SCHEDULING BIOMANUFACTURING OPERATIONS
Getting to the Optimal Solution Faster
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INTRODUCTION

Biopharmaceutical manufacturing facilities are multi-hundred million dollar investments with 20-30 year operational lifetimes, often operating 24/7 and involving hundreds of workers across multiple groups. Maximizing the return on investment in such facilities used to involve producing one or a small handful of blockbuster medicines. However, the advent of biogenerics, expanding pipelines and new therapeutics is bringing increased attention to the efficiency and optimization of these facilities. Plants are being asked to produce multiple products at different scales, efficiently and without disruption, while minimizing wasted raw materials and labor. In this whitepaper, we discuss the role of scheduling in maximizing the use and operational flexibility of critical manufacturing facilities.

SCHEDULING TODAY

Most biomanufacturing planners currently use toolsets like Excel, MS Project, and SchedulePro when doing planning. Such toolsets are ideally suited for simple schedules, where there is little or no process variability, and when less than a dozen major pieces of equipment are being modeled. Examples include high school classroom schedules, or basic chemical processes like bleach production. For biotech facilities, however, such toolsets are unable to accommodate complex manufacturing processes, variability and shared resource constraints. These software packages were not designed as enterprise toolsets, and have a limited number of simultaneous users and groups. Planners are forced to work around such limitations, with varying degrees of success. It is not uncommon for the scheduling group to have invented their own ‘planning boards’, ‘visual schedules’ and data collection systems to collect and reconcile their schedules.

“I want to trust the schedule, but it just does not seem to reflect reality most of the time.”

Manufacturing Technician, Cell Culture Fermentation
Such manual planning systems are time consuming for schedulers, and for the manufacturing staff required to support them. In Figures 1 and 2 we outline the results of a time and motion study of scheduling operations conducted at a large biomanufacturer.

Figure 1 shows a break-down of the ‘average day’ for a scheduler in the study. Approximately 1 hour per day is spent collecting data; 1.9 hours per day is spent in meetings; 3.8 hours is spent creating a feasible schedule, and 0.8 hours is spent on what-if analysis. This data suggests that nearly 50% of a scheduler’s time is spent producing a feasible schedule: a tedious process consisting of checking conflicting equipment and rule constraints, and making manual ‘tweaks’ to the schedule in an attempt to remove them. Such a process typically requires a skilled scheduler with a lot of experience at how to force the software to fix infeasibilities. It is also a highly manual process. This data also suggests that real value-added time for the facility (when schedulers are doing analysis) comprises just 10% of the scheduler’s day.

Figure 2 shows the cumulative number of hours per week, across all full time equivalent staff (FTEs) supporting scheduling. Over 80 hours per week is spent in meetings, discussing the schedule and resolving issues, conflicts and delays. Note that more than 75% of this time is sourced from manufacturing groups, directly impacting staffing levels in those organizations. There are many reasons for these results: schedules are currently so manual to construct, and there are so many discrepancies between the schedule and the manufacturing floor operators, that daily or even twice daily meetings with schedulers and long shift change meetings need to occur. Clearly, there are significant challenges in scheduling biomanufacturing operations that current toolsets are failing to address.

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1 The time and motion study was conducted over a 6-week observation period. The biomanufacturer had approximately 150 direct production staff across three shifts. There were a total of 3 schedulers. All were observed as part of the time and motion study.

2 Note we count 2 FTEs in a meeting for an hour as 2 FTE hours.
VARIABILITY IN BIOMANUFACTURING OPERATIONS

One identified challenge in scheduling is that biomanufacturing facilities exhibit higher variability in operating times (due to titer variability and a host of other factors) than any other industry. Figure 3 shows variability in Unit Operation processing times (due to titer variability) for a chromatography step. Scheduling toolsets that use the median time (5.5 hours) for this activity will require replanning in 50% of cases, while toolsets that use the 90th percentile (11 hours) will mean most downstream equipment sits idle 40-50% of the time.

Variability in Unit Operation Processing Times

Since the scheduling tools that are widely used in biomanufacturing today use only one, deterministic number to plan, the result is that schedules must be constantly adjusted to match conditions on the floor. The challenge then is to reduce the amount of time required to make a change (such as lengthening an activity’s duration) and quickly be able to re-schedule.

INCREASED FOCUS ON ‘OPTIMIZING’ SCHEDULING

The need to quickly be able to re-plan activities and see their impact on the overall schedule seems at first glance to be a trivial task – just change the activity’s duration and publish a new schedule. However, most activities in biomanufacturing plants use a large number of resources (skids, media, buffers, tanks in particular states, and of course, people) that must all be brought together at exactly the right time to start an operation. Delays to an activity propagate through the facility in a complex, and non-linear way that is often difficult to understand. It is this complexity – often across many different tanks, transfer lines, and skids – that must be understood for facilities to successfully optimize a schedule.

Schedulers trying to ‘optimize’ such a schedule today manually check constraints and perform dozens of tweaks to the schedule in order to produce a plan. Most of the logic around how a manufacturing process works is in a planner’s head, using ‘tribal knowledge’ collected from dozens of SMEs over a period of years. A skilled planner will add additional time allowances in areas with high variability, to ‘soak up’ any delays so they don’t propagate. Still, adherence to plan is lower in biotech

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4 Source: Bioproduction Group internal research from customer focus groups, 2010.
than in almost any other industries on a weekly basis. With planners spending almost 80% of their time on average creating plans that are even feasible for all the hundreds of facility constraints, the promise of ‘optimizing’ a plan is far off.

It is ironic that a facility may spend thousands of dollars per kilogram of Protein A resin, while investing minimal time or effort on scheduling methodologies to optimize the use of that resin. Such a task is difficult, but highly valuable – and not capital intensive. Scheduling may not be seen as ‘glamorous’ as manufacturing operations, but it turns out that a badly scheduled facility wastes massive amounts of human resources, raw materials and money. Biomanufacturing’s high levels of variability and complexity require a special approach to scheduling, one that incorporates real-time data and allows for variability within a schedule.

**Towards “Variability Aware, Always Feasible” Scheduling**

The data presented above suggests that there are two major issues with scheduling today: first, the complexity of biomanufacturing processes means that constructing a feasible schedule takes a lot of time; and second the issue of variability in processing times that requires constant re-evaluation of a schedule. Bioproduction Group’s Real-Time Modeling System (RTMS) is designed specifically to manage these two issues. Built on over twenty years of research into finite scheduling and modeling, the toolset brings a new paradigm for scheduling and optimization.

FIGURE 4:
CIP TIMES, SHOWING PROCESS TIME SHIFT FROM 4.5 HOURS TO 2.5 HOURS.

“Biomanufacturing supply chains are complex and highly variable. That’s why we chose a toolset that incorporates data and variability in its design.”

Supply Chain Planner, Top 10 Biopharmaceutical Manufacturer

The first element of “Variability Aware, Always Feasible” scheduling is the ability to automatically see timing data from the facility in real-time, and be able to update models to include not just the latest set of times but the variability in those times. In Figure 4 below we show a chromatography operation, with a clear change in processing times from 3-6 hours (pre 2007) to 0.8-6 hours (post 2007). Variability actually increases in the period after 2007, although the average time decreases (as shown by the trend line). Extracting this data from automation systems, and incorporating such variability in scheduling data is critical to correctly modeling the process. Time and motion studies, and SME estimates, are time intensive ways to collect this data and usually yield less accurate results than the direct approach – since they are both subject to ‘observer bias’. Using timing data from automation systems allows planners to see and update schedules in real-time, rather than in an offline manner as they are told new data. Rather than relying on a third-hand account of the process, Bio-G’s technology allows planners to directly see the process as it occurs on the automation system.
The second element of “Variability Aware, Always Feasible” scheduling is the need to correctly model – without simplifying assumptions – the intricacies of the facility. Figure 5 shows the classic problem with creating such models: an accurate model by definition has hundreds of activities, and hundreds of resources interacting. Bio-G’s patented technology is designed to automatically manage this complexity, to allow the facility to auto-schedule activities on a ‘kanban’ style system that optimizes flexibility and throughput.

This modeling framework allows planners to focus on the critical areas of the process, while leaving the scheduling toolset to auto-schedule the 90% or more of activities (cleaning, preparations, weigh and dispense) that are short and of little importance unless they don’t happen. Such a modeling framework radically changes how planning is performed. Planners are always shown a feasible schedule, since the modeling framework optimally resolves constraints. Planners then focus on the critical value added steps: what-if analysis and human optimization to the schedule.

The final element of “Variability Aware, Always Feasible” scheduling is the ability to rapidly reschedule. One of the most common exercises we ask scheduling teams to do is show us how they would reschedule to respond to a QC delay between the first downstream operation and subsequent steps over 24-48 hours. Such an event is interesting because it affects both the fermentation process (it gets held up) and the downstream process (which is now starved for work). Typically, replanning in such a situation requires at least 60 minutes of juggling schedules for buffer prep and can take up to 8 hours if other schedulers need to be consulted.
Bio-G’s technology breaks this paradigm, allowing immediate replanning for such events (including all related activities: buffer prep, other downstream activities, etc). The planning system is aware of the whole process with all its resources, interconnections, interdependencies, and variability. Immediate replanning becomes possible since the modeling framework automatically constructs an optimal response to events, allowing planners to see the impact on labor loading and subsequent activities. Such an approach is very powerful since it allows the facility to be much more flexible in allowing activities to happen ‘just in time’, since their impact can be evaluated in seconds.

ROI & CONCLUSIONS

Scheduling biomanufacturing facilities is a complex task, requiring the effective understanding and integration of upstream, downstream and process support groups as well as ancillary staff, engineering projects and maintenance. Inherent biological variability confounds the planning problem, requiring schedulers to continually re-plan as campaigns evolve to meet changing conditions on the floor.

Maximizing re-planning speed has immediate benefits for the organization. It decreases the number of hours spent constructing feasible schedules from 50% to around 10%, and it at least doubles the amount of time spent on value-added activities such as ‘what-if’ analysis.

Bio-G experience has shown that re-planning using the Real-Time Modeling System can mean 30-50% less time is spent by groups in reconciliation meetings, with the schedule actually updated in the meeting rather than as an offline activity. Finally, faster re-planning allows the facility as a whole to be more flexible, reacting optimally to adverse events and producing more product.

At one Bio-G customer facility, these benefits resulted in a return on investment (ROI) in excess of $9M in one year. Real-Time Scheduling, as we’ve defined it in this whitepaper has an enormous positive impact by optimizing returns on the major investments biomanufacturers make in their facilities.

FEEDBACK
Please provide your feedback at http://www.zoomerang.com/Survey/WEB22AYVM3VLFC

FURTHER READING

MORE INFORMATION
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