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A MODULAR APPROACH FOR MODELING ACTIVE PHARMACEUTICAL INGREDIENT MANUFACTURING PLANT: A CASE STUDY

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ABSTRACT

Simulating pharmaceutical manufacturing facilities is often quite challenging due to the complexities involved with their chemical processes, material and energy balance issues, equipment sizing concerns, etc. This problem is further exacerbated by uncertainties in operations and logistics. A single simulation model is unlikely to adequately capture the intricacies which exist in both domains (process and operations) within the pharmaceutical environments. Developing independent models using different tools to capture these details is not unique. However, combining information from different models or feeding outputs of a process model to other process / operational models, to address process and operational questions is an uncommon practice. This paper presents a case study wherein outputs from process simulation model acted as inputs to another process model and operational model to study an entire Active Pharmaceutical Ingredient manufacturing plant.

1 INTRODUCTION

A pharmaceutical manufacturing plant has many component parts which must work together, despite numerous constraints, in order to produce a valuable product. At the supply chain level, these component parts may be classified to include raw material supply network, manufacturing of drug substance, which includes Active Pharmaceutical Ingredients (API) production, manufacturing drug products and distribution to final customer. Each of these elements within the supply chain may have intermediate inventories and transportation networks. Additional complexity exists within each of these elements, e.g., production of API involves many different processing equipment, heating and cooling modules, reaction vessels, centrifuges, and dryers, to name a few. Utilities, labor and intermediate test results must be available in a timely manner in order to reliably produce a high quality intermediate or final product. Often multiple equipment are used in parallel to produce at a higher throughput. Inventories of materials in local staging spaces are also needed in order to avoid delays while waiting for key raw materials or allowing for space to empty vessel contents so that the next batch is not delayed.

Modeling and simulations have been used effectively to improve understanding of pharmaceutical systems, and to find means to enhance the design and operations of the constituent parts. However, the wide range of complexity in these systems, both in terms of scope (raw materials through finished product) and in terms of resolution (an individual chemical reaction through inventory management) makes modeling very challenging. Additionally, it is very difficult to find a single modeling tool which can adequately represent the system.

In this paper, a case study is presented wherein the modeling problem is broken into two parts which work together: process (everything that occurs ‘inside the vessel’) and operations (everything that occurs ‘outside the vessel’). Process in this context includes modeling the physical / chemical properties of material, reactions, and utility requirement; whereas operations encompass logistics, equipment

(manufacturing and material handling) need and operating times. The proposed modeling approach of breaking the problem into parts, process and operational, is meant to address different objectives. Subsequently, the results provided by these models can be considered (near) optimal. The case study focuses on one segment of pharmaceutical supply chain, namely, manufacturing of the APIs; and on one challenging problem associated with it – facility modifications required to meet increasing demand.

2 OVERVIEW OF THE PHARMACEUTICAL MANUFACTURING ENVIRONMENT

The pharmaceutical manufacturing environment is a very complex system. This complexity can be attributed not only to the technology involved, but also the constraints imposed by regulatory bodies, such as, FDA (Food and Drug Administration), EMA (European Medicines Agency), WHO (World Health Organization), etc. Additionally, pharmaceutical manufacturing companies have to comply with several regulations and codes as specified in guidance documents, e.g. current Good Manufacturing Practices, Good Laboratory Practices, and Good Engineering Practices, to name a few (Benson and Kulkarni 2011). Besides these regulations, complexity is intensified by stringent quality control (QC) and quality assurance (QA) requirements, limited product shelf life, bottlenecks and yield issues.

A typical pharmaceutical supply chain, at a high level, can be split into three elements – upstream, mid-stream and downstream. The upstream portion mainly includes API manufacturing. The middle portion consists of all activities associated with compounding / mixing of inactive ingredients, blending with APIs, drying, tableting, coating, filling, primary packaging (filling drug product in bottles, blister packs, vials, syringes, etc.), and secondary packaging (packing the filled product in cartons). Distribution, which includes distribution centers, wholesalers and delivery to the end user – hospitals, pharmacies, retailers, direct-to-patient, etc., make up the downstream of the pharmaceutical supply chain.

Usually, the pharmaceutical manufacturing facility will have two sets of buildings – core production building(s), and support building(s) housing functions such as QA / QC labs, warehousing, administrative functions, maintenance shop, etc. Activities within and between these buildings are highly correlated. Broadly speaking, these correlations can be categorized as physical, chemical, biological, operational, and economical. Though these categories to some extent are interrelated, in order to study specifics of a system, these categories should be treated as independent or with minimal commonalities. Subsequently, different measuring instruments, techniques and tools should be employed to study them. Thus, the use of appropriate tools is quintessential, even if that means creating multiple models using different software depending on the tools' capability to address the problem at hand.

These buildings, core and support, experience significant amount of material, people and information flows. In many cases, one or more of these steps may occur in different locations requiring transportation steps in between. Furthermore, depending on the material / product properties, transportation may require temperature and humidity control, additional security measures and continuous monitoring. Also, inventories of materials in warehouses or in local staging areas are used to provide capacitance to allow smoothing of dynamic disturbances and ensure uninterrupted production. The important representative characteristics of pharmaceutical manufacturing environment are summarized below:

- Usually, a single building is incapable of housing all process equipment and procedures required to convert raw materials into finished product. Consequently, the product touches several buildings or suites before it leaves the facility.
- Pharmaceutical manufacturing often occurs in a batch or semi-batch production mode. Campaigning strategies are generally employed in this environment. A campaign is defined as a finite set of production batches of the same product. Each campaign consists of a discrete number of batches (Kulkarni 2015). There is a potential of significant inventory build-up and excessive transportation of inventories due to these campaigns.
- Inventory cannot be held in production area beyond a predetermined time interval. Inventory has to be returned to the warehouse, designated staging spaces, or secured storage locations (in case of controlled material).

- Extensive cleaning activities are performed to avoid contamination. Cleaning is usually performed after a fixed number of batches of the same product; and between two different product campaigns. Cleaning consumes significant amounts of utilities, e.g., treated water, and drastically impacts the overall product lead times.
- Special material handling may be required, e.g., controlled substances move under security; corrosive, flammable or hazardous material (raw material, intermediate, final product or waste) is required to be contained in special containers or in limited quantities; photosensitive material should be appropriately covered, etc.
- Temperature and humidity controlled staging and transportation is required for certain sensitive material. Continuous monitoring of temperature and humidity is critical to ensure product quality is not compromised, to avoid counterfeit products entering the supply chains and to satisfy agency codes and regulations.
- Given the significant potential to cause harm to human life, there are numerous points in the process which require stringent quality checks, i.e., QA and QC activities (Shah 2004).

3 LITERATURE REVIEW

3.1 Pharmaceutical Supply Chain and Manufacturing Strategies

There are many challenges in the pharmaceutical setting including optimal design of the supply chain. An extensive literature review of challenges faced in pharmaceutical supply chains is provided by Shah (2004). Supply chain issues in the process industry, which potentially contribute to the upstream component of the pharmaceutical supply chain have also been researched (Shah 2005). Kallrath (2002a) employed a simultaneous strategic and operational planning approach, based on Mixed Integer Linear Programming (MILP) optimization techniques, to study the supply chain management of a multi-site production network of a chemical plant and calculate Net Present Value (NPV). In this study, material is transferred in pipelines from one reactor to another or from tanks to reactors. Material transfers under such circumstances are (almost) deterministic, and the only variability can be attributed to minor variation in flow rates. Delays due to material unavailability are not considered. Furthermore, variability induced due to cleaning activities between two campaigns or between batches of the same campaign is not addressed. It is important to include these aforementioned aspects in the NPV calculations to get a better handle on financial estimates.

There exist numerous issues when dealing with facilities' operating strategies when the product mix and / or the product batch size is continually changing. One way to address this issue is by improving the campaigning strategies in such environments. Campaign scheduling optimization techniques, such as, MILP, Mixed Integer Nonlinear Programming (MINLP), Discrete Lot Sizing and Scheduling Problems (DLSP), proportional lot sizing and scheduling problems, etc. have been employed in the past. A review of campaign scheduling techniques is presented in Kallrath (2002b). However, determining campaign lengths and scheduling campaigns are usually NP-hard problems with no standard solution technique available (Kallrath 2002a). Subsequently, instead of trying to find an optimal solution, a feasible solution is preferred. Berning et al. (2002) used genetic algorithms to develop schedules at each site and then employed a commercially available collaborative planning tool across sites. Though their study considers routing combinations, unit operations, setups, cleaning regimes, and product batch size, they do not include any logistical constraints e.g. by-product (waste) generation and handling, or any variability in operational times.

Conducting debottlenecking studies using simulations is not uncommon in the pharmaceutical domain. Tan et al. (2006) discuss a case study of debottlenecking an anti-allergic cream production process. They provided economic analysis for different scenarios and a scheme to accommodate future expansion plans. However, their study is restricted to a process occurring within one building, hence is not affected by logistical constraints. They also do not account for any operational or process variability

in their analysis. Papavasileiou et. al. (2007) presented a debottlenecking case study for an OSD (oral solid dosage) plant. They provide analysis for equipment utilization and schedules, utilities consumption and cost analysis. They further combine their results from process simulation models to perform Monte Carlo simulations which include variability in their analysis. However, this analysis only allows them to compute mean, mode, variances, and frequency distribution. Furthermore, Monte Carlo simulations provide limited insight into interactions over time and issues such as staging space constraints, logistics, operator schedules and availability, etc. Kulkarni (2015) developed process models to generate feasible production schedule, understand utilities consumption as a function of this schedule, namely, Water-For-Injection (WFI) and Purified Water (PW), and further use that information to size plumbing in the facility. However, this study does not address the operational and logistical aspects.

Discrete Event Simulation (DES) modeling was used to evaluate WFI performance for future manufacturing needs (Alexander 2006). Haekler et al. (2010) used DES, along with certain Lean techniques, to debottleneck a production line and increase throughput resulting in significant increase in revenue. Saraph (2001) used DES models to study water consumption activities, wherein the continuous supply of water is converted into a discretized version. This study focuses only on water generation and consumption concern, and does not evaluate manufacturing equipment bottlenecks or address operating and scheduling issues. Kulkarni (2014) used DES models, built in FlexSim, to study headcount requirements and potential layout changes for downstream activities in the medicinal food (nutraceutical) industry. But this study is strictly restricted to operations and headcount analysis only. It does not account for any process related or material balancing activities. DES models using FlexSim were used to determine number of weigh dispense suites for an OSD manufacturing environment (Kulkarni 2012). This study too does not consider any process related activities.

It is no surprise that models are created to address specific questions. The tools are also developed and tailored towards the problem instances they are likely to be used in. Even the symbols and graphics used in the modeling and simulation tools are geared towards specific user-groups. Thus, to study an entire manufacturing system, including the operating, logistics, and process issues, more than one model may be required. Additionally, depending on the capabilities of the available modeling tools, use of multiple tools would be essential.

3.2 Modeling and Simulation Tools for the Pharmaceutical Environment

For modeling pharmaceutical environment, it is proposed that simulation models and tools be organized into two categories – process simulations and operations simulations. We define a process model to include everything ‘inside the vessels’. Vessel is a broad term which consists of bioreactors, pipes, reaction tanks, hold tanks, etc. Inside the vessel term comprises of activities such as chemical / biological reactions, consumption or generation of components, mixtures and by-products, physical properties of material, e.g., temperature, specific densities, enthalpy, etc. Operational models, on the other hand, deal with everything that occurs ‘outside the vessels’, e.g. logistics, transportation, physical staging spaces, warehousing activities, headcount, material handling equipment, etc.

Process simulation models can be developed and used throughout the product lifecycle. A brief description of benefits of using process models for process development through product commercialization is provided by Petrides et al. (2002). Typically, process models can be used to understand and generate information on the following:

- Quantities of material consumed and generated per batch – There are numerous steps involved in producing a final product batch, each step consuming specific quantities of material, while generating particular amounts of intermediate material, final product and waste. Process modeling tools are capable of balancing chemical reactions, performing mass and heat balance calculations, computing yield losses, etc. to estimate the quantities consumed or generated.
- Campaigning strategies – Number of batches in a campaign, also known as campaign length, could be dictated by several factors, such as, overall demand, equipment / vessel capacity,

availability of shared resources, etc. Generating a feasible campaigning strategy is one of the important outputs from process models, whereas typically a production schedule acts as an input to the DES models.

- Cleaning regimes – Cleaning affects the products' lead time and is often considered as an essential non-value added activity in the Lean lingo (Benson and Kulkarni 2011). Cleaning regimes are a function of campaigning strategies. Feasible campaigning strategies, often designed to minimize cleaning frequency, can also be provided by process modeling tools.
- Properties of chemical components and mixtures – Physical properties such as heat capacity, density, vapor-liquid equilibrium, bubble / dew-points, etc. can affect stream compositions, temperature, pressure, durations of processing steps, and transfer operations, thereby impacting equipment occupancy and utility requirement.
- Equipment sizing information – It is essential that equipment, e.g. vessels, pumps, bioreactors, tanks, etc. be appropriately sized to meet the planned production. Correct redundancies should also be designed in the system to buffer from unforeseen events. Since a significant number of endothermic / exothermic reactions occur within the vessels, suitable relief systems should also be sized and provided. This sizing and redundancy information can be provided by the process modeling tools, and is seldom an output from the DES models.
- Utility generation and consumption profiles – Many production and cleaning operations require heating and cooling utilities, treated water, and industrial gases. If these resources are unavailable in a timely manner, it may result in production delays.

Operations simulation models, specifically DES models, can be used as stand-alone models or in conjunction with the process models to study the following:

- Variability within the process – This is one of the most important features that can be studied using DES tools. It is very well known that variability has a significant impact on operations including equipment occupancy, resource utilization, throughput, inventory levels, etc. Many process modeling tools do not account for this variability component and fail to capture its impact on operations as time progresses.
- Material movement and handling – Process models do account for material movement to some extent, e.g. tracking material moving within pipes connecting two reactors. However, process models do not provide a complete understanding of material movement and handling that is needed throughout the life cycle of the product, e.g. material moving on conveyors, fork trucks, etc. This shortcoming can be addressed by employing DES tools.
- Staging spaces and inventories – It is very important to include these two features in an operations study. Inventory not only influences staging space sizing, but also ties significant amounts of working capital, impacts throughput, utilization of resources, etc. However, inadequate staging spaces can restrict local inventory storage capability and necessitate increased transportation to replenish material. To understand the dynamics of inventory and staging space requirements DES models prove very useful.
- Labor requirements – Process models typically have limited capability to model labor. Additionally, labor required for any support functions (not directly related to process), such as warehousing, material movement, QA / QC staff, etc. usually are not included in the process models. Since labor contributes to and is affected by variability, a feature not well captured by the process modeling tools, and if the intent is to study labor requirements for support functions as well, it becomes important to study labor using DES models.

On the process front, several commercially available tools such as Aspen Plus (Aspen Technology, Inc.), ChemCAD (Chemstations, Inc.), HYSYS (Hyprotech, Ltd./AEA Engineering Software), ILOG Plant PowerOps (ILOG SA), LINDO (LINDO Systems Inc.), PRO/II (Simulation Sciences, Inc.), SuperPro Designer (Intelligen Inc.), VirtECS Scheduler (Advanced Process Combinatorics, Inc.), etc. have been employed for process simulations and scheduling in the pharmaceutical industry. MS Excel is

another tool that can be used for creating models focusing on material balances, equipment sizing, and cost analysis.

DES have also been used in the pharmaceutical industry to model the operational aspects. Some of the established DES tools used for the aforementioned purpose include, but are not restricted to, Arena and Witness (Rockwell Automation Inc.), Crystal Ball (Decisioneering, Inc.), Extend (Imagine That, Inc.), FlexSim (FlexSim Software Products), ProModel (ProModel Corporation) and Simul8 (SIMUL8 Corporation).

It should be noted that the list of modeling and simulation tools mentioned above is not an exhaustive list of all available tools.

4 CASE STUDY – MODELING API MANUFACTURING PLANT

4.1 Problem Overview

The facility under consideration is a multi-product API manufacturing plant. Raw materials are stored in on-site warehouses, secured locations (for controlled substances), and local staging areas near the production suites. The products made in this facility commonly require the use of one or more previously prepared intermediates (product of one manufacturing building used as an ingredient in another manufacturing building). Raw materials and intermediates are moved throughout the facility as needed and stored in a warehouse or local staging depending on when they will be needed next. Certain materials are moved under stringent security protocols just before the production.

The goals of the project were to identify bottlenecks which may exist in either process or operational domain, and which will be revealed as the demand increases over the next 10 years. It was desired to use models to predict these bottlenecks in advance of the throughput increase so that appropriate measures can be taken to address their impact. A separate goal was documentation of the production processes using these models for audits, operator and engineer training and presentations to potential customers.

The study started by stating the objectives and clearly delineating the boundary conditions. As the next step, we recommend identifying and defining all the relevant factors influencing the system. The modeling strategy calls for categorizing all activities taking place throughout the facility into two major categories – process (inside the vessel) and operational (outside the vessel). This strategy of categorizing activities was beneficial for the following reasons: Firstly, it is very difficult to develop models for the entire facility given the tight schedules and budgets. This strategy allows us to break a complex problem of modeling the entire facility into sub-problems and generate sets of detailed objectives which can be answered by developing specific models. Secondly, there was a clear difference in the needs of the process engineers (plant engineers, chemists, and QA engineers) compared to the needs of operations engineers (logistics and warehouse manager, planning and inventory manager). These two groups were interested in getting solutions to problems in their respective areas. Also, these models were going to be retained and used in the future by these Subject Matter Experts (SMEs) and area owners. Thus, this distinction was helpful as it allowed us to answer domain-specific questions and becomes easier for maintenance and future upgrades. Thirdly, it helped us select the desired modeling tools (software), depending on its capabilities, to answer the given set of objectives.

The remainder of the simulation and modeling study followed steps suggested by Law and Kelton (2000), namely, data collection and data processing, baseline model development, model verification and validation and scenario analysis. This was followed by identifying improvement opportunities and developing an implementation plan, documenting results and lessons learned. It is highly recommended that documentation, an important aspect of any study, should be updated regularly as the study progresses and not at the very end of the study project.

In this case study, following our proposed methodology, we defined the system boundaries and project objectives (see Table 1). As aforementioned, all processes occurring within the vessels, e.g. heat of reactions, heat and material balances, generation / consumption of utilities (e.g. WFI and PW), etc.

were studied using process models; and everything external to these vessels, e.g. all logistics and material handling operations, warehousing policies, inventory needs, etc. were evaluated using operational models.

Table 1: Overall objectives of the simulation study.

Team	Objectives	Tools Employed
Process Engineering	Determine feasibility of adopting new technologies	SuperPro Designer
	Process description and documentation	
	Generate material and energy balances	
	Track yield losses through the process	
Process Engineering and Management	Develop campaigning strategies to meet target throughputs	SchedulePro
	Evaluate product re-assignments to alternate equipment	
	Identify equipment and utility bottlenecks	
Logistics and Warehousing	Determine material handling and delivery strategy to ensure constant supply without increasing on-hand inventory	FlexSim
	Evaluate and compare satellite vs. central warehouse options	
	Assess adequacy of material handling equipment	
	Identify high traffic routes to define alternate transportation routes or propose road widening project	
	Gage capacity of special storage conditions (e.g. corrosives, flammables, hazardous, etc.) within production buildings	

4.2 Data Collection, Model Development and Results

Data collection efforts included extracting information from documentation provided, including batch records, bill of materials, process flow diagrams, interview with SMEs and on-site observations. Numerical data, coupled with the process understanding gained from documents reviewed and SME interviews, were used to develop input tables in MS-Excel. Data elements for process models included process and setup times, utility generation and usage data, physical properties of materials, and tank storage capacities, to name a few. Process constraints were also identified during the interview process.

Data elements collected for operational models included cycle times, current number of equipment, headcount, number of pallet locations, physical space available within production suites, etc. All important activities were closely shadowed to understand the material, people and information flows. Collected information was examined for outliers, documented and verified for accuracy with the SMEs. Wherever possible, data was fitted to an appropriate probability distribution. For those instances where enough data was not available to use distributions, either triangular or uniform distributions were used. Outputs from the process models were used as inputs to either another process model or the operational models. All inputs to and from the process model to the operational models are shown in Figure 1.

Process models were built in SuperPro Designer to solve material and energy balances for every intermediate and final product. A sample process model is shown in Figure 2. This tool accurately estimated the amount of material consumed and generated (by-product or waste) for a given batch of intermediate or final product. Additionally, a feasible schedule of equipment occupancies, linked by transfer operations between equipment, all for a single batch of each product was produced. If multiple batches of the same product are desired, SuperPro will simulate the production of this batch campaign with the batches lined up back-to-back or with any fixed spacing between them.

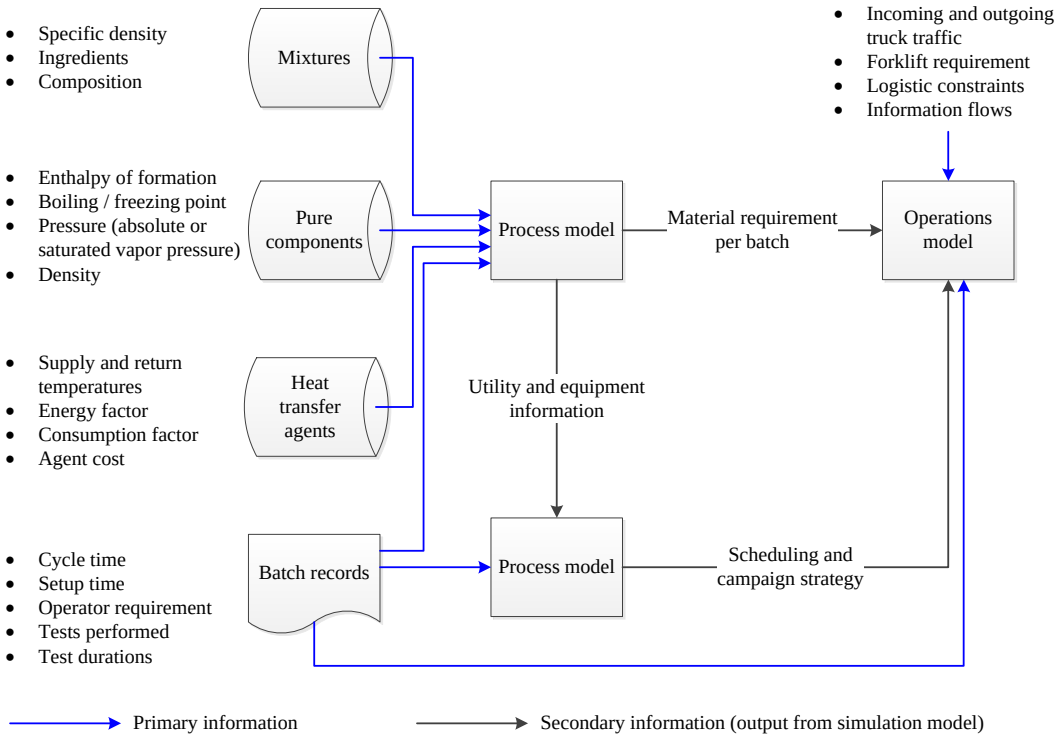

Figure 1: Inputs to process and operations model.

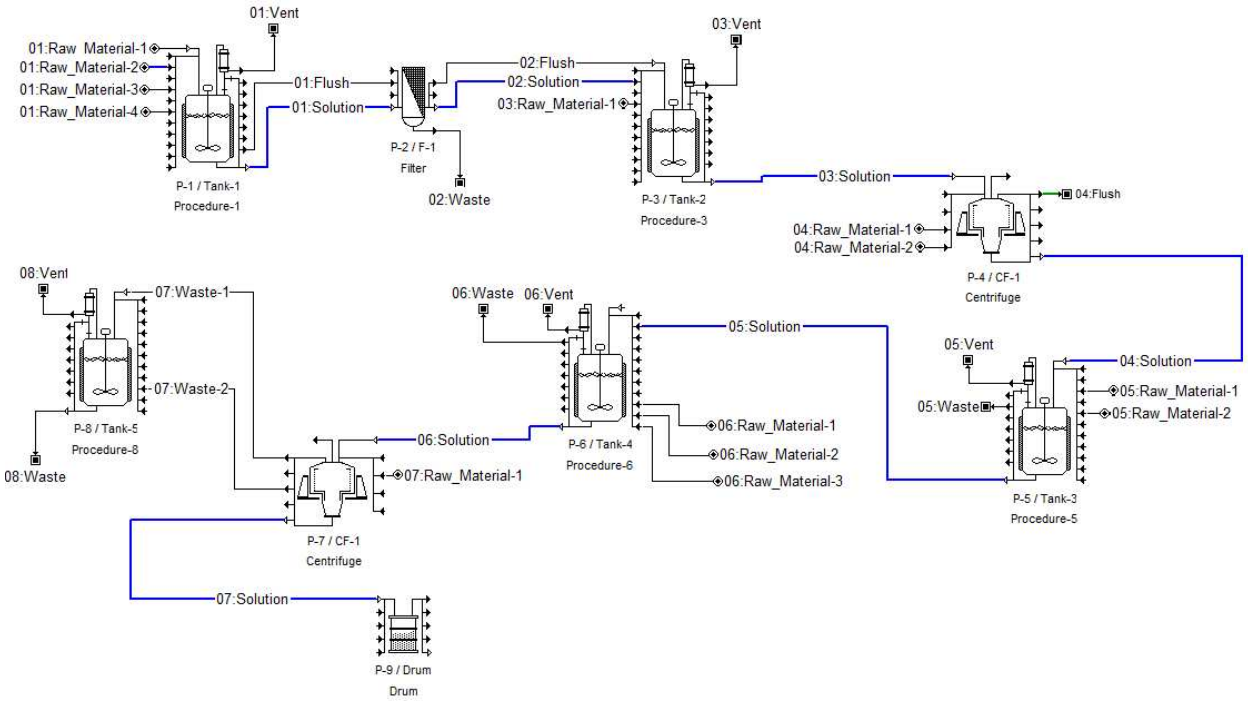

Figure 2: Process model developed in SuperPro Designer.

After addressing the material and energy balancing problem, SchedulePro modeling software was employed. This was particularly important to overcome the single product scheduling issue with SuperPro Designer. Specific outputs from the SuperPro models acted as inputs to the SchedulePro models. Since multiple products are produced in the facility under consideration, SchedulePro was used to develop feasible production schedules (Figure 3). Bottleneck equipment were identified based on the equipment occupancy information generated by SchedulePro.

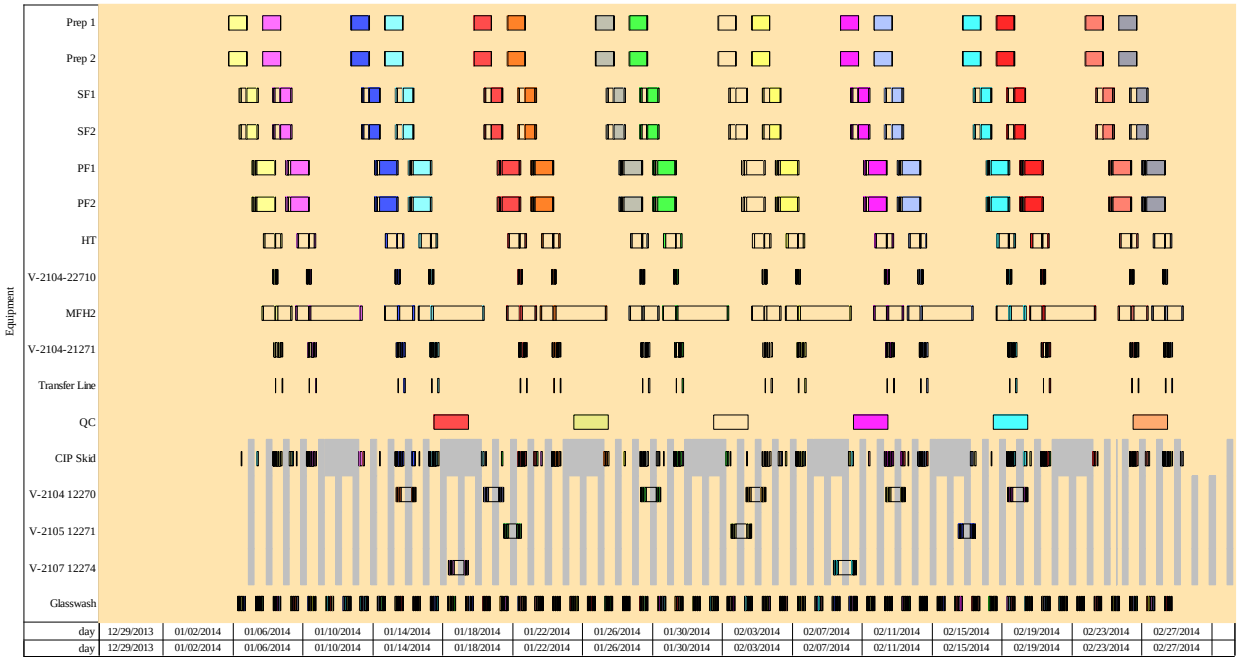

Figure 3: Equipment occupancy chart showing equipment occupancy and estimated campaign length. Each color represents a different intermediate or final product.

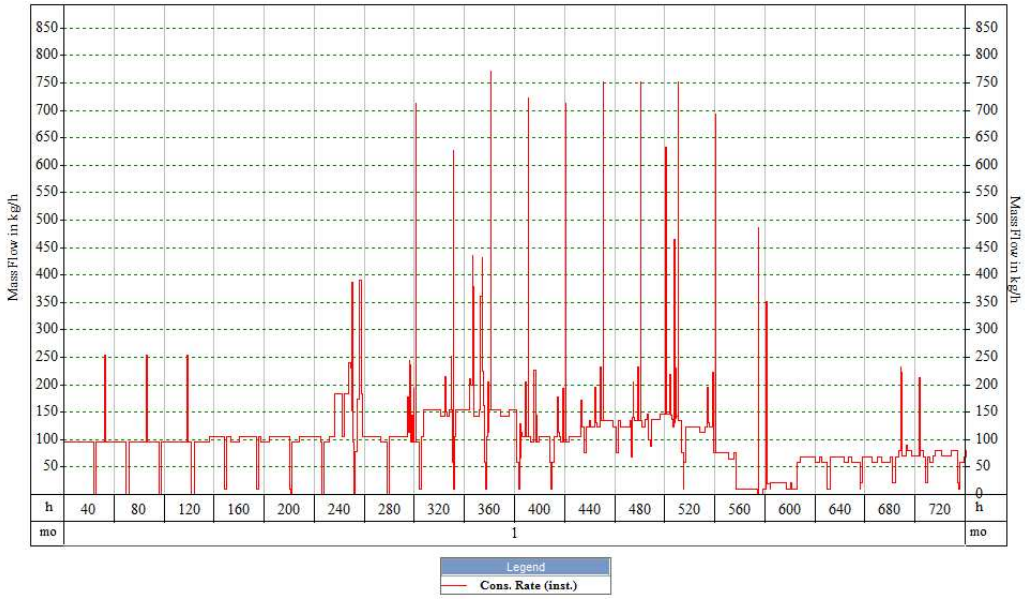

Figure 4: Instantaneous utility demand versus time for the proposed schedule.

Additionally, the models estimated time to complete these campaigns satisfying equipment and resource constraints. SchedulePro was also used to check for equipment and utility requirements as a function of the feasible schedule generated (Figure 4). However, this portion of the effort assumed that material / headcount was available when needed, and that there was sufficient space to move intermediates and final products out of the processing equipment. This shortcoming was addressed by the operational model.

From an operations perspective, to satisfy the logistics and warehousing team's objectives, it was decided to include all the site warehouses, Material Handling & Delivery (MH&D) equipment and personnel, replenishment strategies to individual buildings, and storage locations requiring special safety and containment requirements. The operational models were developed using FlexSim DES software. An actual layout of the entire site was imported in this tool to lay down travel paths for fork trucks, personnel and incoming / outgoing trucks and tanker traffic. A modified snapshot of the FlexSim model is shown in Figure 5.

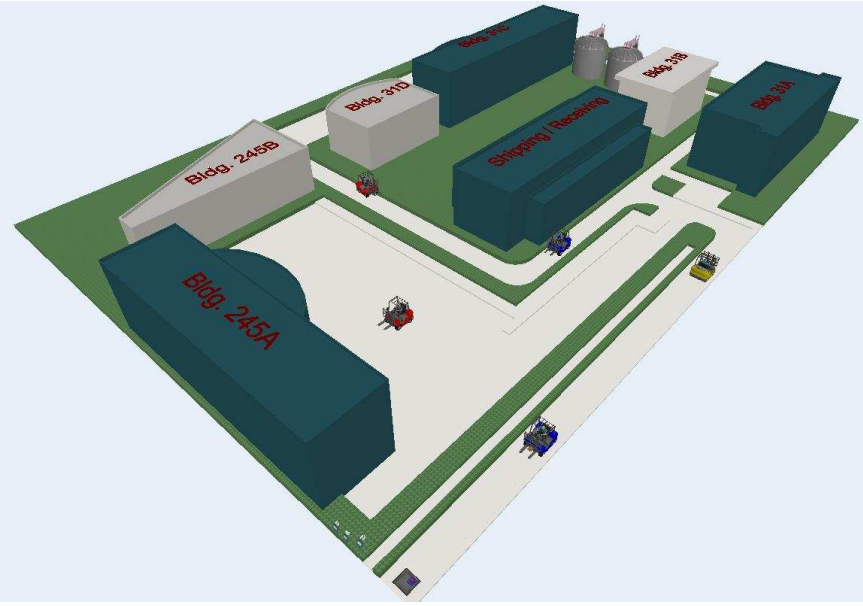

Figure 5: Snapshot of the operations DES model.

Material consumption / generation information (volume) was obtained from the process models. Since all material on the site moved in drums (different type of drums are used for different processes, depending on the type of drum used, the MH&D equipment, and the number of trips to a particular building changed), it was important to understand material consumption and generation rates to estimate number of drums, trips and MH&D equipment needs. The schedule obtained from SchedulePro, including batch start times and durations were passed as inputs into FlexSim. Variability in process durations was included in FlexSim. Raw materials were ordered based on several alternate replenishment algorithms. Also, the (unrealistic) assumptions used in the SchedulePro models regarding resource availability were modeled as hard constraints to account for any production losses due to resource availability issues.

The adopted operational modeling approach was to include one product at a time, verify the flows and overall model for logical accuracy, add another product and repeat the process until all the products were included. This approach greatly simplified model debugging process. The baseline model was validated against current operating conditions and volumes.

These operational models were then used for scenario analysis with an intent to meet the objectives put forth by the logistics and warehousing team. The simulations allowed comparison of alternatives to

understand possible constraints imposed by the transportation network, to estimate necessary local staging and warehouse space required, evaluate their impact on transportation and inventory requirements, and the cost of each scenario. After a thorough analysis, the following outcomes were reached – decision on building a central warehouse, location to construct this central warehouse facility, number of pallet locations, recommendations on MH&D equipment to handle different product mixes, headcount needs, storage space needs within individual buildings, and inputs to vault sizing and racking systems.

Over 50 process models and 7 operational models were created and studied in a span of four months. All the modeling procedures, inputs, assumptions and outputs were documented. Based on the identified equipment bottlenecks, a phased plan was developed to either replace current equipment or add more equipment and headcount over time. Additional engineering changes, e.g. adding mechanical units for certain process buildings, piping changes, installation of water generation systems, etc. were justified. Demolition plan for certain buildings, including two satellite warehouses, were proposed. However, care was taken to ensure that none of these activities would impact ongoing production. Decision to widen the high traffic corridor was taken. Alternate travel paths for MH&D personnel were designated. A group of chemical and industrial engineers, were identified, trained and assigned the responsibility to maintain and update the simulation models.

It should be noted that the site previously did not use simulations to make such decisions. Most of the decisions were based on SMEs' opinion, experience and intuitions. The proposed simulations approach helped the site select and prioritize their projects (different 'what-if' scenarios) and allocate capital budget. Additionally, the approach helped provide accurate, data-drive results in a timely manner, as opposed to the previous intuitive approach the site was using.

5 CONCLUSIONS

Pharmaceutical manufacturing facility is a complex system facing several process, operational and regulatory constraints. Computer aided modeling and simulation is an efficient method of representing this system in order to improve understanding, identify bottlenecks, reduce operational costs and develop rational implementation plans. Literature reviewed is rich with modeling and simulation applications in the pharmaceutical industry. Several different modeling and simulation tools are available which can be employed to study different problems. However, it should be noted that models should be built to answer specific questions, and tools should be selected to facilitate the modeling efforts.

Building a single model which captures all important aspects of manufacturing and the facility can be time-consuming and overly expensive. Additionally, it becomes difficult for multiple modelers to work on the same model at the same. This can increase the time to complete the modeling effort. Furthermore, even if a single model approach were used, the resultant complexity may limit the model's usefulness in the future. For these aforementioned reasons, a method of breaking the problem into two parts, process and operational, is proposed. This division allows each part to be addressed with a software tool which is more appropriate to its characteristics and desired outputs. Also, smaller models are easy to understand and maintain.

As demonstrated with the API manufacturing case study, each model provides its customers with the results they needed while maintaining a common design basis. As seen from the case study, outputs of the process models can act as inputs to other process models and / or operational models. The models were used to create strategic plans to replace or install equipment, add headcount and staging space, address warehousing and logistics needs. These models have been since maintained by the user group and tested to understand impact of significant changes process / operational changes proposed on the facility needs.

Similar classifications schemes can be employed to study other large and complex systems. Depending on the objective of the study, the system can be classified as physical, chemical, biological, operational, and economical systems; and appropriate tools can be employed to study them. The approach used in the case study can be applied to study similar problem instances observed in the chemical, oil, compressed gases, food, and nutraceuticals domain.

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