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 2 – PROCESS DESIGN AND DEPLOYMENT

4. Facility Design – *Understanding fit for purpose*

Without a doubt, the largest source of technical difference of opinion, in the commercialization of a new bioprocess, is the design standard for building a larger-scale facility. The magnitude of the difference of opinion is directly correlated to whether the team members have the capacity to transform and hail from diverse backgrounds (as noted in Lesson #1). Everyone comes with experience and perspective, as well as biases for equipment and vendors, which may or may not be right for the process under development. To understand the source of the conflict, we need to look at what are the most common design standards and how we determine which one is fit for our purpose.

The birth of modern biotechnology began predominantly in the pharmaceutical industry, where the products being made have a very high value and the purity requirements are very strict. Many of these same technologies have been used in the emerging industrial biotechnology industry (biofuels and biochemical), with more recent application to food products. As we look to build large-scale facilities, we will find that the standards (and resulting capital costs) can vary dramatically between each of these platforms. Let's take a look at the requirements for each and what standards would be used to design a fermentation and downstream processing system.

> *Pharmaceutical Standards* – Fermentation used to support pharmaceutical production is usually referred to as sterile or aseptic, meaning that engineering controls are in place to ensure that the process is made

completely sterile before fermentation and remains that way throughout. This means ending a fermentation with only your target organism and no other organisms (aka "a clean batch") is the expectation and typically the standard for most pharmaceutical applications.

The two main techniques that are used to ensure sterility are steam sterilization of the systems prior to use and robust engineering techniques to ensure no viable foreign organisms can enter the system during operation, or build up over time. There is a very specific ASTM standard that outlines these requirements. Additionally, there are strict rules on equipment validation that involve a bureaucratic amount of documentation, certification, and testing.

One easily identifiable attribute of this standard is all process surfaces end up having a near mirror finish. If you look inside a fermenter for a pharmaceutical application, you can usually see your reflection. This is done to ensure small organisms cannot find a surface to adhere and avoid sterilization. Downstream processing systems rely on similar technologies, including disposable systems. There is a trend toward using disposables from fermentation, through downstream processing, to avoid the litany of documentation and testing required to validate equipment for use. The cost to sterilize many types of equipment has made it more cost effective for simply replace versus sterilize.

Industrial Biotechnology Standards – As scale grows in size and output of production, it is not cost effective to build processes to pharmaceutical standards. It is also not usually required, as it is more about controlling the levels and types of other organisms, not their existence. The Pharmaceutical ASTM standard is often used as a guide, but it is adjusted to fit the proposed process. What is standard for a 250 liter packaged aseptic fermenter is not practical or cost effective for a 500,000 liter industrial fermenter. While there is always a desire for a completely clean batch (no competing organisms), it is not usually a requirement in industrial processes. This has generated an industrial biotechnology design standard that takes the basic concepts of high sterility fermentation, but based on risk factors, applies only the portions that are required. In the case of fermenter finish, these seldom are high-polish in large-scale applications, usually a standard milled stainless steel. Large-scale fabricators are often not set up to be able to polish on a large-scale and it can add very significant capital costs.

Food production standards – While the progression from pharmaceutical to industrial biotech was basically a "tweak" or re-application of similar standards, the recent move within the advanced bioeconomy to food applications has brought forward significant design challenges. The basic design concept within food is to ensure there are no pathogens (bad bugs), then limit and control the overall organism count. Food is not produced to be

free of organism, just free of certain bad organisms and below acceptable levels of others.

While the basic concept of the first two standards was sterilization (ability to kill all organisms), food processing is based on the concept of cleanable. Many of the types of equipment used in food processing cannot be steam sterilized, so the applicable standards require it to be completely disassembled and cleaned on a regular basis. This is often quite surprising to technical staff who have not spent time in the food industry.

Comparing these three standards and having experience building and operating facilities under all 3 standards, the most important concept I have learned is determining what is *fit for purpose*. Just because a piece of equipment is designed to a high standard and is more expensive, does not mean is the right equipment for your application. I have seen many cases where very expensive pharmaceutical grade equipment is purchased for a food application and not only was orders of magnitude more expensive than the proper food equipment, it actually did not work as well. The challenge is for staff to rely less on their experience from other industries and be open to learning the needs and applying the appropriate standards of the target industry.

5. Integrating Standard Unit Operations - Standard industrial processes are never standard

This lesson has a special place in my heart, as it is a lesson I have learned the hard way - twice. You generate the core process of your technology, in the case of DMG, fermentation and cell separation, and you look at something like multi-stage evaporation and say to yourself:

- It is done all the time, there is nothing new here
- Our stream is very similar to other streams that use this all the time
- The process is low risk, so we do not need to assign many resources to it

If you have similar thoughts, please don't and here is why. While the technology may be proven and have a long history, it is for a certain type of material. Your feedstock may look similar to you, but when you get into the details, you will find it often is not. For multi-effect evaporation, there could easily be fouling or corrosion issues that can only be identified through fully integrated pilot testing.

The most common example of over confidence on application of a standard industry technology I have seen is purification systems for oils. This technology is commonly referred to as refining, bleaching and deodorizing (RBD) and used interchangeably in the vegetable oil industry with great success. This relies on the fact that one type of natural oil (canola, soy, etc.) is similar to another and there is enough history on

all of them for vendors to make the minor modifications needed. Given the long history and experience on vegetable oils, this has been very successful. The problem comes when applying these technologies to new streams that appear the same, but really are not.

Oils generated from both phototrophic and heterotrophic algae look similar to standard vegetable oils, except when you get to trace contaminants. In the case of phototropic algae there are often various salts and algae made by fermentation have residual sugars and fermentation media. These can be very different than the standard contaminants RBD is set up to deal with. This is one more example of why there is no substitute for fully integrated pilot operations.

6. Location, location, location – *Understand the implications of where you decide to build*

Deciding on where to build the plant is driven by commercial availability and economic considerations, such a simple statement – yet mired in failure points that require mitigation plans that only a Type-A personality can appreciate. Focus here is on ensuring all understand the risks and challenges up front, and are capable of quickly enabling mitigation plans when the inevitable occurs.

Deploying a new technology in the United States is almost always preferable from a project delivery perspective. The ability to source equipment, staff with qualified employees and secure a quality construction contractor are orders of magnitude higher in the US than many parts of the world. As for the specific location your venture selects, that will depend on a handful of factors. Feedstock availability, utilities and proximity to existing operations are typically some of the driving factors. It is important to keep in mind the ability to grow and attract quality technical staff. In many cases, a small idled site in the rural Midwest may make a great demonstration plant, but if the intention is to expand into an eventual commercial operation, availability of utilities and difficulties convincing key technical staff to relocate may inhibit the expansion process. These are examples of risks to consider up front.

There has been a considerable push in recent years to build demonstration and commercial-scale biotechnologies outside of the US, with a primary focus on South America and Asia. These are prime examples of where feedstock supply and funding sources make deployment to these areas very attractive. In those cases, it is then important to understand what the implications are. Beyond the obvious concerns of culture and language, my main lesson learned is that it is much harder than you ever dreamed, for reasons never conceived. It doesn't mean it can't be done, you just need to go in prepared for the level of complexity it will bring. My main takeaways have been:

- It is not just a matter of being in a foreign country, but how rural the site location is. Building a major factory in a rural part of South America or Asia is more difficult to get vendors, equipment and key staff; even housing is a challenge. Be prepared for this as part of the commercialization process.
- Major projects cannot be managed remotely, you need boots on the ground throughout the project. This comes in two forms. You will always need senior in-country staff who are native to the country with a network. Do this up front. The second type of boots on the ground is key technology and engineering staff from your company. There will be hundreds of decisions to be made on a daily basis that cannot be done by phone or skype (if those even happen to be working that day from your remote location in a foreign country).
- Predict the challenges and plan for them. They key to successfully constructing and operating a major facility, especially in a foreign country, is to have a fully committed technical team that understands the challenges and execution plan up front. Finding out late in the process you may need to spend months during startup out of the country does not usually end well, these expectations need to be clearly articulated up front when hiring and staffing the project.
- Hire early and often. It is inevitable you will get attrition from staff that can no longer spend extended time out of the country and you need to have backups ready. This is one of those hidden costs of commercializing overseas. It is critical that there is a fully capable local staff that can handle plant operations and technology transfer to allow your startup team to return home.

I do not mean to infer that projects cannot and should not be done in a foreign country, there are many good commercial reasons. First-hand experience does oblige me to point out there needs to be very compelling reasons though. When in doubt, target the US for all initial operations. If there is a deal you cannot refuse in a foreign country, that's great, but go in with both eyes open.

7. Regulatory – *know what you need to do from day one*

Nobody likes surprises, least of which regulatory surprises that come after you have started commercializing your technology. Getting a good regulatory understanding in the early stages of development is critical. This is driven by the fact that most of the U.S. product regulations were developed over 30 years ago and did not envision the vast expanse of bio-based products. Just because your product is chemically identical to something on the market, does not mean it is regulated the same as the other product. It is unfair and often unreasonable, but unfortunately is a reality that needs to be dealt with.

Given this reality, get advice from someone experienced in the process, sometimes it may be more than one person. The larger regulatory concern in the advanced bioeconomy is whether the organism being used is regulated. If it is genetically modified, the answer is yes. The harder question to answer is what does that mean to your process? This is usually a complex determination, based significantly on how "new" the organism is and whether the organism is a tool to make a product or if it is the final product for a food application. If it is an organism being used to make products in commerce today, the path will be fairly clear. If it is not, then the process required and time needed may not be clearly defined. The key determinations that will come from this process are whether the products can be sold into commerce and what engineering controls are needed to contain the organism. These engineering controls can vary dramatically based on the risk that is determined to be posed by the organism and it is critical this is a design consideration that is known up front. Making changes late in the project can have a significant impact on schedule and cost.

This is a situation where it is best to seek a battle tested veteran who has been through the process before. Look for an independent consultant or often a retired executive who has been through the entire process. The reason for this is there is usually not a clear yes or no answer, and your company will need to make risk based decisions. First-hand experience is very valuable in this situation. The best source of this is someone who has been through it many times. In the overall scope of the project, it is not that much money, and is penny wise.

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.