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TAMING THE SCHEDULING BEAST

By abandoning spreadsheets, Lonza has improved production planning at its Portsmouth facility.

By Jeffrey O'Connor, Lonza Inc., with Andrew Sanford and Floyd Nasuti, AspenTech, Inc.

TWO YEARS ago, Lonza's Portsmouth, N.H.site faced a challenge that most pharmaceutical contract manufacturers would envy: too much business. Our new 275,000-square-foot facility was running near full capacity and had many new customers requesting proposals for production. We needed to boost production and throughput quickly.

One solution was to enhance plant scheduling processes and technology, to squeeze the extra production we needed out of the site. For years, like many producers, we scheduled production at Portsmouth using spreadsheets. The spreadsheets worked fine for a small company producing a few batches of product, but not for our needs.

An additional challenge was something all contract manufacturers must confront—striking a balance between profitable operations and high levels of flexiblity that allow our customers to meet changing patient demand. This balance mandates continuous improvement and operational excellence. Lonza recognized that a new approach to scheduling operations was a pre-requisite for sustained growth.

It was clear that we needed a more sophisticated, electronic production planning system. We began working with Aspen Technology to design and build a scheduling system suitable for the site. The goals of the project: to increase facility production, maintain scheduling staff at current levels, and enhance Lonza's ability to deal with the inevitable hiccups in production that all manufacturers cope with on a daily basis. After 18 months, the new system has been successfully commissioned and is allowing us to achieve these goals.

THE LEGACY OF SPREADSHEETS

The problems we faced had arisen gradually. The Portsmouth facility opened in the 1990s for the production of antibody-based APIs. Over time the site expanded into three production facilities, with one area containing four 20,000-liter production trains consisting of reactors, tanks, filters, lines, and cleaning skids. The site was supplying in-market API for three leading biologics plus numerous other medicines. Production processes at the site became exceedingly complex, consisting of long, linked production chains, complex cleaning and sterilization procedures, and mammalian cell growth.

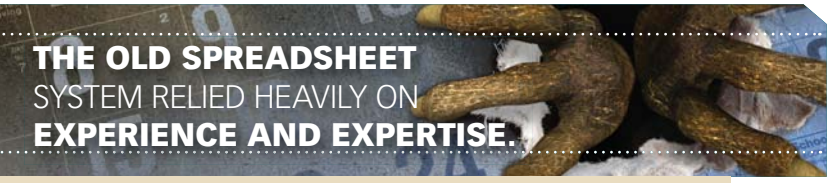
Our previous spreadsheet-based system required an expert scheduler who would enter and refer to data in the spreadsheet to monitor and control the timing of our complex production processes. Typically, the scheduler invested hours in producing an initial schedule each week, then spent additional time each day modifying and tweaking the schedule in response to actual production events and associated cycle variances. Eventually, the scheduler ran out of hours in the day to get the job done.

The key output of the spreadsheet system was a daily production schedule, which served as a guide for manufacturing operators, supervisors and manager. The schedule listed all production activities that were to be completed by date and production unit. Since the schedule produced by the spreadsheet system only had a daily scope, it was left to the shift supervisors to align their intra-day activities against the growth of the API cells and the manpower available on the shift. It was time-consuming, and each intervention created risk.

TAMING COMPLEXITY

Our Portsmouth plant's manufacturing process included three scheduling challenges that are shared by all biopharmaceutical companies: intricate timing of production activities, shared production equipment, and the most confounding of all, growing mammalian cells. These issues made the implementation of advanced scheduling particularly challenging. In Lonza's case, the 275,000-square-foot site houses roughly 200 assets or "facilities" that can be scheduled, with each batch or run comprising anywhere from 400 to 500 activities. Depending on the order(s) being filled, as many as six runs can be on-board at any given time, which means the schedule has to account for up to 3,000 activities. The complexity is astonishing, but even more so when the need to meet Current Good Manufacturing Practices (cGMP) timing constraints is added to the equation.

The first scheduling challenge, timing of production activities, is associated with cGMP guidelines regarding the minimum and maximum time allowed between production activities. For example, a new production activity cannot be started prior to the minimum hold time of the prior activity, and if a batch is held longer than that maximum time it expires and must be discarded, potentially at a large cost to Lonza, to our customers and to patients. Similarly, cleaned or sterilized vessels have expiry dates and must be re-cleaned or re-sterilized when the date is reached, consuming valuable production time and capacity.



Furthermore, expiry time is part of the validated process—any variance over the validated process equates to non-conformance and invokes the associated time-consuming investigation and documentation process. The scheduler must balance the risk of making a batch early (and risking expiry) with the risk of delay, which may make subsequent production activities late and/or infeasible. Within the old spreadsheet system, balancing these risks was a large part of the scheduler's and floor supervisor's duties, and we relied heavily on individual experience and expertise to avoid mistakes.

Our new scheduling system allows us to simulate the timing links between production activities and warns the scheduler of potential issues. In addition, the scheduling simulation provides an additional item called the "target," which represents the ideal or preferred timing for one activity relative to another activity. The AspenTech software uses the target as a starting point for all schedules and adjusts from that point if needed.

DEGREES OF FREEDOM

The second scheduling challenge, dealing with shared production equipment, applies primarily to the Clean-In-Place skids. Due to large amounts of piping and validation required, the CIP skids are assigned to, and shared among, particular pieces of equipment. Since each vessel must be cleaned both before and after use, the skids can and do get overloaded during peak production. During these peak periods, supervisors would often have to make difficult decisions between a pre-clean from the current run and a post-clean from the previous run. In short, the cleaning skids became a bottleneck in the production process, which limited our flexibility and responsiveness.

We recognized prior to starting the advanced scheduling project that dealing with shared equipment constraints, such as the CIP skids, was critical to the success of the project from both a technical and cultural standpoint. Together, Lonza and AspenTech developed functionality based upon a "degrees of freedom" score for scheduled activities. This score represents the amount of time each activity could move without violating the minimum or maximum timing links. Once the system calculates this number, it sorts and places the CIP event according to a sequence, so that the most constrained CIP event is completed first, and the CIP skid's capacity is available. This logic is important to improve throughput while reducing the number of issues on the floor.

Finally, the software had to manage the uncertainty associated with producing a biologics API. The manufacturing process is based on the fermentation of mammalian cells that produce a target protein. Growth of the cells is variable within predefined critical process parameters, and the cells must be transferred from one stage to another while still within the CPP range. Variability in cell growth can cause the cells to be early or late for any stage by as much as 24 hours. This process uncertainty, combined with shared resources and the need to balance "too soon vs. too late" equipment preparation, explains why scheduling at Lonza or any other biopharmaceutical facility is such a challenge.

Our project team created several tools to uniquely address this challenge, such as automated selecting and grouping of activities, and scheduling utilities to apply decisions to these groups. The possible combinations of decisions are almost endless, so we focused on creating a system that allowed the scheduler to make the key decision(s), and then offload the burden of re-scheduling and re-optimizing to the scheduling software. This approach allows schedulers to make changes to the schedule in minutes rather than hours, and trust that their decisions are well informed.

RESULTS

The primary goal of Lonza's advanced scheduling project, and the related process improvements that were implemented, was to increase facility throughput in our near-capacity production situation. Advanced scheduling, combined with aggressive efforts by the manufacturing group to streamline operations, achieved this goal.

Key results of the programs include:

- Batch cycle time has been reduced from seven to less than five days
- Production output has increased by approximately 20%
- No additional scheduling headcount has been required.

One way we achieved the production increase was by reducing manufacturing risk. The scheduling system allows our team to visualize the upcoming production schedule and pinpoint issues in advance. For example, we can identify capacity conflicts in our media make-up area with sufficient lead time to modify batch times, alleviate the bottleneck and avoid product expiry.

Finally, the new system has provided some unanticipated benefits in the areas of resource scheduling and planning. We can better prioritize scheduled activities so that critical activities are completed on-time. In addition, we can more effectively level load production through the plant and more quickly identify plant and process bottlenecks. PM

About the Authors

Jeff O'Connor is scheduling manager for Lonza and has been with the company for the last seven years. Andrew Sanford is senior principal business consultant for Aspen Technology, where he has worked for 14 years. Floyd Nasuti is principal advisor for AspenTech. He has over 26 years of experience and has rotated between development and services roles since joining Aspen 13 years ago.