WHAT MAKES SCALE-UP OF INDUSTRIAL BIOTECHNOLOGY SO DIFFICULT?

Mark Warner, PE
Founder, Warner Advisors LLC

Two questions have dominated the responses received after my Lessons Learned series on commercializing industrial biotechnology (here) and the deep-dive into the industrial biotechnology commercialization process (here), the questions are *what makes scale-up of industrial biotechnology so difficult* and of course *how can risk be reduced in the process*? Looking back at the materials, there are a few areas that need to be expanded in greater detail to answer those questions.

From the Lessons Learned series, the third lesson "***there is no substitute for a fully integrated pilot process"*** generated a lot of discussion on why that is so. Many in our advanced biotechnology industry come from the chemical or petrochemical industries, which are rooted in process modeling as their primary scale-up tool. This is significantly different than advanced biotechnology, where scale-up is based on extended pilot operations. The cost and timeline of building an integrated pilot, or demonstration scale plant, challenges ventures attempting to bypass these steps, which can end badly. Let me focus on what makes biotechnology processes unique and why pilot testing is so critical to a successful scale-up.

First, let's understand how traditional chemical processes are scaled-up by modeling as a comparison. As a chemical process engineer who spent the first portion of his career in the chemical industry, I have been faced with many of the traditional chemical scale-up challenges. Processes such as synthesis of an organic compound and subsequent refinement from a mixture of solvents, where all of the compounds had well documented chemical and physical properties. If there were chemical reactions, it was usually between a limited number of compounds with well-known reaction kinetics and a short list of competing side reactions to be considered. This can be modeled very accurately by process simulation software like Aspen or CHEMCAD. Modeling did not completely replace the need for piloting, but often limited the scope of pilot testing to verification of key parameters. This history of success in using modeling processes and then verifying a few separate operating conditions with piloting, gave confidence in this approach.

Now, let's compare that to industrial fermentation based processes. Industrial fermentation typically starts with feedstocks that are less pure and more complicated from a reaction standpoint than a traditional chemical reaction. Anyone who has seen the massive wall posters of metabolic pathways in very small font knows what I am talking about. It is generally not practical to model the entirety of the individual reactions (and competing side reactions), but rather only practical to generate an average rate equation for the overall process. While this can be used to represent the process from a "macro" perspective, it will not accurately predict the minor constituents in the fermentation broth that can impact both the fermentation and recovery productivity. This example is specific to fermentation, but the principle equally applies to other bio-based processes.

Given this inability to accurately model biotechnology processes, pilot and demonstration plant operation is the only reliable method to generate the information needed to scale and design

equipment. This is why integrated pilot operation is so critical to project success. Here are a handful of my lesson's learned specific to scale up of biologic processes:

Understand your feedstock - If you are planning to use standard industrial sugars like liquid dextrose at commercial scale, you need to make sure your lab and pilot testing accurately represents the feedstock. As an example, if you are buying bags of commercial dextrose crystals to run in your pilot plant, you might be surprised to find out that crystal sugar has a much higher purity (>99.5%) than standard liquid dextrose. Typical liquid dextrose is only 95% dextrose and has 3-5% of other (often unfermentable) sugars including maltose and higher saccharides. These can cause operational issues both in fermentation and downstream recovery. Failing to use representative feedstock during scale-up testing can set you up for big problems later.

The same issues arise when doing fermentation with syngas or digester gas as a feedstock. Often, the commercial business model will be to produce syngas by gasification of biomass or MSW, yet the lab or pilot will operate on syngas generated from natural gas for convenience. Just like the sugar example above, if the feedstock used in the pilot does not represent the reality of commercial scale, there will likely be operations issues that arise.

The liberal media – A reference to the fermentation media, of course. This is a mixture of trace minerals and vitamins added with water and inoculum at the beginning of the fermentation. Just like humans, most organisms need some trace level of these to support metabolic activity. The hard part is determining how much is required and not just liberally adding it to make sure there is plenty. Optimization of media is not generally a priority at lab or pilot scale, but can become a significant cost and supply constraint in a commercial operation. Just like the dextrose example, commercial supplies of the vitamins and minerals are less pure and can bring contaminants and other compounds that can negatively impact the process.

The "other" problem - as discussed above, it is not practical in a commercial biotechnology process predict all compounds generated during the fermentation, or that come along with the feedstock. Typical chemical analysis used in engineering scale-up will identify key compounds, but then everything else that cannot be identified gets lumped into a category of "other", often referred to during the design process as "OS" or "other stuff". It is important to note that these compounds are not inert and usually impact the process. The biggest issue usually comes from the unfermentable sugars and the co-compounds that are generated from side reactions. This is one more case where the only way to determine the impact of these compounds is to run the pilot process.

Don't push the rope – hopefully we all learned at an early age that you cannot push a rope, you need to pull with it. The same principle applies to process scale-up. You need to first determine what your commercial scale facility will look like conceptually and use the pilot operation to prove out key parameters needed to build the process (i.e., "pull" the information needed from the pilot). This involves identifying commercial scale equipment that can perform the unit operations you need and utilizing the pilot to focus on generating the data needed to select and design commercial equipment. Trying to just replicate what you have on a pilot scale, without consideration of what is practical at commercial scale (pushing data forward), will not usually result in a viable process.

Determining your key parameters for scale up – It is critical early in the pilot process to determine what information you will need to design your commercial facility and how to generate what you need. Many times, it is proving out whether a factor will impact your process or not. Think of scaling-up from a standard 300 liter packaged fermenter to a 300,000 liter air lift fermenter. The packaged fermenter is about 5 feet tall and the airlift fermenter could be near 100 feet tall. Consider these questions:

- The pressure at the bottom of the airlift fermenter where the air or syngas is dispersed will much higher than the packaged fermenter. Will the pressure impact how the gas mixtures are absorbed, accessed by the organism and overall fermenter performance?
- Packaged fermenters utilize mechanical mixing while airlift fermenters use the rise of the gas bubbles to induce mixing. How do you determine if the airlift mixing will be adequate?

These are just a few of the items that can only be determined by knowing what you need to prove out for commercial scale and determining how to get the pilot or demonstration operation to generate the information.

Mark Warner is a registered professional engineer with 30 years of experience in process commercialization, focusing for the last 10 years on taking first-of-a-kind-technologies from bench-top to commercial operation. He has worked for four companies who have held the #1 spot in biofuels digest's top company list, in a range of advanced biotechnologies including biodiesel, cellulosic ethanol, phototrophic algae, heterotrophic algae and innovative food products. He is the founder of Warner Advisors, providing consulting services and acting in interim engineering leadership roles for advanced bioeconomy clients. He can be reached at mark@warneradvisorsllc.com or visit www.warneradvisorsllc.com.