Biotechnology Scale-up Hacks

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Not enough time or money to scale-up following the traditional rules of advanced biotechnology (10:1 scale-up factor, 1,000 hours of integrated pilot/demo operation, etc)? Welcome to the reality of the biotechnology start-up world. The common question in that situation is: *if I do not have all the resources to follow the traditional approach, how are my resources best used to reach commercial success*? Let's explore.

I am compelled to start with the disclaimer that streamlined approaches (what I call hacks, but some would characterize as shortcuts) should be consider by need, not as a primary plan. There are risks involved and reasons why the traditional approach should always be the starting point, but reality often requires different approaches. A good place to gain perspective is to look back at the last industrial biotechnology wave and see what lessons can be learned.

The span from 2006 to 2014 was a period of unprecedented growth and expansion in advanced biotechnology, with the last few years being a retreat to focus more on technology development than commercial deployment. The last commercialization wave was fueled significantly by federal stimulus money. While intentions for ensuring projects were ready for prime-time were sincere, the realities of the high influx of grant money pushed many to build larger plants than the technologies or markets warranted. The large size of biofuel facilities, combined with softening oil prices, produced numerous large-scale facilities that were not able to remain viable. This is a scenario we self-committed biotechies do not want to repeat.

Before outlining what some would characterize as short-cuts, it is important to understand the industry accepted practices on scale-up to provide a baseline to start from. The links below are to some key Digest publications on scale-up that are worth review:

- Top 10 Lessons Learned Commercializing Advanced Biotechnologies
- Understanding Advanced Biotechnology Commercialization
- Evaluating Commercial Readiness
- Scaling-up through Contract Manufacturing

When making risk decisions during the scale-up process, it is critical to differentiate outcomes that are undesirable from those that are unacceptable. An example of an undesirable outcome is facility capacity, where you end up with a facility that can only produce a fraction of what it is designed for. This is bad, but usually not catastrophic. The economics will shift some, but as the process is refined, there is potential to ultimately reach design capacity. By contrast, an example of an unacceptable outcome is a process that cannot make product that can be sold. This can be for various reasons, but if not overcome, will cause the venture to fail. As we do risk-based decision making, it is important to focus on items that have undesirable downsides rather than unacceptable ones. With that perspective in mind, let's consider the following hacks that have the potential to provide a faster and less costly route to successful commercial operation.

Go big or go home – How large of a scale-up factor from pilot to demo, or demo to commercial, is a common area of focus. While debt financing looks for a maximum scale-up of 10:1 to limit technology risk, many equity-funded biotechnologies have been able to successfully scale at 100:1. The important point when considering options, is that being too aggressive is more likely to result in a facility that does not provide adequate capacity (undesirable) than a facility that does not produce adequate product quality (unacceptable). This makes scale-up factor a target area if higher risk is acceptable.

How much is enough – Talking about data of course. A critical part of scale-up is not only operating an integrated pilot or demonstration process, but generating enough data to de-risk the scale-up process. The industry standard is for 1,000 hours of continuous operation, or roughly 40 days. The risk involved in reducing operating time is a hybrid of undesirable and unacceptable. The unacceptable risk comes from the period of operation not representing an equilibrium case, which is process specific. Some processes come to equilibrium (including recycle streams) in days, while complex processes can take weeks to reach an equilibrium state. This will determine the level or risk. The undesirable risk comes in the form of capacity of the scaled-up process.

Full integration – Critical during scale-up, is for the entire process to be accurately tested, from feedstock through final product, with recycle streams included. This is the only way to get an accurate representation of what the process will operate like and the product quality standards. Modeling is a great tool, but I can tell you from personal experience, just because a process runs well in a simulation model, does not mean it will run the same in commercial scale equipment. Failure to demonstrate full integration can result in a process that produce product with required specificaiton, an unacceptable outcome. While early stage scale-up may involve processing at multiple sites, care needs to be taken to ensure it accurately represents the integrated process.

Making risk based decisions to optimize scale-up efforts is not preferred, but is often the reality that biotechnology start-ups are faced with. While it is risky to make broad assumptions around the scale-up process, the best approach to optimizing the effort is typically being more aggressive on scale-up factor, with campaign time for pilot process following. The approach with the highest risk involves pilot and demonstration processes that are not fully integrated.

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