TOP TEN LESSONS LEARNED COMMERCIALIZING ADVANCED BIOTECHNOLOGIES

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Spending half a billion dollars placing steel in the ground to commercialize advanced biotechnologies for fuels, chemicals and food applications, is the easy part. Doing it successfully is the hard part – but I have been fortunate to lead many successful projects over the last ten years, and that is what has prompted me to share my personal experience in this three-part series of *Top Ten Lessons Learned*. I have done my best to include real world examples and attributes that make ventures succeed, as well as common pitfalls. My focus is on the technical perspectives of technology deployment, from early stage process development, engineering, and construction to a fully operational commercial facility. This series is for anyone who is passionate about scaling advanced biotechnology dreams.

PART 1 – DEVELOPMENT AND SCALE-UP

1. Build the Team – *Capability, agility, and diversity are critical*

The main lesson I learned, the hard way, is there is not a right or wrong type of experience, it comes down to the capability of the team to transform as broader challenges emerge. The toughest challenges are rarely in proving the technology – it's in scaling and commercializing it. This is a rapid-deployment game, won only by the team whose members have the capacity to listen and learn, the agility to quickly transition, and the desire to embrace diverse backgrounds who will take informed risks to succeed.

As a startup grows and matures, it is inevitable that broader challenges will emerge, many that are not related to the core technology. This often happens when the initial focus of the company is scientific discovery and it transitions to commercial deployment. While a complex scientific problem may be of little to no concern for a senior scientist, determining how that problem can be solved *economically at commercial scale*, including impacts that run the gamut from site selection to marketing, is problematic if the team is not fortified by those who have the skill and will to successfully transform to commercial stages. The scientist cannot be successful without partnering with industrial experience, and vice versa – it is the skill of the team that trumps all. The key is to identify the experience types that cover the range of challenges faced during the lifecycle of commercialization, and to hire individuals who respect that handoffs to others is never in doubt.

The ability to identify when an employee is not a fit for advanced deployment or worse, destructive to the culture, is key. Often, there is a feeling that the specific technical experience the employee brings is critical, but the real test is a leader's capacity to transform the team and the employee's ability to understand the larger purpose which will evolve from its original concept in the lab.

Harmonizing the need for exceptional technical staff who can evolve through rapid growth stages of a startup venture, and transform to long-term key contributors during commercialization, is the key to ultimate success.

2. Process Development – *It's not all about you*

When looking at the long-term challenges that manifest during developing and deploying innovative biotechnologies, it is important to first understand how most biotechnologies are discovered and mature as the venture grows. Most new technologies emerge as a new pathway that is "light-years" ahead of the way things are currently done. The traditional model in the advanced bioeconomy is an organism that can produce a desired compound more efficiently, sustainably, and (hopefully) cost effectively than what is in commerce today.

For our example, let's assume we have discovered a wonder bug that is able to produce our target compound, di-methyl glop (DMG), very efficiently via fermentation. DMG is used in many specialty chemical and commodity applications, and we are confident that if we hit the price projections, we will have an industry-changing venture. We use the positive discovery to form a startup company, get VC funding from a handful of name venture funds and build a world-class team of scientists, with a robust toolkit of genetics and process technology to improve our yield and productivity to the point our fermentation process can be commercially viable. Sounds great, right? It is, but unfortunately, it's only the first leg on the long journey to commercialization. What has been made is a wonderful fermentation broth rich in very valuable DMG, but this now has to be separated and refined to a point it meets industry specifications. It is that second portion of the process that is often the biggest challenge, not because it's necessarily harder, but because it is such a departure from the initial mission of the startup and the organization can struggle to make the shift.

The source of comfort with focusing on the core technology comes during the early development days at a startup, when yields and titers are tracked daily, new versions of the organism are cheered and fermentation results are dutifully reported at every board meeting. The justified pride is such a motivation, the board presentation often includes analytical results only hours old. So what is the problem? As wonderful as the technology is, it will only end up being a single cog in the overall machine that is a fully integrated production process. It is like being a proud parent of a star athlete, you know that your child is the best player on the team, but for the team to win, it may be more important that your child play his or her role as a key member of the integrated team, than be the individual MVP. The same is true for technology. If your ultimate goal is the best overall process for cost and quality of production, it may be more important that your core technology support the overall process, not be the individual star.

3. Scale-up - *There is no substitute for a fully integrated pilot process*

How a process is scaled-up and what constitutes an acceptable risk, to ensure your larger-scale facility operates as predicted, are some of the least appreciated concepts within the advanced bioeconomy. That said, both receive significant focus as companies move into larger-scale production and more importantly, as investors seek more certainty on the probability of a return on their investment.

First, let's start with the basics. It is important to realize the difference between scaling a unit operation and scaling an integrated process. The unit operations are components of the overall process and scaling them individually will seldom result in a properly scaled integrated process. Let's go back to our example of DMG. Our example process consists of four steps:

1. Aerobic fermentation to make DMG
2. Breaking the cells to release DMG into the broth and removing the spent cells
3. Concentration of DMG by multi-stage evaporation
4. Purification of DMG by crystallization

In this process, it is likely that steps #1 and #2 would be done internally at the company pilot plant with fermentation, homogenization and centrifuge equipment. The initial evaporation and crystallization efforts to prove the concept would likely be done at third party vendors. Shipping the purified broth to the evaporation vendor's pilot plant, then shipping that the concentrate to the crystallization vendor. This results in three different portions of the process development. Assuming all three of these individual pilot tests go as planned, generate engineering data (flows, temperatures, concentrations, etc.) and produce in-specification DMG, does this provide "proof of concept"? Absolutely. Is it adequate to scale to a larger facility? No, and here is why.

Proof of concept is very important in the development process, but it only shows that the process can work. It seldom provides enough detail to predict how it will work as an integrated process, taking into consideration items like recycle and byproduct streams and contaminants that may build up over time when recycled. This is why running an integrated process is an indispensable stage in process scale-up. It is when each unit operation is run in series, being interdependent upon each other, that scale-up challenges manifest themselves. Once proof of concept exists, the next critical step is to pilot-scale equipment to bring the concentration and purification steps in house. A general rule of thumb is 500 – 1,000 hours of integrated pilot plant data is a key indicator of readiness for the next level, with a reasonable expectation of success. The jump in scale should not be greater than 10 times the capacity of the unit operations tested in the pilot.

Now you are thinking to yourself, 500 - 1,000 hours of operation and I can only go up 10 times in scale, do I always need to do that? The answer is *usually yes*, but not always. If you are handling complex mixture with solids and liquid materials (like the DMG broth), it would be high risk to go outside of these guidelines. The case where being more aggressive in hours of operation and scale-up factor is when you are dealing primarily with fairly pure liquids and gasses. Much of the scale-up risk on processes comes around material handling and obtaining representative data from samples. In the case of liquids and gasses with a limited number of components, it's much easier. Regardless, there is no substitute for a fully integrated pilot process.

About the author

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.

Special thanks to the large and accomplished team of engineers and scientists I have had the good fortune to work with over the years. This series is a summary of lessons they have all contributed to, but there are far too many to list individually.