Proceedings of the 2002 Winter Simulation Conference
E. Yücesan, C.-H. Chen, J. L. Snowdon, and J. M. Charnes, eds.

CAPACITY ANALYSIS OF MULTI-PRODUCT, MULTI-RESOURCE BIOTECH FACILITY USING DISCRETE EVENT SIMULATION

Prasad V. Saraph

Biological Products,
Bayer Corporation
Berkeley, CA 94701-1986, U.S.A.

ABSTRACT

Use of simulation for capacity analysis is an upcoming field in Biotech industry. This paper discusses an application of discrete event simulation in the multi-product and multi-resource Filling Freeze Drying facility of Bayer Corporation's Berkeley site. The SIGMA® simulation model was used to estimate the current and future throughput capacity by taking into account current operations and various capital and efficiency improvement projects planned for near future. The model also identified certain project clusters with potential for large capacity gains, which otherwise would not have been visible. The model and its outcome are in use since 2001.

1 INTRODUCTION

This paper presents an example of how the capacity analysis was carried out using production schedule simulation for our Filling, Freeze Drying and Plasma processing facility. The modeling was done using SIGMA (Schruben, 1994).

Bayer Corporation's Berkeley facility is the global headquarters for Bayer Biotechnology. The facility houses research as well as manufacturing operations. Currently, the manufacturing operations produce second generation recombinant DNA technology based drug (Kogenate-FS®) to treat Hemophilia that is caused by the lack of factor eight protein. As the drug needs to be administered at regular intervals, manufacturing consistency is the prime objective for Bayer Berkeley facility.

The manufacturing operations are complex not only from the technology point of view but also due to regulatory constraints that have to be meticulously met and documented in accordance with the agreements with regulatory agencies like FDA (Food and Drug Administration).

2 BACKGROUND

Kogenate-FS was commercialized in 1998. Since then the product has enjoyed a healthy growth in demand, being the most advanced drug of its kind on the market.

Growth in demand triggered the need for growth in manufacturing throughput and hence in capacity. The first step was to understand the existing throughput and bottlenecks.

The analysis of existing capacity was relatively straightforward where throughput was directly related to the technical capacity (i.e., machine capacity). But there were some stages where the relationship between throughput and technical capacity was not obvious and hence predicting throughput based on technical capacity was difficult.

One such stage critical to Kogenate-FS was Filling and Freeze Drying operations. For these operations, Kogenate-FS has to share a composite facility with two other products and an intermediate (as well as with the earlier generation of Kogenate). As these operations form the last manufacturing stage (and handle the most concentrated and hence most valuable product), understanding their capacity was critical for our growth plans. Figure 1 illustrates the manufacturing setup for Filling and Freeze Drying operations.

At the same time, there were multiple capital projects and proposed changes to existing operations that were under consideration. The impact of these projects and changes on the throughput was not clear and hence it was proving difficult to prioritize the allocation of personnel, money and time for the implementation of the various projects and changes. Therefore it was important to clarify the impact of various changes.

Having identified these needs, our next step was to choose which approach to use for analysis. We had choices of Simulation, Mathematical Programming, Queuing Theory and some heuristics. We chose Simulation.

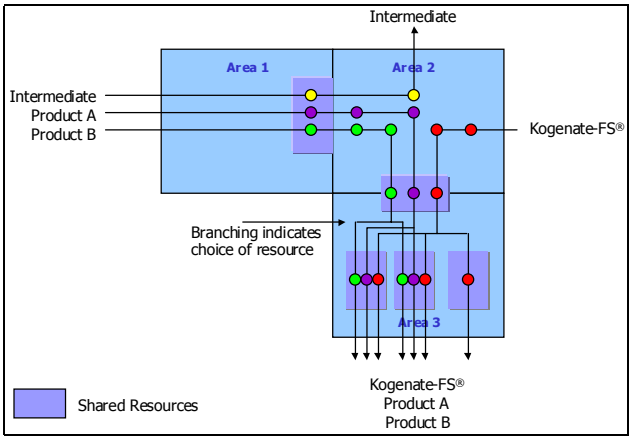

Figure 1: Multi-product, Multi-resource Filling Freeze Drying Facility

3 WHY SIMULATION?

Capacity analysis has been a well-known problem in the field of Industrial Engineering and Operations Research. Mathematical Programming and Queuing Theory have been used extensively to address capacity analysis.

For our problem, the numerous non-linearities, uncertainties and production shift considerations made Mathematical Programming or Queuing Theoretic solutions potentially time consuming, and at the best, only approximate.

Simulation offered us the flexibility to model various constraints and causal relationships in detail and also enabled us to model their interactions. Also, assessing the impact of various projects and changes was easier with the Simulation approach. After deciding on the use of Simulation as an approach, we defined our problem in terms of its objectives, scope and assumptions.

4 OBJECTIVES

Based on the existing and future operating conditions and product mix:

- Estimate Filling Freeze Drying throughput
- Quantify impact of capital projects and proposed changes
- Identify and analyze improvement opportunities

5 SCOPE AND ASSUMPTIONS

We limited our scope to a few aggregated key steps in Filling and Freeze Drying rather than trying to model each and every step (total number of detailed steps cover over 600 pages). Table 1 shows key steps along the critical path.

Table 1: Key Process Steps (Routing)

Product	Step 1	Step 2	Step 3	Step 4	Step 5
KG-FS-I	- -	X	X	X	X
KG-FS-II	- -	X	X	X	X
Intermediate	X	X	X	- -	- -
Product A	X	X	X	X	X
Product B	X	X	X	X	X

For modeling purposes, we chose the operating time span of five months as after every five months, the facility undergoes shutdown and everything starts afresh afterwards.

In terms of events, we modeled all events that affect the manufacturing process and throughput.

As an important assumption, we assumed sufficient availability of personnel and utilities.

The time-span of the shortest activity was about four hours and hence, we modeled all other time durations in multiples of four hours for modeling convenience.

6 MODELING APPROACH

During our discussions with manufacturing, engineering and planning personnel, we identified the production schedule generated by the planning group as the point of control for all production decisions.

The planning group, after receiving intimation of all changes such as equipment failure, material non-availability and urgent needs, generated the current version of the production schedule and communicated it to all stakeholders. This process would repeat itself as often as required (at least once every three working days).

We built a simulation model to mimic the production schedule generation and execution process, with the feedback loops as they exist in reality. Figure 2 illustrates our structure.

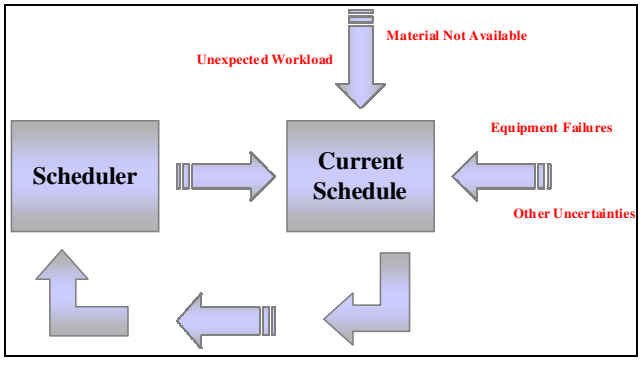

Figure 2: Simulation Model Structure

After deciding upon the model structure, we carried out a number of standard modeling steps, namely, process mapping, data organization, logic development, model

building, validation, experiments, iterative changes, results and analysis.

The process mapping and data organization phases of our modeling efforts helped not only the simulation project but also us as an organization to reach a common understanding of this complex process setup. Data organization in this project was mainly related to capturing the rules and uncertainties of operation. These rules are listed in Appendix-A, while Appendix-B lists the key uncertainties.

Logic development was done over multiple meetings with the planning group to understand the schedule generation and execution process and identify critical issues.

7 MODEL BUILDING

We built the model in phases. To start with, we constructed a model that could build a production calendar. The production calendar identified times of operation (shifts and weekends), certain facility operations that are fixed and independent of production operations, such as cleaning and sanitization processes and planned maintenance on key equipment.

We made sure that the model could generate a feasible production calendar and validated the results with the planning and engineering groups.

Then we modeled the Intermediate product that uses only two out of three areas. Again, we validated the results with stakeholders.

In a similar manner, we introduced the remaining products, one at a time and validated each series of results for feasibility and correctness.

With each additional product and stage that we modeled, we incorporated the constraints and causal relationships specific to that product or stage. Figure 3 shows the final model built using SIGMA.

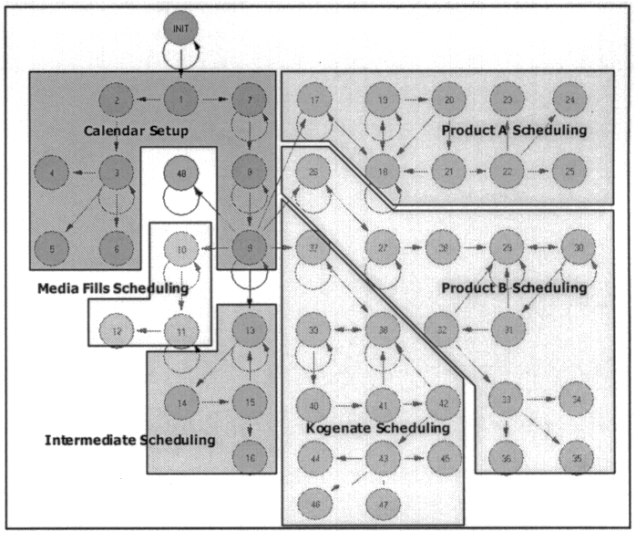

Figure 3: SIGMA Simulation Model

Such phased and modular model building helped expedite the modeling process by reducing errors. After completing the model, we carried out extreme value checks to ensure that the model was free of errors. The next challenge was validation of the model for stakeholders.

8 MODEL VALIDATION

The stakeholders were not simulation experts but experienced personnel from production, engineering and planning. Validating a model from simulation perspective is quite different from validating the model from stakeholder perspective.

Hence, we started to establish the parameters and output formats that the stakeholders were familiar with. An easy set of parameters was the facility output, equipment failures and lost time from the preceding year. Along with these parameters, we developed a small MS Excel® interface that would convert the model output into a production schedule format that was being used by planning group.

The parameter estimation phase of validation had a notable problem. For one particular parameter, namely production volume for Intermediate, the difference between the model estimate and the historical value was 21%. Upon further investigation, we found that the production capacity for the Intermediate was underutilized in the past. In retrospect, the predicted model value was realized as production output for year 2001.

9 EXPERIMENTS

After validating the model, we designed a set of experiments to address our objectives. The first set of experiments was meant to establish existing throughput capacity under different product mix assumptions. It should be noted that though Kogenate-FS is shown as a single product, within this product type there are two sub-types with different processing parameters.

The next set of experiments was meant to analyze the impact of various capital projects and proposed changes on the throughput. The proposed changes arose from compliance requirements in terms of procedures, for example, increased frequency and/or duration of certain cleaning operations.

We carried out these experiments to show the individual impact of each change and project. During this time, we also started to design the experiments for our last objective of identifying and analyzing impact of improvement opportunities.

We did not want to invent improvement opportunities from scratch due to time limitations. Hence, we tried to find clusters of capital projects and proposed changes that would result in maximum increase in throughput. This was the phase of our project that made us realize the value of the software that we were using, SIGMA. We could carry

out numerous experiments, each with enough replications in a short time. For example, 40 replications of our model for any given set of input parameters would take about 30 seconds on a Pentium-II® laptop with 128 MB RAM.

10 RESULTS

We classify the results into three categories, namely, estimates of existing capacity, individual impact of various capital projects and changes and identification of clusters of projects and changes.

10.1 Establishing Existing Capacity

Establishing the existing capacity of the Filling and Freeze Drying operations served as a benchmark for our site capability analysis and future capital projects planning.

Before these efforts, capacity estimates used to be derived from a heuristic method that is popular in pharmaceutical Fill and Freeze-dry operations. The method starts with calculating available time (total time minus planned downtimes, holidays etc.) from the Fill and Freeze-dry resource cluster with emphasis on perceived bottleneck. This available time is then apportioned to workload to calculate the capacity of the operations. On this capacity a utilization factor is applied (based on the experience of people involved in capacity analysis) to account for historically observed uncertainties. The outcome is treated as the realistic capacity of the operations.

The heuristic approach approximates historical capacity quite well, but fails to predict future capacity under different operating conditions with similar accuracy. The three main reasons for such failure are as follows:

- Stochasticity of operations
- Interdependence of resources
- Differences in the ways of working of current operations and future operations

The last reason is worth more discussion. The heuristic approach depends heavily on historical experience with operations. Such experience may not help in predicting operations in future, especially if the rules of operations are going to be changed.

10.2 Impact of Individual Projects and Issues

Clarifying value addition or lack thereof for each individual capital project and proposed change helped us in project management and prioritization. It also helped in substantiating certain changes that were thought to have negative impact on throughput but were found not to have any actual impact in the model (as these changes did not affect the critical path or the bottleneck resources).

At the time of analysis, Filling Freeze Drying area had 11 large projects or concepts in the planning phase. Because each project had different origins and objectives, the impact of these projects on the overall capacity was vague at best and unknown at worst.

In order to analyze the impact of these projects, we analyzed the changes that each project would introduce in operations and capacity. We built many scenarios using our simulation model and showed the impact of each project individually over the base case.

One such project that was perceived as causing a big positive impact on capacity is worth a mention here. This project was going to decrease the unavailable time of one area by 16 hours every week. The general opinion was these 16 hours would linearly impact the capacity of the Fill and Freeze-dry operations. Simulation experiments, however, showed that there was no impact of this change on the throughput.

After going through the detailed performance measures, we realized that this particular area was not the bottleneck for operations and hence increase in non-bottleneck capacity had no impact on the overall capacity.

10.3 Project Clustering Analysis

While analyzing individual projects, we realized the necessity of analyzing the effect of multiple projects, project clusters, on the capacity. Clustering projects was an insight into our plans that was possible only because of the simulation efforts.

We formed the basic project clusters based on timelines and unavoidable precedence. On these basic clusters we added selective projects (mostly through trial and error as the total number of projects was limited) to form the project clusters with maximum impact.

One such cluster identified had the potential of increasing capacity for Filling and Freeze Drying operations by 30% while another cluster showed potential for 50% more capacity. These clusters have been accordingly prioritized now for project management. This is an area worth further analysis.

11 CONCLUSIONS

Discrete event simulation was successfully used to analyze the capability of a multi-product, multi-resource biotech manufacturing facility. The results provided reliable and consistent estimates and also helped the management to prioritize certain project clusters for maximizing the benefit.

The simulation efforts also ended the rule-of-thumb estimates (one of the three causes identified by F W Taylor in 1911 for lower efficiency of organizations in his seminal essay “The Principles of Scientific Management”(Taylor, 1911).

The availability of the simulation model helped us in updating our throughput estimates with minimal additional efforts given the changing business environment. The model and its results are in use now for 1.5 years and the model is still evolving with new information and better understanding of the processes.

This model also sowed the tiny seed for much grander modeling efforts that we undertook over the last two years and which will see completion towards the end of 2002.

ACKNOWLEDGMENTS

The author wishes to thank Bayer Corporation for supporting and believing in Simulation. This piece of work was the result of combined efforts of the 3BU+ team headed by Dr Thomas Bamberger and actively supported by Dr Scott Probst and Alethia DeLéon. The author also wishes to thank all personnel at the Berkeley site that provided the model with active input. Another major contributor to the success of simulation was the availability of SIGMA and the enthusiastic support and help of Prof Lee Schruben of UC Berkeley. Without him, this project may never have been realized.

The author also thanks the anonymous referee whose comments helped significantly to make this paper more complete.

APPENDIX A: KEY SCHEDULING RULES

1. After Step 2 and Step 3 (x_1 hours), Kogenate lot captures the filling (day shift) and then one of the x_{25} Freeze Dryers for x_2 days (x_3 days for KG-2)
2. While one Intermediate lot is undergoing operations (x_4 hours) in Area 2, next lot of Intermediate is released for pasteurization, if feasible
3. Product A and Product B lots are released only when necessary (twice a month and once a month, respectively)
4. Product A and Product B try to progress together through Area 1 and Area 2
5. Product A blocks pasteurizer for x_5 hours and Area 2 for x_6 hours
6. Intermediate blocks pasteurizer for x_7 hours and Area 2 area for x_8 hours
7. Product B blocks pasteurizer for x_9 hours and Area 2 area for x_{10} hours (for purification and freezing) and 4 hours for thaw and Step 3
8. At any given time, there can be either Kogenate or Products A, B in Area 2
9. Product A, B and Intermediate can share Area 2
10. Other products can be present in Area 2 while a product is under process, if and only if, other products are in bulked state
11. Product A filling and freeze drying takes x_{11} days, while Product B filling and freeze drying takes x_{12} days
12. Product B can wait before Step 3 and after pasteurization for x_{13} months
13. Time lag between Step 3 and filling can not exceed x_{14} hours for all products except Product A (x_{15} days)
14. Product A and Product B can be bulked only on the weekdays (Step 2 has to start and end on a weekday)
15. Mandatory Media Fills take place 'y' times a month,
16. About x_{16} media fills per freeze dryer per quarter. QA, QC, Engineering, Validation and Manufacturing also request Media Fills
17. All processes work 24x7 except filling (Day Shift) and Freeze Dryer unloading (Swing Shift) which work in 8x7
18. Freeze Dryer loading starts in parallel with filling and hence there is a overlap of x_{17} hours
19. Kogenate Filling follows Step 3 without any delay for scheduling and operational ease
20. Freeze Dryer unloading can take place only during the swing shift
21. Pasteurization can not start while WFI sanitization is in progress
22. Two freeze dryer unloads on a day plus a fill on the day of unload cancel the fill next day, due to insufficient turnaround time
23. Freeze Dryer 1 and 2 can process any products, while Freeze Dryer 3 can only process Kogenate
24. Kogenate unload cancels the fill on the day of the unload
25. Filling and Freeze Dryer turnaround are either-or activities in the fill area
26. There are x_{18} media fills preceding a shutdown and x_{19} following the shutdown, all of which may not fall within the shut down time span
27. 1 Product B fill corresponds to x_{20} Intermediate II (pasteurization and purification) lots and 1 Intermediate II lot corresponds to x_{21} Intermediate I lots (before pasteurization)

APPENDIX B: KEY UNCERTAINTIES

1. X_{22}% Kogenate fills are cancelled (and hence Step 2 is also cancelled) due to uncertainties (based on 1999 data). These cancellations imply delay of 1 day in the fill and a lost fill slot,
2. X_{23}% Product A and x_{24}% Product B scheduled fills are cancelled (postponed),
3. Model scheduling look ahead period is variable and is currently set at 1 month,

4. X_{25} Freeze dryers put together fail for around x_{26} times a year and each failure lasts for 1 to 4 days, but most commonly observed failure span is 1-2 days,
5. Pasteurizer fails once or twice a year for 1-2 days,
6. Pasteurizer is re-qualified twice a year for 5 days each,
7. There is a delay between two consecutive usage of pasteurize, if there is a mixer failure that happens once or twice per year and causes a delay of x_{27} hours,
8. Mandatory Calibration activities consume x_{28} days per freeze dryer per year lasting for 1-2 days each.

REFERENCES

Schruben, Lee. 1994. *Graphical Simulation Modeling and Analysis: Using Sigma® for Windows (The Scientific Press Series)*. Cambridge, MA: Course Technology, Incorporated.

Taylor, F W. 1911. *The Principles of Scientific Management.* W. W. Norton & Co., NY.

AUTHOR BIOGRAPHY

PRASAD V SARAPH is a Project Manager with Technical Operations of Bayer Corporation's site in Berkeley, CA. He is a Mechanical Engineer by training with a Masters degree in IE from IIT-Mumbai (1995) and MS in IE&OR from University of California at Berkeley (1999). He has worked in Plastics Manufacturing, Corporate Research and Management Consulting. He has a book to his credit "Corporate Restructuring: Crompton Greaves and the challenge of Globalization" (1998). His professional interests are in supply chain optimization and simulation-based process reengineering. His email address is <prasad.saraph.b@bayer.com>.