in which they are modeled is flawed. Referring back to section 4.3.5, the process task times subject to delay were randomized outside of VirtECS® in Excel®. These task times are bundled together as a set of inputs and sent into VirtECS®. All the VirtECS® software sees is a new set of process times that it needs to develop a schedule for. VirtECS® knows what the process task times are before the software begins computing an optimal production schedule. It then produces a schedule optimized with all the given process times - there are no unpredicted delays as the delays are not stochastic from the perspective of the optimizer. In essence, the only impact “delays” have in the model is to occupy the labor and equipment resources with an additional 52 labor-hours per lot. This has the effect of significantly reducing the cycle time and cycle time variation. If BXX wants to make an investment in VirtECS® Scheduler for the purpose of making more exacting strategic decisions, a new computational method will need to be created within VirtECS® to more accurately model delays.

4.4.3. System Output Mismatch with Objective Function

The objective of this project is to reduce overtime, which is assumed to be linked directly to the reduction in average lot cycle time or variation of lot cycle time. Cycle time of each lot is therefore considered the system output. If a scheduling decision in the model improves cycle time, this seen as meeting the goal of this project in terms of reducing overtime. VirtECS®, on the other hand, is trying to optimize for model throughput (the time it takes to execute all activities to be scheduled) and not individual lot cycle times. This difference means that VirtECS® could hypothetically draw out the cycle time of the third lot a day in order to reduce the model throughput by a couple of hours. In effect, the model is applying an optimization that doesn't match with the system output. Because of this mismatch, a validation is needed to ensure that what the model outputs reflects reality (see section 5.2).

4.5 Granularity of the Model

The model that this project developed schedules all production tasks that take 2 hours or greater which accounts for the majority of all production related activities. By contrast, current scheduling methods at BXX account for only main product or filtration activities (5-6 hour activities and up), while simply listing other preparation and breakdown activities in order of priority. The model stops short of tracking smaller components that get washed in a glassware washer or a cleaned out of place (COP) bath, such as beakers, flasks, tubing and valves. The COP baths and glassware washers are not included in the model, as these cleaning resources were found to have very low utilization (25-40%). The model schedules all production activities that can be linked directly to the use of either equipment, labor, or resources such as cleaning

equipment. Overall, this is significant leap from current scheduling practice which formerly accounts for less than 50% of total manufacturing activities when generating production schedules.

5 Analysis

The model created by combining VirtECS® Scheduler with Excel® is used to analyze lot cycle times of both drug substances AA and BB. As a reminder of the problem this project is addressing, Purification currently is operating at 120% labor utilization and needs to reduce their lot cycle times. To this end, the analysis focuses on trying to gain efficiencies out of current production labor, also termed 100% labor utilization. This is done in four phases. The first phase analyzes the case where no delays occur in the schedule and compare to the case where delays occur. The second phase conducts a sensitivity analysis on two of the assumptions made. In the third phase, new decisions are made to optimize the production schedule. The fourth step is to take the decisions that, separately, are effective and combine them. All results are compared to the current state. The system output that is analyzed in each of these phases is lot cycle time. The goal of these phases is to find decisions that are able to reduce the cycle time and its associate variability.

Hiring in the pharmaceutical industry is not done lightly. In Purification's case, employees who are highly cross-trained are especially valuable, given the high variability of the schedule and numerous tasks. It typically takes new hires take about a year to be cross-trained sufficiently such that they can be utilized with some regularity. Thus, this analysis focuses specifically on ways in which Purification can improve their operations with their given resources.

5.1 Analysis Phase 1: Impact of Delays and Labor Constraints

The objective of this phase is to analyze how delays and the labor constraint impacts Purification's cycle time. To do so the model was run in a number of ways. First, the model was run in a deterministic way where no delays are introduced to the model. These deterministic runs capture how BXX could optimally run if no delays occurred. Then the model was run with delays where 200 iterations of the model were run and the aggregates gathered (stochastic method). For both of these methods, the level of labor resource available was set at 100%, 120%, and infinite utilization. 100% utilization is defined as the current level of labor available to Purification without overtime, 120% is with overtime included, and infinite is where the labor constraint is removed to demonstrate equipment/process bottlenecks.

First, a labor utilization analysis is conducted. Purification's goal is to achieve a five day cycle time, the same as the arrival time for new drug substances - one lot per week in a five day work week. Based on the current shift structure, there is approximately

51.2 labor-days available at BXX on a weekly basis (see Table 3) assuming 100% labor capacity available. In the event that no delays occur, the average amount of labor required to execute either drug substance AA or BB on a lot by lot basis can be aggregated from the model (see Table 3). If Purification were to fit all lots into a weekly schedule, they would have a high labor utilization of 95%-96% (Table 3).

Drug Substance	Weekly Labor Capacity (Labor-days)	Avg. Labor Needed per Lot (Labor-days)	Avg. Labor Utilization for 1 week cycle time
AA	51.2	49.3	96%
BB	51.2	48.9	95%

Table 3 - Analysis of labor capacity when 100% of labor is available for production and no delays occur (deterministic model trials).

Next, the effects of the labor resource constraint on cycle time were considered. The model for both drug substances was run twice, both times without delays. The first run removed the labor resource constraint, in effect providing production with infinite labor resource. This is seen as an “equipment constrained” cycle time where the equipment effectively becomes the bottleneck. The second run of the model is with the labor constraint enacted, such as at 100% of the labor resource is available. Results demonstrate that despite the high actual utilization of labor shown in Table 3, when the deterministic model is run with no labor constraint, the corresponding lot times are very nearly the same as when running at 100% labor availability (see Table 4) except for drug substance AA.

AA Lot Cycle Time (No Delays)			BB Lot Cycle Time (No Delays)		
Lot	5x24 Equipment Constrained Cycle Time (days)	Deterministic Cycle Times (days)	Lot	5x24 Equipment Constrained Cycle Time (days)	Deterministic Cycle Times (days)
Lot 1	4.5	4.5	Lot 1	4.3	4.3
Lot 2	5.4	5.4	Lot 2	4.6	4.6
Lot 3	6.5	7.9	Lot 3	7.3	7.3
Lot 4	7.2	7.6	Lot 4	8.0	8.0
Total	23.6	25.4	Total	24.2	24.3

Table 4 - Two separate deterministic runs of AA and BB models where either the production was equipment constrained (removed labor resource constraint) or at 100% availability of labor.

Delays are then introduced to the model. When the delays are added to the 100% labor resource availability scenario, average lot cycle time increases by 14% to 26% (see Table 5 and Table 6). When factoring in the overtime of 20% that Purification typically sees (120% labor utilization), drug substance AA sees the average lot cycle time

reduce to below the levels of the non-delay deterministic case. With 120% labor availability and delays, drug substance BB still sees a slight increase of 4.1% on average of cycle times over the non-delay 100% labor utilization case.

Drug Substance AA - Stochastic

Lot	100% Labor Utilization		120% Labor Utilization	
	Avg Cycle Time (days)	Standard Deviation	Avg Cycle Time (days)	Standard Deviation
Lot 1	4.7	0.5	4.6	0.3
Lot 2	6.2	0.8	5.6	0.5
Lot 3	9.5	1.2	6.6	0.3
Lot 4	9.5	1.7	7.3	0.2
Total	29.8	4.2	24.1	1.4

Table 5 - Drug substance AA's cycle time and standard deviation with stochastic delays. Labor is at 100% and 120% utilization.

Drug Substance BB - Stochastic

Lot	100% Labor Utilization		120% Labor Utilization	
	Avg Cycle Time (days)	Standard Deviation	Avg Cycle Time (days)	Standard Deviation
Lot 1	4.6	0.7	4.4	0.3
Lot 2	5.7	1.5	5.0	0.8
Lot 3	8.3	1.3	7.5	0.4
Lot 4	9.1	1.5	8.4	0.3
Total	27.7	5.0	25.3	1.8

Table 6 - Drug substance BB's cycle time and standard deviation with stochastic delays. Labor is at 100% and 120% utilization.

5.2 Model Validation

Like other models and modeling software, VirtECS® does not have all the capabilities to perfectly model Purification's processes. A number of constraints are not available in VirtECS® Scheduler which BXX observes (section 4.3.3.3) and the objective function is not ideally matched up with the system output (section 4.4.3). This requires some modeling approximation and workarounds whose effects are challenging to isolate in a complicated system. A validation was needed to examine how well the VirtECS® model represents real-world purification production.

Results from section 5.1 were used to provide a partial validation of the model. It is noted that the model predicts the first lot of drug substance AA to be 4.7 days on average with a standard deviation of 0.5 days with Purification running at 100% labor available. Taking the standard deviation as a tight confidence interval, the actual cycle

time data of 4.2 days for a produced lot of AA falls within the confidence interval. For drug substance BB, actual cycle time data of 4.91 days and 5 days fall inside the confidence interval the model's predicted cycle time of 4.6 days plus or minus 0.7 days. This is currently all the data available to validate the model. Thus, any results or solutions from VirtECS® Scheduler can only provide general strategic analysis of Purification's shift structure and operations as opposed to day-to-day operational and specific procedural improvements.

5.3 Analysis Phase 2: Sensitivity of Assumptions

As previously mentioned, the scenario where 100% labor resource is available and delays are included will be the primary point of analysis for determining how to improve Purification's lot cycle time. To this end, a sensitivity analysis is conducted on a few model assumptions: amount of downtime before the first lot, labor available on a shift by shift basis, and the clean hold time. A summary of the sensitivity analysis conducted is highlighted in Table 7. In all, 13 new trials were run. Downtime, or the number of shifts before the week of the first lot, has a nominal value of five shifts and was varied +/- one and two shifts. The number of shift workers for each shift were varied by +/- one worker. The clean hold time, nominally at three days, was reduced to two days.

Sensitivity Analysis	Nominal Value	Values Tested	
Downtime			
		<i>Units: Shifts</i>	
Downtime Before 1st Lot	5	+/- 1	+/- 2
Labor			
		<i>Units: Shift Worker</i>	
Shift 1 Labor	12	+/- 1	
Shift 2 Labor	11	+/- 1	
Shift 3 Labor Tues. thru Thurs.	10	+/- 1	
Shift 3 Labor Mon. and Friday	5	+/- 1	
Hold Times			
		<i>Units: Days</i>	
Clean Hold Time	3	2	

Table 7 - Summary of sensitivity analysis conducted for both AA and BB drug substances.

Results for the sensitivity analyzes are broken down by drug substance and are shown on, Table 8, Table 9, and Table 10. These illustrate the percent change in both lot cycle time and standard deviation of the cycle time for a given week as compared to the baseline case, 100% labor utilization with delays, that was shown earlier in Table 5 and Table 6. These results illustrate that adding a production worker to third

shift's Monday / Friday time slot has the most positive impact from a cycle time perspective for both AA and BB. Adding a shift worker to only Monday and Friday of 3rd shift is basically adding a half an employee or 20 labor-hours to cover those two days, whereas adding a worker to 2nd shift would be adding a full employee for the five days.

Labor Sensitivity - Drug Substance AA

Shift Tested	Cycle Time									
	Average		Lot 1		Lot 2		Lot 3		Lot 4	
	-1	+1	-1	+1	-1	+1	-1	+1	-1	+1
Shift 1	14%	-3%	3%	0%	10%	0%	15%	-4%	22%	-5%
Shift 2	8%	-9%	5%	-1%	8%	-6%	7%	-11%	9%	-12%
Shift 3 T-Th	11%	-4%	7%	0%	12%	-2%	9%	-5%	13%	-6%
Shift 3 M & F	2%	-8%	0%	-2%	1%	-7%	2%	-8%	3%	-11%

Shift Tested	Standard Deviation									
	-1	+1	-1	+1	-1	+1	-1	+1	-1	+1
Shift 1	0%	-1%	41%	0%	9%	1%	-30%	-7%	3%	2%
Shift 2	10%	-2%	49%	-17%	29%	-14%	1%	-6%	-5%	11%
Shift 3 T-Th	9%	1%	60%	-3%	25%	0%	-3%	-5%	-5%	7%
Shift 3 M & F	3%	-7%	4%	-39%	-3%	10%	5%	-19%	4%	4%

Table 8 - Results from labor sensitivity analysis for drug substance AA. Values are in percent change from baseline case.

Labor Sensitivity - Drug Substance BB

Shift Tested	Cycle Time									
	Average		Lot 1		Lot 2		Lot 3		Lot 4	
	-1	+1	-1	+1	-1	+1	-1	+1	-1	+1
Shift 1	16%	-1%	1%	0%	9%	0%	23%	-2%	22%	-2%
Shift 2	4%	-5%	0%	-1%	3%	-4%	6%	-6%	6%	-6%
Shift 3 T-Th	25%	-2%	25%	0%	33%	-1%	23%	-2%	22%	-3%
Shift 3 M & F	3%	-7%	0%	-4%	5%	-9%	3%	-7%	2%	-6%

Shift Tested	Standard Deviation									
	-1	+1	-1	+1	-1	+1	-1	+1	-1	+1
Shift 1	12%	4%	5%	0%	11%	-3%	5%	-12%	24%	26%
Shift 2	18%	-20%	0%	-16%	3%	-19%	15%	-41%	46%	-5%
Shift 3 T-Th	0%	4%	-11%	-3%	-26%	-1%	3%	-9%	28%	21%
Shift 3 M & F	22%	-29%	6%	-61%	23%	-39%	6%	-46%	41%	9%

Table 9 - Results from labor sensitivity analysis for drug substance BB. Values are in percent change from baseline case.

The results from the ramp-up sensitivity analysis can be seen in Table 10. “-2” for example means that the model had 2 less shifts of downtime to prepare for production. All values are in percent change from the average cycle time and average standard deviation of all lots from the baseline case. Drug substance AA ramp-up has a mixed effect on cycle time which is unexpected given that more downtime for production

should give them more time to be ready. For drug substance BB, cycle time improves with more shifts added for downtime on an uneven basis, but the standard deviation trends in the opposite direction.

Ramp-Up Time Sensitivity

Cycle Time

Drug Substance	Number of Additional Ramp-up Shifts			
	-2	-1	+1	+2
AA	-2%	3%	9%	2%
BB	8%	12%	0%	-6%

Standard Deviation

AA	-6%	2%	3%	1%
BB	-9%	-14%	8%	11%

Table 10 - Results from Ramp-up sensitivity analysis in terms of percent change from baseline case.

The final sensitivity analysis with regards to testing hold time was conducted by reducing the testing hold time constraint from 3 days to 2 days. For drug substance BB, this yielded insignificant change to cycle time but reduced variability (standard deviation) by 20%. For AA, this yielded a 3.4% reduction in average lot cycle time reduction but a 13% rise in the average lot cycle time standard deviation. Thus, there are mixed results for this particular variable as well.

5.4 Analysis Phase 3: Testing Shift Schedule Decisions

Three shift scheduling decisions are made for the model to test. Based on the results from the sensitivity analysis in 5.2, it is clear that adding workers to third shift would have the most benefit across both drug substances. There are two decisions tested with this regard as well as an addition decision made about where first shift starts in the week.

The first shift schedule decision is to move a worker from third shift Monday - Thursday (recall that third shift is comprised of two shifts, four days a week, 10 hours a day) to the other third shift from Tuesday through Friday. This was done because third shift is the most insensitive to a reduction in one worker (2-3% increase in average lot cycle time) and had more to gain from adding a worker (7% decrease in average lot cycle time).

The second shift decision tested is to move one worker from second shift to third shift Tuesday through Friday. While the average cycle time would be increased by 8%

for AA and 4% for BB due losing a second shift worker, these loses could be hypothetically balanced out by gaining roughly 7-8% in average cycle time. This would also decrease the standard deviation metric based on results from the sensitivity analysis.

The third decision tested is to move first shift from a Monday through Friday to Tuesday through Saturday. As mentioned in Chapter 4, Purification starts work on Monday and ends work Friday on a weekly basis when no overtime is required. There is a period from Monday until Tuesday afternoon designated as preparation time before Cell Culture releases the lot to Purification. This decision, in effect, tests the preparation Results from the model running the three decisions is shown in Table 11.

Decision	Drug Substance	Average Lot Cycle Time	Average Standard Deviation of Cycle Time
Move 3rd Shift Worker from M-Th to T-F	AA	-3.4%	-10%
	BB	-3.1%	-19%
Move 2nd Shift Worker to 3rd Shift T-F	AA	-1.9%	7%
	BB	-3.5%	-22%
Move whole 1st Shift to Tuesday-Saturday	AA	-1.9%	14%
	BB	-0.4%	-17%

Table 11 - Results from testing scheduling decisions, comparing averages to the baseline case.

5.5 Analysis Phase 4: Combining Shift Decisions

Given the results from Section 5.4, a number of decisions were made in concert. For drug substance AA, the third shift worker was moved from the Monday-Thursday to the Tuesday-Friday shift and the second shift worker was moved to the third shift on Thursday-Friday. Taking only these two decisions for AA were done to maximize improvement in lot cycle time, while trying to balance the variation. BB combined all three decisions, as all had positive effects on cycle time and variation. The results are shown of these two different tests are shown in Table 12.

Drug Substance	Average Lot Cycle Time Change	Average Lot Cycle Time Standard Deviation Change
AA	-5.6%	7.6%
BB	-3.0%	-11.7%

Table 12 - Model results from combining optimal shift decisions.

Drug substance AA's average cycle time clearly benefits from the decision to add two workers to the third shift that operates Tuesday through Friday. BB, while an improvement overall from the baseline case, does not find a better cycle time when using both shift decisions in concert than either of them individually. These particular shift structures only explore one solution in a multi-dimensional solution space. Further

sensitivity would be required to gather information about the solution space contours around this solution.

6 Conclusions and Recommendations

The work done here highlights five important points. 1) labor contributes to the bottleneck of production at BXX, especially when considering the nature of delays, 2) VirtECS® Scheduler has a ways to go to computationally model Purification's stochastic delays and other constraints, 3) a number of simple shift structure decisions appear to reduce both lot cycle time and variability of the cycle time, 4) additional data collection is required to further validate the model and statistical significance of these results and 5) additional modeling is necessary to properly capture the dynamics of purification production.

The weekend is a major disruption to BXX's operations. Only having the Tuesday evening through Friday to execute a highly variable process whereby the standard deviation of the lot cycle time is on the order of 1 day is challenging. The major difference between drug substance AA and BB that is reflected in how they are modeled is the way the drug substances are processed. AA is a discrete batch process and BB has an element of connected processing. This difference leads BB having a set of activities (the connected process) that are both longer than any step in AA and like all activities, cannot be interrupted when started.

BXX's processes are bottlenecked by labor which is estimated to be 95% utilized on a weekly basis in terms of production activities alone (Table 3). The disruption of delays are a significant contributing factor to cycle time increase. There are two ways in which some of these effects could be reduced, one by placing more production workers on third shift and another by moving the start of production later in the week, which could reduce cycle time by 3-5%, while also reducing average cycle time variability. While this is a promising result in terms of the overall goal of reducing overtime, questions of model validation and accuracy still need to be answered.

Additional validation of the model needs to be completed before results and trends from VirtECS® Scheduler can be acted upon. Schedule creep is a trend observed in the model; the cycle time of each subsequent lot increases in magnitude and variability (see Table 4, Table 5, and Table 6). However, the only validation data currently available applies to the first lot. Additional data would need be collected to validate these trends and magnitudes. There is a risk that the model, past the first lot does not properly reflect production scheduling challenges. The software itself has a number of deficiencies that should also be addressed in the future to properly model BXX processes.

VirtECS® Scheduler lacks the appropriate objective function and constraints to capture how Purification operates. A number of manual workarounds are utilized within

this project to mitigate their impact. However, the impact of these challenges is unknown. In the absence of significant data sets to validate a model with possible deficiencies, the model itself should closely follow the physics of the process. Amgen should therefore work with APC, the manufacturer of VirtECS® to enhance the software so it more accurately models BXX Purification. Of primary concern should be altering the objective of the optimization. One way this could be done is to remove the objective to improve “model throughput” and instead minimize the sum of the cycle times of all lots scheduled. In addition, clean hold, dirty hold and maximum hold constraints should be enforced. Finally, schedule delays should be treated as stochastic in VirtECS® as opposed to requiring the use of Excel®.

To better model delays, VirtECS® could offer post optimization processing options that apply random delays. The recommendation is for the software to operate in two stages: initial deterministic schedule creation followed by application of stochastic delays to the resulting schedule. A deterministic schedule would be created by applying constraints, resources, and scheduling rules. After a deterministic schedule is output, the software would step through each activity from start to finish, much like when going through a movie frame by frame. As the software steps to the end of an activity that has a chance of delay, the software would randomly determine if that activity will be delayed (based on a user defined chance of delay or distribution). In the event of a delay, the production schedule from that point forward would be adjusted to take into account that delay.

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Appendix A - Model Assumptions for VirtECS®

The below list is a number of assumptions that were used in constructing the model in VirtECS® Scheduler.

- The normal randomness that occurs when executing any particular process has an insignificant overall impact to the schedule.
- Delays, if they occur, at any particular process are on average the same duration for that particular process.
- Production shifts do not overlap in terms of labor resource available on the floor - the production is seamlessly handed off with no learning curve.
- Shifts operate at 100% labor resource available with no lunch breaks and are perfectly cross-trained.
- All tasks / activities cannot be interrupted and must go to completion once started.
- There is only a minor benefit in campaigning lots versus product changeover in terms of labor resources.
- There is no processing time benefit/reduction to adding additional workers to activities.
- Product steps (purification activities such as chromatography, filtration, etc.), the preparation step immediately preceding the product step, and the breakdown step immediately following the product step are not delayed.
- It takes three days from the time a piece of equipment is cleaned to when it can be released to the floor for use, which is a worst case scenario.
- Cleaning does not fail testing, based on data that less than 1% of cleaning validation tests failed in a similarly run facility.
- Demand for transfer lines, which transport buffer solution and product to different stages, will not be overcapacity.
- Except for product activities, minimal multitasking is allowed.
- Activities take on average two employees to execute, aside from equipment breakdown activities.
- Utilities such as water for injection (WFI) are not capacity constrained.
- The clean out of place (COP) and glassware washers and autoclaves that wash or clean small parts are underutilized to the point where they need not be modeled as a resource. This is based on data which demonstrates these washers are 25%-40% utilized on average.