Throughput Analysis and Debottlenecking of Biomanufacturing Facilities

A Job for Process Simulators

Demetri Petrides, Alexandros Koulouris, and Charles Siletti

Bottlenecks are everywhere, from the freeway overpass during the morning commute to the long lines at the supermarket. But bottlenecks in a manufacturing process are bad for business. Computer models can help you eliminate those conditions or situations that are retarding your progress. Whether the goal is strategic planning, evaluating alternatives, purchasing equipment, appraising a facility, or optimizing production processes, simulation tools can improve your analysis.

Demetri Petrides *is president,* ***Alexandros Koulouris*** *is managing director of Intelligen Europe, and* ***Charles Siletti*** *is director of scheduling and planning applications at Intelligen, Inc., 2326 Morse Avenue, Scotch Plains, NJ 07076, 908.654.0088, fax 908.654.3866, info@intelligen.com, www.intelligen.com.*

Process simulators and other modeling tools are gaining acceptance and popularity in the biotech industry. Such tools are mainly used to evaluate "what-if" scenarios and to optimize integrated processes. Tasks handled by process simulators include material and energy balances of integrated processes, equipment sizing, cost analyses, scheduling of batch operations, environmental impact assessments, throughput analyses, and *debottlenecking* (removing a condition or situation that limits process throughput). Process simulation tools can be used throughout the life cycle of process development and product commercialization (Figure 1).

Using Process Simulation Tools

Simulation tools can be used at many stages during the commercialization process.

Idea generation. When product and process ideas are first conceived, process simulators can be used for project screening and selection and for strategic planning based on preliminary economic analyses.

Process development. During preclinical and clinical testing of a drug candidate compound, a company's process development group is looking into the options available for manufacturing, purifying, and characterizing the drug substance and for formulating it as a drug product. At this stage, the process undergoes many changes. New synthetic routes are investigated: New recovery and purification options are evaluated, and alternative formulations are explored. Typically, many scientists and engineers are involved in improving and optimizing individual processing steps.

Simulation tools used at this stage can introduce a common communication language and facilitate team interaction. A computer model of the entire process can provide a common reference and an evaluation framework that facilitates process development. A model shows the effects of process changes, and those changes can be readily evaluated and systematically documented.

A reliable model can pinpoint the most cost-sensitive areas — the economic hot spots — of a complex process. Those spots are usually capital intensive with high operating cost or with low yields and production throughputs. The findings from such analyses can focus additional lab or pilot-plant studies to optimize those process steps. Experimenting on the computer with alternative process setups and operating conditions allows a company to reduce costly and time-consuming laboratory and pilot plant efforts.

The environmental effect of a process can readily be evaluated with computer models. Material balances calculated for the projected large-scale manufacturing reveal environmental hot spots. Those are usually process steps that require solvents or regulated materials with high disposal costs. Environmental issues not addressed during process development can lead to serious headaches during manufacturing because after a process is approved by regulatory agencies, it is costly and time-consuming to make process changes. That is particularly true for biopharmaceutical production, about which it is commonly said *the process makes the product*.

Facility design and selection. When process development nears completion at the pilot level, simulation tools are used to systematically design and optimize the large-scale process for commercial production. Good computer models can facilitate the transfer of process technology and facilities design. If a new facility needs to be built,

process simulators can be used to size process equipment and supporting utilities and to estimate the required capital investment. Production transfer to existing manufacturing sites can use process simulators to evaluate various sites for capacity and cost and to select the most appropriate facility. The same type of model can be applied to the outsourcing of manufacturing, helping to select a contract manufacturer.

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

Several publications are available that address the use of simulation for evaluating and optimizing integrated biochemical processes (1-4). We focus here on the use of such tools for identifying bottlenecks, reducing cycle times, and increasing the throughput of existing biomanufacturing facilities.

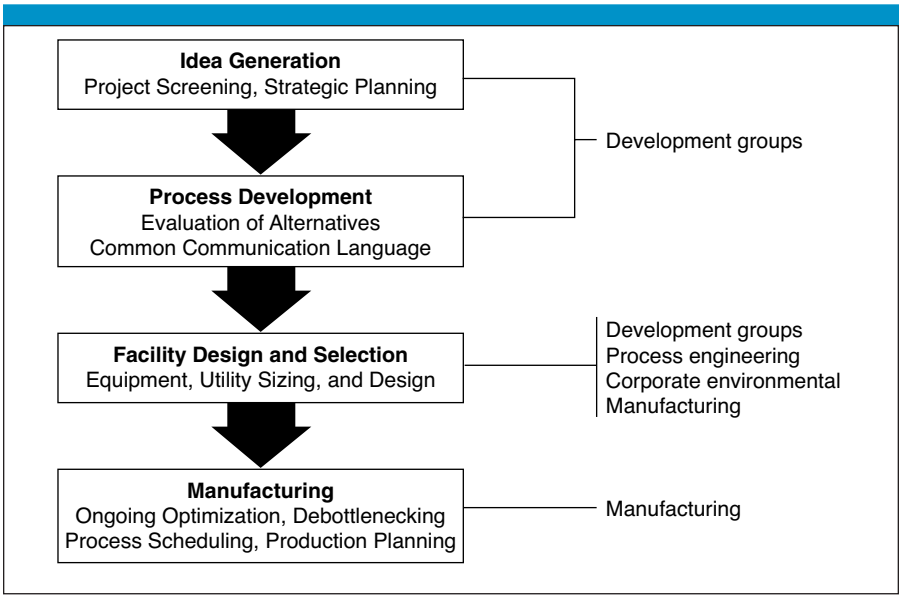

Figure 1. Benefits from the use of bioprocess simulation tools

Using Debottlenecking Theory

The total throughput of a batch plant within a given time period is equal to the *batch size* (the amount of product produced per batch) multiplied by the number of batches executed during that period (Equation 1).

Furthermore, because the number of batches is inversely proportional to the *plant* — or recipe — *cycle time*, which represents the interval between the start of two consecutive batches, the plant throughput becomes proportional to the batch size divided by the plant cycle time (Equation 2).

To increase plant throughput, an increase can be made in either the batch size or the number of batches or both. Increasing those parameters, however, increases the likelihood of running into bottlenecks (process limitations) from either the equipment or the resources. Resources include the demand for various utilities, labor, and raw materials, among others. The bottleneck that limits the number of batches (or the plant cycle time) are known as *time* (or scheduling) *bottlenecks*. Those that limit the batch size are known as *size bottlenecks*.

Equipment-related time (or scheduling) bottlenecks are identified by tracking the uses of the various equipment over time and calculating the equipment cycle time. Figure 2 shows how such information can be graphically displayed using "Equipment Use Gantt Charts." The equipment with the longest cycle time (V-101 in Figure 2) is the time bottleneck that determines the maximum number of batches and the plant cycle time. Auxiliary equipment, such as clean-in-place (CIP) and steam-in-place (SIP) skids, can also become time bottlenecks.

Equation 1

$$\text{Plant throughput} = \text{Batch size} \times \text{Number of batches}$$

Equation 2

$$\text{Plant throughput} \propto \frac{\text{Batch size}}{\text{Plant cycle time}}$$

Equation 3

$$\text{Step batch size} = \text{Cycle size} \times \frac{\text{Number of cycles}}{\text{Batch}}$$

Finding the size bottleneck. Similar to plant throughput (Equation 1), *maximum batch size* (or maximum batch throughput) of a cyclical processing step can be determined as shown in Equation 3.

Batch size of a semicontinuous processing step (such as high-pressure homogenization or disk-stack centrifugation) is determined using Equation 4.

The step that yields the lowest maximum batch size is the size bottleneck and determines the maximum batch size of the entire recipe. An alternative way of identifying size bottlenecks is by calculating the capacity used, the uptime, and the combined use of the various processing steps.

Finding the scheduling bottleneck. The scheduling bottleneck is that step that has the longest *duration* or *step cycle time*. The step duration can be estimated as shown in Equation 5.

Finding equipment use bottlenecks. Each type of equipment is characterized by a unique capacity measurement (such as a reactor's vessel volume, for instance), which determines the maximum load that the equipment can handle per cycle. *Capacity used* is defined as the fraction of an equipment's capacity used during an operation. For instance, if a certain vessel operates with a maximum liquid level of 1,000 L, but the vessel operates at a volume of 500 L, the capacity used is 0.5 or 50%. For equipment that operates in continuous or semicontinuous mode, the capacity used is

Debottlenecking Strategy

If the goal is to increase plant throughput, changes that increase the batch size or reduce the plant cycle time can be effective. In general, we recommend the following strategy.

- Increase batch size until at least one cyclical step operates at 100% use capacity.
- If equipment uptime is low, try increasing the number of cycles per batch for that equipment. This may create opportunities for additional increases in batch size. A side benefit of increased batch size is the reduced cost for quality control (QC) and quality assurance (QA), which depend on the number not the size of the batches.
- If a process operates at its maximum batch size, work to reduce plant cycle time by eliminating time bottlenecks. Long process steps and equipment sharing cause time bottlenecks.
- If bottlenecks are created by equipment sharing install extra equipment that reduces the sharing. The size of the new equipment should be chosen to create opportunities for batch size increases (basing the equipment size on the most demanding step). Rearranging the order in which equipment is used (for shared equipment) can create opportunities for reducing cycle time and sometimes for batch size increases.
- If the time bottleneck is caused by a step that has a very long cycle time, new equipment should be operated in a staggered mode based on the cycle time of the next time bottleneck.
- If the time bottleneck is caused by equipment, it can sometimes be eliminated by moving secondary operations from bottlenecked to nonbottlenecked equipment (1). For instance, instead of heating material in a vessel, heating can be done using an external heat exchanger during the charge and transfer of material into the vessel.
- If bottleneck analysis suggests buying new equipment, the final purchase decision should be based on an evaluation of overall project economic criteria, not simply on throughput considerations.

Reference

(1) T.M. Minnich, "Use Process Integration for Plant Modernization," *Chem. Eng.,* 70-76, (August 2000).

the operating throughput divided by the maximum possible throughput for that particular process material or equipment.

A measure of how effectively a piece of equipment is used is given by the *equipment uptime* defined as the ratio of that equipment's occupancy time over the plant cycle time. For example, if the cycle time is 100 hours, and a certain vessel is only used for 20 hours during a batch, its uptime is 0.2 or 20%. The *equipment occupancy time* is the sum of the time that particular equipment takes to execute the tasks hosted in that equipment.

Combined use is the product of the capacity used and the uptime, and combined use is a clear indicator of how much of the time and capacity of particular equipment is actually being used.

Using these equations as indicators, the processing step with the highest combined use is most likely the batch size bottleneck. Because of time constraints in most plants, we recommend that two approaches (the step batch size and the combined use) be used in conjunction to identify the true batch size bottleneck. We recommend the steps outlined in the "Debottlenecking Strategy" sidebar for biomanufacturing facilities

An Example of Debottlenecking

A cell culture plant that produces a therapeutic monoclonal antibody (MAb) can be used to illustrate throughput analysis methodology. MAbs are used in diagnostic tests as well as for therapeutics. World demand for approved MAbs is now a few kilograms per year. However, with new therapeutic MAbs that require doses between several hundred milligrams and a gram during the course of a therapy, the world demand for MAbs is expected to rise to hundreds of kilograms per year (5).

This example illustrates how to increase plant throughput with only modest capital expenditures. The flowsheet we generated is based on information available in patent and technical literature. We used the SuperPro Designer (Intelligen) simulator in our example. (Readers can obtain an evaluation copy of the software at the company website (www.intelligen.com).

Process description. Our example analyzes the production of a therapeutic monoclonal antibody that is required in large doses. The Figure 3 flowchart shows how approximately 70 kg of purified product is produced each year in 29 batches before debottlenecking strategies are applied. To simplify the flowsheet, the media, buffer, and inoculum preparation steps were removed from the recipe.

The volume of bioreactor broth generated during each batch is about 4,000 L and contains four kg of product (the product titer is 1 g/L). Total volume of the bioreactor vessel (V-101) is 6,500 L. A cycle time of 255 hours (240 hours for fermentation and 15 hours for the turnaround) was estimated for the bioreactor. Because the bioreactor is the time bottleneck, a new batch can begin every 264 hours (11 days). Figure 2 shows the equipment use during two consecutive batches.

Biomass and other suspended compounds generated are removed using a 0.65-μm membrane diafilter (DF-101). Product recovery at this step is 95%. The filtration step takes about 12 hours using a filter with a membrane area of 30 m^2. Clarified solution is concentrated 15-fold using a 50,000 MW cut-off diafilter (DF-102). Recovery yield at this step is 95% and takes 6.35 hours using a filter with an 80-m^2 membrane.

Concentrated product is stored in an agitated tank (V-103) with a total volume of 1,200 L. The bulk of the contaminant proteins are removed using protein A affinity chromatography (C-101). The column handles the material from each batch in two cycles lasting 8.8 hours each. The column has a height of 0.25 m and a diameter of 0.9 m. The binding capacity of the resin is 15 mg of product per mL of resin, and product recovery is 90%. The protein A elution buffer is exchanged with phosphate buffer (P-7) using the same diafilter (DF-102) as in the concentration step (P-4). The multiple rectangles on the Gantt chart at DF-102 (Figure 2) show that the same equipment is used by two different unit procedures. Product recovery at this step is 95%.

Purification continues, using a cation-exchange column (C-102), operated for two

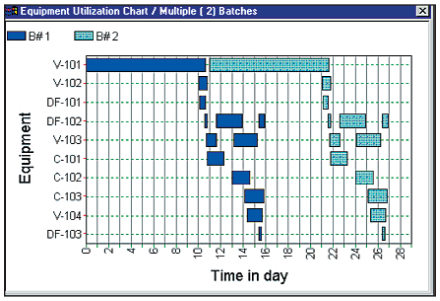

Figure 2. Equipment use chart

cycles lasting 8.95 hours each. The column's height is 0.25 m, and its diameter is 0.8 m. The binding capacity of the resin is 20 mg of product per mL of resin, and the product yield is 90%. Using an agitated tank (V-103), ammonium sulfate is then added to a concentration of 2.0 M, increasing the ionic strength of the solution and preparing it for hydrophobic interaction chromatography (HIC). The HIC column (C-103) handles the batch material in two cycles that each last 20.6 hours. The column has a height of 0.25 m and a diameter of 0.7 m, with a binding capacity of 20 mg of product per mL of resin.

Sodium chloride and acetic acid are added to inactivate any virus particles (P-11/V-104), and the solution is pushed through a 0.1-μm membrane diafilter (DF-103) that captures viral and other suspended particles. As a final diafiltration step (P-13), reusing an existing diafilter (DF-102), the HIC and virus inactivation chemicals are replaced with PBS buffer. Final product solution is about 9.5 g/L, and the final amount of product is 2.3 kg, which corresponds to an overall recovery yield of 56%.

Options for increased throughput. Assuming that the market demand for the product in our example is rising, options need to be considered for increasing the plant's throughput. Figure 4 shows the capacity, time, and combined use for all procedure–equipment pairs as our process now stands. The bioreactor (V-101) has the highest combined use (62.6%) and is identified as the first throughput bottleneck candidate. However, the bioreactor capacity used is only 65.3% because the maximum working volume is 6,175 L (0.95 × 6,500), whereas the broth volume is only 4,000 L,

$$\frac{4{,}000}{6{,}175} = 0.653 \text{ or } 65.3\%$$

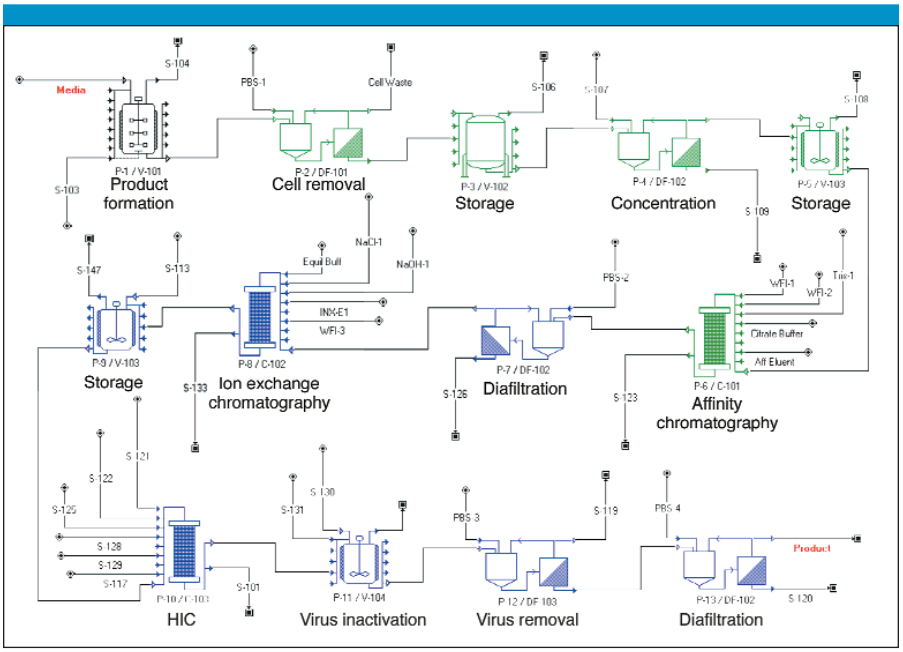

Figure 3. Monoclonal antibody production flowsheet (s = stream, p = procedure, v = vessel, df = diafilter, and c = column)

This provides an opportunity for increasing the batch size by 54.4%. Such a move is in agreement with the debottlenecking strategy that recommends an "increase in batch size until a batch size bottleneck is reached." When that is done, however, all three chromatography columns become unable to handle the amount of material using only the two cycles that was assumed at the beginning (the software we are using displays error messages to warn the user about such discrepancy).

To accommodate the new batch size, the number of cycles per batch for all columns has to increase from two to three. Fortunately, that increase has no negative affect on plant cycle time or the annual number of batches (which remains at 29) because of idle time in downstream processing.

The bioreactor remains the time bottleneck. The new plant throughput is 3.5 kg of product per batch, which translates to 102.8 kg of product per year. This first debottlenecking step clearly shows that oversized equipment offers opportunities for increased plant throughput without capital expenditures. Although the diafilters (DF-101, DF-102, and DF-103) are shown (Figure 4) to be at 100% use capacity use, they are not the batch size bottlenecks because their uptimes are rather low, and increasing their batch size simply increases their uptime.

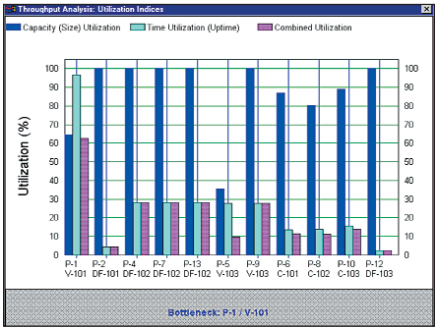

Figure 4. Capacity, time, and combined use chart

After increasing the batch size, the bioreactor (P1/V-101) is fully used both in size (capacity) and in time. At this point, the bioreactor constitutes the batch size as well as the plant throughput bottleneck. The only way to increase plant throughput beyond the current level is by installing extra capacity for procedure P-1 (that is, by installing an additional bioreactor) and by staggering the operation of the second bioreactor so that it starts during the middle of the first bioreactor's cycle time.

Making those changes are not yet feasible because the DF-102, which is the new time bottleneck, has a cycle time (196 hours) that is more than half the cycle time of the P-1 (260 hours). Consequently, the starting times of the two bioreactors are staggered 196 hours apart, and this is the new plant cycle time. Figure 5 shows an equipment use chart for the new scenario. Under these

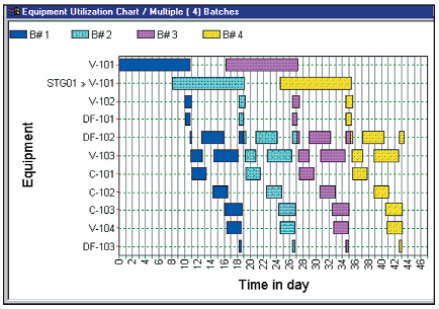

Figure 5. Equipment use chart with two bioreactors operating in staggered mode

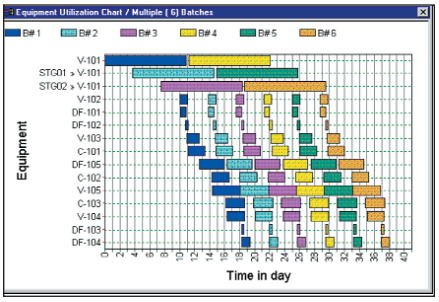

Figure 6. Equipment use chart with three bioreactors and no equipment sharing

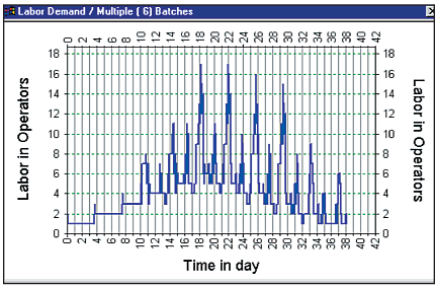

Figure 7. Labor demand as a function of time (six consecutive batches)

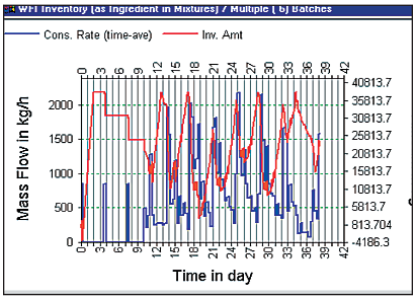

Figure 8. Water-for-injection consumption rate and storage tank levels (six consecutive batches)

conditions, the annual number of batches increases from 29 to 39 and the annual throughput from 102.8 to 138.3 kg.

Figure 5 also shows how the two staggered bioreactors alternate in handling consecutive batches. The first line (V-101) represents the first bioreactor (handling the first and third batches and all subsequent odd-numbered batches), and the second line (STG01>>V-101) represents the second bioreactor (handling the second and fourth batches and all subsequent even-numbered batches). In other words, we use the same recovery train to handle both bioreactors. That is possible because all recovery steps had cycle times considerably lower than the cycle time of the bioreactor.

Removing time bottlenecks. Because the process now operates at its maximum batch size, all additional debottlenecking actions should focus on the elimination of time bottlenecks. Figure 5 clearly shows that the diafilter DF-102 is the current time bottleneck. Addition of a new diafilter to replace DF-102 in P-13 removes that time bottleneck and increases the number of batches to 44 and the annual production to 156 kg. At that point, V-103 becomes the new time bottleneck with a plant cycle time of 171 hours. Adding an extra storage vessel to replace V-103 in P-9 increases the number of batches to 58 and the annual throughput to 205.7 kg. With those changes, the bioreactors (V-101 and STG01>>V-101) again become the time and throughput bottleneck, and the new cycle time has been lowered to 130 hours.

Plant throughput can be increased further with the addition of a new bioreactor and a new diafilter (to replace DF-102 in P-7). Under those conditions, the number of batches becomes 84, and the annual throughput goes up to 298 kg (Figure 6). At this point all steps now use dedicated equipment (no equipment-sharing), and V-105 (a storage tank added to replace V-103 in P-9) becomes the new time bottleneck. However, the bioreactors are again approaching 100% uptime. The same is true for one of the diafilters (DF-105). Furthermore, the chromatography columns are approaching a combined use of 70%. Further throughput increase modifications are probably impractical at this point. If additional plant throughput is required, a new production line should be designed and built.

Floor space. In the previous analysis, we assumed that floor space was available for installing a second and third bioreactor and additional recovery equipment. If that is not the case, then a new building may need to be constructed, and our best throughput scenario may not necessarily be the most economically attractive.

Resource bottlenecks. Another characteristic of batch processing is the variable demand for resources (labor, utilities, and raw materials) as a function of time. For instance, Figure 7 shows the labor demand (expressed in number of operators) for six consecutive batches. As shown, for short periods, up to 17 operators are needed. If that labor is unavailable, then certain operations need to be delayed to distribute the demand for operators more evenly. In such a case, labor can be the time bottleneck.

Labor demand analyses (such as that in Figure 7) are also useful in staffing a facility. If the facility is dedicated to manufacturing a single product, then the number of operators in each shift should be based on the peak demand during that shift. In multiproduct facilities, each production suite can employ a dedicated number of operators and use floating operators during periods of peak demand.

Figure 8 shows the water-for-injection (WFI) demand for six consecutive batches. The blues lines represent the demand for WFI (averaged over an eight-hour period) and correspond with the y-axis on the left side. The red lines represent the liquid level

Equation 4

$$\text{Step batch size} = \text{Continuous throughput} \times \text{Plant cycle time}$$

Equation 5

$$\text{Step duration} = \frac{\text{Step cycle time}}{\text{Number of units available}}$$

Equation 6

$$\text{Combined use} = \text{Capacity used} \times \text{Uptime}$$

in the WFI storage tank and correspond with the y-axis on the right side. WFI demand is a frequent bottleneck in biopharmaceutical manufacturing. It is commonly used during multiple processing steps simultaneously to prepare fermentation media and purification buffers and to make equipment cleaning solutions.

If the WFI storage tank runs dry at a certain point (because of low capacity in the still or the tank), one or more process steps will be delayed, and the WFI can become the time bottleneck. The red lines in Figure 8 (showing the liquid level in the storage tank) stay within certain limits because the WFI still, which has a capacity of 1,000 L/h, was programmed to turn on when the level drops below 35% and to turn off when the level exceeds 85% of the vessel volume of 45,000 L. During retrofit projects, such as the one described in this example, design engineers should consider new utility profiles to make sure adequate production and storage capacity is available to meet new demands. Process simulators can play an important role in retrofit projects by enabling engineers to calculate new profiles and optimize the size of new equipment.

Tooling Up to Maximum Efficiency

Use of computer-aided tools for process design and simulation is increasing in the biotech industry and affecting engineering activities at all stages of commercialization, from initial idea screening to process development and manufacturing.

Simulators that are capable of tracking and displaying the capacity and the time of equipment and resource use can be indispensable in identifying and eliminating bottlenecks. In revamping existing facilities, such tools enable management to visualize the plant operating at maximum practical capacity and to evaluate process modifications required to reach that goal. In designing new facilities, simulation tools can be used to judiciously introduce overcapacity for certain steps and the ability to expand easily for others, so that increased future market demand can be readily accommodated.

Having access to a simulator that quickly performs the repetitive calculations allows facility engineers to focus more of their time on creative aspects of design and to achieve optimized solutions that would be impossible otherwise.

References

(1) D.P. Petrides, J. Calandranis, and C.L. Cooney, "Bioprocess Optimization Via CAPD and Simulation for Product Commercialization," *Genet. Eng. News*, 16(16), 24–40 (1996).

(2) F. Hwang, "Batch Pharmaceutical Process Design and Simulation," *Pharma. Eng.*, 28-43 (January–February 1997).

(3) D.P. Petrides, R. Nir, J. Calandranis, and C.L. Cooney, "Introduction to Bioprocess Simulation," *Manual of Industrial Microbiology and Biotechnology*, A.L. Demain and J.E. Davies, Eds. (ASM Press, Washington, DC, 1999), pp. 289-299.

(4) R.G. Harrison et al., *Bioseparations Science and Engineering* (Oxford University Press, New York), in press. The chapter "BioProcess Design and Economics," is available at www.intelligen.com/literature.htm.

(5) S.S. Seaver, "Monoclonal Antibodies: Using New Techniques to Reduce Development Time," *Genet. Eng. News* 17(1), 13–28 (1997).

BP