SCALING-UP THROUGH CONTRACT MANUFACTURING

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As companies consider options to commercialize their advanced biotechnologies, they are faced with the decision to either build their own demonstration scale facility or utilize existing contract manufacturing operations (CMOs). There are benefits and pitfalls to both approaches, with the correct decision founded in the goals of the organization and specifics of the process. Having successfully scaled advanced biotechnologies through both routes, the following is a primer on key decision factors, and a deeper dive into the scale-up through CMOs.

Understanding what success looks like – before discussing the details of scaling-up and the best option for a process, let's consider what success looks like. What are the goals of the scale-up activities? Is it to prove the process technology, demonstrate production cost targets, produce materials to seed the market, or all of the above? The options cannot be fairly evaluated without first understanding the key criteria and prioritizing must haves. Experience has shown me that every process can usually be scaled-up, the key question is whether it can be done economically to fit the intended market.

Scale-up is more than data – the single largest area of surprise for most ventures scaling-up a process is the conflict between generating the necessary data to demonstrate the viability of the process, and making representative material to seed the market. These are conflicting goals that usually results in a significantly longer period of time for scale-up than anticipated. Let me give you an example:

> *An advanced biotechnology startup has been developing an innovative biotechnology and operating in a pilot fermenter with associated downstream recovery, and has demonstrated 70% of its fermentation titer goal. The start-up recently projected to its board the titer goal (critical to closing the next round of financing) would be demonstrated within 6 months. The CTO reports that a new variation of proprietary organism is forecasted to meet the titer target when optimized through the pilot plant.*
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> *Simultaneously, the head of business development reports that the fortune 100 strategic consumer products client loves the material and needs "hundreds of kilograms" to produce product for a consumer test, which if successful, will result in an offtake agreement. Producing the material for consumer testing will require 4 months of pilot operation.*

These conflicting needs represent reality for most biotechnologies during scale-up: The need to produce consistently representative material to seed the market, and the need to discover and change the process to meet key technical goals. Can they be done at the same time? ***Very unlikely***. When making innovative changes, some will succeed and some will not, it will likely be months of pilot operation until a new strain is making representative (on specification) material. The requirement for interim scale manufacturing can often take much longer than initially projected, to meet both technical and market requirements.

Look at financials from a cash basis – when performing the economic analysis to compare building a demonstration scale facility versus using a CMO, the analysis should also be done on a cash basis. Technically, building a demo facility could be capitalized and depreciated, reality is that once the initial scale-up work is complete, it is a sunk cost that may or may not be utilized further. If the cost is capitalized in the economic analysis, building a facility will appear to be the low cost option, however the reality of scale-up involves a fixed amount of cash and whether it goes towards a capital asset or contract manufacturing does not matter. It is not a P&L statement that is a concern during scale-up, but rather "money in the bank."

Advanced Biotechnology versus Pharma – in my previous series ***"strategic approach to scale-up"***, I introduced *the dollar test*, which provides a basis to differentiate products from various markets (pharma, chemicals and food) and outlines the economically viable options for each. The upshot being that for products such as pharmaceuticals, practically any biotechnology option is available, but foods and commodity chemicals have economics that limit the practicality of many technologies. This applies directly to the world of CMO options. Most contract manufacturing options within advanced biotechnology are built and operated to pharmaceutical standards and have a cost structure often 5-10 times higher than CMO's built and operated to non-pharma standards. This makes pharma style CMO's an option for initial screening (say 500 – 5,000 liter fermentation scale), but they become economically prohibitive when moving into demonstration or commercial scale (25,000 liter or greater).

Pros and Cons of Contract Manufacturing – The decision on whether to build a demonstration facility or use a CMO is a combination of cost and ability of each to meet the goals discussed previously.

Advantages

- Likely faster time to market if CMO does not require major equipment modification
- Less up-front cash, limited capital investment and cost incurred as CMO operates
- Benefit from experience of others, not required to be experts on all unit operations

Disadvantages

- Less control, inability to control schedule and specific way equipment is operated
- Higher marginal production cost and higher overall cost for lengthy operations
- Hidden costs of staff time and travel required to provide on-site supervision

The CMO world is getting smaller – most contract manufacturing operations for advanced biotechnology were not built with the intent to be a CMO, they ended up in this mode of operation due to loss of their primary product. This is not a bad thing, but since the facility was not likely built to be a CMO, it likely does not have all the flexibility required. The second reality is that since there have not been as many facilities built in recent years, the available world of CMO's for advanced biotechnology companies continues to get smaller. Contract manufactures seek long term (multi-year) manufacturing arrangements, while biotechnology startups often seek a very discrete and less predictable operational period.

Using a CMO for process scale-up can be the lowest cost option when the time period is shorter (typically 1-2 years max) and the facility can host the process without significant new equipment or investment. Scale-up periods of longer than 1-2 years or that require significant capital equipment

installed at the CMO will typically be more favorable towards building a dedicated demonstration facility.

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.