Adapt or Fall Behind: Surviving and Thriving in the Competitive Jungle of Plant Operations Scheduling and IIoT

A White Paper by Rick Johnston

Abstract

Biopharmaceutical manufacturing has required significant technological developments in the area of cell culture, chromatography, and purification. It is no small miracle that every day across the world, millions of liters of cell culture capacity generates life-saving medicines for the patients who need it. The bio-manufacturing process is unique in its need for—

- Tight regulation of an inherently variable process
- Rigidly controlled environmental conditions to make an imperfectly characterized living cell
- A large number of groups responsible for making, testing, validating, and releasing bio-manufacturing products

However, as teams increasingly “normalize” this bio-manufacturing process, an increased focus exists for categorizing and reducing variability. Nowhere is this more visible than in scheduling—because this is the part of the process where variability is seen first and foremost. Delays in processes, re-work, and last-minute re-planning and schedule changes are a visible “yardstick” of a non-optimized process. By closely observing these delays and the causes behind them, operation teams can begin to make concrete improvements to their manufacturing processes. Such an approach has been extremely successful in the semiconductor manufacturing sector in which significant improvements in process efficiency have been realized. In this white paper, we discuss how focusing on optimizing detailed process schedules—along with the tools for such optimization—can provide critical insights into processes and help optimize bio-manufacturing operations.

Process Delays: A “Yardstick” for Manufacturing Inefficiency

One of the most difficult issues in complex bio-manufacturing processes is identifying operational inefficiencies to improve run rates and lower total production costs. Modern biopharmaceutical manufacturing is a capital-intensive process, consisting of many facilities that cost hundreds of millions of dollars to construct and require dozens or hundreds of staff to run. While many other industries are highly automated with few or even no human workforce, biotech facilities require significant manual labor to manage the manufacturing process. This requirement exists in part because of the inherent variability in biopharmaceutical processes: in-process sampling as well as process adjustments must be made when executing recipes, each of which requires documentation, validation, and (at times) active process adjustment. However, even when accounting for this “inherent biological variability,” a significant variation between batches in process durations prevails.
Figure 1 shows an indicative distribution of the observed times for a media preparation recipe, collected from a manufacturing execution system (MES). As illustrated, while the average time to prepare a batch of media is 4 hours, durations as low as 2 hours and as high as 11.5 hours are historically observed. (This data excludes media hold times but includes in-process sampling activities.)

![Media Prep Times, for 2KL Bioreactor](image)

**Figure 1. Distribution in 2KL Production Bioreactor Media Prep Times**

This data suggests that significant process variation and potential inefficiencies exist—even with outside activities and biological product contact. Schedulers trying to plan for this activity need to either allow a long period of time (8+ hours) to make the media batch to ensure it will be available, or use lower time that risks the material from not being ready when scheduled. The standard deviation of this process (a measurement of how variable this process is) is around 2.2 hours.

Contrast this with data collected in the semiconductor industry in which the duration of all photolithography steps (one of the key manufacturing processes) is approximately 8 hours. In this semiconductor example, we see a similar pattern of variation, but with almost no variation in manufacturing times. The standard deviation of this process is 2 minutes, nearly 1/100th that of the biotech process.

While there are many potential causes for variability in operational process times, one of the critical observations made by Applied Materials in the semiconductor industry was to focus the manufacturing organization around identifying causes for and reducing root causes of time-based...
variation. The reason is simple: activities with large variations in process step durations either reduce capacity or decrease process robustness, or both. By focusing operational groups around process time variation as a metric for performance, it provides concrete—

- Real-time feedback on which processes are performing poorly
- Measurements on “how bad” the performance is
- Details (by comparing to median process times) on what the impact will be on activities that follow

Such an approach provides bio-manufacturers with a data-rich solution that can be used as a yardstick for measuring and identifying inefficiencies in process steps. In the semiconductor industry this approach has been tremendously successful in eliminating time-based variability as well as reducing the indirect forms of waste that are introduced to the process to manage variability, such as additional intermediate inventories, additional hold times, and excess capacity.

**Measuring Process Delays: From Stop-Watches to Automated Data Collection**

While bio-manufacturers have significantly more manual and person-driven process steps than semiconductor manufacturing, both industries have sophisticated approaches for collecting data. With the need to collect a significant number of process variables during the course of producing a batch, as well as the need for validated systems that meet regulatory requirements, bio-manufacturers have invested in control systems and hardware that provide a rich source of data to operations teams. Distributed control systems (DCS), manufacturing execution systems (MES), as well as OLE for process control (OPC), and other standards have helped create an environment in which almost every manufacturing step, operation, and phase time is collected and stored—often in multiple systems of record. This source of data is “free” to manufacturing groups or software products that collect it (because it is required by quality) and guaranteed to be accurate because the same systems that observe the process, control it. This means that manufacturers can easily collect this time-based data and use it to measure process delays at a highly granular (operation, phase) level.

Applied Materials’ *Analytics and Control* provides functionality to integrate with DCS, MES, and other systems through OPC, direct connect, or a variety of other integration methods. We have over three decades of experience in systematizing the extraction and analysis of time-based data for manufacturing. Our software allows users to automatically stream, collect, and analyze the sources in timing variability data—and use this data to drive standard work, “lean,” Kanban, or other initiatives.

**From Process Time Measurement to Schedule-Based Control**

In order to effectively reduce variability to improve manufacturing processes, measuring delays is an important first step. However, manufacturers need to understand not the magnitude of the delay when it occurs, but rather its impact on the overall processing times of this and future batches. Some areas of the manufacturing process can tolerate variation in process times due to timing or capacity “buffers,” while other parts cannot. To effectively understand this, manufacturers use finite scheduling software to first plot the sequence of events and dependencies between equipment and operations, and then predict the impact of delays on manufacturing operations.

Figure 3 outlines an evolutionary map for how finite scheduling software can be introduced into a bio-manufacturing organization to drive improvements in process metrics. This approach is based on Applied’s *SmartFactory Operations Productivity* software, which has been used by nearly 100% of the top-25 semiconductor manufacturers to perform scheduling. This evolution transitions in stages from primarily measuring timing data to increasingly sophisticated control strategies to manage delays in processes.
MANUALLY COLLECT MANUFACTURING TIMING DATA. At the beginning of a manufacturer’s journey, operators typically focus on setting up systems that allow them to evaluate manufacturing timing data as part of a project. This “hot spot” analysis uses Applied’s SmartFactory Analytics and Control to help identify key areas of the manufacturing process that need additional attention or focus. The outcome of such analysis is a series of projects to correct obvious issues with operating procedures (SOPs), recipes, or hardware that cause the variability. Existing DCS and MES databases, as well as time-based historians such as OSIsoft PI, are typically used for this analysis.

AUTOMATE PRICING TIMING DATA COLLECTION/REPORTING. As manufacturers see benefit from measuring duration based metrics and timing data, a need exists to automate the collection of this detailed data and to report outliers as they occur. A variety of statistical approaches can be used here including Shewart plots to detect trends and patterns. Applied Materials’ SmartFactory Analytics and Control software is used to provide reporting and alerting functionality to operators.

USE PROCESS TIMING TO SCHEDULE FACILITY AND PREDICT IMPACT. Manufacturers can then plug these time-based metrics into a finite scheduling application like SmartFactory Operations Productivity, which can indicate the impact of delays on overall capacity. Depending on the configuration of the equipment of that facility, as well as bottlenecks and critical paths, this provides critical information on where delays will have the largest impact on metrics like throughput and cycle time vs. where delays carry little or no cost. Little or no thought is given in this analysis to the response to delays or to optimizing processes (by delaying, prioritizing, or batching).

GENERATE OPTIMIZED SCHEDULES. As using scheduling software becomes more sophisticated, manufacturers focus less on generating “feasible” schedules (that are typically only reactive in the case of delays) and increasingly on adjusting schedules that are optimized either to minimize the impact of a delay should it occur, or to otherwise proactively optimize capacity. Such a scheduling tool typically uses a mixed-integer optimizer or other optimization techniques to generate the best schedule against a metric-like throughput or cycle time. At this level, schedules are typically at the procedure or unit-procedure level, with little or no visibility into operation or phase level information.

GENERATE DISPATCH DATA AND RESPOND TO REAL-TIME DATA. The final phase of evolution is characterized by increased control by a scheduling tool over the minutiae of the bio-manufacturing process, both in terms of increased resolution (operations, phases), incorporating “soft” constraints and preferences in the manufacturing process, as well as the direct assignment of people to tasks. By generating schedule and dispatch data, the scheduling application can directly track individual users and their execution of tasks, which is typically beyond the scope of information collected by
MES or DCS. *SmartFactory Operations Productivity* includes an integrated scheduler and dispatcher that can respond to real-time data, allowing faster recovery from adverse events.

By following this evolution from process time measurement to schedule-based control, bio-manufacturers can transition their organizations from today’s process-driven culture to a performance-based driven organization that adheres more strictly to manufacturing schedules and actively drives process-time variability from their respective areas of focus.

This has significant benefits to organizations that implement it. In the semiconductor industry, such an approach towards “standard work” and automated strategy execution (in the case of adverse events) has resulted in multi-million dollar improvements in cycle time and reduction in rework and scrap.

**A Day in the Life: Biotech vs Semiconductor**

Figure 4 summarizes a day in the life of scheduling a biotech manufacturing process. Red activities represent adverse events, orange represents flow-on delays and impacts, and green activities represent event resolution. Two adverse events—a CIP failure early in the day and a clean hold expiry in the early afternoon—delay the start of a Protein A Chromatography step by nearly 14 hours. It is common to see such “cascading” sets of delays in bio-manufacturing facilities due to clean or sterile hold expiries, which limit the amount of time vessels can be held before they must be re-cleaned. Note also that the schedule is refreshed multiple times throughout the day in a reactive manner to delays, with schedulers scrambling to understand the impact and effect of process issues.

![Figure 4. A Sample Day in the Life of a Biotech Purification Process](image)

Contrast this with Figure 5, which shows a typical day in a semiconductor manufacturing process. While adverse events still occur, the optimal response to those events occurs quickly—a minute or two after the event is reported to a control system. This means that optimal rebalancing of the manufacturing line can be done, limiting impact to other production systems. Re-optimization is performed as additional information about the issue is discovered, using an automated rules-based approach that limits manual re-planning. This way, semiconductor manufacturers can make real-time adjustments without operator intervention to their schedules, leaving schedulers to perform critical communication tasks to resolve crises quickly and effectively.
Conclusion

Variations in processing time are an inevitable part of any manufacturing process, but are particularly prevalent in biopharmaceutical manufacturing. Many manufacturers are beginning to understand that collecting information about where delays occur, what impact the delays caused, and root causes behind delays can be critical in improving overall process efficiency and product quality. In the semiconductor industry, a “laser focus” on time-based variability has helped manufacturers make significant improvements in their operations. Through a systematic approach to data collection, risk identification, and sophisticated scheduling, semiconductor manufacturers have built processes that are nearly deterministic and highly optimized.

While there remains significant work to do in the pharmaceutical industry to achieve the same kinds of results, the path to improved manufacturing is clear from the semiconductor industry. With an integrated approach to data collection, analysis, scheduling, and dispatching, manufacturers can automate the response to many common kinds of adverse events. Applied Materials’ integrated tool suite is designed specifically to enable this institutional learning, enabling data collection and insights as well as scheduling and optimization. By implementing “rule based” scheduling and dispatching, manufacturing organizations can quickly and effectively respond to almost any kind of problem on the manufacturing floor. And by reducing process time variability, other process variability is also reduced—with significant impact on business operations, manufacturing productivity, and overall supply chain health.

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