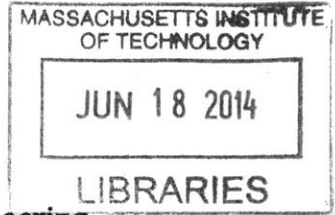


A Practical Application of Simulation for Production Planning in a Flexible Pharmaceutical Manufacturing Environment

ARCHIVES



by

Christopher J. Wilson
B.S. Engineering, Trinity College, 2007

Submitted to the MIT Sloan School of Management and the Mechanical Engineering Department in Partial Fulfillment of the Requirements for the Degrees of

**Master of Business Administration and
Master of Science in Mechanical Engineering**

In conjunction with the Leaders for Global Operations Program at the Massachusetts Institute of Technology

June 2014

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Abstract

In pursuit of Novartis Pharmaceutical's vision to "Make Quality Medicine-On Time, Every Time" Novartis Ringaskiddy Limited (NRL), is pursuing Class A Manufacturing (MRP II) certification. Achieving Class A certification requires production plans be established and met with great accuracy. The Multi Synthesis Production Unit (MSPU) at NRL sets rolling eighteen month production commitments on a semi-annual basis. During planning a rudimentary tool is used to allocate production campaigns for over 40 different Active Pharmaceutical Ingredients (API) and intermediate products across roughly 200 pieces of equipment. This manual tool is time intensive to operate, prone to errors, and requires extensive knowledge of the facility. To address this problem, a simulation based model was developed using the software package, SchedulePro™. The aim of this project was to create a system to support more effective and reliable production planning. The approach requires accuracy in modeling, a process to deploy the tool and a connection to people who use and benefit from the process.

In order to evaluate the proposed model and understand potential benefits to Novartis, five case studies are used to compare the proposed planning process with traditional methods. First, when planning a future production year the proposed planning process demonstrates a reduction in required time as well as an increase in accuracy. Second, when evaluating the response to a change in demand a user with little knowledge of the plant can attain comparable response time as an experienced user of traditional methods. Third, when faced with an unplanned equipment failure the user is able to explore alternative production plans which minimize disturbance to the established production plan. Fourth, through the evaluation of alternative resource allocation plans the user can determine the lowest cost approach. Finally, when applied to a product launch evaluation the model is shown to reduce the number of planning cycles, focusing specifically on the ability of the site to support a product launch in a previously allocated year.

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Glossary

API – Active Pharmaceutical Ingredient

NRL-Novartis Ringaskiddy Limited

MSPU – Multi Synthesis Production Unit

ChemOps – The division of Novartis Pharma responsible for API production through chemical synthesis

QUOTIF – Quantity on time and in full

SCP – SchedulePro™ software from Intelligen

IP – Ingress Protection rating used to specify environmental protection of electrical enclosure or electrical equipment

PU- Production unit

1 Introduction

1.1 Context and Thesis Summary

1.1.1 Multi Synthesis Production Unit

The Multi Synthesis Production Unit (MSPU) within Novartis Ringaskiddy Limited (NRL) houses over 200 pieces of equipment which can be configured in a variety of ways to produce a range of APIs and intermediates. Beyond the physical limitations of the equipment in the plant, production capacity is constrained by staffing, cleaning, changeovers, preventative maintenance routines, raw material supply, and Quality Control testing. Eighteen month production commitments are typically made during a semi-annual planning meeting. Ensuring the feasibility of this capacity commitment requires equipment to be allocated to production campaigns, in an accurate manner. The current methodology uses a time intensive, manual approach, which is prone to errors and difficult to revise. Further, the process relies heavily on the planning team's prior knowledge and experience to ensure technical feasibility.

1.1.2 Summary of Work

To address this scheduling problem, a simulation based model was developed using the software package, SchedulePro™. The aim of this project was to create a system to support more effective and reliable production planning. The approach requires accuracy in modeling, a process to deploy the tool and a connection to people who use and benefit from the process.

The first goal of accuracy is accomplished by creating a master data set representing both: production resources, such as labor and equipment, and production requirements, such as product recipes. The representation of the production environment allows for proper resource accounting and allocation during subsequent planning.

Second, the process begins with product demand, and generates a rough cut plan. The use of defined recipes, ensures accurate resource allocation and allows the user to explore a variety of production scenarios while maintaining a complete picture of production requirements.

The third goal is that the system look at the human requirements for successful implementation. This is achieved through the modification and use of a well-established change management framework which considers a new technology, the people who use the technology and the process by which the technology is used.

In order to evaluate the proposed model and understand potential benefits to Novartis, five case studies are used to compare the proposed planning process with traditional methods. First, when planning a future production year the proposed planning process demonstrates a reduction in required time as well as an increase in accuracy. Second, when evaluating the response to a change in demand, a user with little knowledge of the plant can attain comparable response time as an experienced user of traditional methods. Third, when faced with an unplanned equipment failure the user is able to explore alternative production plans which minimize disturbance to the established production plan. Fourth, through the evaluation of alternative resource allocation plans the user can determine the lowest cost approach. Finally, when applied to a product launch evaluation the model is shown to reduce the number of planning cycles, focusing specifically on the ability of the site to support a product launch in a previously allocated year.

Based on the results of this proof of concept, the site plans to integrate this work into future production planning and looks to explore potential synergistic opportunities at other multi product facilities.

1.2 The Multi Production Planning Problem

1.2.1 The Need for Flexibility

Traditionally the pharmaceutical industry has focused heavily on research and development as a source of future profits. However, as fewer marketable drugs are being discovered, industry trends have shifted placing greater value on maximizing competitiveness of existing product lines. With this has come increased focus on the optimization of existing production processes[1].

To compete in this new market Pharmaceutical companies are finding it necessary to shift to a more nimble model. Traditional API manufacturing of large batch sizes on

dedicated equipment is transitioning to generic and contract manufacturing, and much of the focus of the larger companies is shifting to higher value products. The production of specialized drugs with smaller markets and higher potency products, favors smaller production runs. Uncertainty with regard to demand forecasts and a focus on reducing inventories also favors shorter production runs. Achieving this goal of smaller batch sizes and shorter production runs requires a manufacturing system that can operate in a variety of configurations. The combination of a desire to achieve high utilization and maintain flexibility introduces significant complexity and uncertainty into the planning process.

1.3 Project Purpose

1.3.1 Objectives

The primary goal of this project was to provide NRL with a robust and repeatable methodology for equipment scheduling and production planning in the MSPU. Further the project sought to increase efficiency and transparency, and enable reliable planning in support of the broader Novartis Pharma goal of achieving Class A MRP II status by January of 2015.

1.3.2 Scope

The scope of this project was to produce a methodology/process to provide the planning team with the capability to perform production equipment allocation, while considering technical feasibility, human resource requirements, preventative maintenance constraints and changeover requirements in a manner that is consistent and repeatable. While aiming to provide a clear picture of the production environment the models developed do not: 1) focus on the planning of QC testing, 2) focus on the management of raw materials, 3) develop a detailed changeover plan, or 4) generate a preventative maintenance plan, as these are all currently performed in the ERP system.

1.4 The Hypothesis

The hypothesis of this work is that production planning for a flexible manufacturing environment can be improved through the use of simulation tools and that the practical

application of this improvement can be made possible by considering the planning environment as a system consisting of the planning tool, a process to use the tool and the people who execute the process

1.5 Research Methodology

This work was executed in three main phases, 1) data collection/current state analysis, 2) pilot and 3) scale up.

Current state:

To improve the planning process it was deemed critical to first understand the current state of the production planning environment. This analysis began with an assessment of the existing production planning process as well as a review of the data captured during that process. The current state analysis was also used to define user and business requirements for the production plan as well as targets in terms of process improvement.

Pilot:

The pilot phase focused on determining the best methodology for modeling the production environment and used 3 product lines to validate the modeling approach. It also served to determine if the proposed tool could meet the established needs of the planning team.

Scale up and implementation:

Once the methods and assumptions were deemed suitable the model was expanded to capture the complete production environment. Along with scaling of the model came a focus on implementation. Through evaluating the requirements to transition to the proposed planning process and the current capabilities for planning in the PU risks were identified and mitigation strategies established.

2 Literature Review

2.1 Production Planning/Optimization Approaches

In the context of planning manufacturing activities, planning and scheduling deal with the utilization of resources and timespan of manufacturing operation.[2] The plans created during the planning phase are prone to change and modification during the execution phase due to system variance and uncertainty[2] [3]. The inevitable changes to a production plan do not diminish the need for a plan but rather indicate the importance of a responsive and robust planning process that can accurately react to fluctuations in demand[3]. Planning is critical as it ensures that production capacity is aligned with the organization's needs[4].

Traditional methods of production planning such as MRP and MRP II rely heavily on accurate forecasts and are prone to difficulty when presented with uncertainties or frequent changes[5]. To address this problem of randomness in the MRP system, optimization, simulation and other forms of math modeling have been extensively studied. [6][7][8][9]. For example Grasso and Taylor show how a GRASP-VI simulator can be used to explore the impact of uncertainty on the MRP system[10]. Lee et al use a custom developed simulation to examine the impact of demand forecast error on the MRP system [6]. Wemmerlov again uses simulation to look further at demand uncertainty[11].To overcome the challenges of deterministic models Factor Physics Inc. developed dynamic risk based scheduling as presented by Sun et al [5]. The complementary nature of simulation as tool to support the MRP system and aide the production planner in modeling uncertainty is well understood.

Methods for simulation of the production environment vary and include custom built solutions as well as prebuilt software packages. A spread-sheet model developed by Taj et al [12] presents a straight forward method of modeling and planning production in a multi-product single line environment. While Lee and Kim propose a technique to address the complexities inherent to large manufacturing systems such as those used in semiconductor manufacturing[13], Taj et al note that a simple SW package would be preferred for a practical application [12].

Commercially available simulation and scheduling tools and their use in pharmaceutical manufacturing are described at length by Petrides and Carmichael [14], who in particular highlight the capabilities of finite capacity scheduling tools for the planning API manufacturing.

3 Data Collection and Analysis

3.1 Current State Analysis

3.1.1 Planning process

An understanding of the current state of the production planning process was developed from a series of interviews and observations. Interviews took place with production coordinators, process managers, production planners, QC planners, logistics managers, change-over coordinators, and process engineers. Observations were collected during a variety of production planning meetings, including the daily production meeting, weekly and monthly planning meetings as well as the multi day annual planning session.

An overview of the current state of production planning in NRL's MSPU is shown below in Figure 1 - Current State Planning Process Flow. The supply chain group contains product specialists who manage demand and inventory forecasts for all of the chemically synthesized products. Supply chain provides these to each of the manufacturing sites and production units one of which is the MSPU at NRL. The planning team responsible for performing the equipment allocation uses a combination of prior knowledge and Microsoft Excel to assign product campaigns to equipment and create a production plan which meets demand.

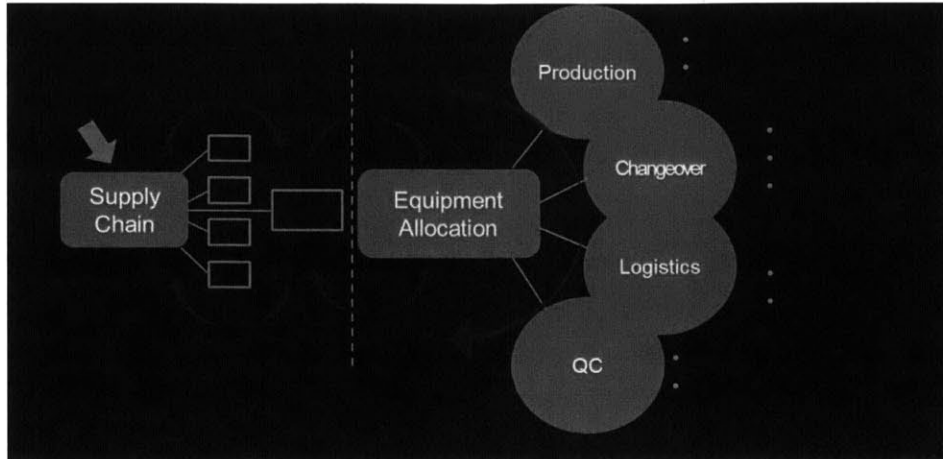


Figure 1 - Current State Planning Process Flow

3.1.2 Example of planning for a single product

To provide further understanding of the planning process a fictitious product called D41 demonstrates the type of production requirements and decisions a planner might face.

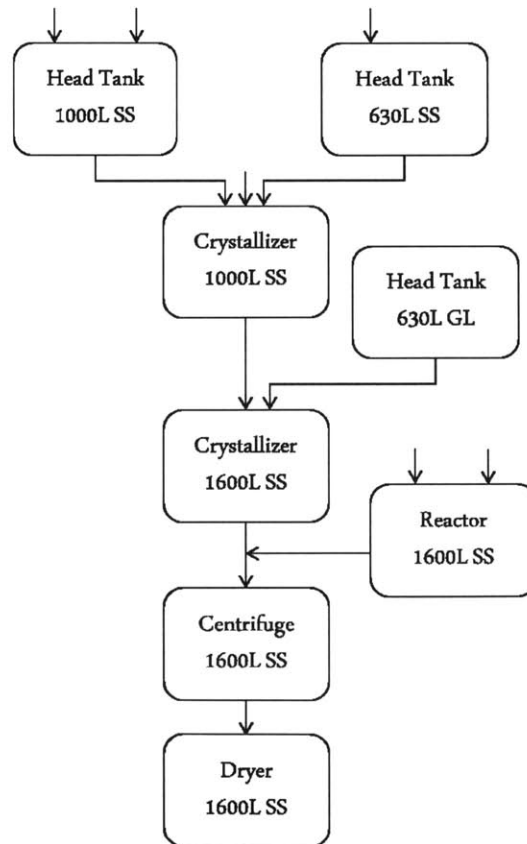


Figure 2 - Sample Recipe (product D41) with Equipment Requirement

Further detail of this representative sample and the how the planning process is applied can be found in Appendix 1. This sample recipe is used to demonstrate how the planning is executed in Excel. If a planner were to plan a 4 week campaign of sample product D41 he/she must first allocate the necessary equipment. The sample plant shown in Table 1 contains 19 pieces of equipment 6 head tanks, 4 reactors, 5 crystallisers, 2 centrifuges and 2 dryers. Based on the requirements highlighted in Figure 2 above, the planner must determine which pieces of equipment to allocate to the production of D41.

Table 1 - Equipment list of Sample Production Plant

Head Tanks	Size	MOC	Crystalliser	Size	MOC
1	630	SS	1	1000	SS
2	630	SS	2	1000	GL
3	630	GL	3	1600	SS
4	1000	SS	4	1600	SS
5	1000	SS	5	1600	GL
6	1000	GL	Centrifuge		
Reactor			1	1000	SS
1	1000	SS	2	1000	SS
2	1000	GL	Dryer		
3	1600	SS	1	1600	SS
4	1600	SS	2	1600	SS

A network map is shown in Figure 3, describes the options presented to the planner. Equipment items are represented by nodes and the path between nodes indicates possible configurations for producing product D.

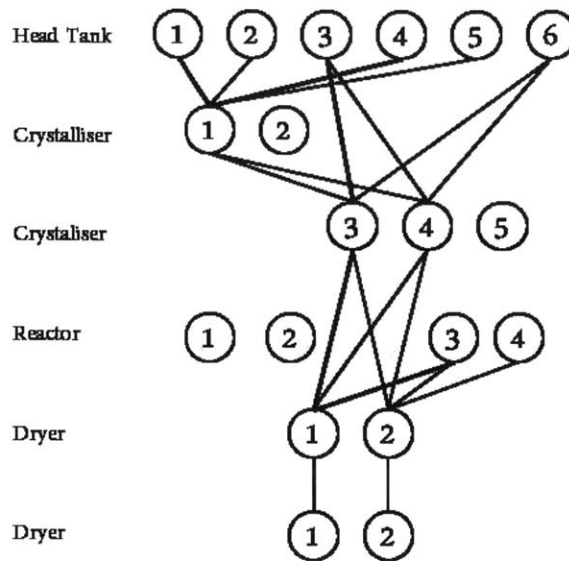


Figure 3 - Product D Configuration Options

For a planner in the MSPU to allocate production of this sample product to the equipment he/she must consider the production requirements and select the appropriate equipment. For the representative case of D41 the planner must allocate production to 8 pieces of equipment and is constrained by size and material of construction. The planner in a real facility faces many more constraints such as proximity of equipment (feasibility of transfers between items) IP ratings, containment capabilities and more. Historically much of this information has existed in the planner's head.

Once the equipment is allocated the planner must determine the length of the campaign, labor requirements, and establish a changeover window. The fully constructed plan representative of the production of a single campaign of D41 is shown in Table 14 in Appendix 1.

For planning in the MSPU the process previously described for a single product must be replicated for up to 40 products/process steps. Further, as market needs change and product demands shift, the planner must address requests for alternative production scenarios. The submission of a change request to evaluate a different production scenario in terms of product mix or quantity of a product means the process must be repeated and all the appropriate parties consulted to evaluate constraints.

As the production plan changes from one year to the next very little information as to how the plan was created is captured. Thus, when a new planner takes on the planning role he/she faces a steep learning curve and has little information as to how previous plans were formulated.

3.1.3 Challenges presented by current process

The challenges presented by this highly iterative Excel based planning method and evidence supporting these challenges are discussed in the following section.

Manual and time intensive

The Excel method requires that the user maintain an equipment allocation sheet, a labor plan, a batch count sheet and a change-over planning sheet. Each of these worksheets functions independently of the others so that any changes to the plan on one sheet require manual updates to the other sheets. Previous attempts have been made to link these sheets, however maintaining the linked workbooks has proven difficult as different stakeholders tend to focus on only one worksheet and eventually break the links.

Given the multiplicity of stakeholders and number iterations a typical plan runs through there are many opportunities for error to be introduced into the plan, for example:

- Campaign length varies from one sheet to the next
- The number of batches per week is inconsistent (discussed more under throughput)
- Equipment items dropped from a campaign
- Assumptions behind a decision are lost
- Lack of clarity around when and where a changeover takes place

Further, this process requires the planner to have significant knowledge of the facility and process requirements. When an employee who had previously worked outside of the production unit stepped into the planning function he lacked the in-depth knowledge to appropriately plan production. Ultimately this led to the commitment of a second resource with a long history in the production unit to support the equipment allocation and changeover planning function.

3.1.4 Comparison of plan and actual production

To further understand the current planning process the throughput of actual production batches was compared to planned production. For any instance where a batch was not produced on the expected date a reason for the variance was collected. This information is presented in Figure 4. The leading cause for misalignment between actual production and planned production was faster throughput than planned; this is followed by delays due to equipment issues and then slower throughput than planned.

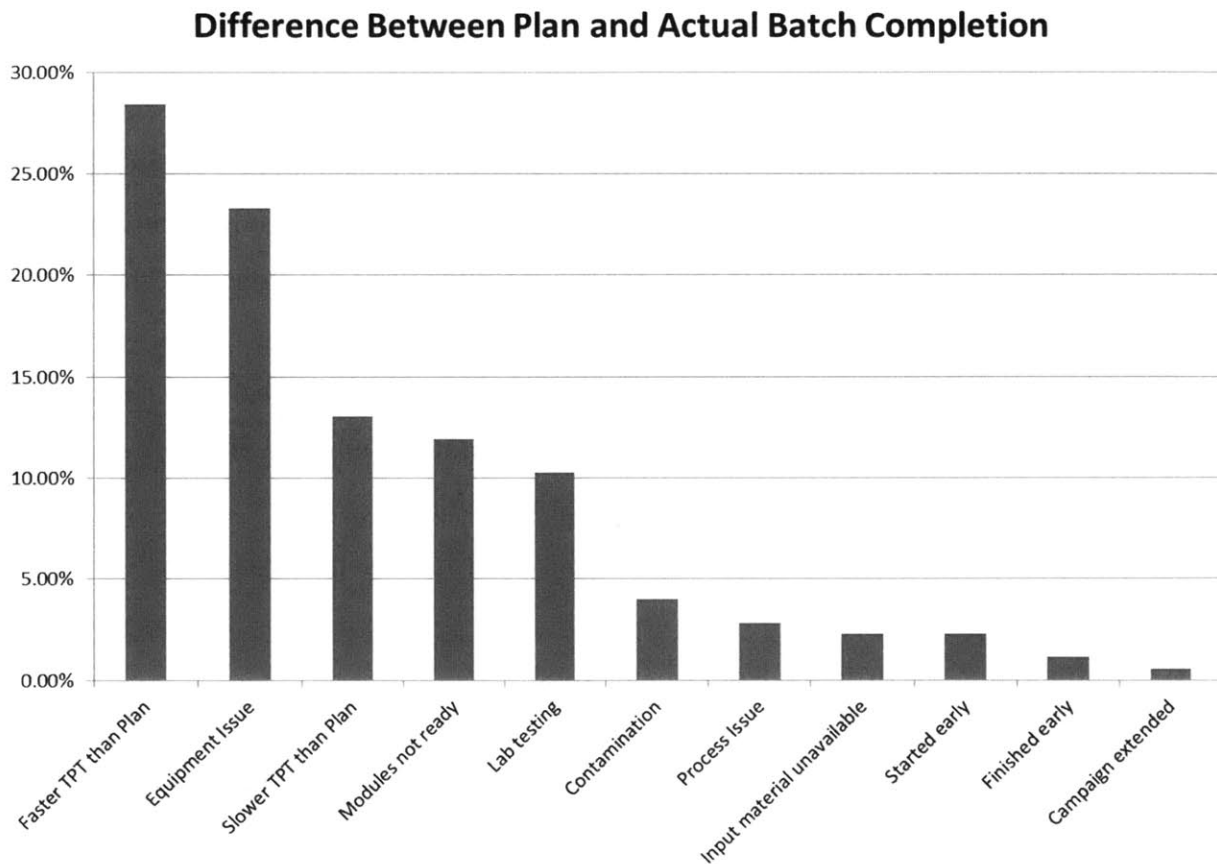


Figure 4 -Sources of Variance between plan and actual batch production

It was clear from this information that a major source of challenges facing the current planning process is variability or lack of understanding in the throughput times. This reinforces the need for a scheduling tool that can capture dynamic change easily to permit operating adjustments in real-time.

Throughput times

Given that 40% of the batches which failed to complete on time were due to faster or slower throughput than planned, the throughput times for each product type were examined. First, the data used by the planners was compared to the data input into the ERP system. A significant amount of variability was found, the distribution of this variability is shown below in Figure 5. This distribution is fairly normal about a mean of 0.68. This indicates that on average the ERP data reflects a higher throughput than what the planning team is currently using to plan. While this highlights the potential opportunity for increased plant capacity through better planning, it also is clear indication that the two information systems are misaligned and contain very different sets of information.

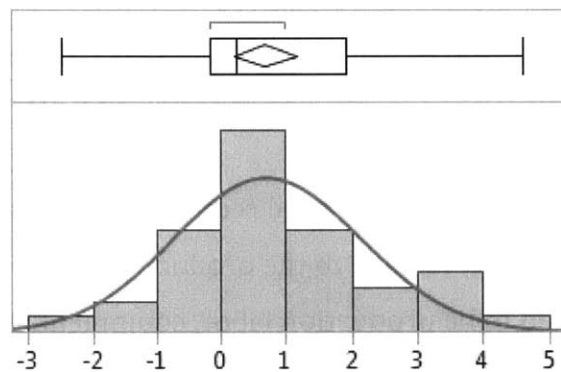


Figure 5 - Distribution of difference in batches per week between ERP and Excel TPT data

Next the data in the two systems was compared to the actual tpt times found in production. Figure 6 reflects a comparison of the planned throughput time to the actual mean throughput for each product. This distribution indicates that in some instances the mean actual throughput is slower than planned (negative value) and that the mean actual throughput can also be faster than planned. This information is supported by the data previously shown in Figure 4, which highlights both faster and slower throughput time as the major reasons for actual production varying from planned production.

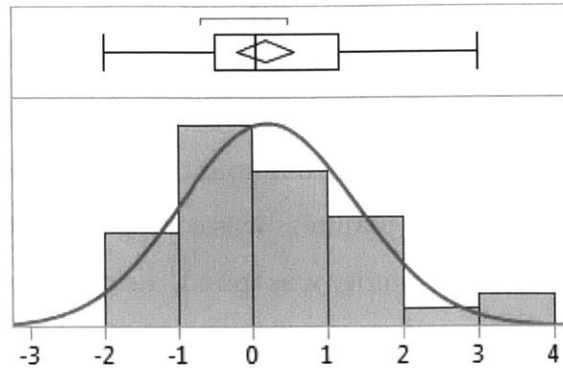


Figure 6 - Distribution of difference between planned TPT and actual mean TPT for each product

3.2 Business Requirements

To ensure alignment and the practicality of the model, close consideration was given to business and user requirements specific to the organization. High level business requirements, discussed below, were established and used to help guide the software selection and initial testing.

Feasible

For the model to be applied one critical requirement was that any proposed production plan be feasible with respect to the production constraints of the facility. In this case these were determined to be production labor, equipment changeover time and labor, and equipment/facility outages.

Flexible

The unique nature of the MSPU was identified to be flexibility. This flexibility relies on a plant with a range of equipment with respect to size and material of construction and a substantial network of manifolds and interconnects. The third business requirement for a planning model was that the model be able to represent the flexible nature of the MSPU production environment.

Repeatable

For the model to have a practical application it was key that it not only represent the current state of the facility, but also that the model remains accurate into the future. This

means the ability to update with the addition or removal of equipment from the production environment, the ability to update, add, or remove recipes, and the ability to add new users trained on the tool.

3.3 Key Performance Metrics

Metrics were established to aide in the measurement of changes and determination of overall improvement to the planning process.

Create annual plan

One measurement looks at the amount of time required to create an annual plan. This is defined as the time in terms of full time equivalent (FTE) required to create an annual production plan. This is defined as starting with demand information, in terms of quantity and QUOTIF dates for all desired products and generating a rough cut production plan for the given production window.

Changes to plan

Another important measurement is the ability to evaluate changes to an established production plan. As a change can be due to a variety of reasons, relevant scenarios are used to look at different situations. Changes to the plan are measured in time to evaluate a change in terms of FTEs.

Number of revisions per year

Another way to measure the ability of the model to evaluate changes is to look at the number of schedule revisions per year, in other words to ask if the use of a simulation model in the planning process can identify situations which will impact the production schedule earlier and reduce the need for retroactive revisions to the production plan. This is evaluated by examining a prior production plan and revisions to the plan.

Ability to test scenarios.

The measure of scenario tests is a binary one which under the Excel based planning methodology is severely limited in terms of sensitivity analysis or scenario testing.

Scenarios are used to highlight the difference in planning methodology but the key performance metric tests if scenario evaluation is even a possibility.

4 Modeling

4.1 Software Selection

4.1.1 Software Evaluation

As a part of an MIT LGO internship at a different Novartis manufacturing site, Shai Assia performed a substantial evaluation of simulation software. A summary of this evaluation is presented in Appendix 2. Assia indicates that SchedulePro™ is the appropriate software for the simulation and tactical planning work in the BioPharmaceutical manufacturing context[15]. Assia's evaluation combined with prior work done internally at NRL led to the decision to use the SchedulePro™ software package as a modeling tool for this project.

4.2 Model Layout

Full explanation of the software package, construct and general use of SchedulePro™ can be found in the Instruction Manual for the software. The following discussion will present the details of this application of SchedulePro™ and review the key assumptions used in this specific application.

Data

There is significant metadata required to drive this model and these data can be categorized into three groups, 1)Facility Data, 2)Recipe Data, and 3)Production Plan.

Facility

The facility is a representation of the resources available to perform the activities associated with the production of APIs. This includes a list of all relevant production equipment used for planning. Examples of equipment captured in this list are Head Tanks, Reactors, Crystallisers, Dissolvers, Separators, Centrifuges, Nutsche type Dryers and Filter

Dryers. Auxiliary equipment such as Powder Transfer Systems, Heating Skids, and Hoppers are also included. Additional equipment used in the production process, such as waste vessels, motors, pumps and transfer lines are typically dedicated to the larger items categorized above and are not included in this list.

In addition to the categories described above each item of equipment has unique characteristics including size, material of construction and location in the plant. This information is contained in the equipment description as well as the name of the equipment. A sample of this naming convention can be found in Table 13 of Appendix 1. The final piece of information stored within the equipment data are the standard changeover times, defined by equipment category for that piece of equipment. The data and assumptions around changeovers are discussed further in section 4.3 Assumptions and Benchmarks.

The other production resource within the facility is labor. Labor is categorized into two types, production operators and changeover operators. When planning production each type must be accounted for. This segmentation is necessary as the two groups use different resources and are constrained by different schedules, production is 7 x 24 and changeovers follow a day shift pattern.

Recipe

The recipe contains the information about how resources are consumed during production. Recipes are defined for each product type, which in the case of the MSPU are not only drug substance but also the steps required for the site to produce intermediate products used in API production.

The recipe is broken into procedures representing the different pieces of equipment necessary for production. Each procedure contains an equipment pool which is a collection of all the equipment capable of performing a particular production step.

Procedures are further broken into individual operations. For this application each procedure consists of one operation. For further explanation see the discussion around the use of bottleneck cycle time for recipes. The operation contains information about the time required to perform each step, which in this case is simply the bottleneck cycle time. The operation also contains information about the number of production operators required to

produce a given recipe. An example of the recipe structure used for the representative product D41 is shown in Appendix 1.

Production Plan

The third part the model in Schedule Pro™ is the production plan. The facility and recipes are built with data that can be maintained on an annual basis. The production plan is used to combine this resource data to create meaningful scenarios representative of the production environment.

The production plan requires information: 1) about the quantity of a given product, 2) if production of that product should start after or end before a given date, 3) if production of that product should follow completion of or run in parallel with other campaigns, and 4) if a campaign will require a changeover and what kind of changeover resources will be needed.

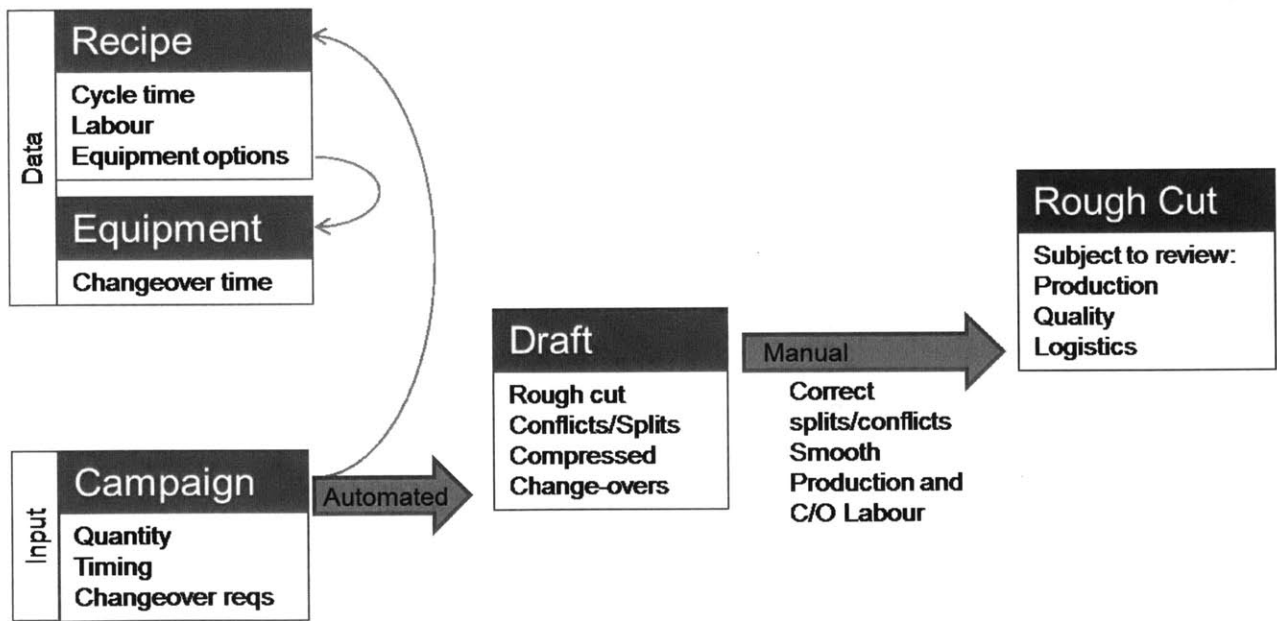


Figure 7 - Planning Process Flow

Planning Process flow

To create a production scenario or plan, the scheduling algorithm must be run. SchedulePro™ uses the inputs in the production plan to determine which resources must be allocated to production. The recipe establishes the parameters such as cycletime, labor

and necessary equipment. Once equipment is identified for use within a campaign the changeover window and labor requirements are also determined.

For this application it was found that following the first cut of the SchedulePro™ scheduling tool, the equipment allocation and production plan required additional manual manipulation to create a feasible plan. In some cases equipment conflicts were left unresolved by the scheduling tool and the planners preferred to manually balance the changeover plan to meet the constraints of the MSPU. The process flow for creating a rough cut plan in SchedulePro™ is shown above in Figure 7.

4.3 Assumptions and Benchmarks

Data Sources

The information input into SchedulePro™ as described above was gathered from a variety of sources. An overview of these sources is provided below in Table 2. The following discussion will review the assumptions made to determine the appropriate inputs for the model.

Table 2 - Overview of Data and Sources

Item	Source
Batch Throughput	PI, Excel, SAP
Batch Throughput (actual)	SAP (ERP system)
Batch Size	SAP
Equipment	Historic Plans
Equipment	Master Manufacturing Plan
Equipment	Human (Process Engineers)
Production Labor	Historic Plans
Production Labor	SAP
Change Over	Human (Planners)

4.3.1 Assumptions

Batch Size:

The amount of product to be produced by each batch is subject to some variability, however, typical batch sizes are well understood, tracked by product managers and planners, and maintained in the site ERP system. The information contained in the ERP system served as the source of information for the size of a batch

Batch Throughput:

The batch throughput time and associated data were previously shown to be subject to a high degree of variability. The planning team worked closely with process managers to review the historic batch throughput times as well as simulated throughput times to determine a “demonstrated throughput” for use in the SchedulePro™ tool as well as other planning activities.

Bottleneck cycle time:

The recipes used in the model are based on bottleneck cycle time. This is say that if the bottleneck cycle time of a batch is 24 hours then a batch will be completed every 24 hours during a campaign or that there will be 7 batches produced per week. For planning production on the 12-18 month horizon this level of detail was determined to be appropriate for the MSPU and has been indicated as an appropriate assumption for the 12-18 month planning horizon[14].

Production Labor:

Operator requirements for production labor, established in the recipe are based on the number of operators required per shift while the product in is production. For planning purposes and the needs of the facility this level of accuracy is currently sufficient though may be an area for future development. A more accurate and detailed approach would consider the labor required to perform specific tasks such as solvent transfers, liquid transfers and splits, and product off loads.

Changeover hours:

The time required to prepare a piece of equipment for a new campaign is not something that has been historically well planed or tracked, however discussions with

planners and operators familiar with the site have shown that the changeover time is dependent on a variety of factors. These include the product last produced in a vessel or equipment, the next product to be produced in the vessel, duration of idle time, and characteristics unique to the vessel, such as the transfer lines and connections. For the purpose of long term planning and this model a baseline changeover time was established for each category of vessel. Vessel categories are broken into Head Tank, Reactors, Crystallisers, Seperators, Centrifuge, Dryer, Nutsche, Vaccuum pump and Powder Transfer System. An example summary of these hours is shown in Table 3 below.

Table 3- Changeover Hour Baseline

	Representative data (example)
Head Tank	4 hours
Reactor	150 hours
Seperator	200 hours
Centrifuge	150 hours

Equipment:

The model is structured such that equipment used by a recipe is occupied throughout the duration of a campaign. In reality an item such as the dryer in D41 may be used during certain periods of production and spend time sitting idle between batches, however, the nature of the changeover requirments under the current operation of the facility is such that equipment remains dedicated to a campaign during that campaign’s production window.

Blank Batch:

Typically the facility plans for a week of blank batching prior to production and allocates one production operator during that time. The model does provide for a window of time for blank batching between changeovers and production, however, it doesn’t assign an operator to this task. This should be corrected in the detailed labor forecast.

Post Campaign Flush:

Similar to the blank batch the facility plans for a week of post campaign flushing. The model can retain a 1 week window for post campaign flush activities but does not account for proper labor requirements. This should be corrected in the detailed labor forecast.

4.4 Data Verification

To verify the data and modeling tool output, the resourcing requirements established by SchedulePro™ are compared to the resourcing requirements predicted by traditional planning methods. The 2013 production plan was used for verification, which looked at projected changeover hours, production hours, and volume of API to be produced. While total hours have been removed for confidentiality, a summary of this result is shown in Table 4.

Table 4 - Model Verification Comparison

	2013 Plan	SchedulePro™	Delta
Change Over (hrs)	XXXXXX	YYYYYY	-2.5%
Production (hrs)	XXXX	XXXX	-2%
Batches Produced	XXX	XXX	0

Examination of the 2.5% difference in changeover hours reveals that the 2013 changeover hour forecast includes additional project work not captured in the SchedulePro™ model.

Examination of the production hours reveals that 2% difference in forecast production labor hours is due to the lack of labor resources assigned during the blank

batch and post campaign flush process. While this time is blocked off in the production plan the model cannot easily allocate appropriate resources as discussed in the previous section. This difference can however be accounted for in the detailed labor forecast performed later in the planning process. It is shown that the data in the model is in line with the current planning methods and the ability of the model to accurately predict the requirements of a given production plan is appropriate for the planning group's needs.

4.5 Model Limitations

The model limitations can be grouped into two categories, those purposefully placed out of scope and those discovered during model development and testing. These limitations as a result of project scope, previously discussed in detail, are summarized as follows: 1) the planning of QC testing, 2) management of raw materials, 3) creation of a detailed changeover plan, and 4) generation of a preventative maintenance plan.

The limitations of the model inherent to the SchedulePro™ software are summarized below. First, the software does not optimize campaign length, in other words the user must intentionally select and evaluate options such as producing a product in one long campaign or through multiple shorter campaigns. In addition switching production equipment mid campaign is difficult and best performed by creating a new campaign. With respect to campaign start up the model is limited in that recipes assume constant throughput time. In reality the first one or two batches of a campaign tend to take longer than the majority of the batches. This ramp up must be manually accounted for in detailed planning rounds.

Further the model is limited in areas of labor allocation and forecasting. In particular it is difficult to allocate labor to other tasks outside of production, such as CIP activities supporting project work. When planning labor it is difficult to treat overtime as an independent constraint, as well as properly account for the additional costs associated with overtime. These detailed planning activities must be performed outside of any SchedulePro™ models and should be a part of subsequent detailed planning activities.

5 Scenario Analysis

5.1 Planning a Year's Production

5.1.1 Relevance

The creation of a rough cut production plan for a year is a critical requirement of this project. The yearly production plan is something the planners must create every year and is core to the planner's role. All other scenarios discussed in this paper first require an accurate annual production plan to serve as the basis of further evaluation. The first part of a rough cut production plan for a given year X is typically created during the fourth quarter two years prior (Q4 of X - 2). This plan is revised in the second quarter of the prior year (Q2 of X - 1). This case compares the use of SchedulePro™ to Excel in planning a year's production.

5.1.2 Description

The annual planning round in November of 2013 was dedicated to the planning of production for the 2015 year. A sample, representative of the type of demand requirements presented to the planners is shown below in Table 5.

Table 5 - 2015 Product Demand Forecast (representative)

Product	Quantity (kgs)
Product A	56,000
Product C	12,000
Product B	31,300
Product D	3000
Product P	2,000
Product G	33,000
Product J	200
Product K	4,000

The planners were asked to produce a rough cut production plan to create the products and quantities similar to those mentioned Table 5. In addition it was requested that the plan have no production or changeover labor overtime.

5.1.3 Modeling in Excel

A draft 2015 production plan was created using the traditional Excel based method similar to the method previously described in Section 3.1.2. This session was broken up into the following activities:

- Produce equipment plan or equipment occupancy chart
- Create operator view to represent operation labor requirements.
- Create batch/production view, to show the number of batches of each process step to be completed per week.
- Create changeover plan.

The time and resource requirements in terms of Full Time Equivalent (FTEs) to complete various tasks were recorded throughout the planning round, the results of which are shown in Table 6 below.

Note: Prior to this session significant time was spent preparing a rough equipment plan based on expectations though the time spent on this work is listed as uncertain in Table 6 shown below.

Table 6 - Annual Production Planning in Excel

Task	Time (hrs)	Resources (FTE)
Prior Equipment prep work	??	1
Produce viable plan	4	3
Operator view	1	2
Batch view	1	2
Create changeover plan	8+	1
Total	24+	1

5.1.4 Modeling in SchedulePro™

To produce the rough cut plan using SCP the demand forecasts shown in Table 5, were input to the scheduling tool and a plan was created following the process previously outlined in Figure 7. The time and resources required to complete this work in FTEs were recorded and are shown in Table 7 below.

Table 7 – Annual production planning in SchedulePro™

Task	Time (hrs)	Resources (FTE)
Prior Equipment prep work	n/a	0
Produce viable plan	2.5	1
Operator view	0	1
Batch view	.1	1
Create changeover plan	0	1
Total	2.6	1

5.1.5 Results

Examination of the time and resource requirements reveals that the use of SchedulePro™ to create an annual production plan can yield at least an 89% reduction in the resource requirements to create a rough cut annual plan.

Table 8 - Comparison of resources requirements for planning in Excel and SCP

	Excel	SchedulePro™	Delta
Total Hours/FTE	24+	2.6	>89%

The other meaningful result shown by this work relates to the accuracy of each method. To assess the accuracy of each method, the production plan created in Excel was replicated using SchedulePro™ and the two outputs were compared. Through this comparison eleven equipment errors were found in the Excel based plan. These were typically cases of an equipment item being dropped during the scheduling process as a campaign was moved from one date to the next. Further, four campaign length errors were found, meaning that a campaign was too long or short on one of the 4 worksheets associated with the plan.

5.1.6 Discussion

While the value of a reduction in planning resource requirements is quite clear there is additional value in the knowledge capture that takes place through the use of this tool, this is discussed further in the subsequent scenarios.

The second important improvement is the increase in accuracy. What is shown in this scenario is the errors that occur tend to be dropped equipment and a loss of assumptions. The value of this is difficult to measure as it is rare that errors such as dropped equipment will remain in the plan to the point that the error impacts production. However, the plan

with errors may be approved and published with corrections to the plan taking place after plan approval. This type of correction leads to a lack of trust in planning among the engineering and product managers.

5.2 Unplanned Outage

5.2.1 Relevance

In the production environment unplanned equipment outages are inevitable. These type of outages are also something that planning and scheduling cannot control. Though preventative maintenance programs are in place to reduce the frequency of delays due to equipment issues, unplanned equipment issues contributed to 24% of delays in 2013 (see Figure 4). The following scenario serves to demonstrate how a planner might address an equipment issue using the proposed tools as well as the Excel based method.

5.2.2 Description

During the completion of a campaign of H1 the screen on a Nutsche filter was damaged beyond repair. Examination of the spare parts stores revealed that after the same screen was damaged in 2008 a replacement screen was never ordered. With regard to acquiring a replacement the engineers indicated it would take roughly 12 weeks to manufacture/deliver and another 4 weeks to install the replacement screen. The challenge for production was that this particular unit was planned to be used in two process steps, H2 and H2v5 during the following two months. A 5 week production run of H2 was due to start in two weeks, the time required to complete necessary changeover activities to prepare for production of H2. Following the completion of H2 was another 6 weeks of idle time and then a 6 week production run of H2 V5.

5.2.3 Modeling in SchedulePro™™

To evaluate the equipment outage in SCP the user first creates an outage on the relevant equipment item. In this case a 16 week outage on Nutsche number 067 must be created. Following this all production planned for equipment item 067 becomes conflicted. The conflict is resolved either automatically or by the user manually working through each campaign. In either approach the planner quickly learns that no feasible options exist in the current model. The planner must approach the engineers to identify other equipment

options for production of H2 and H2v5. Once these options are reviewed the planner is able to update the equipment options in the recipe and quickly discover a possible solution. The solution requires moving production of 5 process steps into other equipment items as well as a two week delay in the production of Q8 and Q9.

5.2.4 Modeling in Excel

To evaluate this outage through the Excel method the planner must undertake an iterative process and resolve each conflict individually. While there are many possible solutions, the following is one possible approach the planner might take to solving the previously described problem.

The obvious option when looking at the schedule is to move H2 into equipment 064 and H2v5 into 068. This means production of H2 would face a delay of one week. Further, the use 064 also leads to a delay in production of H3, H4, H3v5 and H4v5.

This is not the whole picture and the planner must look to the rest of the schedule to see how the delays of H3, H4, H3v5 and H4v5 impact other areas of production. A map of these connections is shown below in Figure 8. The knock on effect of these options carries through 15 different products or process steps and impacts the schedule through the end of the production year.

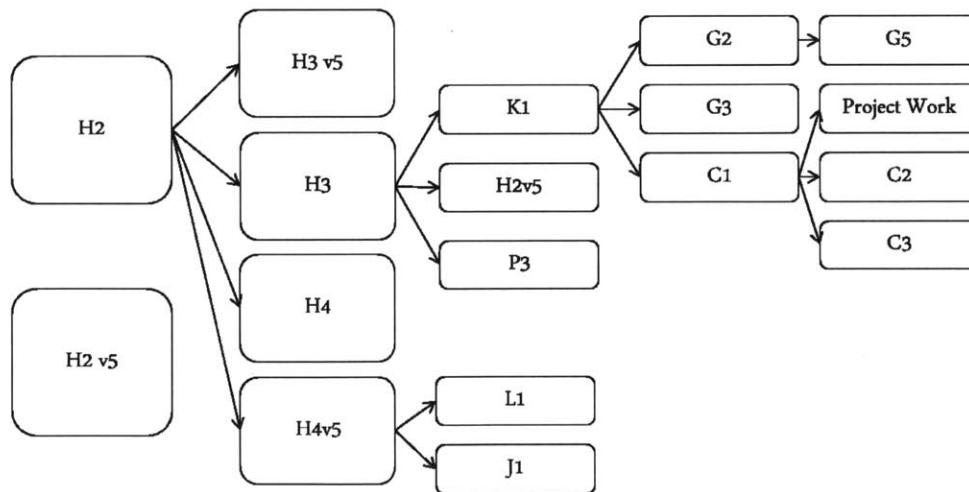


Figure 8 - Product delay impacts do to changing equipment

If these delays are deemed unacceptable the planner must further explore alternatives such as selecting alternative equipment, which was not explored as part of this scenario.

5.2.5 Results

Table 9 - Results from evaluation of equipment delay

	SCP	Excel
Conflicts examined/resolved	113	17
Iterations to complete	2	5
Changes to schedule (dates)	3	18

To solve the equipment outage in SchedulePro™ the user must go through two iterations. First to realize there is no obvious alternative equipment options for H2 and H2v5. The second iteration is re-running the schedule once the alternative equipment for H2 and H2 v5 are discussed with engineering and incorporated into the model. During the second iteration, SchedulePro™ explored 112 alternatives to find a feasible solution.

In solving the outage in Excel the user follows the most obvious path which after 5 iterations has only explored 17 conflicts and found a suboptimal solution in terms of number of changes to the previously planned schedule.

5.2.6 Discussion

In this case both approaches require the planner to seek outside input from the engineering staff, however, it is important to consider how this would unfold had the equipment alternatives already been input into SCP. In this case there would have been two conflicts and these would have been resolved in one iteration. As more equipment combinations are evaluated and captured in the SCP recipes overtime, the possible options available for conflict resolution will continue to grow. Under the Excel method none of the conflict resolution is captured and future planners facing similar problems do not benefit from the work of prior planners.

5.3 Evaluation of a Product Launch

5.3.1 Relevance

As previously discussed the ability to launch new products is a key factor in the competitive strategy of future Pharmaceutical production. In particular, the ability to accurately and consistently evaluate product launch is something critical to the flexible manufacturing group.

5.3.2 Description

Novartis's product development group inquired about the ability of the MSPU to support a new product launch. In this representative case the group would like to know if the MSPU can accommodate the launch of ICE9 (fictional product) during the 2014 production plan. The equipment requirements and information are shown in Table 11 below. ICE9 produces 170kgs per batch and has an expected throughput of 5 batches per week.

Table 10 -Equipment requirements for ICE 9

Vessel	MOC , Size
Reactor 1	GL, >650L
Reactor 2	GL, >1000L
Reactor 3	GL, > 5500L
Centrifuge	HST
Paddle dryer	SS, 2500L
Scrubber	
PTS	HST
Head tank 1	GL, 1000L
Head tank 2	GL, 630 L
Seed Pot	

5.3.3 Modeling in SchedulePro™

The first step to evaluate the launch of ICE 9 is the creation of a new recipe. Table 10 contains relevant recipe information. The planner must first work with a process engineer to identify equipment options and update the previous table with equipment options as shown below.

Table 11 - ICE 9 equipment options

Vessel	Size	Equipment options
Reactor 1	GL >650L	010,021,044
Reactor 2	GL >1000L
Reactor 3	GL > 5500L
Centrifuge	HST
Paddle dryer	SS 2500L
Scrubber	
PTS	HST
Head tank 1	GL 1000L
Head tank 2	GL 630 L

Seed Pot	
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The recipe is constructed by creating a recipe with the 10 procedures outlined in the previous table. For the SCP model each procedure should have a single operation with a cycle time of 5 batches per week or 33.6 hours per batch. Each procedure must also point to all the relevant equipment options shown in Table 11. The recipe must also contain information about the production labor requirements. In the case of ICE 9, 2 operators will be assigned to production.

The planner creates a campaign using the new recipe and depending on the year of evaluation assigns the appropriate demand values and desired delivery date. The planner can then use the SCP scheduling tool to search for possible production windows during the planned year. In this case a window was found in April of the given year and the evaluation was able to progress further.

5.3.4 Modeling in Excel

The traditional method of evaluation for product launch is an iterative process. The planner/engineer takes the highest utilized equipment in the plant, in this case reactor 2 and looks for possible production windows on similar reactors. From here the planner looks for corresponding windows on the other reactors. Then the evaluation would continue by searching equipment that is capable of serving as reactor 3, then centrifuge and so on. For this launch evaluation the iterative cycle would take 10 turns to find a complete equipment window.

5.3.5 Discussion

Completing a launch evaluation in SchedulePro™ requires the planners and engineers to first create a recipe and with that identify capable production equipment and labor requirements. At first this creates a perception of more time to complete an evaluation in SchedulePro™.

The traditional method of evaluation, through examination of the bottleneck equipment, appears to save time initially as the planner can quickly determine that the launch is not possible. In practice this is highly subjective and typically leads to a significant amount of rework.

The value of getting a definitive answer and ability to continue to evaluate a product as the production schedule changes is the significant advantage of completing the launch evaluation in SchedulePro™.

5.4 Change in Throughput Time

5.4.1 Relevance

Evaluating a change in throughput time is critical to this application. Variability in the process, process improvements and resource reallocation are all potential causes for a change in batch cycle time. While efforts to reduce this variability are in place, it remains an area for further improvement. This scenario looks closely at changes to the throughput time as a result of resource reallocation, however, the approach and results would be similar if changing the throughput time for other reasons.

5.4.2 Description

Due to efforts to balance labor resources the production coordination team is considering reducing the number of operators dedicated to the operation of lyophilizers during the production of product B3. Product B3 has a demonstrated throughput of 21 batches per week and requires 4 operators. The team is considering reducing the number of dedicated operators on the process to 2 which would reduce the throughput to 14 batches per week.

5.4.3 Modeling in SchedulePro™

To evaluate this scenario in SchedulePro™ the planner creates a copy of the current recipe for B3. This recipe is subsequently modified to reflect the reduced throughput by changing the duration of the operation to reflect the new output of 12 batches per week. Second the recipe labor requirements are reduced from 4 to 2 operators.

Once the new recipe is created the planner must correct the production plan by modifying the properties of the planned campaign of B3 to point to the new recipe for modified B3. Next the planner reschedules the campaign and is able to immediately see the new labor requirements as well as extended campaign length.

5.4.4 Modeling in Excel

To evaluate this scenario in Excel, the planner must first change the batch planning sheet to show the reduced output of 12 batches per week. Second they must extend the campaign by the necessary length, in this case 3 weeks. Next the planner modifies the labor planning sheet to reflect the reduction to 2 operators and must also remember to extend the campaign by three weeks. Finally the planner must open the equipment allocation sheet and extend the campaign of B3 by three weeks for all included equipment.

5.4.5 Discussion

To evaluate the two methods we can look at time to create the scenario, accuracy during the evaluations, and overall control around the process. As the time and accuracy between the two methods have been discussed using previous scenarios, this discussion will focus on the control which exists between the methods.

What we see with two methods is that in using SchedulePro™ the planner must execute five steps 1) copy the recipe, 2) change throughput, 3) change labor, 4) modify campaign, and 5) reschedule the campaign. In working in Excel the planner must execute three main steps 1) update the batch sheet, 2) update the labor sheet, and 3) update the equipment sheet.

To evaluate this scenario in SchedulePro™ the planner must complete all five steps in the same order. In the case of Excel the planner can choose complete the steps in any order and there is no requirement for all three to be completed. This allows for subjective decision making which fails to examine the full implications of a scenario. The fixed process inherent to the use of SchedulePro™ ensures consistency during scenario evaluation thus reducing the opportunity for mistakes.

5.5 Change in Demand

5.5.1 Relevance

Change requests relating to product demand occur during and outside of the planning round. These types of request requiring modifications to the planned production quantity are a common request in the MSPU. In 2013 there were a significant number of revisions to the production plan involving extension or reduction of a campaign length. Though steps are being taken to reduce the number of change requests from the supply

chain, the ability to respond to demand changes accurately will remain critical to the planning team in the near future.

5.5.2 Description

During the annual planning round year the supply chain indicated there was a need for an additional 1,000kgs of product P5 to be delivered before the end of 2015. At the time of request a campaign of P5 was slated for the 2014 production year, however, there were no campaigns of P5 planned for 2015.

Production of P5 consists of 4 intermediate process steps run in series and the final step which produces 340 kgs of P5 per batch. The question the planner must address is whether to extend the production planned for 2014 or include an additional campaign into 2015 production.

5.5.3 Modeling in SchedulePro™

To evaluate the request in SchedulePro™ the user must model two scenarios one with an extended campaign in 2014 and one which looks at the addition of a campaign during 2015. Further consideration must be given to the production of the necessary intermediate process steps.

We first look at the extension of the 2014 campaign. To do this the user modifies the campaign properties to increase the quantity to be produced by 1,000kgs. As the recipe for P5 indicates, one batch will produce 340 kgs. The tool calculates that 3 additional batches are needed to meet the request. The intermediate process steps must also be extended, in this case by 1 week each, to supply the requested quantity. The extension of these campaigns creates equipment conflicts as a crystalliser is shared between P2 and P3 and the centrifuge and dryer are shared between process steps P2, P3, and P4. The resolution of this conflict requires shifting the start of production P3 by 1 week which requires production of P4 to shift by two weeks. This compounding of delays ultimately results in shifting the production of P5 by 3 weeks.

To model the additional production of P5 during 2015, production is modeled through the creation of a new set of P5 campaigns. This is done by adding the five process steps to the 2015 production plan. In this case the planner is able to copy the previously planned campaign of P5 from 2014 and modify the delivery dates and quantities as needed.

Since the only time constraint is for P5 delivery by the end of 2015 the scheduling tool is used to find the optimal window to include the production and necessary change overs.

5.5.4 Modeling in Excel

Evaluation of this request using the Excel based method requires the planner to again examine both options of extending the 2014 production of P5 as well as the addition of a campaign to 2015 production. To first model the extension of the 2014 campaigns the user must calculate how many weeks to extend the P5 campaign to produce the desired quantity. Following this the equipment occupancy sheet and the production labor worksheet must be updated. This must be done for all 5 production steps. Following the extension of P5 production, the equipment conflicts for each of the five campaigns must be resolved by shifting campaign start times. This requires the modification of the production plan for 34 different equipment items as well as the labor plan across 5 campaigns.

To model the addition of P5 during 2015 production, the user must introduce the additional campaign into the Excel plan for 2015. This requires the user to identify a potential production window in terms of production labor, changeovers and all required equipment. This translates to allocation across 34 items of equipment 4 changeovers and 5 labor windows.

5.5.5 Results

Table 12 - Evaluation of Change in Demand Request

	Evaluation in SCP	Evaluation in Excel	Errors in Excel
Extend 2014 Campaign	1 hour	1.5 hours	2
Add Campaign 2015	0.5 hours	2	4

5.5.6 Discussion

Both methods of evaluation indicate a preference for production of the additional production of P5 during 2015. The main reason for this being the delivery requirements previously established during 2014 cannot be moved. It is important to consider that the addition of P5 to 2015 requires the addition of 4 changeovers while extending 2014 production requires zero additional changeovers.

The use of SCP to evaluate this scenario indicates a reduction in evaluation time, as well as an improvement in the accuracy of the evaluation as shown in Table 12. The Excel method produced 2 errors when extending the campaign in 2014 and 4 errors when adding a campaign to 2015.

6 Implementation Strategy

When considering the application of an enabling technology the ability of a business to effectively deploy and utilize the technology is a critical consideration. We suggest that the implementation should be looked at as a system which can be broken into three parts; the people who use the tool, the plant or the tool, and the process by which the tool is used and verified. For each of these categories we can identify system capabilities or requirements as well as challenges or risks they pose to implementation.

For the application of SchedulePro™ as a planning tool for a Multi-Product Chemical Synthesis Plant the approach to the implementation builds on a well-established framework commonly used during the implementation of information technology and knowledge management projects. In 1965 Harold Leavitt developed a model for analyzing change management which is now commonly referred to as Leavitt's Diamond[16], [17]. Leavitt presents technology, tasks, people and structure as independent variables which can be seen as the four points of a diamond[17]. Overtime Levitt's Diamond has been adapted to what is referred to as the Triangle[18], [19]. The Triangle shown in Figure 9 is a generally well-accepted framework in the IT community and is a popular structure when implementing business process enabling technologies of programs.

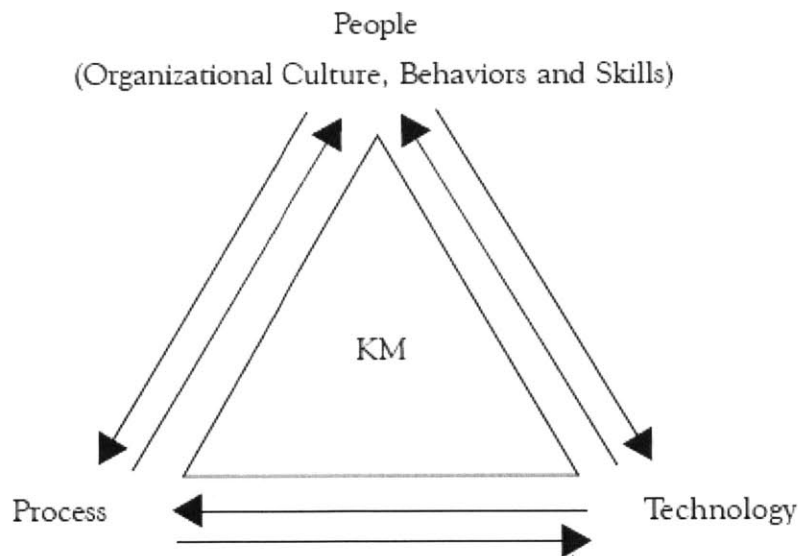


Figure 9 - Traditional structure of the Triangle Framework[18]

For this application we built on the traditional triangle structure shown in Figure 9. The triangle model was modified through the addition of linkages between the “corners” of the triangle as shown in Figure 10 - Modified triangle model.

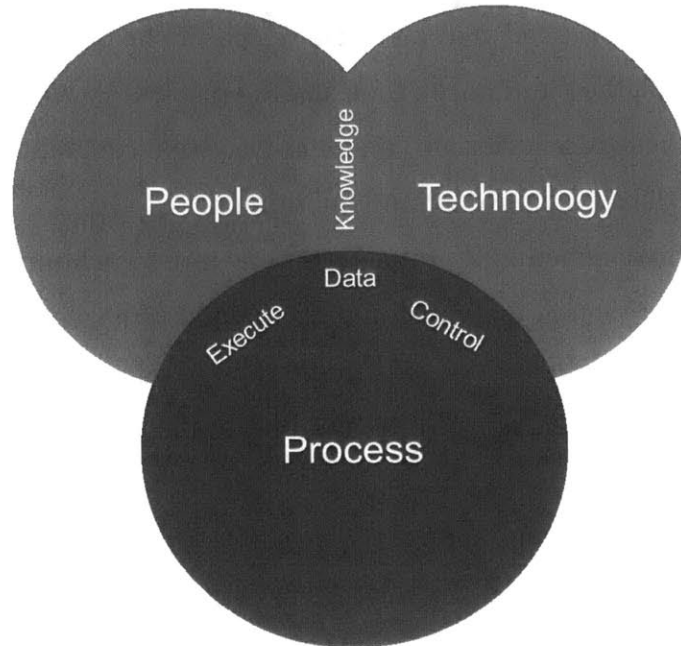


Figure 10 - Modified triangle model

The purpose of these connections between the points of the triangle was to establish both requirements and assess the current capabilities of the people, process and the technology in the system. Mapping the requirements and current capabilities provides a basis for performing a gap analysis to identify the major risks to a successful implementation. From this identification of risks, a mitigation strategy in the form of action plans is developed.

6.1 Technology

The technology in this case is the software package or modeling tool, the three critical links to the system are data, control and knowledge

Requirements

Data are core to the system as it links all three parts of the system. In terms of SchedulePro™ tool data are core to functionality. This requires a system is in place to store data, that updates to the data or models can be captured, and that relevant data are accurate and up to date.

Control is the main linkage between the process and the plant. To ensure consistent reliable results the software must allow for consistent use, reliable revision control and produce a clear result.

The main link between people and plant is knowledge, the plant or tool must be easy to use and allow a user to quickly learn and understand how to use the tool. The tool should also provide a user with an increased knowledge of the production environment.

Risks

In terms of the data the greatest risk is that the data are maintained and accurately reflects the production environment. New equipment will be installed and older items removed, process throughput times will change, new products will launch and changeover times will change. This risk can be mitigated through consistent execution of the process.

Looking at the software from the perspective of control, the greatest challenge is the variability in the production environment. As previously discussed the flexible production environment has high variability. The continued pressure for high utilization of equipment and people will not reduce this variability. Outside activities, such as the Class A work at NRL to understand and address this variability are a key strategy to mitigate some of this risk.

While the software is intended to enhance the knowledge and understanding of the user, there is also a requirement that the user possess knowledge of how to use the tool. There is a risk that this knowledge will be lost as people change roles and move through the company.

6.2 Process

The process or the methods by which SchedulePro™ is used, is linked to the system through data, execution and control.

Capabilities

The process outlined in Figure 7 - Planning Process Flow requires that data for the model are updated prior to the initiation of planning. Further, during execution the process must allow for not only the creation of a draft plan, but also revisions and changes to a plan. Finally, the process should produce a plan which can be verified as 90% complete.

Challenges/Risks

The greatest risk to the process is ensuring that data are updated prior to the start of planning. In particular production requirements in terms of both quantity and delivery date are inputs to the system and historically undergo frequent changes.

In terms of execution there is a learning curve associated with the new process/tool, and this, combined with people's inherent resistance to change, creates a significant risk to implementation.

In terms of control, a risk under the proposed process is ensuring that the master plan is maintained in the simulation tool. Once revisions or changes take place outside the simulation tool it is time consuming to pull them back into the process, and without an accurate representation of the plan the tool will quickly become outdated.

6.3 People

Though the triangle model presents a balanced system it is often the case that people can be the greatest challenge to a successful implementation. Perhaps this contradiction is due to the inherent capability gap that is presented by a need to learn a new tool and process. For this model people are linked to the rest of the system through data, execution of the process and knowledge of the technology.

Capabilities/Requirements

The requirements of the people in the system with respect to the *data* are that 1) recipes are maintained, 2) equipment lists are accurate and reflect the current state of the

true plant, and 3) that changeover data are maintained and updated with process improvements.

To *execute* the process people must be able to collect the necessary data and use the tool to develop a plan. Further, the process is not firm and requires significant problem solving, thus the planner should be a curious problem solver with a deep interest in exploring alternative solutions.

Finally all stakeholders involved must be capable of interpreting the production plan and identifying relevant problems.

Risks/Challenges

Challenges associated with the people involved in the process span the data, execution and knowledge links. Data maintenance is a risk, as collection of proper inputs is something that may be difficult for the planners to drive. Resistance to change is perhaps the greatest risk to the entire implementation. Though fraught with challenges the existing planning process is well adopted by the organization. High levels of workload and pressure to continually deliver results leaves the individual with little capacity to learn and adopt the new process. Though this tool takes steps to reduce knowledge loss, history has shown that people have a tendency to move within the organization. The risk of knowledge loss through this movement is far greater than the risk from resistance to change and should be a key motivator to capture knowledge of the system and planning process.

7 Conclusions

7.1 Specific recommendations re: research findings

This work has presented a system that may be used for planning the production of active pharmaceutical ingredients in a batch production process. The approach and assumptions are based on planning production for a highly flexible manufacturing facility. This work has shown that through the use of process simulation software the time required to create a feasible production plan can be dramatically reduced while increasing the reliability of the planning process. Further, it has been shown that this model can be used to evaluate additional production scenarios to answer questions common to the multi-product production facility. This includes addressing variability in the process throughput time, unplanned equipment failures, and the evaluation of capability to support new product launches.

Through the use of this model and process, the firm will be able to increase the reliability of the planning process, and enter the future better equipped to evaluate alternative production configurations. This could include alternative resourcing plans, the addition of new equipment or technologies to the facility or a change in product mix.

Finally, this research has shown that process improvement such as the type investigated during this work requires a significant amount of time and resources. It is important to consider the inertia that exists within an established organization and remain aware of the time and energy required to uncover and implement improvements.

7.2 General implications for other firms/industries

While the system developed and presented in this work is focused on the practical application of simulation tools to a specific production facility, the challenges facing the planning group are not unique. In particular, the ability to track assumptions, capture knowledge, and properly account for constraints throughout the planning process are common to many organizations. Planners and Supply Chain Managers working in a flexible manufacturing setting should find similar benefits from simulation tools and techniques.

The second important lesson presented in this work is the criticality of people as a factor in organizational change. This work has shown the validity of the triangle model and

presented a case where this model is used to assess the requirements of a process improvement against the organizations capabilities to reduce risk and improve implementation outcomes.

7.3 Remaining questions for further research/future theses

As the organization moves ahead with the use of simulation during production planning, key areas of focus include: implementation, process improvement, resource allocation, and evaluation of alternative production configurations.

Implementation

The groundwork for a successful implementation is currently in place, the people behind the process have a strong understanding of the use of the tool, and management is aware of the value of these techniques. Management can encourage this success by continuing to ask questions such as those highlighted below, and by allocating sufficient time and resources to explore these questions.

Process Improvement

Continued improvement of the planning process should be a key goal in the future. This could include:

- Integration of the tools presented in this work with the existing ERP system.
- Incorporation of raw materials and/or preventative maintenance planning.
- Ongoing or periodic review and update of the data behind the key assumptions in these models, such as throughput time and changeover time.
- Application of similar techniques to the Quality Control testing planning process.

Resource Allocation

One focus area for improvement should be the allocation of production resources; this could include both the use of production operators as well as the use of changeover operators. What was seen through this work is that resources are currently the bottleneck in terms of plant capacity. Improvement of plant throughput or utilization will come from better use of the human resources.

References

- [1] K. Chin, "The changing face of chemical engineering," *Chem. Eng. Prog.*, vol. 100, no. 4, pp. 5–5, Apr. 2004.
- [2] H. T. N. Nejad, N. Sugimura, and K. Iwamura, "Agent-based dynamic integrated process planning and scheduling in flexible manufacturing systems," *Int. J. Prod. Res.*, vol. 49, no. 5, pp. 1373–1389, Mar. 2011.
- [3] P. Feng, J. Zhang, Z. Wu, and D. Yu, "An improved production planning method for process industries," *Int. J. Prod. Res.*, vol. 49, no. 14, pp. 4223–4243, Jul. 2011.
- [4] A. Sundaramoorthy, J. M. B. Evans, and P. I. Barton, "Capacity Planning under Clinical Trials Uncertainty in Continuous Pharmaceutical Manufacturing, 1: Mathematical Framework," *Ind. Eng. Chem. Res.*, vol. 51, no. 42, pp. 13692–13702, Oct. 2012.
- [5] L. Sun, S. S. Heragu, L. Chen, and M. L. Spearman, "Comparing dynamic risk-based scheduling methods with MRP via simulation," *Int. J. Prod. Res.*, vol. 50, no. 4, pp. 921–937, Feb. 2012.
- [6] T. s. Lee and E. E. Adam Jr., "Forecasting Error Evaluation in Material Requirements Planning (mrp) Production-Inventory Systems," *Manag. Sci.*, vol. 32, no. 9, p. 1186, Sep. 1986.
- [7] C.-J. Ho, T. C. Ireland, and T. c. Ireland, "Correlating MRP system nervousness with forecast errors," *Int. J. Prod. Res.*, vol. 36, no. 8, Aug. 1998.
- [8] J. H. Y. Yeung and W. C. K. Wong, "Parameters affecting the effectiveness of MRP systems: a review," *Int. J. Prod. Res.*, vol. 36, no. 2, pp. 313–332, Feb. 1998.
- [9] S. T. Enns, "MRP performance effects due to lot size and planned lead time settings," *Int. J. Prod. Res.*, vol. 39, no. 3, pp. 461–480, Feb. 2001.
- [10] E. T. Grasso and B. W. Taylor III, "A simulation-based experimental investigation of supply/timing uncertainty in MRP systems," *Int. J. Prod. Res.*, vol. 22, no. 3, p. 485, Jun. 1984.
- [11] U. Wemmerlöv, "A time-phased order-point system in environments with and without demand uncertainty: a comparative analysis of non-monetary performance variable," *Int. J. Prod. Res.*, vol. 24, no. 2, p. 343, Apr. 1986.
- [12] S. Taj, G. N. Nedeltcheva, G. Pfeil, and M. Roumaya, "A spread-sheet model for efficient production and scheduling of a manufacturing line/cell," *Int. J. Prod. Res.*, vol. 50, no. 4, pp. 1141–1154, Feb. 2012.
- [13] C. Kim and T.-E. Lee, "Modelling and simulation of automated manufacturing systems for evaluation of complex schedules," *Int. J. Prod. Res.*, vol. 51, no. 12, pp. 3734–3747, Jun. 2013.
- [14] D. Petrides and D. Carmichael, "Role of simulation and scheduling tools in bioprocess development and manufacturing," *Abstr. Pap. Am. Chem. Soc.*, vol. 245, Apr. 2013.
- [15] S. Assia, "Tactical Planning Optimization for Campaign Scheduling of Active Pharmaceutical Ingredient Production Based on Monoclonal Antibodies."
- [16] H. J. Leavitt, *Applied Organizational Change in Industry: structural, technical and human approaches, Handbook of Orgaizations*. Skokie, IL.: Rand McNally, 1965.
- [17] "Leavitt's Diamond," *Bloomsbury Bus. Libr. - Bus. Manag. Dict.*, pp. 4321–4321, Jan. 2007.
- [18] D. Christopher and A. Tanwar, "Knowledge Management in Outsourcing Environment: People Empowering People," *IUP J. Knowl. Manag.*, vol. 10, no. 2, pp. 61–86, Apr. 2012.

[19] J. Edwards, "A Process View of Knowledge Management: It Ain't What you do, it's the way That you do it," *Electron. J. Knowl. Manag.*, vol. 9, no. 4, p. 297, Dec. 2011.

Appendix 1

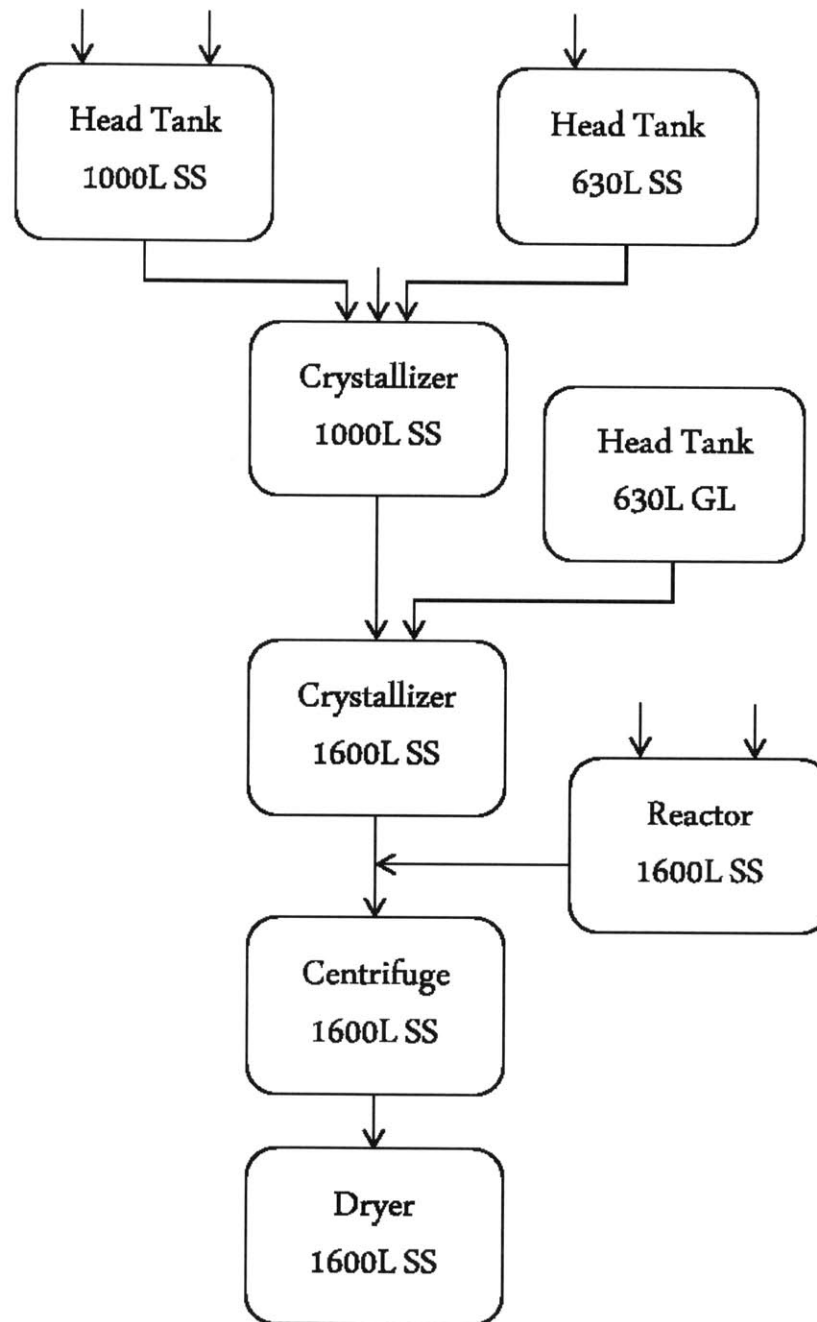


Figure 11 - Process flow/equipment requirement of example product D41

Product D41 is a representative product to highlight how information is used in Excel and SchedulePro™. For this example PS4 has a batch cycle time of 36 hours and requires 2 operators during production.

Table 13 - Equipment list for example plant

Equipment in SchedulePro™	Equipment list in Excel		
Equipment ID	Head Tanks	Size (L)	MOC
HT.SS.630.001	1	630	SS
HT.SS.630.002	2	630	SS
HT.GL.630.003	3	630	GL
HT.SS.1000.004	4	1000	SS
HT.SS.1000.005	5	1000	SS
HT.SS.1000.006	6	1000	GL
	Reactor		
R.SS.1000.001	1	1000	SS
R.GL.1000.002	2	1000	GL
R.SS.1600.003	3	1600	SS
R.SS.1600.004	4	1600	SS
	Crystalliser		
C.SS.1000.001	1	1000	SS
C.GL.1000.002	2	1000	GL
C.SS.1600.003	3	1600	SS
C.SS.1600.004	4	1600	SS
C.GL.1600.005	5	1600	GL
	Centrifuge		
Cent.SS.1000.001	1	1000	SS
Cent.SS.1000.002	2	1000	SS
	Dryer		
Dryer.SS.1600.001	1	1600	SS
Dryer.SS.1600.002	2	1600	SS

Table 13 is a list of the equipment in the sample production plant. This also indicates how equipment information such as size and material of construction is incorporated into the SchedulePro™ Equipment ID.

Table 14 - Sample production plan with Excel method

		Weeks	1	2	3	4	5	6	7	8	9
Head Tanks	Size	MOC									
1	630	SS			D41						
2	630	SS									
3	630	GL			D41						
4	1000	SS			D41						
5	1000	SS									
6	1000	GL									
Reactor											
1	1000	SS									
2	1000	GL									
3	1600	SS			D41						
4	1600	SS									
Crystalliser											
1	1000	SS			D41						
2	1000	GL									
3	1600	SS			D41						
4	1600	SS									
5	1600	GL									
Centrifuge											
1	1000	SS			D41						
2	1000	SS									
Dryer											
1	1600	SS			D41						
2	1600	SS									

Table 14 shows the Excel type production plan for a four week campaign to produce D41. Table 15 and Table 16 show the information that would be used to create the batch production and labor plans.

Table 15 - Sample production plan with Excel method

Product	Weeks	1	2	3	4	5	6	7	8	9
D41	Batches/wk			4	5	5	4			

Table 16 - Sample labor plan with Excel method

Product	Weeks	1	2	3	4	5	6	7	8	9
D41	Ops/wk			2	2	2	2			

Table 17 represents the SchedulePro™ recipe information for the production of D41. Each equipment item is a procedure and each procedure has one operation. The equipment indicates which equipment is capable of performing a given procedure.

Table 17 - Sample SchedulePro™ recipe information

Procedure	Equipment		Duration	Labor
Head Tank 1	HT.SS.630.001; HT.SS.630.002	op1	36 hrs	2 (operators)
Head Tank 2	HT.SS.1000.004; HT.SS.1000.005	op1	linked to Batch Start of op1 in Procedure 1	
Head Tank 3	HT.GL.630.003	op1	linked to Batch Start of op1 in Procedure 1	
Reactor	R.SS.1600.003; R.SS.1600.004	op1	linked to Batch Start of op1 in Procedure 1	
Crystalliser 1	C.SS.1000.001	op1	linked to Batch Start of op1 in Procedure 1	
Crystalliser 2	C.SS.1600.003; C.SS.1600.004	op1	linked to Batch Start of op1 in Procedure 1	
Centrifuge	Cent.SS.1000.001; Cent.SS.1000.002	op1	linked to Batch Start of op1 in Procedure 1	
Dryer	Dryer.SS.1600.001; Dryer.SS.1600.002	op1	linked to Batch Start of op1 in Procedure 1	

Appendix 2

Bio-G	
Real-Time Modeling System that consolidates supply chain and manufacturing operations data, providing outcomes like quality by design (QbD), real-time scheduling, debottlenecking etc., across a facility or network	
Pros: <ul style="list-style-type: none"> • Operations Research experts dedicated to biotech • Link to multiple data sources (SAP, Delta-V) • Feedback mechanism for real-time schedule control 	Cons: <ul style="list-style-type: none"> • External consulting, requires Novartis to rely on a 3rd party for modifications and/or new products • Cost
SuperPro Designer + SchedulePro	
SW suite to facilitates modeling, evaluation and simulation of integrated processes, compatible with biotech batch and semi-continuous production. Cost of Goods analysis, cycle time reduction, environmental impact assessment, and other tasks. Suited for multi-product manufacturing facilities.	
Pros: <ul style="list-style-type: none"> • +120 build-in templates for mAb (batch & semi-cont.) • Automatic link between tactical & operational plans • Sensitivity analyses: Capacity, COGS, resources, HR • Campaign scheduling optimization for multiproduct 	Cons: <ul style="list-style-type: none"> • Highly customized and sophisticated, this SW requires configuration of the operation processes and a learning curve
Aspen Tech Inc.	
Integrated SW solutions, customized to various industries for process optimization and production planning. The aspenONE Production Management & Execution module targets end-to-end operational efficiency	
Pros: <ul style="list-style-type: none"> • Fully Functional (similar to SuperPro+SchedulePro) • Adapted to many industries, including pharmaceutical 	Cons: <ul style="list-style-type: none"> • More complicated and expensive than the Intelligen Suite without an additional value
MS Excel (Solver) + MS Project	
Currently in place at BPO Huningue are Excel spreadsheets and Project Gantt charts. The Solver application is an Excel Add-In that can be used for what-if analyses and optimization of a target objective function	
Pros: <ul style="list-style-type: none"> • Simple to use, short learning curve • Already implemented in the plant • No capital investment required for SW license 	Cons: <ul style="list-style-type: none"> • Operations / unit-procedures are not optimized • No link between tactical and operational planning • Limited capability / information • Model must be build from scratch
BioSolver	
An Excel-based COGS model that provides user configurable process sequences and manufacturing cost calculations, aimed at modeling biotech processes	
Pros: <ul style="list-style-type: none"> • Commonly accepted cost values for bench marking • Relatively easy to use, compared to customized tools • Software costs are lower 	Cons: <ul style="list-style-type: none"> • Limited capabilities on the operational level • Analyses are done per product (no multiproduct) • Not suited for campaign scheduling
SAP Advanced Planner & Optimizer (APO)	
Production Planning and Detailed Scheduling (PP/DS component) enables multi-site production optimization while simultaneously taking into account product and capacity availability	
Pros: <ul style="list-style-type: none"> • SAP is already available in the system • Planners are more familiar with its various functions (purchasing, maintenance scheduling) 	Cons: <ul style="list-style-type: none"> • Not designed specifically for Biotech, therefore still requires large customization. • Core competencies are not within tactical planning