28

THE ROLE OF SIMULATION AND SCHEDULING TOOLS IN THE DEVELOPMENT AND MANUFACTURING OF ACTIVE PHARMACEUTICAL INGREDIENTS

DEMETRI PETRIDES
Intelligen, Inc., Scotch Plains, NJ, USA

ALEXANDROS KOULOURIS
A.T.E.I. of Thessaloniki, Thessaloniki, Greece

CHARLES SILETTI
Intelligen, Inc., Mt. Laurel, NJ, USA

JOSÉ O. JIMÉNEZ
Intelligen, Inc., Amsterdam, The Netherlands

PERICLES T. LAGONIKOS
Merck & Co., Union, NJ, USA

28.1 INTRODUCTION

The global competition in the pharmaceutical industry and the increasing demands by governments and citizens for affordable medicines have driven the industry's attention toward manufacturing efficiency. In this new era, improvements in process and product development approaches and streamlining of manufacturing operations can have a profound impact on the bottom line. Process simulation and scheduling tools can play an important role in this endeavor. The role of such tools in the development and manufacturing of pharmaceutical products has already been reviewed in the past [1]. This chapter focuses on the role of these tools in the development and manufacturing of active pharmaceutical ingredients (APIs), and specifically on small-molecule APIs that are produced through organic synthesis. Information on the role of such tools in the development and manufacturing of biologics is also available in Ref. 2.

Process simulation and scheduling tools serve a variety of purposes throughout the life cycle of product development and commercialization in the pharmaceutical industry [2–6]. During process development, process simulators are used to facilitate the following tasks:

- Represent the entire process on the computer
- Perform material and energy balances
- Estimate the size of equipment
- Calculate demand for labor and utilities as a function of time
- Estimate the cycle time of the process
- Perform cost analysis
- Assess features such as environmental impact

The availability of a good computer-based model improves the understanding of the entire process by the team members and facilitates communication. What-if and sensitivity

Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing Edited by David J. am Ende

analyses are greatly facilitated by such tools. The objective of such studies is to evaluate the impact of critical parameters on various key performance indicators (KPIs), such as production cost, cycle times, and plant throughput. If there is uncertainty for certain input parameters, sensitivity analysis can be supplemented with Monte Carlo simulation to quantify the impact of uncertainty. Cost analysis, especially capital cost estimation, facilitates decisions related to in-house manufacturing versus outsourcing. Estimation of the cost of goods identifies the expensive processing steps and the information generated is used to guide R&D work in a judicious way.

When a process is ready to move from development to manufacturing, process simulation facilitates technology transfer and process fitting. A detailed computer model provides a thorough description of a process in a way that can be readily understood and adjusted by the recipients. Process adjustments are commonly required when a new process is moved into an existing facility whose equipment is not ideally sized for the new process. The simulation model is then used to adjust batch sizes, figure out cycling of certain steps (for equipment that cannot handle a batch in one cycle), estimate recipe cycle times, and so on.

Production scheduling tools play an important role in manufacturing (large scale as well as clinical). They are used to generate production schedules on an ongoing basis in a way that does not violate constraints related to the limited availability of equipment, labor resources, utilities, inventories of materials, and so on. Production scheduling tools close the gap between ERP/MRP-II tools and the plant floor [7, 8]. Production schedules generated by ERP (enterprise resource planning) and MRP-II (manufacturing resource planning) tools are typically based on coarse process representations and approximate plant capacities and, as a result, solutions generated by these tools may not be feasible, especially for multiproduct facilities that operate at high capacity utilization. That often leads to late orders that require expediting and/or to large inventories in order to maintain customer responsiveness. "Lean manufacturing" principles, such as just-in-time production, low work in progress (WIP), and low product inventories cannot be implemented without good production scheduling tools that can accurately estimate capacity.

28.2 COMMERCIALLY AVAILABLE SIMULATION AND SCHEDULING TOOLS

Computer-aided process design and simulation tools have been used in the chemical and petrochemical industries since the early 1960s. Simulators for these industries have been designed to model continuous processes and their transient behavior for process control purposes. Most APIs, however, are produced in batch and semicontinuous modes. Such processes are best modeled with batch process simulators that account for time-dependency and sequencing of events. *Batches* from Batch Process Technologies, Inc. (West Lafayette, IN) was the first simulator specific to batch processing. It was commercialized in the mid-1980s. All of its operation models are dynamic and simulation always involves integration of differential equations over a period of time. In the mid-1990s, Aspen Technology (Burlington, MA) introduced *Batch Plus*, a recipe-driven simulator that targeted batch pharmaceutical processes. Around the same time, Intelligen, Inc. (Scotch Plains, NJ) 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 API and secondary pharmaceutical manufacturing processes.

Discrete-event simulators have also 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, UT), Arena and Witness from Rockwell Automation, Inc. (Milwaukee, WI), and Extend from Imagine That, Inc. (San Jose, CA). The focus of models developed with such tools is usually on the minute-by-minute time-dependency of events and the animation of the process. 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, PA) belongs to this category.

In terms of production scheduling, established tools include *Optiflex* from i2 Technologies, Inc. (Irving, TX), *SAP APO* from SAP AG (Walldorf, Germany), *ILOG* Plant PowerOps from ILOG SA (Gentilly, France), and *Aspen SCM* (formerly Aspen MIMI) from Aspen Technology, Inc. (Burlington, MA). Their success in the pharmaceutical industry, however, has been rather limited so far. Their primary focus on discrete manufacturing (as opposed to batch chemical manufacturing) and their approach to scheduling from a mathematical optimization viewpoint are some of the reasons of the limited market penetration.

SchedulePro from Intelligen, Inc. (Scotch Plains, NJ) is a finite capacity scheduling tool that focuses on scheduling of batch and semicontinuous chemical and related processes. It

is a recipe-driven tool with emphasis on generation of feasible solutions that can be readily improved by the user in an interactive manner.

28.3 MODELING AND ANALYSIS OF AN API MANUFACTURING PROCESS

The steps involved during the development of a model will be illustrated with a simple process that represents the manufacturing of an active compound for skin care applications.

The first step in building a simulation model is always the collection of information about the process. Engineers rely on draft versions of process descriptions, block flow diagrams, and batch sheets from past runs, which contain information on material inputs and operating conditions, among others. Reasonable assumptions are then made for missing data.

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 (see Figure 28.1) is developed by putting together the required unit procedures and joining them with material flow streams. Operations are then added to unit procedures (see the following 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 [9]. A batch process model is in essence a batch recipe that describes how to make a certain quantity of a specific product. The set of operations that comprise a processing step is called a "unit procedure" (as opposed to a unit operation that is a term used for continuous processes). The individual tasks contained in a procedure are called "operations." A unit procedure is represented on the screen with a single equipment-looking icon. Figure 28.2 displays the dialogue through which operations are added to a vessel unit procedure. On the left-hand side of that dialogue, 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 (Charge Quinaldine, Charge Chlorine, Charge Na2CO3, Agitate, etc.). The two-level representation of 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 includes a mathematical model that performs material and energy balance calculations. Based on the material balances, it performs equipment-sizing calculations. 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 and, hence, not overfilled during any operation, but it is no larger than necessary (in order to minimize capital costs). If the equipment size is specified by the user, the simulator checks to make sure that the vessel is not overfilled. In addition, the tool checks to ensure that the vessel contents do not fall below a user-specified minimum volume (e.g., a minimum stirring volume) for applicable operations.

In addition to material balances, equipment sizing, and cycle time analysis, the simulator can be used to carry out cost-of-goods analysis and project economic evaluation. The following sections provide illustrative examples for these features.

Having developed a good model using a process simulator, the user may begin experimenting on the simulator with alternative process setups and operating conditions. This has the potential of reducing the costly and time-consuming laboratory and pilot plant effort. Of course, the GIGO (garbage in, garbage out) principle applies to all computer models. If critical assumptions and input data are incorrect, so will be the outcome of the simulation.

When modeling an existing process, input data required by the model can be extracted from the data recorded by the actual process. A communication channel must, therefore, be established between the modeler and the operations department. The application of some data mining technique is usually required to transform the process data to the form required by the model. When designing a new plant, experience from similar projects can be used to fill in the information gaps. In all cases, a certain level of model verification is necessary after the model is developed. In its simplest form, a review of the results by an experienced engineer can play the role of verification. Running a sensitivity analysis on key input variables can reveal the parameters with the greatest impact on the model's most important outputs. These parameters would then constitute the focal points in the data acquisition effort in an attempt to estimate their values and uncertainty limits with the best possible accuracy.

28.3.1 Design Basis and Process Description

A simple batch process is used to illustrate the steps involved in building a model with SuperPro Designer. It is assumed that the process has been developed at the pilot plant and it is ready to be moved to large-scale manufacturing. Based on input from the marketing department, the objective is to produce at least 27,000 kg of active ingredient per year at a cost of no more than $330 per kilogram. A production suite can be dedicated to this process that includes two 3800 L reactors (R-101 and R-102), one 2.5 m^2 Nutsche filter (NFD-101), and a 10 m^2 tray dryer (TDR-101).

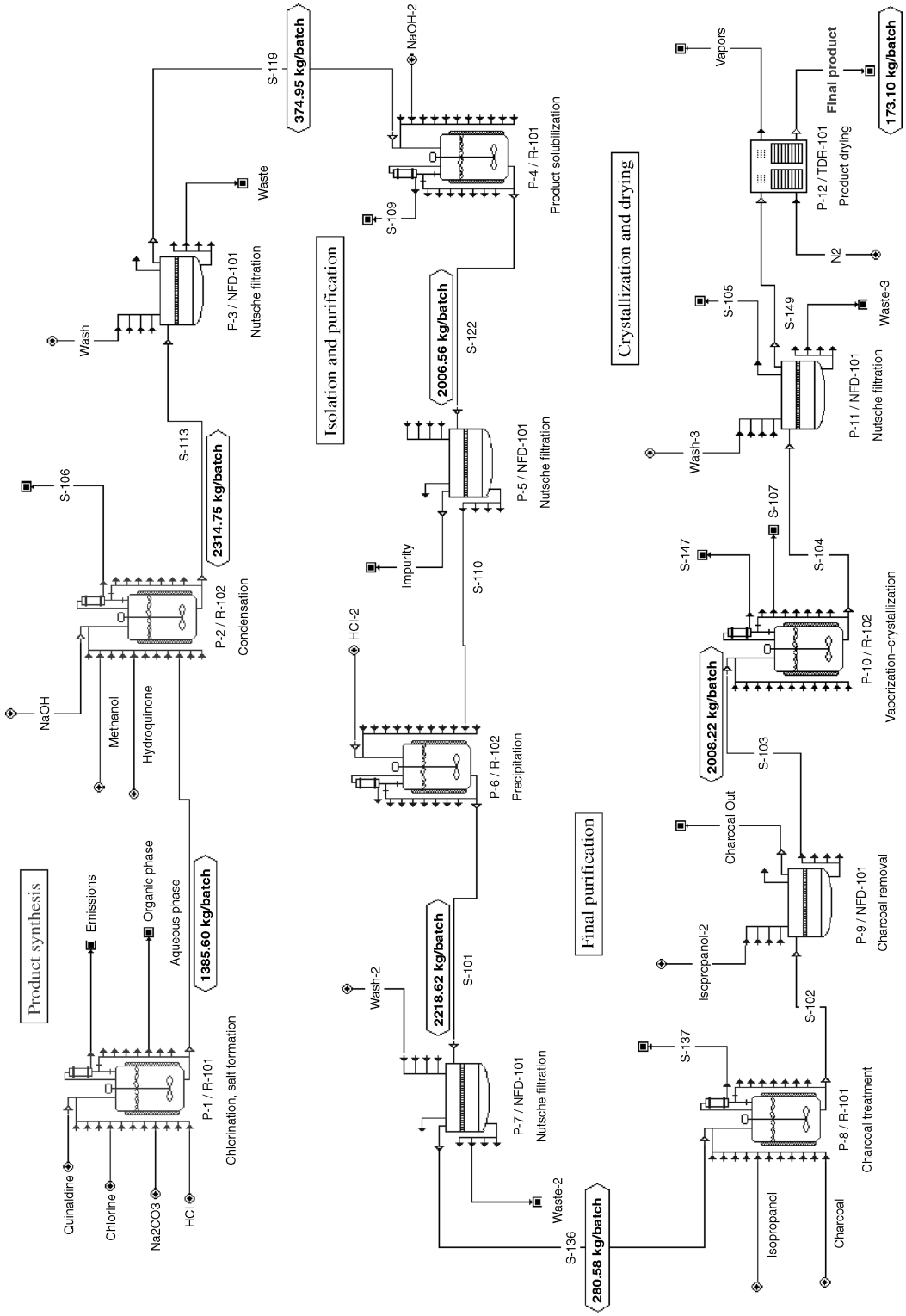

FIGURE 28.1 Flow diagram of the API process.

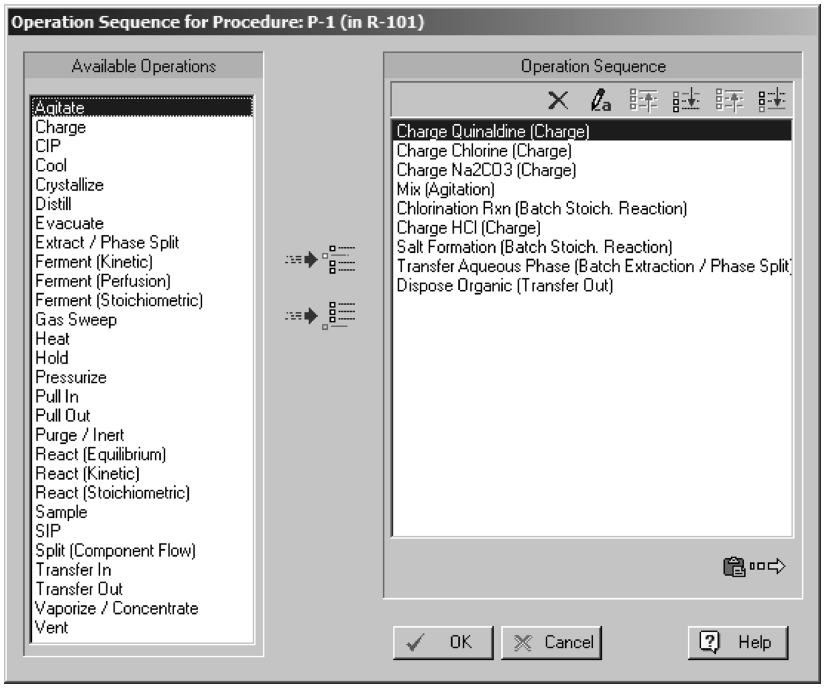

FIGURE 28.2 The operations associated with the first unit procedure in Figure 28.1.

The entire flow sheet of the batch process is shown in Figure 28.1. It is divided into four sections: (1) Product synthesis; (2) Isolation and purification; (3) Final purification; and (4) Crystallization and drying. A flow sheet section in SuperPro Designer is simply a group of unit procedures (processing steps).

The formation of the final product in this example involves 12 unit procedures. The first reaction step (procedure P-1) involves the chlorination of quinaldine. Quinaldine is dissolved in carbon tetrachloride (CCl_4) and reacts with gaseous Cl_2 to form chloroquinaldine[1]. The conversion of the reaction is around 98% (based on amount of quanaldine fed). The generated HCl is then neutralized using Na_2CO_3. The stoichiometry of these reactions is as follows:

$$\text{Quinaldine} + Cl_2 \rightarrow \text{Chloroquinaldine} + HCl$$

$$Na_2CO_3 + HCl \rightarrow NaHCO_3 + NaCl$$

$$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$$

Small amounts of unreacted Cl_2, generated CO_2, and volatilized CCl_4 are vented. The above three reactions occur sequentially in the first reactor vessel (R-101). Next, HCl is added in order to produce chloroquinaldine-HCl. The HCl first neutralizes the remaining $NaHCO_3$ and then reacts with chloroquinaldine to form its salt, according to the following stoichiometries:

$$NaHCO_3 + HCl \rightarrow NaCl + H_2O + CO_2$$

$$\text{Chloroquinaldine} + HCl \rightarrow \text{Chloroquinaldine.HCl}$$

Small amounts of generated CO_2 and volatilized CCl_4 are vented. The presence of water (added with HCl as hydrochloric acid solution) and CCl_4 leads to the formation of two liquid phases. Then, small amounts of unreacted quinaldine and chloroquinaldine are removed with the organic phase. The chloroquinaldine-HCl remains in the aqueous phase. This sequence of operations (including all charges and transfers) requires about 14.5 h.

After removal of the unreacted quinaldine, the condensation of chloroquinaldine and hydroquinone takes place in reactor R-102 (procedure P-2). First, the salt chloroquinaldine-HCl is converted back to chloroquinaldine using NaOH. Then, hydroquinone reacts with NaOH and yields hydroquinone-Na. Finally, chloroquinaldine and hydroquinone-Na react and yield the desired intermediate product. Along with product formation, roughly 2% of chloroquinaldine dimerizes and forms an undesirable by-product impurity. This series of reactions and transfers takes roughly 13.3 h. The stoichiometry of these reactions is as follows:

[1] Note that carbon tetrachloride is an ideal solvent for this specific reaction from a chemistry perspective, but this solvent is considered highly undesirable from an environmental, health, and safety perspective.

$$\text{Chloroquinaldine-HCl} + \text{NaOH} \rightarrow \text{NaCl} + \text{H}_2\text{O} + \text{Chloroquinaldine}$$

$$2\text{Chloroquinaldine} + 2\text{NaOH} \rightarrow 2\text{H}_2\text{O} + 2\text{NaCl} + \text{Impurity}$$

$$\text{Hydroquinone} + \text{NaOH} \rightarrow \text{H}_2\text{O} + \text{Hydroquinone-Na}$$

$$\text{Chloroquinaldine} + \text{Hydroquinone-Na} \rightarrow \text{Product} + \text{NaCl}$$

Both the product and the impurity molecules formed during the condensation reaction precipitate out of solution and are recovered using a Nutsche filter (procedure P-3, filter NFD-101). The product recovery yield is 90%. The filtration, wash, and cake transfer time is 6.4 h.

Next, the product/impurity cake recovered by filtration is added into a NaOH solution in reactor R-101 (procedure P-4). The product molecules react with NaOH to form product-Na, which is soluble in water. The Impurity molecules remain in the solid phase, and are subsequently removed during procedure P-5 in filter NFD-101. The product remains dissolved in the liquors. Procedure P-4 takes about 10 h, and procedure P-5 takes approximately 4 h.

Notice that the single filter (NFD-101) is used by several different procedures. The two reactors are also used for multiple procedures during each batch. Please note that the equipment icons in Figure 28.1 represent unit procedures (processing steps), as opposed to unique pieces of equipment. The procedure names (P-1, P-3, etc.) below the icons refer to the unit procedures, whereas the equipment tag names (R-101, R-102, etc.) refer to the actual physical pieces of equipment. The process flow diagram in SuperPro designer is essentially a graphical representation of the batch "recipe" that displays the execution sequence of the various steps.

After the filtration in procedure P-5, the excess NaOH is neutralized using HCl and the product-Na salt is converted back to product in reactor R-102 (procedure P-6). Since the product is insoluble in water, it precipitates out of solution. The product is then recovered using another filtration step in (procedure P-7). The product recovery yield is 90%. The precipitation procedure takes roughly 10.7 h, and the filtration takes about 5.7 h. The recovered product cake is then dissolved in isopropanol and treated with charcoal to remove coloration. This takes place in reactor R-101 under procedure P-8. After charcoal treatment, the solid carbon particles are removed using another filtration step in (procedure P-9). The time required for charcoal treatment and filtration is 15.9 h and 5 h, respectively.

In the next step (procedure P-10), the solvent is distilled off until the solution is half its original volume. The product is then crystallized in the same vessel with a yield of 97%. The crystalline product is recovered with a 90% yield using a final filtration step (procedure P-11). The distillation and crystallization steps take approximately 18.3 h, and the filtration requires roughly 3.3 h. The recovered product crystals are then dried in a tray dryer (procedure P-12, TDR-101). This takes an additional 15.6 h. The amount of purified product generated per batch is 173.1 kg.

TABLE 28.1 Raw Material Requirements

Material	kg/batch	kg/kg MP
Carbon	497.31	2.87
Quinaldine	148.63	0.86
Water	3621.44	20.92
Chlorine	89.52	0.52
Na_2CO_3	105.06	0.61
HCl (20% w/w)	357.44	2.07
NaOH (50% w/w)	204.52	1.18
Methanol	553.26	3.20
Hydroquinone	171.45	0.99
Sodium hydroxid	74.16	0.43
HCl (37% w/w)	217.57	1.26
Isopropanol	2232.14	12.90
Charcoal	15.85	0.09
Nitrogen	1111.49	6.42
Total	9399.84	54.30

Table 28.1 displays the raw material requirements in kilogram per batch and per kilogram of main product (MP = purified product) that correspond to the maximum batch size achievable with the available equipment. Note that around 54.3 kg of raw materials (solvents, reagents, etc.) are used per kilogram of main product produced. Thus, the product to raw material ratio is only 1.84%, an indication that large amounts of waste are generated by this process. A more detailed description of this process along with information on how the pilot plant process is transferred to the large-scale manufacturing facility is available in Ref. 10.

28.3.2 Process Scheduling and Cycle Time Reduction

Figure 28.3 displays the equipment occupancy chart for three consecutive batches (each color represents a different batch). The process batch time is approximately 92 h. This is the total time between the start of the first step of a batch and the end of the last step of that batch. However, since most of the equipment items are utilized for shorter periods within a batch, a new batch can be initiated every 62 h, which is known as the minimum cycle time of the process. Multiple bars on the same line (e.g., for R-101, R-102, and NFD-101) represent reuse (sharing) of equipment by multiple procedures. If the cycle times of procedures that share the same equipment overlap, scheduling with the assumed equipment designation is infeasible. White space between the bars represents idle time. The equipment with the least idle time between the consecutive batches is the *time (or scheduling) bottleneck* (R-102 in this case) that determines the maximum number of batches per year. Its occupancy time (approximately 62 h) is the minimum possible time between the consecutive batches.

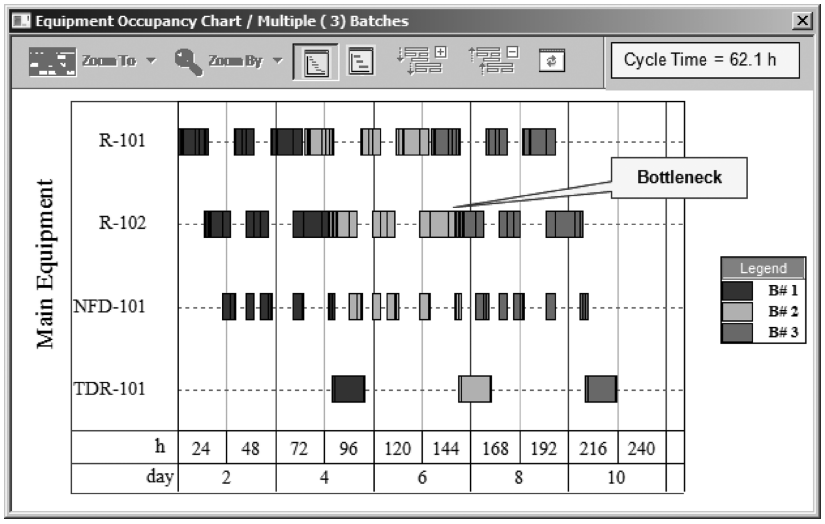

FIGURE 28.3 Equipment occupancy chart for three consecutive batches.

Scheduling in the context of a simulator is fully process driven and the impact of process changes can be analyzed in a matter of seconds. For instance, the impact of an increase in batch size (that affects the duration of charge, transfer, filtration, distillation, and other scale-dependent operations) on the plant batch time and the maximum number of batches can be seen instantly. Due to the many interacting factors involved with even a relatively simple process, simulation tools that allow users to describe their processes in detail, and to quickly perform what-if analyses, can be extremely useful.

If this production line operated around the clock for 330 days a year (7920 h) with its minimum cycle time of 62 h, its maximum annual number of batches would be 126, leading to an annual production of 21,810 kg of API (126 batches $\times$ 173.1 kg/batch), which is less than the project's objective of 27,000 kg. And since the process operates at its maximum possible batch size, the only way to increase production is by reducing the process cycle time and thus increasing the number of batches per year. The cycle time can be reduced through process changes or by addition of extra equipment. However, major process changes in GMP manufacturing usually require regulatory approval and are avoided in practice. Addition of extra equipment is the practical way for cycle time reduction. Since R-102 is the current bottleneck, addition of an extra reactor can shift the bottleneck to another unit. Figure 28.4 displays the effect of the addition of an extra reactor (R-103). Please note that under the new conditions, each reactor handles two procedures instead of three.

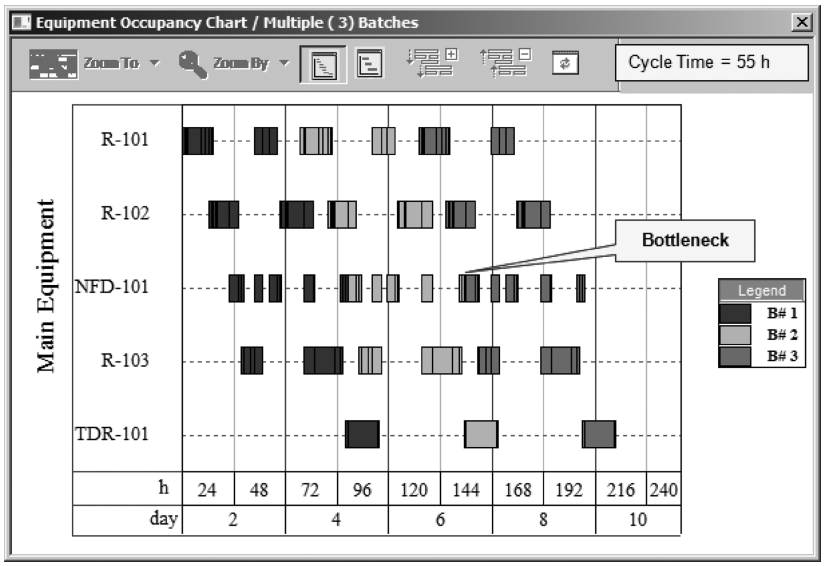

FIGURE 28.4 Equipment occupancy chart for the case with three reactors.

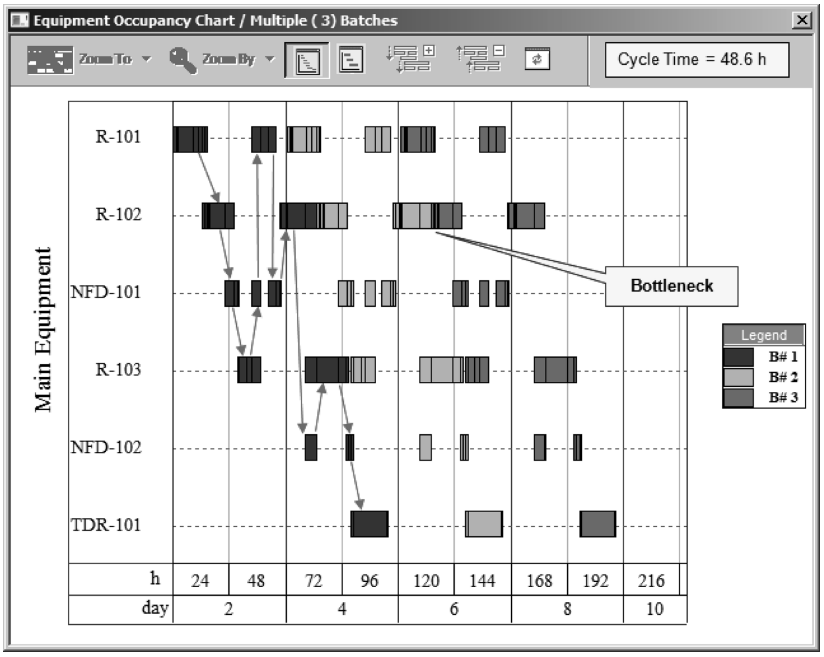

FIGURE 28.5 Equipment occupancy chart for the case with three reactors and two filters.

The addition of R-103 reduces the cycle time of the process to 55 h, resulting in 143 batches per year and annual throughput of 24,753 kg. Under these conditions, the bottleneck shifts to NFD-101. Since the annual throughput is still below the desired amount of 27,000 kg/year, addition of an extra Nutsche filter to eliminate the current bottleneck is the next logical step. Figure 28.5 shows the results of that scenario. In this scenario, the first Nutsche filter (NFD-101) is used for the first three filtration procedures (P-3, P-5, and P-7) and the second filter (NFD-102) handles the last two filtration procedures (P-9 and P-11). Under these conditions, the process cycle time goes down to 48.6 h, resulting in 162 batches per year and annual throughput of 28,042 kg, which meets the production objective of the project. The arrows in Figure 28.5 represent the flow of material through the equipment for the first batch.

Debottlenecking projects that involve installation of additional equipment provide an opportunity for batch size increases that can lead to substantial throughput increase. More specifically, if the size of the new reactor (R-103) is selected to accommodate the needs of the most demanding vessel procedure (based on volumetric utilization) in a way that shifts the batch size bottleneck to another procedure, then, that creates an opportunity for batch size increase. Additional information on debottlenecking and throughput increase options can be found in Refs 11,12.

28.3.3 Cost Analysis

Cost analysis and project economic evaluation is important for a number of reasons. If a company lacks a suitable manufacturing facility with available capacity to accommodate a new product, it must decide whether to build a new plant or outsource the production. Building a new plant is a major capital expenditure and a lengthy process. To make a decision, management must have information on capital investment required and time to complete the facility. To outsource the production, one must still do a cost analysis and use it as a basis for negotiation with contract manufacturers. A sufficiently detailed computer model can be used as the basis for the discussion and negotiation of the terms. Contract manufacturers usually base their estimates on requirements of equipment utilization and labor per batch, which is information that is provided by a good model. SuperPro Designer performs thorough cost analysis and project economic evaluation calculations and estimates capital as well as operating costs. The cost of equipment is estimated using built-in cost correlations that are based on data derived from a number of vendors and literature sources. The fixed capital investment is estimated based on total equipment cost using various multipliers, some of which are equipment specific (e. g., installation cost) while others are plant specific (e.g., cost of piping and buildings). The approach is described in detail in Refs 10, 13. The rest of this section provides a summary of the cost analysis results for this example process.

Table 28.2 shows the key economic evaluation results for this project. Key assumptions for the economic evaluations include (1) a new plant will be built and dedicated to the manufacturing of this product (2) the entire direct fixed capital is depreciated linearly over a period of 12 years; (3) the project lifetime is 15 years, and 27,000 kg of final product will be produced per year.

TABLE 28.2 Key Economic Evaluation Results

Total capital investment	$19.5 million
Plant throughput	27,000 kg/year
Manufacturing cost	$8.6 million/year
Unit production cost	$318/kg
Selling price	$450/kg
Revenues	$12.2 million/year
Gross margin	29.3%
Taxes (40%)	$1.1 million/year
IRR (after taxes)	14.0%
NPV (for 7% discount interest)	$8.5 million

For a plant of this capacity, the total capital investment is around $19.5 million. The unit production cost is $318/kg of product, which satisfies the project's objective for a unit cost of under $330/kg. Assuming a selling price of $450/kg, the project yields an after-tax internal rate of return (IRR) of 14% and a net present value (NPV) of $8.5 million (assuming a discount interest of 7%).

Figure 28.6 breaks down the manufacturing cost. The facility-dependent cost, which primarily accounts for the depreciation and maintenance of the plant, is the most important item accounting for 35.74% of the overall cost. This is common for high-value products that are produced in small facilities. This cost can be reduced by manufacturing the product at a facility whose equipment has already been depreciated. Raw material is the second most important cost item accounting for 32.12% of the total manufacturing cost. Furthermore, if we look more closely at the raw material cost breakdown, it becomes evident that quinaldine, hydroquinone, and isopropanol make up more than 80% of this cost (see Table 28.3). If a lower priced quinaldine vendor could be found, the overall manufacturing cost would be reduced significantly.

Labor is the third important cost item accounting for 18.8% of the overall cost. The program estimates that 12 operators are required to run the plant around the clock supported by three QC/QA scientists. This cost can be reduced by increasing automation or by locating the facility in a region of low labor cost.

28.4 UNCERTAINTY AND VARIABILITY ANALYSIS

Process simulation tools typically used for batch process design, debottlenecking, and cost estimation employ deterministic models. They model the "average" or "expected" situation commonly referred to as the base case or most likely scenario. Modeling a variety of cases can help determine the range of performance with respect to key process parameters. However, such an approach does not account for the relative likelihood of the various cases. Monte Carlo simulation is a practical means of quantifying the risk associated with uncertainty in process parameters [14]. In a Monte Carlo simulation, uncertain input variables are represented with probability distributions. A simulation calculates numerous scenarios of a model by repeatedly picking values from a user defined probability distribution for the uncertain variables. It then uses those values in the model to calculate and analyze the outputs in a statistical way in order to quantify risk. The outcome of this analysis is the estimation of the confidence by which desired values of key performance indicators can be achieved. Inversely, the analysis can help identify the input parameters with the greatest effect on the bottom line and the input value ranges that minimize output uncertainty.

In batch pharmaceutical processing, uncertainty can emerge in operation or market-related parameters. Process times, equipment sizes, material purchasing, and product

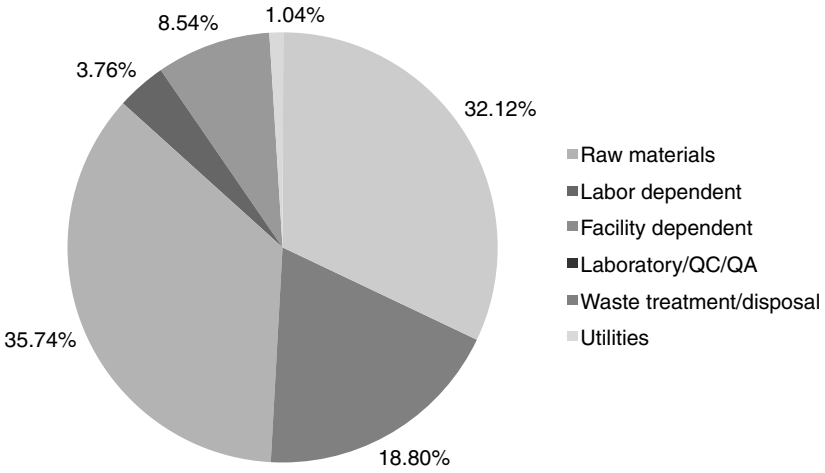

FIGURE 28.6 Manufacturing cost breakdown.

TABLE 28.3 Raw Material Requirements and Costs

Bulk Material	Unit Cost ($/kg)	Annual Amount (kg)	Annual Cost ($)	%
Carbon tetrachloride	0.80	77,581	62,065	2.25
Quinaldine	60.00	23,187	1,391,215	50.40
Water	0.10	564,944	56,494	2.05
Chlorine	3.30	13,965	46,083	1.67
Na_2CO_3	6.50	16,389	106,528	3.86
NaOH (50% w/w)	0.15	31,905	4,786	0.17
Methanol	0.24	86,308	20,714	0.75
Hydroquinone	18.00	26,746	481,427	17.44
Sodium hydroxide	2.00	11,569	23,138	0.84
HCl (37% w/w)	0.17	33,942	5,770	0.21
Isopropanol	1.10	348,214	383,035	13.88
Charcoal	2.20	2,473	5,440	0.20
Nitrogen	1.00	173,393	173,393	6.28
TOTAL		1,466,376	2,760,088	100.00

selling prices are common uncertain variables. Performing a stochastic analysis early on in the design phase increases the model's robustness and minimizes the risk of encountering unpleasant surprises later on.

For models developed in SuperPro Designer, Monte Carlo simulation can be performed by combining SuperPro Designer with *Crystal Ball* from Decissioneering, Inc. (Denver, Colorado). Crystal Ball is an Excel add-in application that facilitates Monte Carlo simulation. It enables the user to designate the uncertain input variables, specify their probability distributions and select the output (decision) variables whose values are recorded and analyzed during the simulation. For each simulation trial (scenario), Crystal Ball generates random values for the uncertain input variables selected in frequency dictated by their probability distributions using the Monte Carlo method. Crystal Ball also calculates the uncertainty involved in the outputs in terms of their statistical properties, mean, median, mode, variance, standard deviation, and frequency distribution.

Section 28.3.3 discusses the production and cost objectives of the project (27,000 kg/year of API for less than $330/kg) based on the assumed operating parameters and material unit costs. If the variability related to process parameters and uncertainty related to cost parameters can be represented with probability distributions, Monte Carlo simulation can estimate the certainty with which the project objectives can be met. For this exercise, a normal distribution was assumed for the price of quinaldine, which is the most expensive raw material, with a mean value equal to that of the base case ($60/kg).

The annual throughput (or number of batches per year) is determined by the process cycle time. Since procedure P-8 that utilizes vessel R-102 is the time bottleneck, any variability in the completion of P-8 leads to uncertainty in the annual throughput. Variability in the completion of P-8 can be caused by variability in the operations of P-8 as well as by variability in the operations of procedures upstream of P-8. Common sources of process time variability in chemical manufacturing are as follows:

(1). Fouling of heat transfer areas that affect duration of heating and reaction operations
(2). Fouling of filters that affect duration of filtration operations
(3). Presence of impurities in raw materials that affect reaction rates
(4). Off-spec materials that require rework
(5). Random power outages and equipment or utility failures
(6). Differences in skills of operators that affect setup and operation of equipment
(7). Availability of operators

TABLE 28.4 The Input Parameters Used for the Monte Carlo Simulation and Their Variation

Variable	Base Case Value	Distribution	Variation and Range
Quinaldine cost	60 ($/kg)	Normal	S.D. = 10 (30–90)
Chlorination reaction time (in P-1)	6 h	Triangular	(4–8)
Condensation reaction time (in P-2)	6 h	Triangular	(4–8)
Cloth filtration flux in P3, P5, P7, P9	200 (L/m^2-h)	Triangular	(150–250)

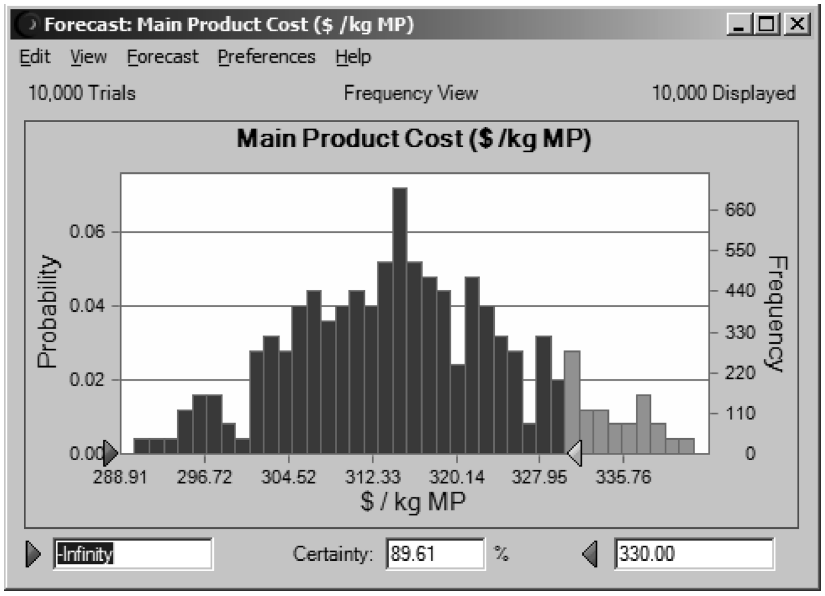

FIGURE 28.7 Probability distribution of the unit production cost (10,000 trials) (mean = 315.52; median = 315.03; S.D. = 10.49; range = 290.19–342.25).

Triangular probability distributions were assumed for the duration of the two main reaction operations and the filtration steps that precede P-8 (Table 28.4). Even though variability distributions were assigned to specific operations, it may be deemed more accurate to assume that they account for the composite variability of their procedures. If this type of analysis is done for an existing facility, historical data should be used to derive the probability distributions. Crystal Ball has the capability to fit experimental data.

The two decision variables considered in this study are the number of batches that can be processed per year and the unit production cost. These are key performance indicators important for production planning and project economics. The output variables of the combined SuperPro Designer–Crystal Ball simulation are quantified in terms of their mean, median, mode, variance, and standard deviation. These results are shown in Figures 28.7 and 28.8 for the "unit production cost" and the "number of batches," respectively. Based on the

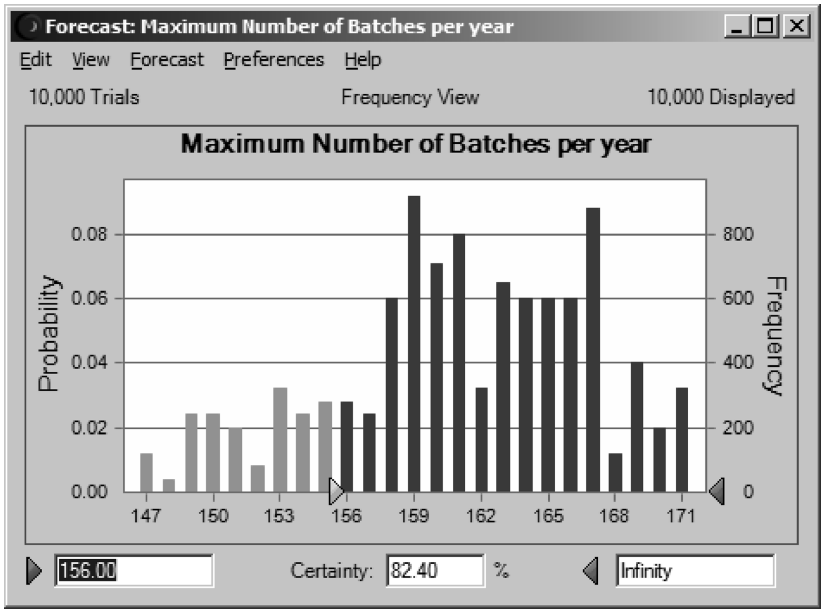

FIGURE 28.8 Probability distribution of the annual number of batches (10,000 trials) (mean = 161.0; median = 161, mode = 159, S.D. = 5.72, range = 147–171).

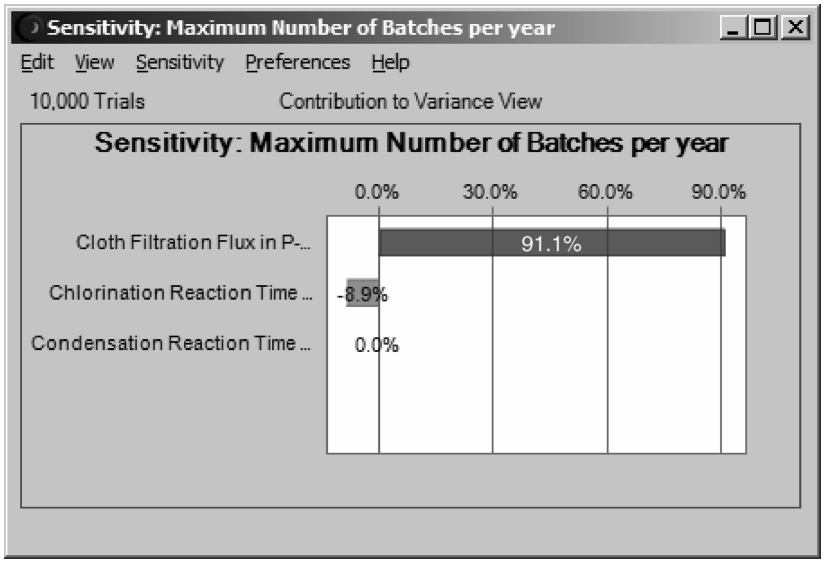

FIGURE 28.9 Contribution of uncertain parameters to the variance of the annual number of batches.

assumptions for the variation of the input variables we note that average values (mean/median/mode) calculated for the decision variables satisfy the objective. The certainty analysis reveals that we can meet the unit production cost goal (unit cost of under $330/kg) with a certainty of 89.6% (black area in Figure 28.7). The certainty of meeting the production volume goal (of 27,000 kg or 156 batches) is only 82.4% (black area in Figure 28.8). Such findings constitute a quantification of the risk associated with a process and can assist the management of a company in making decisions on whether to proceed or not with a project idea.

The dynamic sensitivity charts provide useful insight for understanding the variation of the process. They illustrate the impact of the input parameters on the variance (with respect to the base case) of the final process output, when these parameters are perturbed simultaneously. This allows us to identify which process parameters have the greatest contribution to the variance of the process and thus focus on them for process improvement. The sensitivity analysis for the *maximum number of batches per year* is displayed in Figure 28.9. The flux of the filtration operations has the greatest impact on the number of batches and consequently the annual throughput. If the management of the company is seriously committed to the annual production target, it would be wise to allocate R&D resources to the optimization of the filtration operations.

28.5 PRODUCTION SCHEDULING

After the process is developed and transferred to a manufacturing facility for clinical or commercial production, it becomes the job of the scheduler to ensure that all the activities are correctly sequenced and that the necessary labor, materials, and equipment are available when needed. The short-term schedule includes the upcoming production campaigns and may span from a week to several months. The general workflow begins with the long-term plan that describes how much of each product should be made over the planning period. The long-term plan, which is described in the next section, is based on approximate batch or campaign starts and does not include details about process activities. The scheduler uses the plan and knowledge about the process and available equipment and resources to generate a detailed production plan, that is, the short-term schedule, and communicate it to the appropriate staff. As the schedule is executed, there may be deviations between the schedule and the actual process execution. Tests, for example, may need to be redone, operations may take longer than the time assumed, or equipment may fail. The scheduler must recalculate the production schedule to reflect changes in resource availability and notify the staff.

Pharmaceutical companies use a variety of plant systems. Enterprise or manufacturing resource planning (ERP/MRP) systems keep track of the quantity of resources, such as materials or labor. Manufacturing execution systems (MES) ensure that the process proceeds according to precise specifications. Process control systems interface with the equipment and sensors to carry out steps and to maintain the process parameters according to specification [15]. Short-term scheduling is often managed manually or with stand-alone systems, but it could potentially interface with ERP/MRP and even MES programs.

The following example introduces SchedulePro as a scheduling tool. SchedulePro does not model the process itself with respect to its material and energy balances; it is

mainly concerned with the time and resources that tasks consume. If a user is interested in both process modeling and scheduling, he/she can generate the process model in SuperPro Designer, perform the material and energy balances there, and then export it as a recipe to SchedulePro for a thorough capacity planning or scheduling analysis in the context of a multiproduct facility. Within SchedulePro, capacity/scheduling information imported from SuperPro related to processing tasks can be expanded in the following ways:

- For every procedure, an equipment pool can be defined representing the list of alternative equipment that could potentially host that procedure.
- Auxiliary equipment can be assigned, possibly through pools, to operations.
- Materials supplied or generated through operations can be linked to supply, deposit or intermediate storage units.
- The rigidity in recipe execution is relaxed with the introduction of the ability to delay the start or break the execution of an operation (if the resources it requires are not available).

The inclusion in the production model of this additional information is motivated mainly by the needs of the pharmaceutical/biotech industry where it is known that quite frequently the bottlenecks exist in the use of auxiliary equipment (e.g., CIP skids, transfer panels) or are related to support activities (e.g., cleaning, buffer preparation) that tend to have flexible execution.

With the resources and facilities in place, simulation of the production activity in SchedulePro can proceed through the definition and scheduling of campaigns. A *campaign* is defined as a series of batches of a given recipe leading to the production of a given quantity of product. A series of campaigns organized in a priority list constitute the production plan that needs to be realized. As a finite capacity tool, SchedulePro attempts to schedule production of campaigns while respecting capacity constraints stemming from resource unavailability (e.g., facility or equipment outages) or availability limitations (e.g., equipment can only be used by only one procedure at a time). Conflicts (i.e., violations of constraints) can be resolved by exploiting alternative resources declared as candidates in pools, introducing delays or breaks if this flexibility has been declared in the corresponding operations, or moving the start of a campaign or batch at a time where the required resources are available. The automatically generated schedule can subsequently be interactively modified by the user through local or global interventions in every scheduling decision. Through a mix of automated and manual scheduling, users can formulate a production plan that is feasible and satisfies their production objectives.

28.5.1 Illustrative Example

This example uses the optimized version of the pharmaceutical intermediate process described above. The objective in this example is to create a schedule for the month of October. Specifically, the process is the three-reactor, two-filter case outlined in Figure 28.5. SchedulePro serves as the scheduling tool. The scheduling model or recipe captures the step-by-step timing and the use of equipment, materials, utilities and labor. Table 28.5 shows a recipe representation for the product dissolution step (procedure P-4).

Pharmaceutical process scheduling is unlike scheduling general work activities because tasks are generally assumed to progress one after the other without delay or interruption. Due to chemical stability limitations, delays in the process are defined and limited. The recipe representation of an allowed delay or safe-hold is the *flexible shift*. In this example, when the product is in a solid form, it may be held for up to 6 h.

The plant scheduler must create a schedule that meets product demand and respects the resource limitations of the facility. The target, plan is for 15 batches with an average

TABLE 28.5 Sample Scheduling Recipe

Operation	Description	Scheduling and Timing	Operators
Cake charge	Transfer in for 233 min from NFD-101 (in P-3) to R-103 (in P-4).	Starts concurrently with TRANSFER-OUT-1 in P-3. The duration matches the duration from TRANSFER-OUT-1 in P-3 to TRANSFER-OUT-2 in P-3	2.0
NaOH charge	Charge 1740 kg of mixture to R-103 (in P-4), using stream NaOH-2.	Starts at the end of cake charge in P-4. Duration is 3.233 h	2.0
Product solubilization	React in batch mode for 2 h., at 50°C and pressure of 2.5 bar.	Starts at the end of NaOH in P-4. Duration is 2 h	1.0
Transfer to filter	Transfer 100% from R-103 (in P-4) to NFD-101 (in P-5) for 253 min.	Starts at the end of product solubilization in P-4. The duration matches the duration of impurity removal in P-5	2.0

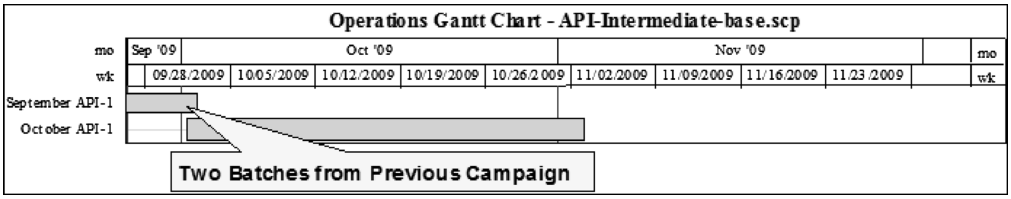

FIGURE 28.10 Campaign to produce 15 batches in October.

cycle time of 50 h. The suite has a crew of seven operators, three reactors, two Nutsche filters and a tray dryer. The scheduler creates a campaign of 15 batches starting at 8:00 on October 1. The last two batches of the October campaign finish in November. This is balanced by the October completion of the final two batches of the September campaign. The two campaigns are shown in the Gantt chart in Figure 28.10.

28.5.1.1 Labor Shortages Under normal circumstances, seven operators are required. Figure 28.11 shows the typical operator demand for 1 week. The horizontal line indicates the limit of seven operators. The thin line shows the average labor requirement.

Short-term schedulers often need to account for labor availability. In this case, a training program during the week of October 12 effectively reduces the crew size to six. The scheduler must decide whether or not to request overtime operators. Rescheduling with the new temporary limit produces the result shown in Figure 28.12. The scheduling tool manages the temporary labor constraint by delaying the start times of the two batches that begin during the week of October 12.

The revised schedule still meets the 15-batch goal for the month of October; however, the completion of the final batch is delayed by about 1 day.

28.5.1.2 Maintaining the Schedule Time does not always specify the completion of an operation in pharmaceutical processing. The concentration of a key component may, for example, be the primary specification. The durations of actual operations may therefore vary from those in the scheduling recipe. The scheduler must, therefore, regularly update the schedule based on new information about the status of the batches. For example, suppose the scheduler updates the schedule on Tuesday, October 27 at 5:00 and learns that batches 12 and 13 are in progress. Furthermore in batch 12, the evaporation step (P-10 in R-103) was delayed by 3 h due to some mechanical issues. The scheduler sets the current time in the schedule and updates the status by entering the actual duration for the vaporization in batch 12. The scheduling tool predicts that R-103 will be overallocated by 11:30.

Figure 28.13 shows the conflicted schedule. The diagonal hatch indicates activities that are in progress. Overallocated or conflicted equipment is shown as an additional line on the chart and the conflicted procedures are outlined.

To resolve the conflict, the scheduler has the scheduling tool attempt. The scheduling tool takes advantage of the safe hold point in the process to delay the transfer of batch 13 material to R-103. Figure 28.14 shows the result. This solution does not affect the production target.

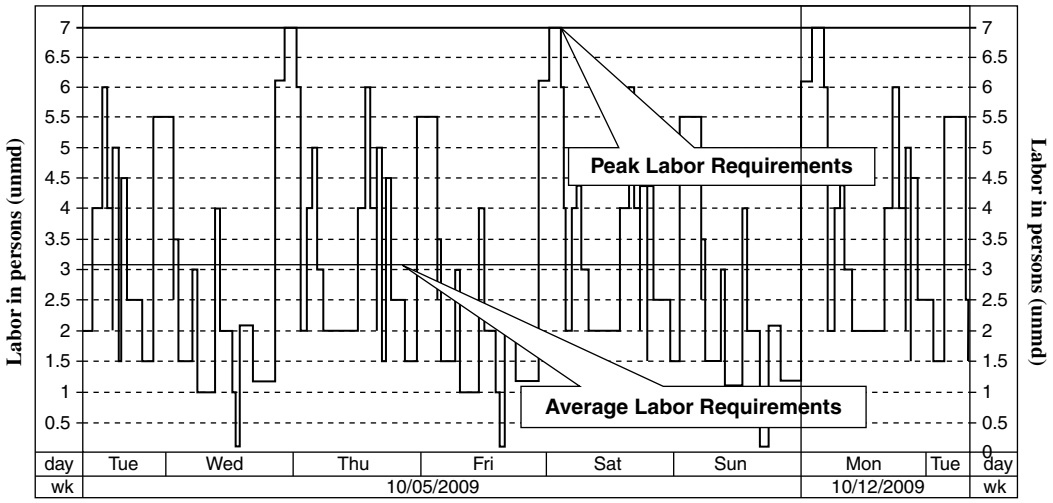

FIGURE 28.11 Typical labor demand for 1 week.

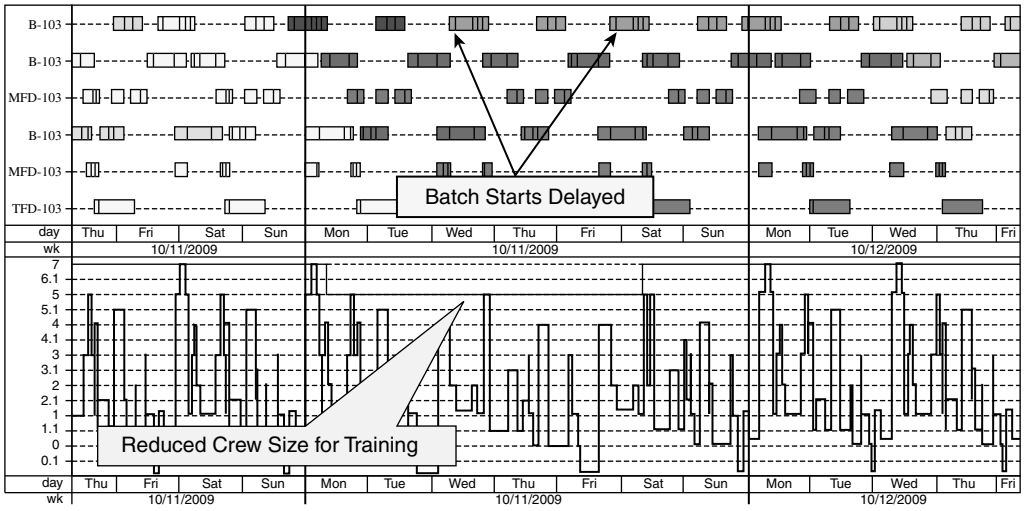

FIGURE 28.12 Equipment occupancy (top) and labor demand (bottom).

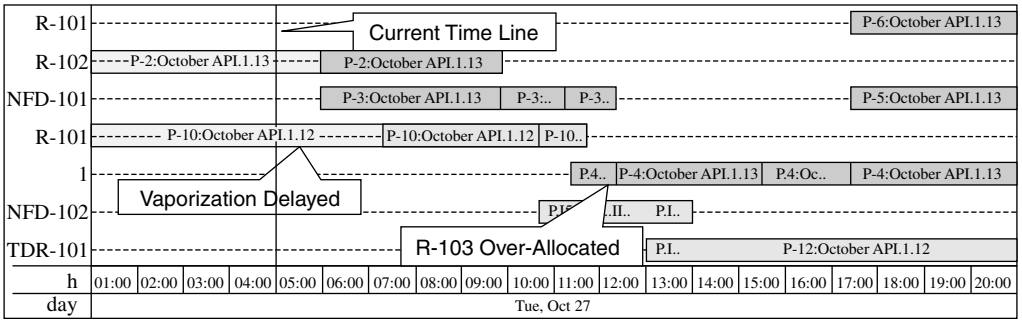

FIGURE 28.13 Conflict with R-103 in batch 13.

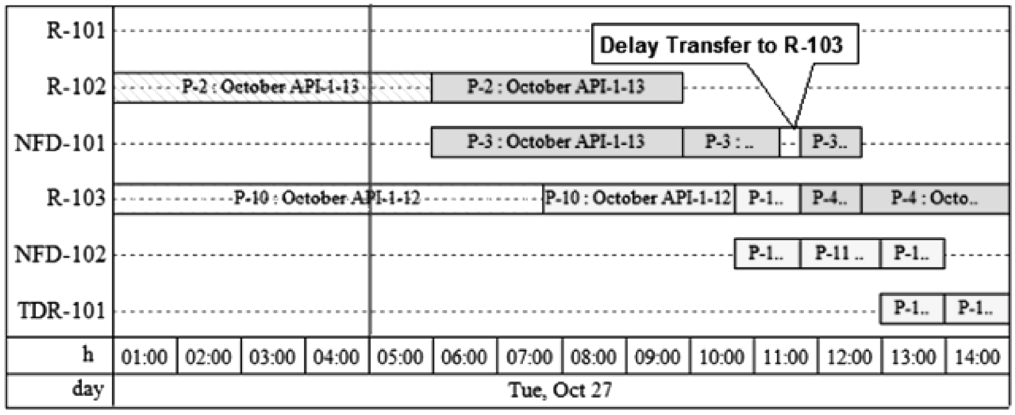

FIGURE 28.14 Conflict resolved with a hold in P-3.

28.5.1.3 Accounting for Equipment Outages Scheduling around equipment maintenance is one of the scheduler's routine tasks. From a scheduling standpoint, preventative maintenance (PM) represents periods of unavailability. Maintenance may be fixed to a particular date or it may be floating. Figure 28.15 illustrates each type. The dryer, TDR-101, has a firm maintenance outage on Monday, October 19. The scheduling tool "plans around" the outage by delaying

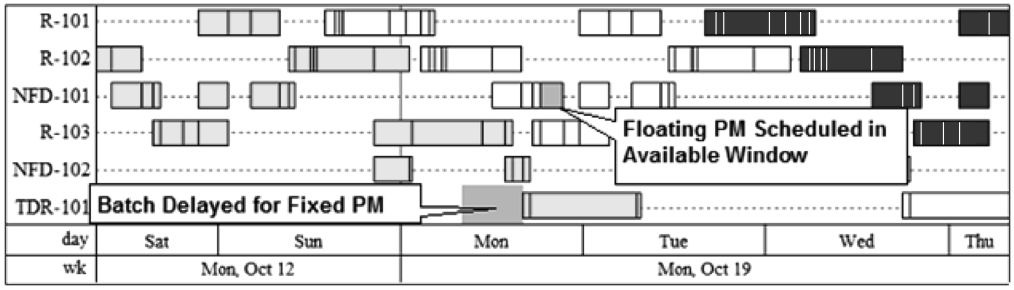

FIGURE 28.15 Maintenance outages for NFD-101 and TDR-101 (gray areas).

the batch that uses the dryer. The Nutsche filter, NFD-101 requires a 4 h preventive maintenance before November but after 10:00 on October 19. The scheduler creates a "batch" of maintenance and schedules it during the first convenient window of opportunity in October.

28.5.2 Tracking

The scheduler's focus is usually limited to the immediate future. The scheduler usually deletes completed batches because they no longer affect the current or future scheduling. Electronic batch records are maintained in other systems that are focused on permanence and security [16] and are not well suited to the fast-changing environment of short-term scheduling. However, the scheduler may wish to recall an earlier version of a production schedule. For example, if the scheduler wants to track planned versus actual completion dates, there must be a repository for scheduled campaigns. The schedule changes as batches are made, so the repository may store multiple versions of the schedule.

Table 28.6 displays the results of a simple report. The first row corresponds to the originally planned date for the campaign. The second row corresponds to the same campaign just before it begins. The delay is due to resource constraints from other campaigns. The third row corresponds to the completed campaign. The new end date is delayed due to constraints that arose during manufacturing.

28.5.2.1 Connection to Planning Systems The short-term scheduler usually starts with a rough production plan that is based on product demand, estimated plant capacity, and/or inventory constraints. Planners generally use separate systems, often part of ERP, that do not require all the resource and timing details. As the next section shows, a scheduling tool with simplified recipes can be an effective planning system. Regardless of the specific planning system used, an automated link between planning and scheduling, can streamline both the planning and the scheduling processes. For example, the scheduler may download campaign information with estimated dates from the planning system. As the schedule progresses, the scheduler uploads revised date and production information to the planning system.

TABLE 28.6 Campaign Status History

Campaign	Start Date	End Date	Entry Date	Comment
October API-1	10/01/2009	11/04/2009	09/15/2009	Original Plan
October API-1	10/05/2009	11/06/2009	10/18/2009	Before Start
October API-1	10/05/2009	11/07/2009	11/26/2009	Completed

28.6 CAPACITY ANALYSIS AND PRODUCTION PLANNING

Capacity is a measure of how much product a manufacturing system can make. The amount of product manufactured in a given time period (hour, day, week, etc.) or the time required to produce a given quantity of product are the most intuitive and commonly used measures of capacity. The capacity of a manufacturing system should exceed demand at least over the long run. On the other hand, excess capacity is costly [17]. Increasing capacity to meet demand might require capital investments in equipment and buildings or extending the manufacturing time (through labor overtime or additional shifts). *Effective capacity* is the actual capacity achieved in practice. Due to equipment maintenance or unexpected breakdowns, scheduling inefficiencies, and labor unavailability among others, the effective capacity is usually less than the nominal plant capacity.

The need for an estimate of the plant capacity arises in different activities of supply chain management. In aggregate planning, the objective is to generate feasible long-range or medium- range production plans that can satisfy expected lumped demand for a range of aggregate products. The validity of these plans depends on the accuracy of the aggregate plant capacity estimates. If an MRP-II approach is used to create a master production plan and more detailed production orders, the feasibility of the generated schedules should be checked against the plant capacity, this time measured with greater detail and for each product separately. Inventory management, batch sizing, and operation

scheduling are other examples of activities that relate to capacity analysis.

Depending on the complexity of the production system, the range of different products produced and the diversification of their routings (recipes), the level of difficulty in estimating a plant's capacity can vary from trivial to formidable. The capacity of a single-product batch plant depends only on the batch size, the cycle time, and the allocation of production time. If greater capacity is required, either the production time should be extended or the cycle time should be reduced by removing bottlenecks. In multiproduct or multipurpose facilities, however, with complex material flows, multiple equipment used in parallel, shared resources and sequence-dependent changeover and cleaning times, the estimation of the capacity is far from trivial. In fact, in these cases, capacity estimates emerge through the same activities that capacity analysis is supposed to serve, that is, planning and scheduling. In other words, only after specific production planning and scheduling scenarios have been laid out, can capacity be estimated. Capacity analysis is, therefore, interlinked with the production planning and scheduling activities providing important data to carry out these activities and simultaneously emerging as their outcome. This is the reason why in this section capacity analysis and production planning are treated simultaneously.

Both production planning and capacity analysis, in different contexts, have been the subject of intense research and industrial activity for many years. It is now recognized that there is no solution to these problems that can fit all cases; there is too much variability in the problem structure for a single solution to cover all aspects. The differences between process industries and discrete manufacturing industries have also been investigated and the applicability in the process industries, of the methods developed mainly for discrete manufacturing, has been questioned (see, for example, Refs [18–20].)

Pharmaceutical manufacturing facilities are typically multipurpose plants equipped with multiple production lines that share utilities, labor resources, and auxiliary equipment, such as CIP skids, transfer panels, delivery lines, and occasionally main equipment. Production is typically campaigned. Considerable changeover time is often required between campaigns of different products. API synthesis, in particular, is characterized by complex material flows and the need to handle and store a variety of required intermediates.

Simulation is an appropriate tool to cope with the complexity of production planning and capacity analysis in pharmaceutical manufacturing. Rather than attempting to formalize a single model and come up with a single solution as optimization-based methods do, simulation allows the planner to formulate and analyze different scenarios and select the one that best fits the objectives and constraints of the problem. Such "what-if" analyses can generate feasible production plans utilizing the available capacity or provide justifications for facility expansions and/or outsourcing of production. The types of capacity analysis questions that can be answered using simulation will be demonstrated in this section with the use of the software tool SchedulePro.

28.6.1 Simulating the Production Process

Production planning is the activity of assigning facility resources to processing tasks. This makes a scheduling tool appropriate because it manages timing and resources without the necessity of engineering calculations.

A simulation-based approach can be used to support both planning/capacity analysis and scheduling activities. The level of detail included in the simulation model is the only difference between the two. In planning, the recipe representations are coarse, products could be lumped in aggregates with similar production recipes and only the most basic resources are considered. In scheduling, recipes are expanded to their fullest detail, products are differentiated and all potentially limiting resources are included. The following example will demonstrate the use of simulation for planning and the types of what-if scenarios that can be investigated under different assumptions and objectives.

28.6.2 Capacity Analysis Example

In this example, we will consider the last three steps required for the production of a small-molecule API assuming that any required raw or intermediate material is supplied from external sources. Based on detailed process analysis done in a process simulator such as SuperPro Designer, the amount of raw material and the amount of product produced in each step have been calculated. By considering the main plant resources, the cycle time of each step has also been estimated. This is shown in Figure 28.16. The material denoted as SM in the figure is the raw material supplied externally (e.g., by a contract manufacturer); Int-1 and Int-2 are the two stable isolated intermediates, which can be stored until turned into the final product FP. Step-1 takes 975 kg of SM as input per batch and generates 1500 kg of Int-1 as output. Step-2 takes

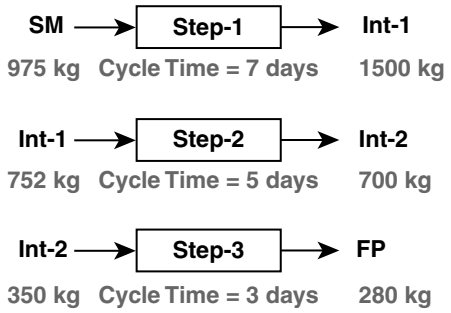

FIGURE 28.16 Cycle time, input amount, and output amount for the three chemical steps.

752 kg of Int-1 per batch and generates 700 kg of Int-2. Finally, Step-3 takes 350 kg of Int-2 and generates 280 kg of FP per batch. The cycle times for the three steps are 7, 5, and 3 days, respectively.

The objective of this study is to find out whether 35,000 kg of FP (corresponding to the anticipated demand) can be produced per year if three independent production areas ("Train-1," "Train-2," and "Train-FP") can be made available to this synthesis route. Since the output of Step-3 is 280 kg of FP per batch, the required number of batches of Step-3 per year is 125 (= 35,000/280). For Step-2, the required amount of produced Int-2 is 43,750 kg (= 35,000*350/280) and the corresponding number of batches per year is 63 (= 43,750/700). Finally, for Step-1 the required amount of produced Int-1 is 47000 (= 43,750*752/700) and the corresponding number of batches per year is 32 (= 47,000/1500).

In SchedulePro's terminology, each step corresponds to a separate recipe. For the purposes of this long-term planning study, it suffices to represent each step as a single-procedure recipe that utilizes one of the available production trains. In other words, the entire recipe is abstracted to a single processing task and all resources are represented through a single resource corresponding to each plant. Assuming that the capacity of each plant to execute each detailed step recipe has been checked, the above simplification comes at no loss of generality. The advantages of faster implementation and production plan development exceed by far the effects of possible inaccuracies (such as end effects in the planning horizon's beginning or end) caused by the simplified representation.

In this representation, each procedure is assigned a duration equal to the step's cycle time (as reported earlier) and a pool of equipment representing each of the three available plants. It should be noted that the reported cycle times are a bit longer than the minimum (optimal) cycle times calculated by the step's detailed analysis. Operating at a cycle time that is somewhat larger than the minimum enables the schedule to absorb any delays without long deviations from the original plan.

Under the above assumptions, it is quite easy to calculate the required capacity (measured in production days) for the required quantity of the final product. For 32 batches of Step-1, 224 days (= 32 × 7) are required. Similarly, for Step-2 and Step-3 the corresponding duration is 315 (= 63 × 5) and 375 (= 125 × 3). Adding the time required to produce the first batch of Int-1 so that Step-2 can start and the time to produce the first batch of Int-2 so that Step-3 can start, brings the total campaign make span beyond the desired 365-day completion horizon.

The above simple calculations can be easily verified with a simulation of this case scenario in SchedulePro. The equipment occupancy chart in Figure 28.17 is generated under the assumption that each step is executed independently in the three separate lines named (Train-1 for Step-1, Train-2 for Step-2, and Train-FP for Step-3). The total make span of the production schedule is approximately 56 weeks.

The implementation of the above schedule requires large inventories for Int-1 and Int-2 since they are produced at a much faster pace than they can be consumed by the subsequent steps. This is clearly demonstrated in Figure 28.18a,b where the inventories of Int-1 and Int-2 are shown. Storage capacity of over 15,000 kg for Int-1 and 8000 kg for Int-2 will be required to implement this production plan.

On the other hand, the capacity of the available trains dedicated to the production of intermediates is underutilized (see Figure 28.17) and the objective of completing the production campaign in less than a year is not satisfied. Modifications on the above basic scenario can be driven by two different objectives: reduction of storage capacity and reduction of total make span.

The key to satisfy the make span objective is better plant capacity utilization. The underutilization of capacity in Train-1 and Train-2 creates the possibility of exploiting that excess capacity for Step-3 that is responsible for the delay. Please recall the initial assumption that each production train can be used interchangeably for every step. The base case can therefore be modified by inserting Train-1 (with the lowest utilization) into the pool of candidate trains for executing

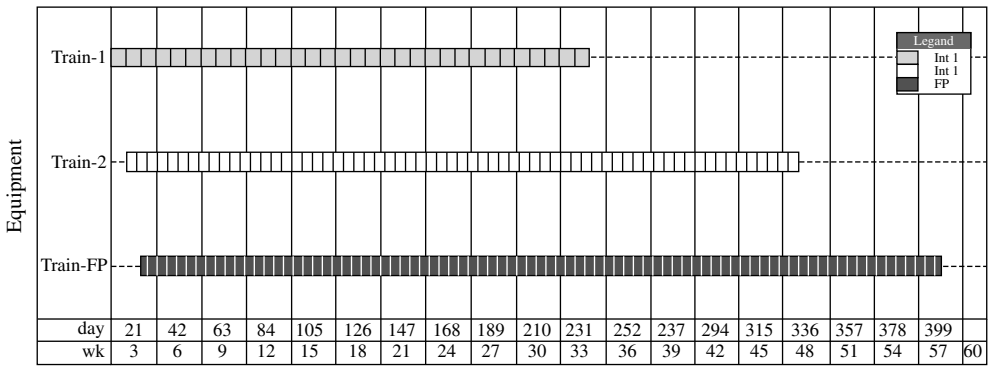

FIGURE 28.17 Equipment occupancy chart for the base production scenario.

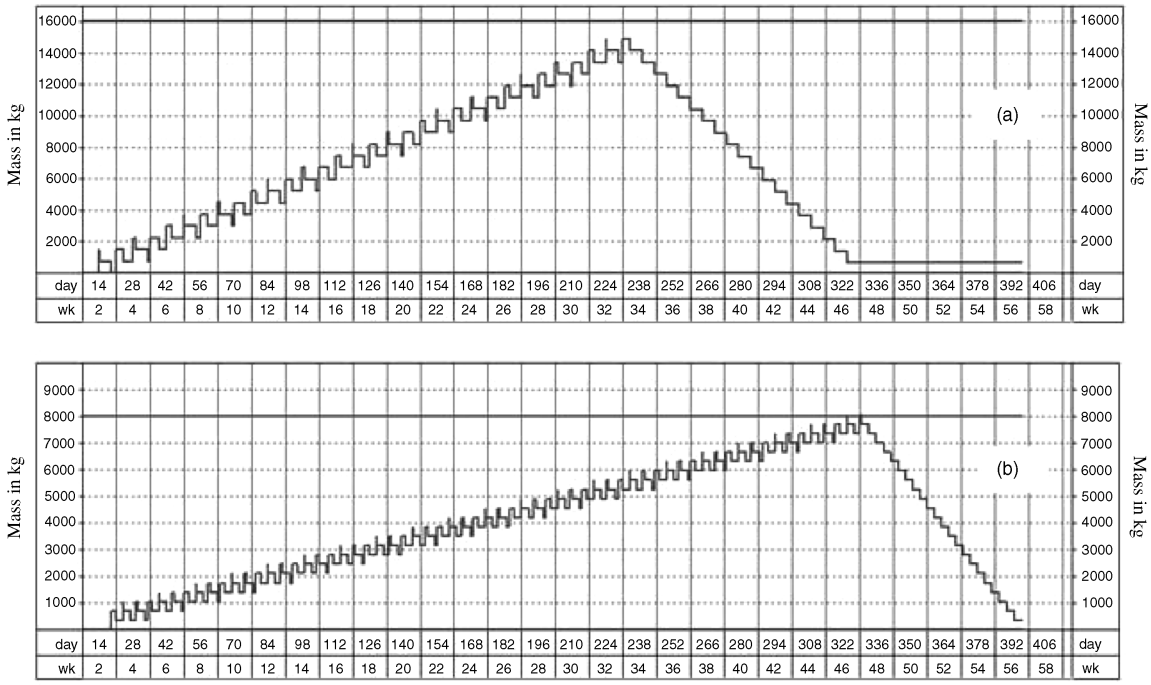

FIGURE 28.18 Inventories of Int-1 (a) and Int-2 (b).

Step-3. Initially, it will be assumed that an extended (5-week period) is required for a thorough cleaning/changeover when switching campaigns within a train—a constraint that makes alternation of batches of different steps within the same train prohibitive. The generated production plan under these assumptions is shown in Figure 28.19.

In this case, the excess Train-1 capacity is utilized to host some of the Step-3 campaign batches after campaign Step-1 is completed and following the extensive cleaning of the line. As a result, the make span is significantly reduced to less than 47 weeks and the production objective is satisfied. This change has not affected the demand for intermediate storage, though, which remains high at the levels previously shown in Figure 28.18.

The potential to satisfy the production make span objective while minimizing inventories exist only if it is possible to alternate batches of different steps within a single line. If we assume that the cleaning required when switching products is not as extensive as before, it is possible to break the long 32-batch campaign of Step-1 in multiple shorter campaigns which can be spread throughout the year and interject batches of Step-3 in the time gaps. With this strategy, it is expected that both objectives can be met.

To implement this scenario, it is assumed that the Step-1 campaign is split into four 8-batch campaigns released every 11 weeks and 3 days of cleaning are required before and after switching products within a plant. Figure 28.20 shows the updated schedule. The total make span is again shorter than a

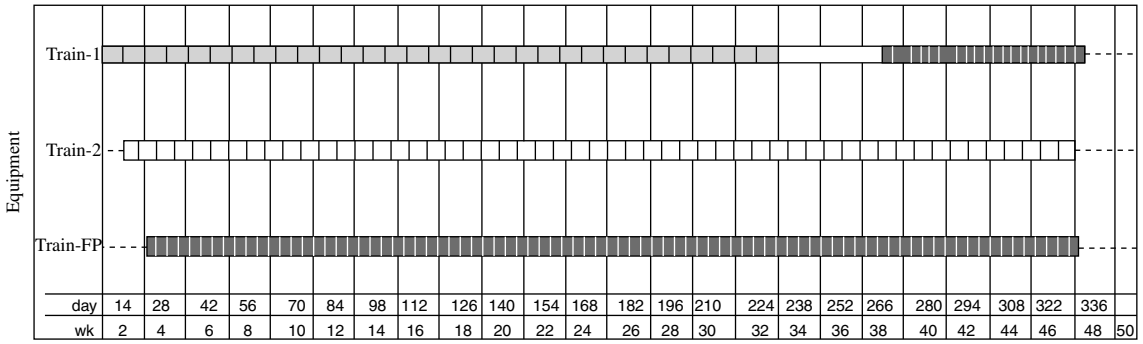

FIGURE 28.19 Equipment occupancy chart with Step-3 batches following Step-1 batches in Train-1.

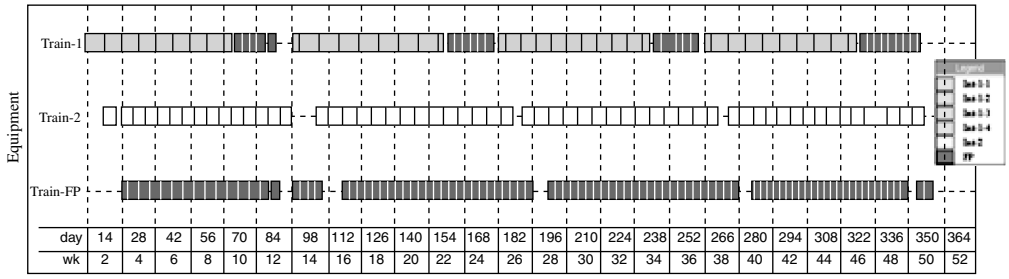

FIGURE 28.20 Equipment occupancy chart with Step-1 and Step-3 campaigns alternating in Train-1.

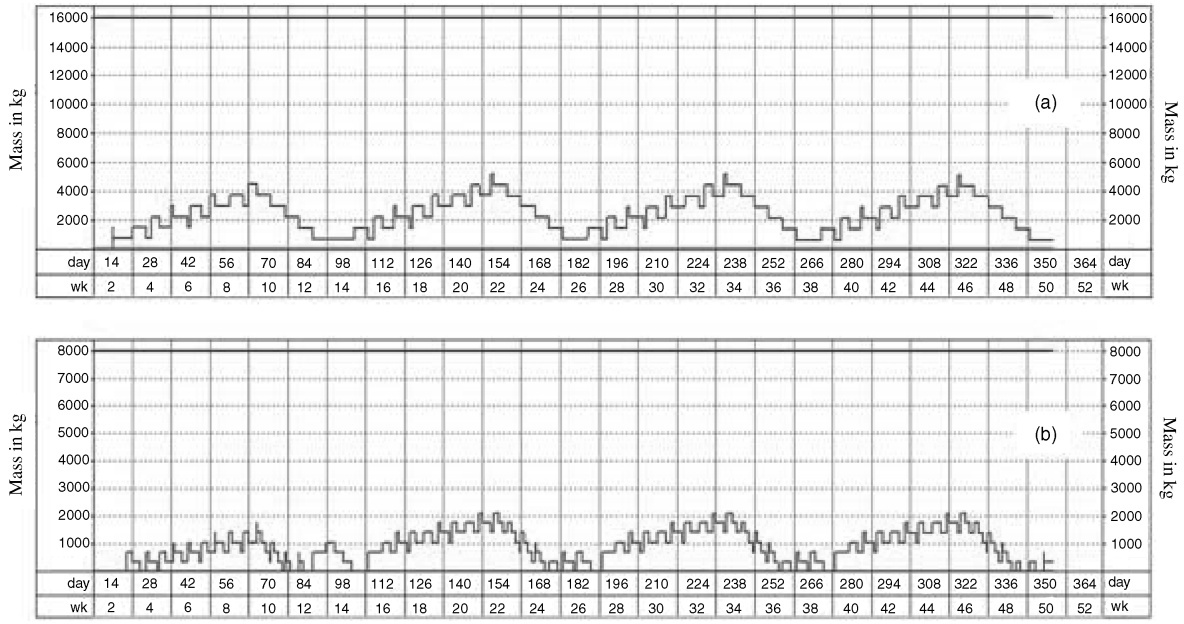

FIGURE 28.21 Inventories of Int-1(a) and Int-2 (b) with Step-1 and Step-3 campaigns alternating in Train-1.

year, but, unlike the previous scenario, it is now possible to reduce considerably the inventory of intermediates. As shown in Figure 28.21, the required storage capacity has dropped from 16,000 kg to less than 5000 kg for Int-1 and from 8000 kg to about 2000 kg for Int-2.

Note that in the attempt to satisfy the inventory constraints, the scheduling of Step-2 and Step-3 batches has become more challenging and less obvious. The existence of adequate intermediate inventory now determines the start of these batches. Nevertheless, at the expense of less regular scheduling, this scenario has indeed proved capable of satisfying both the make span and the reduced inventory objectives.

One could think of infinite variations for the scenarios above under different assumptions and objectives. As long as the capacity and planning constraints can be intuitively captured, formulating and developing feasible and satisfactory solutions under variable assumptions and objectives can be easily performed in a simulation environment.

28.7 SUMMARY

Process simulation and production scheduling tools can play an important role throughout the life cycle of product development and commercialization. In process development, process simulation tools are becoming increasingly useful as a means to analyze, communicate, and document process changes. During the transition from development to manufacturing, they facilitate technology transfer and process fitting. Production scheduling tools play a valuable role in manufacturing. They are used to generate production schedules based on the accurate estimation of plant capacity, thus minimizing late orders and reducing inventories. Such

tools also facilitate capacity analysis and debottlenecking tasks. The pharmaceutical industry has only recently begun making significant use of process simulation and scheduling tools. Increasingly, universities are incorporating the use of such tools in their curricula. In the future, we can expect to see increased use of these technologies and tighter integration with other enabling IT technologies, such as supply chain tools, MES, batch process control systems, process analytics tools (PAT), and so on. The result will be more robust processes and efficient manufacturing leading to more affordable medicines.

REFERENCES

1. Papavasileiou V, Koulouris A, Siletti CA, Petrides D. Optimize manufacturing of pharmaceutical products with process simulation and production scheduling tools. *Chem. Eng. Res. Des.* 2007;85(A7):1–12.
2. Petrides DP, Calandranis J, Cooney CL. Bioprocess optimization via CAPD and simulation for product commercialization. *Genet. Eng. News* 1996;16(16):24–40.
3. Petrides DP, Koulouris A, Lagonikos PT. The role of process simulation in pharmaceutical process development and product commercialization. *Pharm. Eng.* 2002;22(1).
4. Petrides DP, Calandranis J, Cooney CL. Bioprocess optimization via CAPD and simulation for product commercialization. *Genet. Eng. News* 1996;16:24–40.
5. Hwang F. Batch pharmaceutical process design and simulation. *Pharm. Eng.* 1997;17(1):28–43.
6. Thomas CJ. A design approach to biotech process simulations. *BioProcess International*, October, 2003, pp. 2–9.
7. Petrides DP, Siletti CA. The role of process simulation and scheduling tools in the development and manufacturing of biopharmaceutical. In: Ingalls RG, Rossetti MD, Smith JS, Peters BA, editors, *Proceedings of the 2004 Winter Simulation Conference*, 2004, pp. 2046–2051.
8. Plenert G, Kirchmier B. *Finite Capacity Scheduling: Management, Selection, and Implementation*, John Wiley & Sons, 2000.
9. Parshall J, Lamb L. *Applying S88: Batch Control From a User's Perspective*, ISA, 2000.
10. Intelligen. User's guide of SuperPro Designer, Chapter 2. http://www.intelligen.com/demo. 2007.
11. Petrides D, Koulouris A, Siletti C. Throughput analysis and debottlenecking of biomanufacturing facilities: a job for process simulators, *BioPharm*, August 2002.
12. Tan J, Foo DCY, Kumaresan S, Aziz RA. Debottlenecking of a batch pharmaceutical cream production. *Pharm. Eng.* 2006;26(4):72–82.
13. Harrison RG, Todd P, Rudge SR, Petrides DP. *Bioseparations Science and Engineering*, Oxford University Press, 2003.
14. Achilleos EC, Calandranis JC, Petrides DP. Quantifying the impact of uncertain parameters in the batch manufacturing of active pharmaceutical ingredients. *Pharm. Eng.* 2006; 26(4):34–40.
15. Abel J. Enterprise knowledge management for operational excellence. *Pharma. Eng.* 2008;28:1–6.
16. Abel J, LeBlanc L. Specifying a batch management system for electronic records and signatures: a checklist for compliance with 21-CFR Part 11. *Pharm. Eng.* 1999;19(4):1–9.
17. Sipper D, Bulfin R. *Production: Planning, Control and Integration*, McGraw-Hill International Editions, Singapore, 1997.
18. Crama Y, Pochet Y, Wera Y.A discussion of production planning approaches in the process industry, Université Catholique de Louvain, Center for Operations Research and Econometrics, CORE discussion papers No. 2001042, 2001.
19. Kallrath J. Planning and scheduling in the process industry. *OR Spectrum* 2002;24; 219–250.
20. Schuster EW, Allen SJ. A new framework for production planning in the process industries. *38th APICS Conf. Proc.* 1995: 31–35.