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This article presents a case study focusing on the design and optimization of a large scale biopharmaceutical facility using process simulation and scheduling tools.

Design and Optimization of a Large Scale Biopharmaceutical Facility Using Process Simulation and Scheduling Tools

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Introduction

The global competition in the biopharmaceutical industry and the increased demand for affordable and effective medicines has shifted the industry's focus on manufacturing efficiency. Therefore, process development and design are gaining importance. For new products, it is crucial to minimize market entry time without compromising product and process quality. This is particularly true for biopharmaceuticals for which it is commonly said that "the process makes the product" and process changes are very difficult to implement after the regulatory approval of a new product.

Process development scientists have a short time window to optimize the process of a promising new molecule. Similarly, engineering teams face challenges within the design and construction of new production lines and facilities required for manufacturing newly developed products. The challenges of both groups can be lessened by the use of appropriate computer aids, such as process simulators and production scheduling tools.[1,2,3,4]

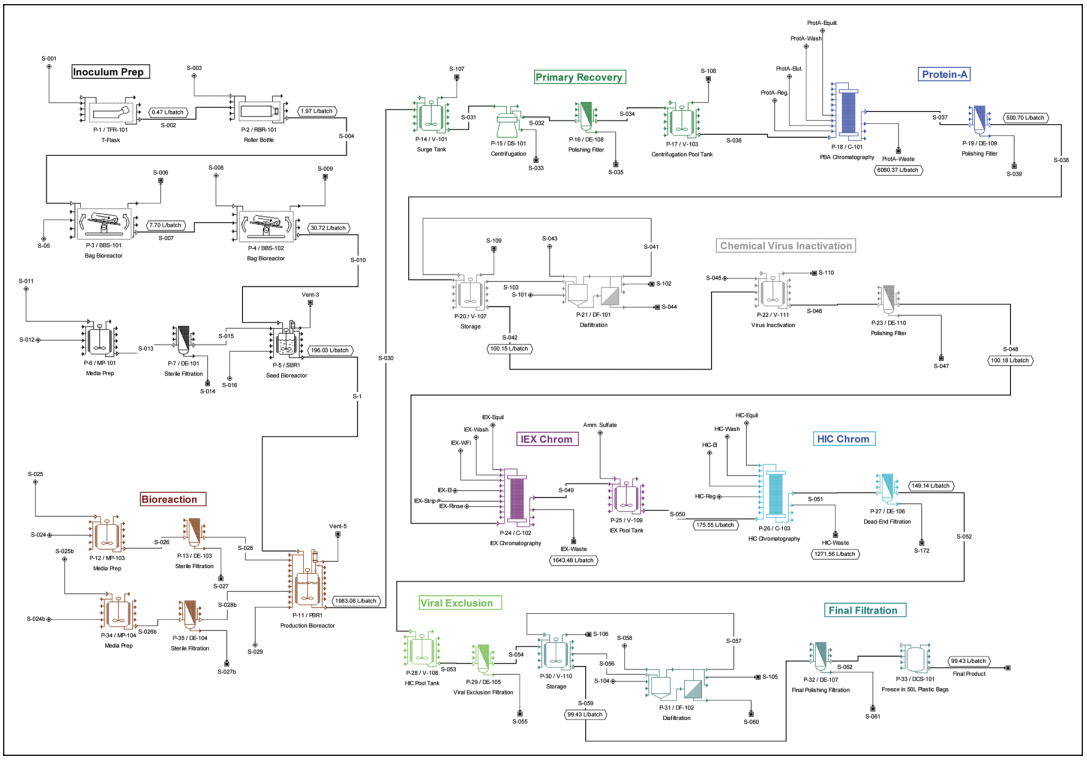

Figure 1. Monoclonal antibody production flowsheet.

The objective of our Large Scale Biotech (LSB) project was to support the design of a new production facility at an existing manufacturing site of Merck Serono (Vevey, Switzerland). The plant will initially be dedicated to the parallel production of two different molecules, a Monoclonal Antibody (MAb) and a fusion protein. Additional MAb and related molecules from the Merck Serono pipeline are expected to be manufactured in the same facility in the future. The limited space available for the construction of the new facility made the design very challenging and the project highly complex. A computerized process model was developed at an early stage of the basic design phase of the project to support all design activities and facilitate scenario analysis and evaluation. This article describes the strategy followed for the development of the model, the challenges faced, and the benefits derived from this effort.

Monoclonal Antibody Production

Monoclonal Antibodies (MAbs) are large protein molecules used to treat a wide variety of illnesses, such as rheumatoid arthritis, psoriasis, Crohn's disease, transplant rejection, and a variety of cancers. They constitute the fastest growing segment in the biopharmaceutical industry. More than 20 MAbs and fusion proteins are approved for sale in the United States and Europe[5,6] and approximately 200 MAbs are in clinical trials for a wide variety of indications.[5,7] The market is growing by more than 15% per year and is expected to exceed $30 billion in 2010.[8,9,10,11]

Figure 1 displays the flow diagram of a typical MAb process. The left-hand-side of the diagram displays the seed train (for inoculum preparation) and the production bioreactor(s). Such processes include several cell expansion steps as well as two to three seed bioreactor steps to expand the volume of the inoculum. Cell growth and product formation in the production bioreactor takes usually 11 days. Considering the time for cleaning and turnaround activities, the overall cycle time of the production bioreactors that operate in fed-batch mode is around 14 days. That includes some idle time to synchronize the cycle time and to accommodate batch to batch changes in fermentation time in a way that a fixed amount of batches are produced every week. After a production bioreactor run is completed, primary recovery is initiated, which typically includes centrifugation for cell removal followed by filtration. The purification part of the process that follows usually includes three chromatography steps, dia-filtration/concentration steps, and virus removal/inactivation steps. The overall product recovery yield is around 70 to 80%.

Such processes utilize a large number of buffer and cleaning solutions (usually 20 to 30) that must be prepared on time and be ready for delivery when required by the main process. The preparation and storage of such buffers involve a large number of tanks. Most of the tanks are used for the preparation and storage of multiple solutions and require cleaning after each use. Estimating the number and size of such tanks is a challenging task during the design of such facilities. Figure 1 does not display buffer preparation and holding activities. However, such activities were taken into account in the models developed for the needs of this project.

Our design project involved the modeling and optimization of a facility equipped with two production lines, each capable of producing a different MAb. Each line includes four production bioreactors feeding a single purification train. The two production lines have their own independent main equipment, but share tanks for media and buffer preparation. They also share all utilities, such as steam, Water for Injection (WFI), Highly Purified Water (HPW), waste collection, and treatment systems, etc.

Process Simulation Tools – Evaluation and Selection

Computer-aided process design and simulation tools have been used in the chemical and petrochemical industries since the early 1960s. Simulators for those industries have been designed to model continuous processes and their transient behavior. However, most biopharmaceutical products are produced in batch and semi-continuous mode. Such processes are best modeled with batch process simulators that account for time-dependency and sequencing of events. In the mid 1990s, Aspen Technology, Inc. introduced *Batch Plus* (now called Aspen Batch Process Developer) a recipe-driven simulator that targeted batch pharmaceutical processes. Around the same time, Intelligen, Inc. (Scotch Plains, New Jersey) introduced *SuperPro Designer*. The initial focus of SuperPro was on bioprocessing. Over the years, its scope has been expanded to include modeling of small-molecule Active Pharmaceutical Ingredients (APIs) and secondary pharmaceutical manufacturing processes. In 2005, Intelligen introduced *SchedulePro*, a production planning and scheduling tool. SchedulePro also functions as a modeling tool that facilitates design, debottlenecking, and capacity analysis of multi-product facilities that operate in batch and semi-continuous mode.

Discrete-event simulators also have found applications in the pharmaceutical industry, especially in the modeling of secondary pharmaceutical manufacturing processes. Established tools of this type include *ProModel* from ProModel Corporation (Orem, Utah), *Arena* and *Witness* from Rockwell Automation, Inc. (Milwaukee, Wisconsin), and *Extend* from Imagine That, Inc. (San Jose, California). The focus of models developed with such tools is usually on the minute-by-minute time-dependency of events and on animation of the process. Discrete event simulators are often used to evaluate the impact of variation on step duration and random events, such as equipment failures and process delays. Material balances, equipment sizing, and cost analysis tasks are usually out of the scope of such models. Some of these tools are quite customizable and third party companies occasionally use them as platforms to create industry-specific modules. For instance, BioPharm Services, Ltd. (Bucks, UK) have created an Extend-based module with emphasis on biopharmaceutical processes.

Microsoft Excel is another common platform for creating models for pharmaceutical processes that focus on material balances, equipment sizing, and cost analysis. Some companies have even developed models in Excel that capture the

time-dependency of batch processes. This is typically done by writing extensive code (in the form of macros and subroutines) in Visual Basic for Applications (VBA) that comes with Excel. *K-TOPS* from Biokinetics, Inc. (Philadelphia, Pennsylvania) belongs to this category.

Engineers at Merck KGaA (the parent company of Merck Serono) have had experience with chemical/pharmaceutical process simulators like Batch Plus and planning tools like *Orion-Pi* from Axxom Software AG (Munich, Germany) and *SimPlan* from SimPlan AG (Munich, Germany). Batch Plus was initially considered for the project, but it was not finally adopted because of its limited bioprocess modeling and advanced scheduling capabilities. Instead, SuperPro Designer and SchedulePro were selected because the combination of the two tools satisfied both the modeling as well as the scheduling objectives of the project. SuperPro Designer can effectively model the bioprocess recipes, which can then be exported to SchedulePro to generate representative production schedules for the combined operation of the two production lines, thus enabling visualization of the utilization of shared resources, such as buffer preparation tanks and utilities. Another reason for the selection of these tools was the fact that SuperPro and SchedulePro had already been adopted by the research and engineering departments at the Vevey site of Merck Serono where the new facility was going to be constructed. The adoption of common tools by multiple departments created a common platform of communication among the various teams and provided assurance that the start-up and handover phases would be smooth.

Building a Model in a Batch Process Simulator

The first step in building a simulation model is always the collection of information about the process. In this case, draft versions of process descriptions and block flow diagrams, which contained information about material inputs and operating parameters, were available. Missing data forced the team to make assumptions after consulting with the operations department. Rough estimates were used at the start of the project for unknown process parameters and operating times. As the project progressed, the assumptions were updated several times and were thoroughly documented in order to comprehend and track the development of the various models.

The steps of building a batch process model are generally the same for all batch process simulation tools. The best practice is to build the model step-by-step, gradually checking the functionality of its parts. The registration of materials (pure components and mixtures) is usually the first step. Next, the flow diagram (Figure 1) is developed by putting together the required unit procedures and joining them with material flow streams. Operations are added to unit procedures (see next paragraph for explanation) and their operating conditions and performance parameters are specified.

In SuperPro Designer, the representation of a batch process model is loosely based on the ISA S-88 standards for batch recipe representation.[12] A batch process model is in essence a batch recipe that describes how to a make a certain quantity of a specific product. A single basic processing step is called a "unit procedure" as opposed to a "unit operation," which is a term used for continuous processes. The individual tasks contained in a procedure (e.g., Transfer in, Ferment, Transfer Out, CIP, etc.) are called "operations." A unit procedure is represented on the flowsheet with a single icon that represents the main equipment used. Figure 2 displays the dialog through which operations are added to a vessel unit procedure. On the left-hand side of that dialog, the program displays the operations that are available in the context of a vessel procedure; on the right-hand side, it displays the registered operations for the edited procedure. The two-level representation of processing tasks (operations in the context of unit procedures) enables users to describe and model batch processes in detail.

For every operation within a unit procedure, the simulator solves a mathematical model representing the material and energy balance equations. Equipment-sizing calculations are performed based on the results obtained by the material balances. If multiple operations within a unit procedure dictate different sizes for a certain piece of equipment, the software reconciles the different demands and selects an equipment size that is appropriate for all operations. The equipment is sized so that it is large enough (e.g., vessels are not overfilled during any operation), but not larger than necessary (in order to minimize capital costs). Equipment sizes also can be specified by the user, in which case, the simulator checks to make sure that the provided size is adequate. For certain types of equipment, minimum size requirements also are taken into account in order to satisfy constraints, such as minimum stirring volume in vessels.

The outputs of batch process simulators include the following:

- visual representation of the entire process
- material and energy balances
- sizing of equipment and utilities
- estimation of capital and operating costs
- process scheduling and cycle time analysis

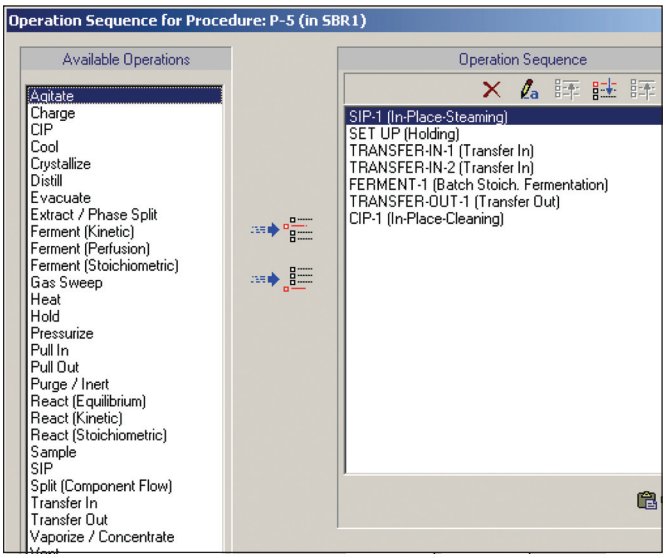

Figure 2. Specifying the operations of a unit procedure.

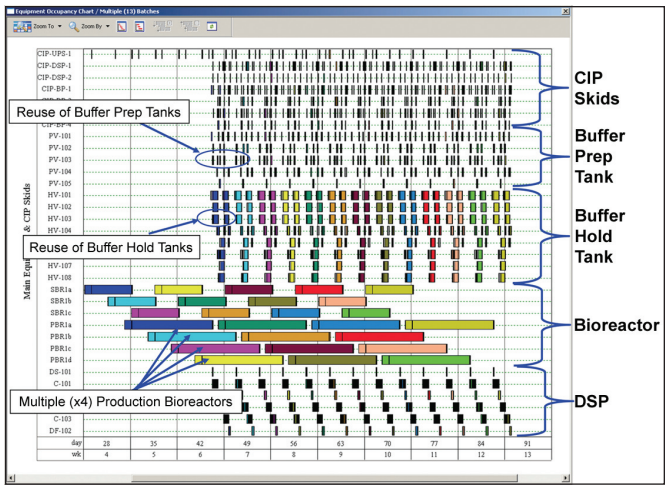

Figure 3. Equipment occupancy chart.

- throughput analysis
- environmental impact assessment

With respect to process scheduling and cycle time analysis, the results are typically visualized with Gantt charts that display equipment occupancy as a function of time - *Figure 3*. Equipment items grouped by type are listed on the y-axis and time is on the x-axis. The horizontal bars in the chart represent occupancy of the corresponding equipment by a procedure during a time interval. Different colors are used to represent different batches. Multiple bars of the same color on the same line represent reuse of a piece of equipment within a batch, while bars of different colors correspond to activities (unit procedures) of different batches. Scheduling conflicts arising from overlapping activities that share the same equipment are displayed with multiple lines (one for each conflicting activity) and exclamation marks on the y-axis. This type of chart enables engineers to resolve scheduling conflicts and optimize the cycle time of the process.

Modeling the Multi-Product Facility

After the SuperPro Designer models had been developed, the individual process models (recipes) were exported to SchedulePro for the generation of the multi-product model. Within SchedulePro, scheduling information imported from SuperPro Designer related to processing tasks can be expanded in the following ways:

- For every procedure, an equipment pool (instead of a single equipment) can be declared representing the list of alternative equipment that could potentially host that procedure.
- Auxiliary equipment (e.g., rinse in place skids and transfer panels) can be assigned, possibly through pools to operations.
- Flexible delays (i.e., the ability to delay the start of an operation if the resources it requires are not available) can be declared, thus relaxing the rigidity in executing a recipe.
- The general availability of resources in time can be declared through a calendar.

All these extra features proved very useful especially in modeling the media and buffer preparation tasks. The multi-product model offered us the ability to represent and visualize the demand of shared resources, such as media and buffer preparation tanks, utility generation systems, and bio-waste treatment systems. The structure and boundaries of the multi-product model are shown in Figure 4.

As soon as the multi-product model was constructed, it was used to answer a wide variety of questions concerning utility and raw material consumption, potential scheduling conflicts, and plant capacity issues.

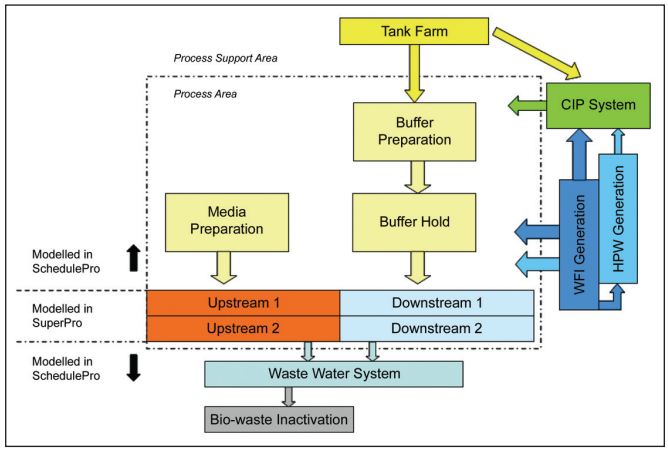

Figure 4. Structure and boundaries of the multi-product model.

Challenges Related to Model Development and Validation

The processes that were analyzed in this project have been developed using a platform technology approach that aims to standardize the number and the sequence of the production steps as well as the media and buffer solutions used. All process parameters that affect product quality (e.g., bed height of chromatography purification steps) were fixed by the end of process development. Such process parameters were not altered during the scope of this project. Instead, the focus was on engineering parameters that affect capital cost and capacity (e.g., number and size of vessels for buffer preparation and storage, requirement for transfer lines, cleaning skids, etc.).

Keeping the models up to date proved to be quite challenging because the design of the facility underwent many changes. The collection of information concerning changes in the processes and the general plant design is a tedious and time-consuming task, due to the fact that many people are involved. It would be advisable, for future practitioners, to develop an appropriate information workflow and change-management process that includes the simulation team, thus enabling the members of the simulation team to have constant access to the latest process and plant information.

The validation of the model was based on information that was available to the team (e.g., process description, op-

erational experience based on past runs, analytical results, etc.). The validation of the process parameters was based on batch records from previous runs carried out by the process development department. Values from existing processes were used as a first approximation for operations that are similar in other bioprocesses, such as buffer/media preparation and CIP/SIP activities.

The modeling of the buffer preparation area was one of the most challenging tasks of the simulation. That was due to the fact that many constraints had to be taken into account - *Figure 5*. In terms of main equipment, this area included several buffer preparation vessels. The list of auxiliary equipment included three closed powder transfer systems and two Rinse-in-Place (RIP) skids. The model included interfaces to the utilities that are used in buffer preparation and an interface to the tank farm. The preparation of the 40 different buffers required by the two processes was represented with 40 different recipes. The large number of buffers required, even though platform technology is adopted, is due to the different physical properties of the two products (the first product is a monoclonal antibody and the second is a fusion protein). Modeling of buffer preparation and hold activities was particularly challenging because it involved numerous connectivity constraints. For example, if a certain ingredient from the tank farm was required for the preparation of a certain buffer, but not all preparation vessels were equipped with a supply line from the tank farm for this certain ingredient, then some of the preparation vessels could not be used for preparing that specific buffer. These constraints were modeled by specifying appropriate equipment pools for the various buffer preparation procedures.

The handling of shift constraints also was quite challenging. Since certain areas of the production facility were planned to operate in a two-shift-mode, appropriate outages (downtime) had to be specified for the involved equipment, and flexible delays had to be added to some of the operations. Using flexible delays, the tool was able to automatically shift the start of an operation (or interrupt an operation) in order to accommodate facility downtime and/or unavailability of required resources. The tool also is able to handle material supply, utility, and personnel constraints. However, such constraints add to the complexity of the model and increase the computation time significantly. If a problem is over constrained, the tool may even fail to generate a meaningful solution.

Discussion of Results

The models were mainly used to size shared resources (e.g., utilities and media/buffer preparation tanks) and evaluate various capacity scenarios. The impact of different shift patterns on equipment demand for buffer preparation also was evaluated. Using such tools it is easy to quantify the trade-off between labor cost and capital investment when management wants to decide whether buffers should only be prepared during the day shifts or around the clock. The former option involves lower labor cost, but higher capital investment. However, it also constitutes a solution of higher inherent capacity. More specifically, if product titers increase

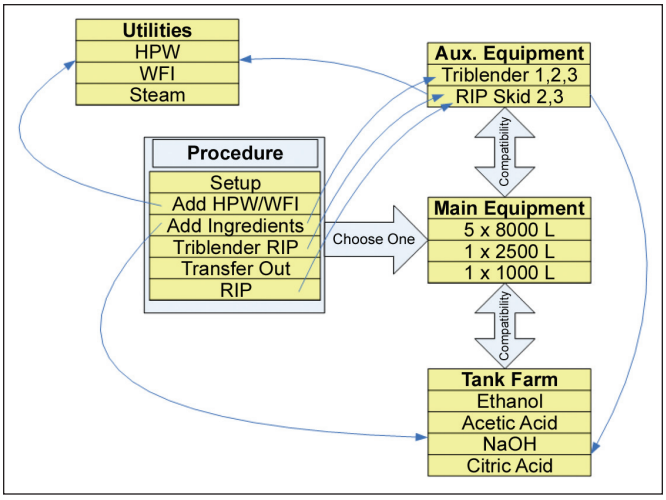

Figure 5. Buffer preparation constraints.

in the future and there is a need for reduced purification cycle times, the plant may switch to a three-shift operation for buffer preparation in order to accommodate the increased demands of the purification trains.

Sizing of WFI systems is simplified considerably using these tools. A WFI system consists of a still that generates the distilled water, a surge tank, and a circulation loop for delivering the material around the plant. Plant capacity may be limited by any of the following:

- The plant cannot, on average, consume more water than the still can generate.
- The peak demand cannot exceed the capacity of the circulation system.
- The surge vessel must be large enough to maintain capacity during peak demand.
- Periodic circulation loop sanitization cycles may interrupt all WFI draws.

Process simulation can provide reasonable estimates for the sizes of the still, the surge tank, and the pumping capacity of the circulation loop. Figure 6 displays the demand of WFI for

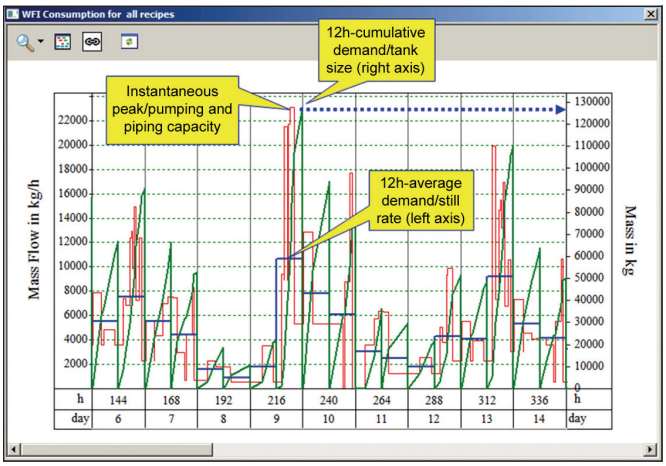

Figure 6. Instantaneous (red lines), 12-h averaged (blue lines), and 12-h cumulative (green lines) WFI demand as a function of time.

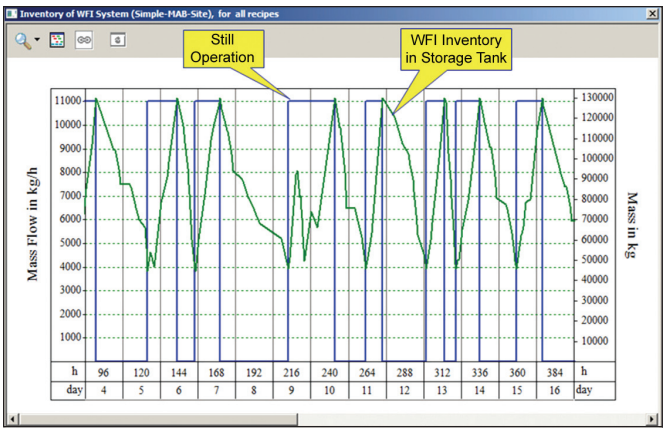

Figure 7. WFI inventory (green lines) and operating frequency of still (blue lines).

such a plant. The chart shows the instantaneous (red lines) and the 12-h average (blue lines) demands. The chart also shows the 12-h cumulative demand (green lines) that corresponds to the y-axis on the right. The peak instantaneous demand indicates the minimum pumping capacity for the system (23,000 kg/h). The peak 12-h average rate provides an estimate for the still capacity (10,600 kg/h) and the corresponding 12-h cumulative peak is an estimate of the surge tank capacity of 128,000 L. The trade-off between still rate and surge capacity can be examined by changing the averaging time. Selecting a longer period predicts a larger surge tank and a lower still rate. Figure 7 displays the inventory profile of WFI in the surge tank (green lines) for a tank size of 130,000 L and a still rate of 11,000 L/h. The still is turned on when the level in the tank falls below 35% and it remains on until the tank is full. The operation rate and frequency of the still is depicted by the blue step-function lines.

Sizing of bio-waste treatment systems can be handled in a similar way. Such systems typically involve two tanks that alternate in operation periodically (while one is receiving, the other is treating a batch of waste material). The peak cumulative amount for the alternating period indicates the minimum capacity of each tank.

The tools also were used to analyze the impact of buffer

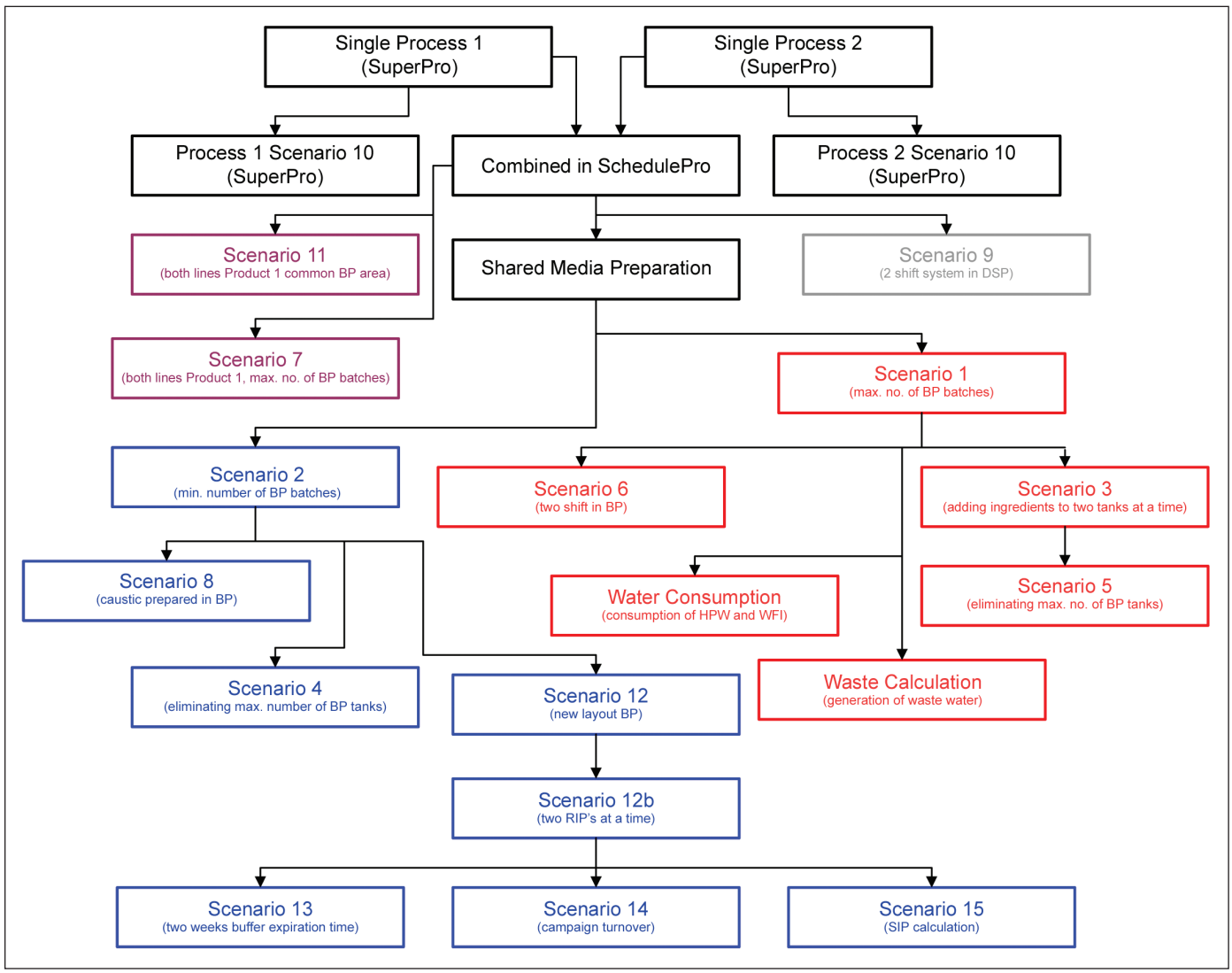

Figure 8. File diagram representing the evolution of the scenarios: Buffer Hold (BH), Buffer Preparation (BP), Rinsing in Place (RIP), and Sterilization in Place (SIP).

expiration times, shift patterns, equipment sizes, and number of equipment items. Approximately, 35 different scenarios were evaluated during the project and most of the scenarios included major model updates. As the project evolved, the team's understanding of the processes, the facility, the underlying links, and constraints improved, and the knowledge gain was used to improve the models. Figure 8 shows the evolution of the models up to scenario No. 15.

As mentioned before, the initial stages of the project focused on the development of the SuperPro models of the two processes (one for each product). The SuperPro models were then combined in SchedulePro to generate the first multi-product model. Next, a rough model representing media preparation was added to the multi-product model. Two different options for buffer preparation and holding were evaluated. Option number one involved refilling of the buffer hold tanks after every batch of the corresponding main process. That led to a set of scenarios where the maximum number of buffer preparation batches was performed (red scenarios in Figure 8). Option number two involved the preparation of larger buffer batches that could supply multiple batches of the main process. That led to a set of scenarios where the minimum number of buffer preparation batches was performed (blue scenarios in Figure 8). The final design evolved out of the blue set of scenarios.

The simulation of the process support areas was quite challenging and required an iterative approach. The buffer preparation area was initially represented with a simplified model. Next, minimum cycle times for each process were specified and the tool was used to generate feasible solutions. Experienced manufacturing engineers were then asked to evaluate the results and confirm that the generated solutions would work out in practice. For questionable solutions, improvements were proposed involving rearrangement of existing equipment or installation of additional equipment. Then, the changes were incorporated into the model and feasibility was checked once again. That worked very well for the buffer preparation area and valuable results were gained from the model. The final model also contained constraints for the delivery lines, the Rinse-in-Place (RIP) skids, the powder transfer systems, the connectivity to the tank farm, and the personnel resources, including shift patterns.

Using the model, a number of potential bottlenecks mainly associated with cleaning equipment and delivery lines were identified and resolved. Capacity analysis enabled the team to identify a number of opportunities for equipment savings. That approach worked especially well for areas with multiple parallel equipment items, such as media and buffer preparation. When analysis revealed that spare capacity existed, resources were gradually removed from the equipment pool and feasibility rechecked. That eventually resulted in infeasible situations. Addition of an extra resource item led to the optimal solution.

Return on Investment

Table A summarizes the subjects that were analyzed and the benefits that were derived from the use of simulation tools. The core of the analysis was done during a period of 12 months. Besides the financial aspects, there were additional benefits that are hard to quantify, but are equally valuable. The common language of communication that process simulation brings to the different stakeholders was probably the most important qualitative benefit. The members of the various teams involved with plant design and operations were able to communicate effectively despite the fact that they were looking at the plant from different points of view: engineering vs. operations vs. maintenance. It was recognized that the graphical presentations generated by such tools helped stakeholders to visualize the problems and come up with solutions more efficiently.

Model Lifecycle Management and Hand-Over to the Operations Team

The simulation work was intended to support the engineering team during the detailed design phase. However, the simulation model continues to live and evolve in the operations

No.	Subject	Initial Approach	Benefits
1	Vessels for the buffer preparation area	The initial number had been estimated using basic engineering assumptions and conservative design.	The detailed model enabled the team to eliminate one 2,500 L and two 8,000 L tanks, resulting in savings of more than $1.2 million (€0.85 million).
2	Sharing of the bulk filtration unit	The initial design assumed a bulk filtration unit for each production line.	Simulation showed that sharing of the unit by the two production lines is feasible, leading to savings of $1.4 million (€1 million).
3	Sizing of HPW and WFI supply systems	The initial design was based on overall averaged demand without taking into account the demand as a function of time.	The detailed simulation model enabled the team to size these systems more accurately.
4	Sizing of waste treatment systems	The initial design was based on simplified spreadsheet models.	The detailed simulation model enabled the team to size these systems more accurately and reduce capital expenditures.
5	Tank farm sizing	In the plant, basic chemicals are stored in the tank farm. The number of tanks and their sizes had been estimated using crude spreadsheet models.	The detailed simulation model enabled the team to size the tanks and the delivery lines more accurately and confirm the reliable supply of these chemicals to the production lines.
6	RIP routing in buffer preparation and holding areas	The initial piping design for this area was so crowded that the simulation team had been asked to evaluate the impact of an alternative piping design which uses fewer pipes and couples the usage of two RIP stations.	The process simulation model showed that this is achievable even with additional rinsing of the tri-blender (a closed introduction system for buffer preparation).

Table A. Subjects analyzed and benefits derived.

department. The detailed model, which constitutes a virtual plant, was handed over to the operations team to help in preparing the personnel for the start-up of the plant and its "routine" production schedule.

The model developed in SchedulePro by importing the SuperPro Designer recipes of the two processes will be transferred into the new production facility and serve as a basis for the scheduling of the future production activities. However, many details included in the model are not necessary for on-going scheduling purposes and lead to long calculation times (several minutes) every time a new production schedule is generated. Currently, a new "simpler" model is under development in SchedulePro to support the scheduling of the future production activities. Less detail will be specified in each unit procedure; for example, the typical operations of a chromatography cycle (e.g., load, wash, elution, regeneration, etc.) will be lumped into a "cycle" activity and consequently a chromatography procedure will be represented as a sequence of the following events: equilibration, cycle-1, cycle-2, … cycle-n, and sanitization. Similar simplifications will be implemented in the procedures that represent buffer preparation and holding activities. The simplified model is intended to be used by the operations department to:

- plan the activities during the start-up of the new production facility
- analyze the bottlenecks at full production capacity
- analyze and schedule changeovers (change from one process to another on a production line)
- consider the impact of equipment maintenance on production schedule
- analyze the influence of a failure or delay of one step on the following steps of a batch and on the scheduling of subsequent batches
- understand interdependencies between shared areas and production lines

Conclusions

When applied early, simulation tools can support plant design and technology transfer and can facilitate the communication between the engineering and operations teams. In this project, process simulation was started early during basic engineering and valuable results were obtained from the process modeling effort. The insight that modeling provided for the design of the support areas, such as buffer preparation and holding, utilities, and equipment cleaning requirements, was of particular importance. In general, process simulation tools, such as SuperPro Designer, are useful for understanding and improving a process whereas process scheduling tools, such as SchedulePro, are beneficial for estimating equipment and utility requirements for multi-product facilities. Scheduling tools also facilitate production planning and scheduling of operating facilities on an on-going basis. Future practitioners are advised to apply process simulation tools as early as possible in a project. That way, more synergies can be achieved. The use of process simulation in this biopharmaceutical project was a success. It provided additional insights on how a design could work in reality. The final models have been handed over to the operations team to be maintained and for future use. The scheduling models can be used for production and maintenance planning as well as scheduling in the future. They might also prove valuable for bringing new products into the facility. The SuperPro process models might serve as basis of decision making for future process changes.

References

1. Petrides, D., Koulouris, A., and Lagonikos, P., "The Role of Process Simulation in Pharmaceutical Process Development and Product Commercialization," *Pharmaceutical Engineering*, January/February 2002, Vol. 22, No. 1, www.ispe.org.
2. Petrides, D., Koulouris, A., and Siletti, C., "Throughput Analysis and Debottlenecking of Biomanufacturing Facilities, A Job for Process Simulators," *BioPharm*, August 2002.
3. Petrides, D., and Siletti, C., "The Role of Process Simulation and Scheduling Tools in the Development and Manufacturing of Biopharmaceuticals, *Proceedings of the 2004 Winter Simulation Conference*, Ingalls, R.G., Rossetti, M. D., Smith, J. S., and Peters, B. A., eds., pp. 2046-2051.
4. Tan, J., Foo, D.C.Y., Kumaresan, S., and Aziz, R.A., "Debottlenecking of a Batch Pharmaceutical Cream Production," *Pharmaceutical Engineering*, July/August 2006, Vol. 26 No. 4, pp. 72-82, www.ispe.org.
5. Pharmaceutical Research and Manufacturers of America, Biotechnology Research Continues to Bolster Arsenal Against Disease with 633 Medicines in Development, PhRMA 2008 survey, www.phrma.org.
6. Walsh, G., "Biopharmaceutical Benchmarks 2006," *Nat. Biotech*, 24(7) 2006:769-775.
7. Farid, S.S., "Established Bioprocesses for Producing Antibodies as a Basis for Future Planning," *Advances in Biochemical Engineering / Biotechnology*, (2006) 101: 1-42, published online 8 June 2006.
8. Pavlou, A.K., Belsey, M.J., "The Therapeutic Antibodies Market to 2008," *European Journal of Pharmaceutics and Biopharmaceutics*, 59(3) 2005:389-396.
9. Jagschies, G., "Where is Biopharmaceutical Manufacturing Heading?," *BioPharm International*, 21(10), October 2008.
10. Farid, S.S., "Economic Drivers and Trade-Offs in Antibody Purification Processes," *BioPharm International,* http://biopharminternational.findpharma.com/biopharm/Downstream+Processing/Economic-Drivers-and-Trade-Offs-in-Antibody-Purifi/ArticleStandard/Article/detail/633295, 2 October 2009.
11. Low, D., O'Leary, R., Pujar, N.S., "Future of Antibody Production," *Journal of Chromatography*, B 848(1), 2007:48-63.

12. Parshall, J., Lamb, L., Applying S88 – Batch Control from a User's Perspective, Instrument Society of America (ISA), Research Triangle Park, North Carolina, USA, 2000.

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