PROS AND CONS OF ENGINEERING RUNS

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An engineering run (ER), executed either as part of process development or afterward, once the consolidation run (combining upstream processing and downstream processing) is complete, ensures the scale-up process works for biopharmaceutical manufacturing. The ER is run at GMP scale (e.g., 500L, 1000L, 2000L, etc.) and, as such, demands the same resources as a GMP run. Thus, biopharma companies and their CDMO partners must make a risk- and evidence-based decision whether conducting an ER is in the best interest of their project.

At stake in this decision are project costs and timelines – including, potentially, first-to-market status – as well as confidence in the GMP production process and brand reputation. Assessing ER pros and cons is a must-do exercise for any project, but the significance assigned to each element (e.g., the cost, timeline, or risk of GMP run failure) varies on a case-by-case basis. To some extent, the decision also is affected by the type of company.

For example, some organizations may lack extensive experience: they either do not know or have insufficient knowledge to be confident about how their cell line will react at a large scale and require an engineering run for confirmation. Conversely, a company may desire an engineering run but is unable to bear the cost of executing one (i.e., essentially the same cost as executing a GMP run). Other biopharma companies have extensive product development experience and a high level of confidence in their product and process, so they perceive skipping an ER as a low-risk decision. Or, an experienced biopharma may be confident in its process and product but still desires an ER because it realizes its molecule is complicated and/or difficult to work with.

Whatever the rationale, executing or skipping an ER is a consequential decision for any biopharma or CDMO and should be supported by all available data as well as a thorough risk assessment. This analysis requires an understanding of the benefits and pitfalls of an ER in the context of the organization's particular circumstances.

ERs CAN REFINE PROCESSES, EXPOSE SHORTCOMINGS

The key benefit of an ER is the opportunity to eliminate almost all deviations and limitations from a process. As the run is executed, operators can track ups and downs, monitoring where glitches exist and minimizing or removing any risk they may introduce. ERs also allow for refinement of documentation (e.g., batch records) – more so than if it was left to be completed during/after GMP runs – because the ER provides an opportunity to redline aberrations in the paperwork and identify areas that require an update.

Additionally, an ER gives every team member hands-on experience relevant to the specific product's GMP run. A seemingly well-understood process is much like an automobile: each one is very similar (four wheels, internal combustion engine, door locks), but each vehicle also exhibits its own quirks. Consider that monoclonal antibody (mAb) development is a standard process; fed batch usually is a standard process; perfusion is a standard process. But experience with a specific molecule, a specific set of equipment, and a specific group of operators working in unison provides more complete insight into that process' nuance – facilitating identification of opportunities for training, workflow optimization, and maintenance.

ERs also can result in a greatly reduced sampling regime that still provides the sought-after information. Sampling experimentation during the ER allows operators to examine analytical material and

determine what information it will provide, as well as what must be done (and by whom) to glean that information. For example, a sampling regime originally planned to take place every two hours might be altered to take place every 24 hours after the ER shows less frequent sampling will result in the same information, depicting the same trend. Combined with process and workflow optimization, this leads to more efficient use of materials and time, with fewer perturbations to the system, during subsequent GMP runs.

Finally, ERs provide confirmation of harmonious consolidation, evidence that upstream processes and downstream processes all work together. This surety reduces the risk of a failed GMP run almost completely (no process is ever 100% risk free; living things don't always behave the way we want or expect them to behave). In fact, many larger biopharma organizations — those with the vast resources to do so — consider it sensible practice (if not always a necessity) to conduct multiple ERs for each project to refine their production processes. However, not all organizations have the resources, or desire, to sustain such a convention.

ERs CAN BE COSTLY AND TIME-CONSUMING

Budget almost always is a significant factor in the decision to conduct or skip an ER. The cost to execute the run is not paltry: it's essentially the same as a GMP run. For example, if a project is estimated to cost $5M, adding an engineering run might make it $6M. Many organizations want to limit, as much as possible, the use of materials and people's time.

Sometimes, companies "split the difference," saving money by just executing an upstream engineering run and skipping the downstream portions (e.g., purification steps), particularly if they have a well-known or a relatively common process for downstream. Upstream activities dealing with more in-depth biological processes tend to be more complicated. Companies simply seeking confirmation their equipment functions as intended (i.e., they already have confidence in their cell line) also can save money by performing the ER using water or plain media. These companies don't need to spend time and money growing cells and expanding them simply to dial in sparger settings or confirm the pH monitor is accurate.

Regardless of its extent, an ER is executed under the same structure as a GMP run, but without the same restrictions since the run does not have to adhere to GMP regulatory standards. It can be conducted beginning-to-end, nonstop, while tracking pitfalls and challenges encountered, as well as the time the run takes to execute. Prep work, such as growing cells, plus the ER itself are likely to add a month or more to the development process. Plus, if viable material is used to execute the run, the resulting product usually is lost, since it was not produced according to GMP standards.

Supply chain also can impact — and be impacted by — ERs. As supply chain issues around the world worsen, this consideration is becoming more vital for biopharma organizations and their partners. In addition to the media used for both ERs and GMP runs, shortages can strike single-use (SU) disposable bags, tubing, filters, or any other commodity necessary for manufacture. A diligent CDMO will ensure all necessary materials are available (in-house) before starting a run so, if a problem is encountered, subsequent runs will not have to wait for new materials to arrive.

Lastly, it warrants mention that the time and cost associated with an ER can be exacerbated by too much focus on extraneous details. From a desire to dot every "I" and cross every "T" on batch records to hyper-specificity on key parameters, it can be easy to lose sight of the key function of the ER: building confidence and working out kinks in the process. Digging into details regarding equipment RPMs, fiddling with the type of impeller used to keep the cells suspended, or tinkering with the volume and the rate of spargers all add time to the ER.

SKIPPING THE ER: RISK VS. REWARD

A mAb is, for the most part, a platform process. Many organizations have an established small-scale process wherein they have determined most key parameters, which they are confident will work for a GMP run, emboldening them to skip an ER. As a drug product progresses into phase two and phase three, though, ERs become more common (i.e., faults become apparent, and more development work may be applied to smooth out issues).

In any case, skipping an engineering run is a calculated risk. The biopharma company acknowledges and accepts that, if something goes wrong with the GMP run, the consequences could be severe. However, there is no way to attribute a hard number to the amount of time or money that could be lost. It partially depends on where the error occurs. For example, if

a problem occurs at the end of the run, the amount of time lost is effectively doubled (i.e., one to two months could be necessary to complete an entirely new run). If it occurs in the beginning of the run – say, the first 10 days – the project loses 10 days, but can start again (though all of the material used is still lost).

Added to this time loss – depending on how far the failed GMP run progressed and the company's quality system – could be a failure modes effect analysis (FMEA). The investigation into, for example, pressure testing all equipment connections to determine why the run failed, can take anywhere from several days (if rushed) to several weeks. While the company may decide to begin a new run as the investigation is ongoing, it accepts additional risk if a clear answer and solution have not been determined by the time the next run is ready.

Moreover, many CDMOs book GMP slots back-to-back, so if an organization misses its scheduled GMP run, another slot may not be immediately available. The delay could be substantial depending on how the CDMO books its GMP slots. Some CDMOs prepare for this possibility by setting up two cultures a week apart. That way, if something goes wrong when the initial culture is placed in a larger reactor, only one week is lost before another can be inserted. Some companies see this strategy as a viable fail-safe, while others view it as a waste of material and time.

THE RIGHT CDMO MINIMIZES ER-RELATED RISK

To speed project timelines and minimize the risk of bypassing an ER, it is advantageous to partner with a CDMO that has experience in your molecule and potentially even your process. This technical fit builds client confidence that the CDMO understands the science behind the molecule – experienced personnel who can say, "I've worked with this molecule type for years; this is how it should work. This project fits within our scope of operations and capability."

In early discussions, biopharma clients want to know about a CDMO's experience and expertise. This conversation can have imprecise results, since the CDMO cannot divulge information about previous client successes or failures – only the types of molecules it has developed/produced and the extent of that experience. Thus, other than big-name organizations whose reputations are well-established, CDMOs must strive to establish relationships with their clients through presentations, facility tours, and conversations that build comfort with the scientific group.

These interactions, combined with open conversations about the pros and cons of ERs relevant to their goals, resources, and molecule/process, can help a biopharma company determine whether a CDMO partner is well-positioned to help it succeed in GMP runs, regardless of the path it takes before executing those runs. For more information, visit Northway Biotech online at www.northwaybiotech.com.

ABOUT THE AUTHOR

Francis B. Maddalo, is Site Head and Director of U.S. Operations for Northway Biotech. He is a highly experienced manager with over 25 years of experience in different areas of the manufacture of biologics, drugs, and medical devices. His areas of expertise include process optimization, product development, CMC regulatory, and others. Francis holds a MSc in Physiology/Virology and a BSc in Biology.

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.).

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