BIOPHARMA PROCESS DEVELOPMENT: UNDERSTANDING ITS IMPORTANCE AND PROPER EXECUTION

NORTHWAY® BIOTECH

BIOPHARMA PROCESS DEVELOPMENT: UNDERSTANDING ITS IMPORTANCE AND PROPER EXECUTION

High-quality process development aims to maintain a consistent process from toxicology through to GMP production runs, and can be aided by a capable, adaptable CDMO.

By Nerijus Makauskas and André Markmann, Northway Biotech

Implementing high-quality process development that considers GMP manufacturing from the start is critical to reducing costs and timeline disruptions associated with raw material supply chain insecurity, adhering to regulatory compliance, and avoiding process redesign at a later stage.

However, ambitious biopharmaceutical product development timelines often overlook the importance of a process well-suited for GMP production. Their key milestone usually is to achieve production during a pre-booked GMP slot – ideally, driving first-to-clinical Phase I status. All biopharma company development teams are aware of this time crunch, understanding that the industry's manufacturing capacity (as a whole) typically is booked full months, or even more than one year, in advance. So, a missed GMP slot is difficult, time-consuming, and costly to reschedule.

Unfortunately, in the rush to meet these timelines, biopharma companies and their partners may overlook factors like raw material (e.g., resins, media, or single-use bags) availability and lead times. For example, some resins may only be readily available in small amounts, prohibiting their use for a scaled-up version of a process in a timely manner. Or, a biopharma company's process may not be compatible with its intended manufacturer's equipment and facility. For example, in Phase I, only a portion of upstream process (USP) material is used to run the downstream process (DSP), since not a lot of material is needed at this phase. Then, at commercial scale, it is realized the process has a scalability issue.

In some cases, the biopharma company may be working with a CRO whose key objectives differ (i.e., they are focused solely on developing the drug substance process for early-phase development, allowing the sponsor to test the protein´s/antibody´s mode of action in a research environment). Sponsors can be complicit in this oversight, striving to progress through Phase I, Phase II, and even Phase III on time to achieve their pre-set milestones, but sacrificing fully fledged process development in that effort – often resulting in yield or purity shortcomings or a non-scalable/non-robust process. Only afterward do they begin to concern themselves with scale-up and commercialization,

as well as how to reduce process costs (i.e., increase efficiencies).

The consequences of inadequate process development are severe. If significant process redesign is needed, toxicology and Phase I/Phase II studies may have to be repeated. That loss of time and money is compounded by further reducing time for commercialization until patent expiration — if such detours need to be made. This volatile situation is likely to make finding a licensing partner for commercialization difficult, even if the product's scientific mode of action is persuasive. For that partner, the cost of goods sold (COGS), potentially within a shorter commercialization phase due to the impending patent expiration date, does not justify the investment necessary to redesign a suboptimal process for GMP production.

Ultimately, high-quality process development aims to maintain a consistent process from toxicology through to GMP production runs. While a tech transfer or scale-up can normally be expected to require process adaptations to facilitate higher yield, greater purity, or a more stable supply chain (i.e., changing to a resin with a shorter lead time), significant changes will invite additional regulatory scrutiny.

ENGAGE A CDMO PARTNER ASAP

It is vital to secure a CDMO partner as early in a project as possible to allow time for thorough, well-considered process development. More often than not, a biopharmaceutical company does so with the understanding the process they have in mind is not ideal and will require external expertise to optimize. This leads to productive initial conversations between the CDMO and its client, ranging from ways to improve yield and purity to how much time and money the biopharma company wishes to invest in that effort and its exact desired outcomes (e.g., an accelerated production timeline). An experienced CDMO will recognize which process steps already are optimized and can focus on those that warrant attention, determining how they can be substantially improved.

Conversely, some biopharma companies already have invested heavily in a process and demand it be run exactly as designed following tech transfer or scale-up. Or, they are concerned that changes may trigger regulatory compliance-related delays. For example, a company might object to the substitution of different filters used for intermediate filtration; they may have no experience with the type of filter suggested by the CDMO partner and be uncomfortable with its use, despite the fact it is more readily available. As a consequence, supply chain issues may plague the original filter, causing the company to miss its scheduled GMP run, despite the issue being preventable.

Even if the GMP run takes place on time, issues may arise exposing the process as less than ideal for the scale, equipment, or facility (e.g., efficient mixing temperature or duration may change at larger scale, affecting the entire process). Thus, whether the CDMO joins a project at its genesis or midstream, any discussion of necessary or optimization changes is viewed through the lens of how it will affect yields and purity.

PICKING THE RIGHT CDMO PARTNER

Generally, a biopharma company knows in advance the type of CDMO it wishes to work with (e.g., a large- or medium-sized CDMO). From there, the decision-making process usually delves into candidate CDMOs' level of expertise and experience — their potential know-how — with a certain process or protein.

However, no CDMO ever is going to have experience with a potential client's exact process or specific protein. Accordingly, the key differentiator between CDMOs becomes their capability and adaptability in working with diverse types of molecules. Northway Biotech excels in this regard, working regularly not only with common monoclonal antibodies (mAbs), but also with bispecific and trispecific antibodies.

Additionally, about half of Northway Biotech's projects involve microbially produced recombinant proteins. Such proteins differ extensively from one another in terms of structure, pI value, hydrophobic interactions, etc. and, as such, cannot be "plugged into" a platform technology/process like one might apply to a mAb. Thus, the purification of recombinant proteins differs significantly from protein to protein and is not comparable to the purification of monoclonal antibodies.

Northway Biotech's knowledge and experience in developing processes for a variety of structurally dif-

ferent proteins apply directly to our capability to handle different types of antibodies, refining the production process to overcome specific problems or designing new processes to be optimized from the start. This capability is facilitated by in-house depth of understanding regarding any potential limitations of our equipment (relevant to specific processes or process steps), supply chain, and facility, eliminating the possibility of developing a process ill-suited for GMP-scale manufacture.

FINAL THOUGHTS

Do not underestimate the importance of fully fledged process development. A process that is adequate in early stages to produce small amounts of material or to prove mode of action in a small-scale laboratory setting may not always respond well to GMP manufacturing and scale-up. This can lead to a range of hurdles, up to and including process redesign that triggers regulatory intervention (e.g., a request for evidence the GMP materials are comparable to materials used for toxicology studies, which may necessitate re-doing some studies). This outcome leads to additional costs and time loss.

Accordingly, process development is critical not only to on-time GMP production, but as a cornerstone of presenting a complete package if a smaller company strives to be acquired or work alongside a larger partner. To learn more, contact the authors and visit https://www.northwaybiotech.com/.

ABOUT THE AUTHORS

André Markmann is VP of Business Development at Northway Biotech.

Nerijus Makauskas is Chief Technology Officer & Head of the DSP Department at Northway Biotech.

ABOUT NORTHWAY BIOTECH

Northway Biotech is a leading CDMO supporting customers worldwide. Its highly experienced, professional team executes projects at any stage, from cell line construction and process development to cGMP manufacturing of biopharmaceutical products. The company's wide-ranging expertise and vertically integrated service offering translate to the ability to rapidly execute multiple projects from its state-of-the-art GMP facilities while ensuring full process and product compliance at all stages of research, development, and commercial manufacturing. Northway Biotech is a privately owned company founded in 2004 and located in Vilnius, Lithuania; London, UK; and Waltham, MA (U.S.).

NORTHWAY® BIOTECH