The Role of Process Simulation in Pharmaceutical Process Development and Product Commercialization

by Demetri P. Petrides, Alexandros Koulouris, and Pericles T. Lagonikos

Introduction

The development and commercialization of a new pharmaceutical product is a painstaking process that takes 7 to 12 years to complete requiring sizable investments ranging from $100 million to $500 million. In addition, 80 to 85% of products in development fail somewhere in the development pipeline, often after undergoing expensive clinical trials. The pharmaceutical industry spends considerably more on the development and evaluation of products that eventually fail than on successful products. Consequently, any methodologies and tools that can be used to evaluate alternatives and speed up the development effort can have a tremendous impact on the bottom line.

Computer Aided Process Design (CAPD) and simulation tools have been successfully used in the chemical and oil industries since the early 60s to expedite development and optimize the design and operation of integrated processes. Similar benefits can be expected from the application of CAPD and simulation in the pharmaceutical industries. The primary emphasis of this article is on the role of CAPD and simulation in expediting process development. The responsibilities of process development include:

- Characterization of the process
- Identification of critical process parameters
- Optimization of process conditions
- Process design and equipment selection
- Process control

These responsibilities require a thorough understanding of the process and its underlying mechanisms. Process simulation tools can provide a powerful means to achieve these objectives.

Figure 1. Addition of unit procedures and stream lines to the flowsheet.
Process Simulation

Process simulation tools can be used throughout the life cycle of process development and product commercialization. The benefits at the various stages of the commercialization process are explained below.

**Idea Generation**
When product and process ideas are first conceived, process simulation is used for project screening/selection and strategic planning based on preliminary economic analyses.

**Process Development**
While the pre-clinical and clinical testing of the candidate drug compound is going on, the company's process development group is looking into the many options available for manufacturing, purifying, characterizing the drug substance, and formulating it as a drug product. At this stage, the process undergoes constant changes. New synthetic routes are being investigated. New recovery and purification options are evaluated. Alternative formulations are also explored. Typically, a large number of scientists and engineers are involved in the improvement and optimization of individual processing steps. Simulation tools at this point can introduce a common language of communication and facilitate team interaction. A computer model of the entire process can provide a common reference and evaluation framework to facilitate process development. The impact of process changes can be readily evaluated and documented in a systematic way. Once a reliable model is available, it can be used to pinpoint the most cost-sensitive areas — the economic "hot-spots" — of a complex process. These are usually steps of high capital and operating cost or low yield and production throughput. The findings from such analyses can be used to judiciously focus further lab and pilot plant studies in order to optimize those portions of the process. Being able to experiment on the computer with alternative process setups and operating conditions reduces the costly and time-consuming laboratory and pilot plant effort. The environmental impact of a process is another issue that can be readily evaluated with computer models. Material balances calculated for the projected large scale manufacturing can reveal the environmental hot-spots. These are usually solvents and regulated materials that are costly to dispose of. Environmental issues not addressed during process development may lead to serious headaches during manufacturing. This is the case because after a process has been approved by the regulatory agencies, it is extremely costly and time-consuming to make process changes. This is particularly true for biopharmaceuticals where it is commonly said that "the process makes the product."

**Facility Design and/or Selection**
With process development nearing completion at the pilot plant level, CAPD and simulation tools are used to systematically design and optimize the process for commercial production. Availability of a good computer model can facilitate the transfer of process technology and facility design. If a new facility needs to be built, process simulators can be used to size process equipment and supporting utilities, and estimate the required capital investment. In transferring production to existing manufacturing sites, process simulators can be used to evaluate the various sites from a capacity and cost point of view and select the most appropriate one. The same can apply to outsourcing of manufacturing to contract manufacturers.

**Manufacturing**
In large scale manufacturing, simulation tools are primarily used for process scheduling, debottlenecking, and on-going process optimization. Simulation tools that are capable of tracking equipment utilization for overlapping batches can identify bottleneck candidates and guide the user through the debottlenecking effort.

**Commercially Available Tools**
Process simulators for continuous chemical processes have been in use in the petrochemical industries since the early 1960s. Established simulators for the petrochemical industries include: Aspen Plus (from Aspen Technology, Inc.), ChemCAD (from Chemstations, Inc.), HYSYS (from Hyprotech, Ltd./AEA Engineering Software), and PRO/II (from Simulation Sciences, Inc.).

The time-dependency of batch processes makes development of batch process simulators more challenging. "Batches" from Batch Process Technologies (West Lafayette, IN - www.bpptech.com) was the first simulator specific to batch processes. 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. This simulator has found applications in pharmaceuticals, biochemicals, and food processing.1

In the mid 1990s, Aspen Technology, Inc. (Cambridge, MA - www.aspentech.com) introduced Batch Plus, a recipe-driven simulator that targeted batch pharmaceutical processes. At around the same time, Intelligem, Inc. (Scotch Plains, NJ - www.intelligem.com) introduced SuperPro Designer. SuperPro has its roots in BioPro Designer, the development of which was initiated at MIT in the late 1980s to address the needs of the
biopharmaceutical industries. SuperProDesigner was created to address other related industries (e.g., synthetic pharmaceuticals, agrochemicals, food processes, etc.) as well as water purification and end-of-pipe treatment processes. More recently (late 1990s), Hyprotech, Ltd. (a subsidiary of AEA EngineeringSoftware- www.hyprotech.com) introduced Batch Design Kit (BDK), a tool originally developed at MIT which is quite similar in philosophy and functionality to Batch Plus.

Batch Plus, BDK, and SuperPro Designer differ from “Batches” in their basic approach to modeling. More specifically, most of their unit operation models are not dynamic, but rather simple algebraic models, whose solution does not require integration of differential equations. This shortens the computation time and enables the user to evaluate a larger number of scenarios in a shorter period. Batch Plus is recipe driven. In other words, the user develops a model by creating a text recipe (similar to a batch sheet), and the modeling engine creates a Process Flow Diagram (PFD) as an output. BDK and SuperPro Designer build their process models using a graphical user interface with a PFD view. A batch sheet is generated as an output report. SuperPro Designer can handle batch and continuous processes equally well; whereas the other three tools are practically limited to batch processes.

SuperPro Designer will be used to illustrate the role of process simulators in the design and development of bulk synthetic pharmaceutical processes. Information on the role of process simulators in the design and development of biopharmaceuticals can be found in the literature.4

Generation of a Batch Process Simulation Model

To model an integrated process on the computer, the user starts by developing a flowsheet that represents the overall process. Figure 1, for instance, displays part of the flowsheet of a synthetic pharmaceutical process. The flowsheet is developed by putting together the required unit procedures (see next paragraph for explanation), and joining them with material flow streams. Next, the user initializes the flowsheet by registering the various materials that are used in the process and specifying operating conditions and performance parameters for the various operations. The simulator is equipped with two component databases, its own of 450 compounds and a version of DIPPR that includes 1,700 compounds. It also comes with a user database where modified and newly created compounds can be registered. All database files are in MS Access format.

Most bulk pharmaceutical processes operate in batch or semi-continuous mode. This is in contrast to petrochemical and other industries that handle large throughputs and use continuous processes. In continuous operations, a piece of equipment performs the same action all the time (which is consistent with the notion of unit operations). In batch processing, on the other hand, a piece of equipment goes through a cycle of operations. For instance, a typical Nutsche filtration cycle includes charge of slurry, filtration under vacuum or pressure, cakewashing, occasionally cakedrying, and removal of cake. In SuperPro, the set of operations that comprise a processing step is called a “unit procedure” (as opposed to a unit operation). Each unit procedure contains individual tasks (e.g., charge, heat, react, etc.) called operations. A unit procedure is represented on the screen with a single equipment icon (for example, P-1/R-101 in Figure 1 represents the first procedure P-1 that takes place in stirred-tank reactor R-101). In essence, a unit procedure is the recipe of a processing step that describes the sequence of actions required to complete that step. Figure 2 displays the dialog through which the recipe of a vessel unit procedure is specified. On the left-hand side of that dialog, the program displays the operations that are available in a vessel procedure; on the right-hand side, it displays the registered operations. The significance of the unit procedure is that it enables the user to describe and model the various activities of batch processing steps 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. Unlike typical models where batch time is specified, this simulator provides the ability to calculate batch cycle time by estimating the cycle-time of scale-dependent unit operations. 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. In other words, the equipment is sized so that it is large enough that it will not be overfilled during any operation, but it is no larger than necessary (in order to minimize capital costs). In addition, the software checks to ensure that the vessel contents will not fall below a user-specified minimum volume (e.g., a minimum stir volume) for applicable operations.

Before any simulation calculations can be done, the user must initialize the various operations by specifying operating conditions and performance parameters through appropriate dialog windows. After initialization of the operations, the simulator performs material and energy balances for the entire process, and estimates the required sizes of equipment and the batch cycle time. Optionally, the simulator may be used to carry out cost analysis and economic evaluation calculations. The fundamentals of process economics are described in the literature.4

Other tasks that can be handled by process simulators include process scheduling, environmental impact assessment, debottlenecking, and throughput analysis. Issues of process scheduling and environmental impact assessment will be addressed in the next section. In throughput analysis and debottlenecking, the engineer analyzes the capacity and time utilization of equipment and resources (e.g., utilities, labor, raw materials), and tries to identify opportunities for increasing throughput with the minimum possible capital investment.

Having developed a good model using a process simulator, the user may begin experimenting on the computer with alternative process setups and operating conditions. This has the potential of reducing the costly and time-consuming laboratory and pilot plant effort. Please be aware that the Garbage-
In Garbage-Out (GIGO) principle applies to all computer models. If some of the assumptions and input data are incorrect, so will be the outcome of the simulation. Consequently, a certain level of model validation is necessary. In its simplest form, a review of the results by an experienced engineer can play the role of validation.

Illustrative Example
The objective of this example is to illustrate how batch process simulators can be used to model, visualize, and analyze bulk pharmaceutical processes. This example deals with the production of around 171 kg per batch of an intermediate pharmaceutical compound. This task is accomplished using three 1,000 gal reactors, two 4 m² filters, and one 10 m² tray dryer.

Process Description
The entire flowsheet of the batch process is shown in Figure 3. It is divided into four sections: 1) Product Synthesis, 2) Isolation and Purification, 3) Final Purification, and 4) Crystallization and Drying. A flowsheet section in SuperPro is simply a set of unit procedures (processing steps). The unit procedures of each section are marked by distinct colors (green, blue, purple, and black for section one, two, three, and four, respectively). Due to space limitations, the description below is not comprehensive and is not intended to be an exact representation of the actual process. The following sections are merely intended to illustrate the usage of a simulation tool in designing and analyzing a sample process.

The formation of the desired 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 (CCl₄) and reacts with gaseous Cl₂ to form chloroquinaldine. The conversion of the reaction is around 98% (based on amount of quinaldine fed). The generated HCl is neutralized using Na₂CO₃. The stoichiometry of these reactions follows:

\[
\text{Quinaldine} + \text{Cl}_2 \rightarrow \text{Chloroquinaldine} + \text{HCl}
\]
\[
\text{Na}_2\text{CO}_3 + \text{HCl} \rightarrow \text{NaHCO}_3 + \text{NaCl}
\]
\[
\text{NaHCO}_3 + \text{HCl} \rightarrow \text{NaCl} + \text{H}_2\text{O} + \text{CO}_2
\]

The small amounts of unreacted Cl₂, generated CO₂, and volatilized CCl₄ 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 NaHCO₃ and then reacts with chloroquinaldine to form its salt, according to the following stoichiometries:
NaHCO₃ + HCl $\rightarrow$ NaCl + H₂O + CO₂
Chloroquinaldine + HCl $\rightarrow$ Chloroquinaldine.HCl

The small amounts of generated CO₂ and volatilized CCl₄ are vented. The presence of water (added with HCl as hydrochloric acid solution) and CCl₄ leads to the formation of two liquid phases. Then the 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 15.8 hours.

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 the chloroquinaldine dimerizes and forms an undesirable by-product impurity. This series of reactions and transfers takes roughly 16.3 hours. The stoichiometry of these reactions follows:

Chloroquinaldine.HCl + NaOH $\rightarrow$ NaCl + H₂O + Chloroquinaldine
2Chloroquinaldine + 2NaOH $\rightarrow$ 2H₂O + 2NaCl + Impurity
Hydroquinone + NaOH $\rightarrow$ H₂O + Hydroquinone.Na
Chloroquinaldine + Hydroquinone.Na $\rightarrow$ Product + NaCl

Both the Product and 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 5.4 hours.

Next, the product/impurity cake recovered by filtration is added into a NaOH solution in reactor R-103 (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 recovery yield is 90%. The filtration takes about 8.1 hours, and the precipitation and filtrations takes approximately 4.8 hours. The recovered product cake is then solubilized in isopropanol and treated with charcoal to remove coloration. This takes place in reactor R-102 under procedure P-8. After charcoal treatment, the solid carbon particles are removed using another filtration step in NFD-102 (procedure P-9). The times required for charcoal treatment and filtration are 17.6 hours and 4.4 hours, 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 into the same vessel with a yield of 97%. The crystalline product is recovered with a 90% yield using a final filtration step in NFD-102 (procedure P-11). The crystallization step takes approximately 13.1 hours, and the filtration requires roughly 3.6 hours per cycle. The recovered product crystals are then dried in a tray dryer (procedure P-12, TDR-101). This takes an additional 12.4 hours.

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>kg/Year</th>
<th>kg/Batch</th>
<th>kg/kg MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorine</td>
<td>14,534</td>
<td>89</td>
<td>0.52</td>
</tr>
<tr>
<td>Na₂CO₃</td>
<td>17,057</td>
<td>104</td>
<td>0.61</td>
</tr>
<tr>
<td>USP Water</td>
<td>481,484</td>
<td>2,936</td>
<td>17.12</td>
</tr>
<tr>
<td>HCl (20% w/w)</td>
<td>58,034</td>
<td>354</td>
<td>2.06</td>
</tr>
<tr>
<td>NaOH (50% w/w)</td>
<td>33,206</td>
<td>202</td>
<td>1.18</td>
</tr>
<tr>
<td>Methanol</td>
<td>89,827</td>
<td>548</td>
<td>3.19</td>
</tr>
<tr>
<td>Hydroquinone</td>
<td>27,836</td>
<td>170</td>
<td>0.99</td>
</tr>
<tr>
<td>Carb. TetraCh</td>
<td>80,743</td>
<td>492</td>
<td>2.87</td>
</tr>
<tr>
<td>Quinaldine</td>
<td>24,132</td>
<td>147</td>
<td>0.86</td>
</tr>
<tr>
<td>Sodium Hydroxide</td>
<td>12,041</td>
<td>73</td>
<td>0.43</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>322,303</td>
<td>2,15</td>
<td>11.46</td>
</tr>
<tr>
<td>Charcoal</td>
<td>2,574</td>
<td>16</td>
<td>0.09</td>
</tr>
<tr>
<td>HCl (37% w/w)</td>
<td>35,325</td>
<td>215</td>
<td>1.26</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>180,336</td>
<td>1,100</td>
<td>6.41</td>
</tr>
</tbody>
</table>

Total 1,379,432 8,411 49.05

Table A. Raw material requirements (1 batch = 171 kg MP).

unit procedures, 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. In other words, the process flow diagram in this simulator is essentially a graphical representation of the batch “recipe” that shows the sequence of execution 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-101 (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 NFD-101 (procedure P-7). The product recovery yield is 90%. The precipitation procedure takes roughly 8.1 hours, and the filtration takes about 4.8 hours. The recovered product cake is then solubilized in isopropanol and treated with charcoal to remove coloration. This takes place in reactor R-102 under procedure P-8. After charcoal treatment, the solid carbon particles are removed using another filtration step in NFD-102 (procedure P-9). The times required for charcoal treatment and filtration are 17.6 hours and 4.4 hours, 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 in NFD-102 (procedure P-11). The distillation and crystallization step takes approximately 13.1 hours, and the filtration requires roughly 3.6 hours per cycle. The recovered product crystals are then dried in a tray dryer (procedure P-12, TDR-101). This takes an additional 12.4 hours.
between 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 44.2 hours) is the minimum possible time between consecutive batches (also known as Minimum Effective Plant Batch Time). This plant operates around the clock and processes 164 batches per year. The simulator also keeps track and displays the utilization of auxiliary equipment, such as Clean-In-Place (CIP) and Steam-In-Place (SIP) skids.

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.

Another characteristic of batch processing is the variable demand for resources (e.g., labor, utilities, and raw materials) as a function of time. For instance, Figure 5 displays the demand for Purified Water for five consecutive batches. The red lines represent the instantaneous demand; whereas the green line represents the cumulative demand and corresponds to the y-axis on the right-hand side. The blue line corresponds to daily demand (the averaging period can be adjusted by the user). High purity water is a common potential bottleneck in biopharmaceutical processes. It is commonly used for multiple processing steps simultaneously in activities such as fermentation media preparation, buffer making, and equipment cleaning. If not enough instantaneous (or cumulative) capacity is available, one or more process steps may be delayed, possibly with severe consequences. The graph of Figure 5 along with the raw material inventory graph (not shown here) play a crucial role in the sizing of utilities for a batch manufacturing facility. The program generates similar graphs for any raw material, heating and cooling utilities, and electric power consumption.

In addition to instantaneous demand of resources, the simulator provides the means to track the volumetric utilization of all vessels throughout the batch cycle. This allows the user to track maximum working volumes over time, and ensure that the minimum stir volume is always met at any relevant point in a process. The volume content of vessels is also used in sizing new vessels and calculating the capacity utilization of existing vessels.

**Economic Evaluation**

Cost analysis and project economic evaluation is important for a number of reasons. For a new product, if the company lacks a suitable manufacturing facility that has available capacity, 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 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. The simulator performs thorough cost analysis and
project economic evaluation calculations. It estimates capital as well as operating cost. The cost of equipment is estimated using built-in cost correlations that are based on data derived from a number of vendors and sometimes literature sources. The fixed capital investment is estimated based on total equipment cost and using various multipliers, some of which are equipment specific (e.g., installation cost) while others are plant specific (e.g., cost of piping, buildings, etc.). The approach is described in detail in the literature. The rest of this section provides a summary of the cost analysis results for this example process.

Table B shows the key economic evaluation results for this project. Key assumptions for the economic evaluations include: 1) a new manufacturing facility will be built and dedicated to production of this product; 2) the entire direct fixed capital is depreciated linearly over a period of 10 years; 3) the project lifetime is 15 years, and 4) 28,120 kg of final product will be produced per year.

For a plant of this capacity, the total capital investment is around $10.7 million. The unit production cost is $257/kg of product. Assuming a selling price of $500/kg, the project yields an after-tax Internal Rate of Return (IRR) of 34% and a Net Present Value (NPV) of $22.3 million (assuming a discount interest of 7%). Based on these results, this project represents an attractive investment. However, if amortization of up-front R&D cost is considered in the economic evaluation, the numbers change dramatically. For instance, a modest amount of $10 million cost for up-front R&D amortized over a period of 10 years reduces the IRR to 15.3%. This reinforces the point that R&D expenditures should be considered in estimating and justifying the pricing of pharmaceuticals.

Table C breaks down the manufacturing cost. Labor is the most important cost item accounting for 35% of the overall cost. The program estimated that 16 operators are required to run the plant around the clock supported by four QC/QA scientists. This cost can be reduced by increasing automation or by locating the facility in a region of low labor cost. The facility-dependent cost, which primarily accounts for the depreciation and maintenance of the plant, is in the second position (25% of total). This is common for high-value products that are produced in single-product, small facilities. To reduce the impact of this cost, the pharmaceutical industry tends to use flexible, multi-product facilities, where a number of products are manufactured in campaigns throughout the year. Raw materials also make up a large portion of the manufacturing cost. Furthermore, if we look more closely at the raw material cost breakdown, it becomes evident that quinaldine and isopropanol make up by far the largest portions of this cost. Table D. Together they account for approximately 64% of raw materials cost. If a lower-priced quinaldine vendor could be found, the overall manufacturing cost would be reduced significantly. In terms of the isopropanol cost, perhaps the charcoal treatment procedure should be studied to determine whether the amount of this solvent could be reduced. Decreasing the amount of isopropanol would significantly improve the overall process economics because it would decrease the waste disposal costs as well as the raw material costs. Alternatively, perhaps some of the waste solvent which is currently being discarded could be purified and reused. This would decrease both disposal costs and raw material costs.

After a computer model for the entire process is developed, process simulators can be used to ask and readily answer “what if” questions and carry out sensitivity analyses with respect to key design variables. In this example, we looked at the impact of production scale on unit manufacturing cost. When a new drug is commercialized, it takes years to fully penetrate the market. During that period, production is gradually ramped up to meet demand. If the facility is designed to meet demand at full market penetration, then, in the interim it is underutilized. The unit production cost as a function of production scale in the interim period is shown in Figure 6. It was assumed that at lower production scale the plant simply processes fewer batches per year (e.g., two per week instead of one every two days) without handling any other products. At lower annual throughputs the unit cost increases substantially because the same fixed cost is charged to a lower amount of product.

**Summary**

Simulation tools can play an important role throughout the commercialization process. In process development, they 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 facility selection or construction. In manufacturing, they assist engineers in dealing with production scheduling and planning, throughput analysis and debottlenecking, and on-going process optimization.

Batch industries such as pharmaceuticals have just begun making significant use of process simulation to support process development and optimize manufacturing. Increasingly, universities are incorporating the use of batch process simulators in design courses. In the future, we can expect to see increased use of this technology and integration with other enabling technologies, such as advanced process control, computerized batch recipe generation, and on-line analysis and optimization. The result will be more robust processes developed faster and at a lower cost; making higher quality products.

**References**


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