It’s Not Magic: Optimum Buffers Delivered Just-In-Time

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The Biopharma Scheduling Challenge

Manufacturing biopharmaceuticals (e.g. therapeutic proteins) requires many capital-intensive, complex steps that use numerous associated resources, including equipment, material, and labor. In large molecule drug substance manufacturing, these proteins are typically produced in two major steps and then prepared for use in patients. First, genetically engineered cells are grown in “upstream processing.” Next, the proteins are recovered from the cells and purified in processing steps collectively referred to as “downstream processing.” Finally, the protein is prepared for patient use in manufacturing steps called formulation, fill, and finish. The focus of this white paper is to address the scheduling challenges associated with “downstream processing” including the makeup of the WIP materials, or buffer, required for protein recovery and purification.

Applied Materials is focused on designing a downstream schedule that “senses and responds” to the real-time changes in the factory and automatically optimizes the production schedule, maximizing plant capacity and throughput. The downstream schedule contains two parts: (1) a drug substance (DS) schedule and (2) a buffer schedule. In both cases, the buffer schedule should never delay the DS schedule.

Figure 1 shows a conceptual process flow diagram that illustrates the complexity of the scheduling buffer material makeup for two DS batches. The chromatography steps (green) recover and purify the DS in multiple cycles and require buffer. Buffer batches (BB - blue) are prepared just in time. As shown, BBs can service multiple steps within the same batch and across multiple DS batches.

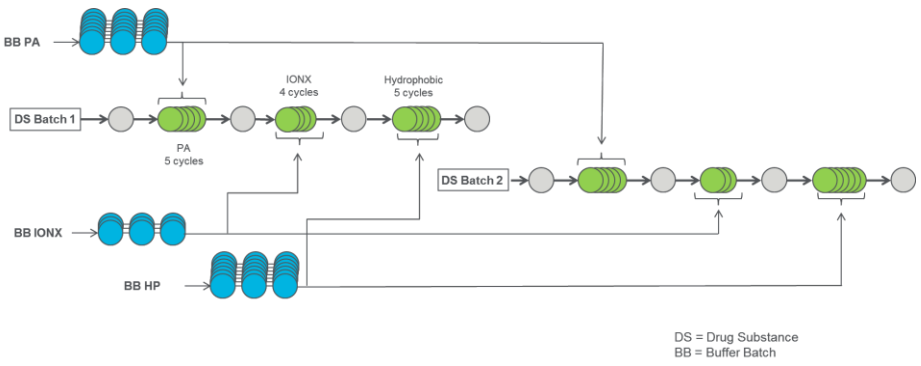

Figure 1. Conceptual Process Flow Diagram of Drug Substance Flow and Buffer Requirements

Addressing the Buffer Bottleneck

Buffers are a common bottleneck in large molecule facilities. To minimize this bottleneck, buffers should be made in a coordinated manner to be ready for consumption, otherwise they “expire” and must be re-made. The role of buffer solutions is to assist with chemical isolation of the drug substance from other cells, proteins, and contaminants in the solution in combination with filtration, capture, and chromatography process steps. Buffer solutions must be precisely prepared in prep tanks and then stored in separate hold tanks (typically stainless steel, but occasionally bags are used) in advance of the drug substance process step where they are needed. Often prep and hold tanks are limited resources and must be cleaned after use, so they can be used for the next buffer solution.

Today, the industry relies on multiple experts to manually create production and buffer schedules for a single campaign. A **campaign** is a series of batches for the same drug product; a campaign schedule takes multiple weeks to assemble and is incredibly complex.

To optimize the buffer manufacturing process, both hard and soft constraints must be considered, and they contribute to the high degree of complexity in the buffer area. **Hard constraints** include a limited quantity of buffer prep and hold tanks, volumetric capacity of tanks to prep and hold buffers, piping constraints, buffer expiry times, etc. **Soft constraints**, or manufacturing preferences, offer options to combine like buffer lots in the same tank, minimize waste, and reduce the quantity of buffer cycles, the use of bags vs. hold tanks, etc.

The Industry Approach to Scheduling Today

Today, demand is reflective of the global patient population, and manufacturing will interpret this into a set number of campaigns to satisfy this demand over the course of a quarter or year. In most companies, MS Excel is the scheduling tool of choice. Creating an initial campaign schedule takes 1–2 weeks, and it is continually adjusted throughout production because in-process step durations, variations, and unforeseen events transpire. In a typical working day, 10–15+ changes are made to the schedule, sometimes requiring adjustments to other activities “downstream” of the activity being moved. It requires a herculean effort to maintain a “near real-time” schedule because hundreds of rules and constraints exist and many are known only by the scheduler.

During a campaign, the scheduler proactively works with plant personnel to make updates to the schedule as quickly as possible. During a normal campaign, there is a continuous flow of unplanned events including: equipment downs, personnel issues, material delays, and other process anomalies. Often, re-planning may take hours or even days for large scale disruptions, during which time the facility cannot optimally process material.

Annual Opportunity: Faster Throughput for Reaching More Patients

- Increase capacity and throughput by 10+% per line
- Minimize business impact of major and minor events between 30–60%
- Reduce buffer cycles and waste generation by 10+%
- Focus scheduling team efforts on business improvement projects
- Reduce supervisor's time managing unscheduled events
- Reduce step time variability in production process

Why Does Applied Materials Offers the Best Solution

With over 30 years’ experience in semiconductor, we have the technology components and application experience to implement an automatic “sense and respond” approach to solve this

scheduling problem. This means that a scheduler doesn't have to remember all the rules, and the best response to an issue will be implemented as the event occurs.

Applied Materials has the integration experience to connect to real-time plant control systems, so we can capture and maintain real-time batch and equipment state models. The real-time state model allows the implementation of "sense and respond" so adaptive scheduling is automatic and continuously updated, based on real-time manufacturing events.

We offer many optimization options for the industry. When there are many manufacturing preferences, an Analytical Hierarchy Method (AHP) can be leveraged for optimization. An AHP considers both hard and soft constraints optimization techniques. Soft constraints allow customers to apply weighting factors to influence the output. Our unique approach incorporates an algorithm that calculates the ideal volume of buffer required for optimum hold tank selection and to minimize buffer waste. When there is a robust data infrastructure and an MES, the linear program model can be considered to find the most optimal schedule for maximizing throughput. All optimization options enable the schedule to consider the future, so it optimizes buffer prep and hold tank decisions, optimizes run rate, eliminates bottlenecks, provides buffers just-in-time, and reduces the overall time to provide lifesaving therapies to patients.

Summary: An Industry-wide Impact Opportunity

Applied offers the most advanced scheduling solution in the market to enable the biotech industry to reduce overall production cycle duration, reclaiming $10s of millions in hidden capacity in every facility: greenfield or brownfield. In automating the production schedule and connecting it to the business systems that understand the current state of the factory, the industry will reduce in process step variability and remove the human element from scheduling. Our solution is in place in 100% of 300mm semiconductor fabs worldwide. The impact this presence has had on the industry is greater than 30% increased throughput improvement cumulatively. We are ready to enable the biopharma industry to realize the same benefits.

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