Regulatory Insights for Converting Batch to Continuous Biomanufacturing Processes

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Biologics are foundational therapies for addressing the health needs of patients. In 2013 only 20% of FDA approved drugs were biologics but this figure has risen to 48% by 2023. FDA approvals for biologics have increased by over 450% in the last 10 years. Yet despite this impressive growth there are many countries where patients do not have access to these medicines. PD-1 antibodies, for example, a type of immune checkpoint inhibitor, are not available in many countries across Africa, Southeast Asia, and parts of South America.[1,2] The biopharmaceutical industry must find ways of making these medicines more affordable if they are to deliver their full potential in improving global health.

Just – Evotec Biologics is a technology-forward company that provides contract development and manufacturing services to partners. The company mission is to design and apply innovative technologies to expand global access to biotherapeutics. One of its key technologies is a fully continuous manufacturing platform. This platform allows the production process to be highly intensified. It can be installed into agile facilities allowing a reduced clean room footprint and lower running costs. Just – Evotec Biologics' GMP biomanufacturing plants, called J.POD® facilities, utilize G-CON's production on demand (POD) pre-fabricated cleanroom modules.

J.POD facilities can reduce the cost of goods manufactured (COGM) from the industry standard of $200 per gram to as little as $50 per gram or less. The company can construct these facilities at a significantly lower cost than a traditional stainless-steel facility and in a much shorter time. This dramatically increases biomanufacturing agility, allowing companies developing biopharmaceuticals to ramp up production rapidly to address global health emergencies such as pandemics or in response to fluctuating market demand forecasts.

Converting from Batch to Continuous Biomanufacturing Processes

While some biopharmaceutical companies adopt continuous manufacturing platforms for first-in-human manufacturing and early clinical supply,[3] many companies have progressed through early phase development with a fed-batch process only to later recognize that a more efficient and agile process is needed

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for commercial manufacturing. Often, what's holding them back from exploring the possibility of transitioning to a continuous process are the time, costs, and perceived comparability risks associated with running large-scale development batches.

However, sponsor companies typically cannot avoid scaling up their process if they want to meet commercial supply demands, so they will be facing these investment decisions, anyway. Simple, low-cost, and low-risk feasibility studies can be run to assess whether their fed-batch process is suitable for conversion to a continuous manufacturing process. Feasibility studies allow scientists and engineers to evaluate whether expected increases in productivity are likely to materialize and if equivalent product quality profiles can be achieved.

Meeting Regulatory Expectations

When contemplating the switch from a batch process to a continuous process, a sponsor is already thinking ahead to how they will successfully address the change in subsequent regulatory filings.

"A regulatory agency will expect a sponsor company to collate and submit a comprehensive comparability package when a firm is making a substantial change to their process, whether it be a change from batch to continuous processing, a change in scale, and/or a change in manufacturing site. These types of changes are not uncommon. In fact, most companies will need to make changes that require a demonstration of comparability at some point in a product's lifecycle, and it most often occurs when a sponsor is preparing for late stage clinical and commercial production demands." says Tracy Janus, Senior Vice President of Regulatory Affairs & CMC at GLOBAL Regulatory Writing and Consulting (GLOBAL).

GLOBAL is a boutique consultancy firm specializing in the regulatory strategy and authoring of communications with regulatory agencies including, submission documents. The firm helps CMC teams prepare for their next regulatory milestone ensuring that they have performed the proper work packages and risk assessments, then translate these into robust, phase-appropriate control strategies. They have considerable experience in supporting clients throughout the development life cycle and in navigating process changes such as these.

"Timing is often critical to the overall development program, and we encourage sponsors to make these more substantial process changes before the start of Phase III clinical trials, during which pivotal registrational data will be collected." explains Janus, "The more patients receiving investigational product manufactured by the intended commercial process, the stronger the justification for their commercial control strategy can be at the time of licensure."

The Importance of Risk Assessments and a Solid Comparability Package

Janus recommends that, "Before any substantial manufacturing change is undertaken, scientific teams need to perform a risk assessment to gain a full understanding of the potential impact of the proposed changes and to identify all their critical process parameters (CPPs), ie, which operating parameters, or group of parameters, influence the product's critical quality attributes (CQAs). This list of CPPs and CQAs (at minimum) require acceptance ranges be established for manufacturing and will be the focal point of any good comparability demonstration."

The reason comparability studies are so important, she explains, is that "As soon as you've begun your nonclinical animal studies, you have already started building your product's safety database, and this database continues to grow with each in vivo study, animal and human. You don't want to break the link between the materials that were used in these studies and the materials intended for a future clinical study or for the market – breaking the link meaning that the pre-change and post-change materials are found to not be similar enough. If this happens, you could find yourself in a difficult situation with regulators where you can't proceed until you've generated adequate safety data on the post-change materials, for example, having to repeat animal studies or potentially getting kicked back to Phase 1."

Demonstrating compatibility between an existing process and a new process does not come down to the process operating in the exact same way or that the pre-change and post-change products are identical. "That's pretty much impossible, anyway," she says, "But, what it does mean is that the material is 'highly similar,' in that its quality attributes fall within certain predefined ranges around historical means. How tight those ranges need to be will depend on the attribute."

Aligning CPPs between the current and new processes is also important. However, while some CPPs from the fed-batch process might be the same at several points as those for the continuous process, not all will be, so CMC teams should consider and create a plan for those points in the operation that might require extra development work. Understanding what needs to be adjusted, and in what way, will help to ensure that the new process will perform as expected.

Demonstrating Comparability

Sponsors will want to execute engineering and/or GMP runs at-scale to generate the necessary data for analytical comparisons and having more than one batch of post-change material has the best chance of convincing regulators to buy in to your claim of comparability.

"You have the opportunity on your next at-scale run to adapt process parameter ranges if they see the process is running a little on the high-side or the low-side, but the focus will be on the product quality," Janus says. "This focus on product quality means preparing a comparability protocol and collecting those data. These will include a release panel, a characterization panel and ideally some stability data even if this is accelerated stress stability, which will show whether the degradation pathways have stayed the same."

"Making the transition from a fed-batch to a continuous process is about understanding the process well. Organizations like Just – Evotec Biologics really understand the science and can anticipate which areas are important and will need work packages in focused areas to make sure the transition is seamless," she explains.

"Just – Evotec Biologics has a proven track record of taking our partners' early-phase fed-batch process and converting them to a continuous bioprocess for late phase development and then commercialization. We have a deep understanding of our continuous manufacturing platform and an experienced team that can guide partners through the comparability process. This is allowing our partners to commercialize antibodies without having to perform dramatic increases in scale and yet provides them with significantly higher manufacturing agility and the lowest cost of goods," concludes Randal Bass, Executive Vice President of Process Design & Biotherapeutic Operations.

To see a case study demonstrating how Just – Evotec Biologics has converted an intensified fed-batch process to a continuous biomanufacturing process watch our on-demand webinar: https://www.evotec.com/en/events/conversion-of-an-intensified-fed-batch-to-an-integrated-continuous-bioprocess-webinar

References

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3. Evotec.com – OncoResponse chose Just – Evotec Biologics for the Phase 1 clinical manufacturing of their cancer-fighting antibody | Science Pool

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