TAKE THE TEST - *EVALUATING COMMERCIAL READINESS*

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In my previous series *what makes the scale-up of industrial biotechnology so difficult*, I discussed the need for a fully integrated pilot plant and reviewed common pitfalls that companies face on their path to commercialization. The series generated the obvious question as to how and when a company can be confident it is prepared to take the leap of faith and spend big money on commercializing its technology. The focus of this series will be to provide a framework to allow ventures to assess their current state of process development and whether they are ready to make the next step on the commercialization path from a technology standpoint. There are significant product sales and commercial issues that need to be considered in any commercialization determination which drive technical requirements; however this series will focus just on the technology portion of the evaluation. The final installment of the series will provide a self-assessment tool to evaluate overall readiness and highlight gaps.

The evaluation process begins by determining expectations. Ventures come prepared to present a large data set of fermentation titers, unit operation yields and throughputs, along with product quality information, asking if they are ready to take the next step in commercialization. While technical data is important to the evaluation process, the first question to be answered is *what does success look like*? A company cannot determine if they are ready to start the next step in the commercialization journey unless they understand the realistic goal. If the decision is made to build a demonstration or commercial scale plant, what are their expectations that define success? The more rigid and aspirational the expectations, the longer it will take and the less likely the venture is to meet the goal. Many years commercializing advanced biotechnology has taught me that being aggressive or conservative are both valid commercialization strategies, as long as the approach to commercialization matches the company goals and the expectation of success, let me explain.

The most common factors that come into play when determining expectation of scaling-up a process are capital cost, project timeline, manufacturing cost and projected production capacity. The level of certainty that is required for each of these criteria at the front-end of the process will set the overall definition of success. This can generally be broken into 3 categories:

High probability (slow and easy wins the race) – having a high confidence in the capital cost, project timeline, manufacturing cost and ultimate capacity of the facility before commercialization begins. Common among large, establish businesses. There is an expectation that the project cost will be fixed, the timeline highly probable and the facility will produce near capacity soon after being released for operations. This is the typical expectation for debt funded projects like traditional corn ethanol, but is generally

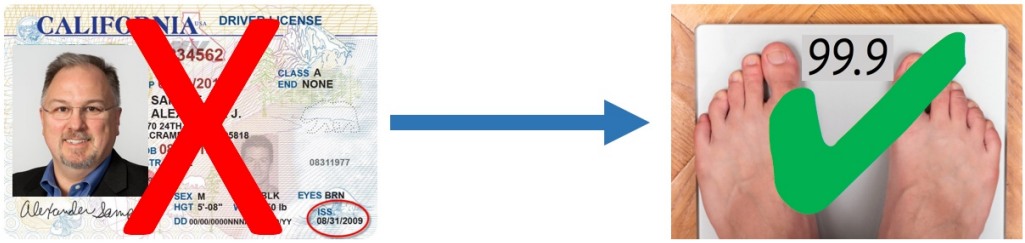
aspirational for advanced biotechnologies. As new biotechnologies represent processes that have never before been built, the technology risk makes reaching this standard very difficult.

Balanced (no risk, no reward) – willing to accept some level of uncertainly in capital cost, timeline, manufacturing cost and schedule, usually dependent on risk-based decisions and trying to bound the uncertainty. Company has reasonable equity reserves to be able to take modest risks and can absorb increased capital cost, extended timeline and slower than projected production ramp-up. Project can be done quicker than the high probability approach, if level of uncertainty is acceptable.

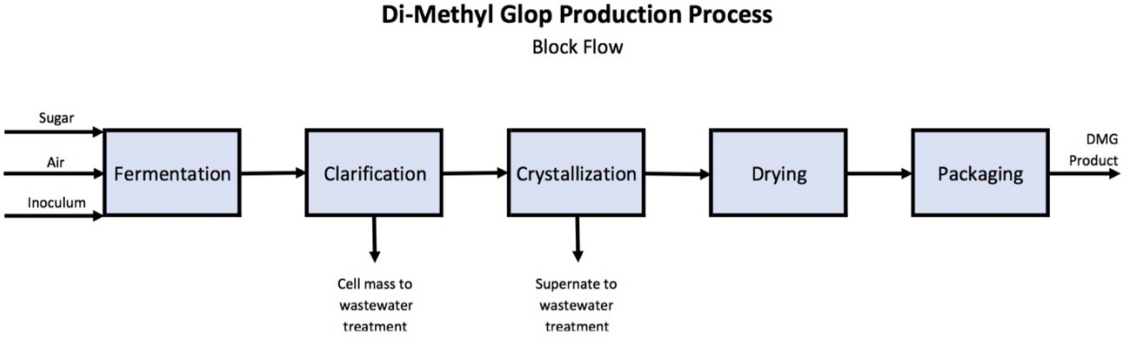
Speed to Market (ready, fire, aim) – ability and willingness to accept higher level of risk in commercialization to keep first mover advantage. Often early leaders in technology areas that are able to raise significant venture funding have such a forward lean towards rapid commercialization, they are willing to accept cost, schedule and production risks to get product on the market as soon a possible and keep their first-mover advantage over competitors. This typically involves making the go/no-go on major portions of the facility when they are ready and filling in the gaps (hopefully) during engineering and construction. Only a viable option for equity funded projects.

As noted previously, each of these approaches has advantages and disadvantages. There is no generic "best" option, but rather the option selected must fit the company business objectives. The problem comes when companies want the high probability outcome without putting the time and resources in up front.

One final point I want to make in preparation for the technology readiness assessment that will come in subsequent parts of the series is what I call the ***drivers license test***. There will be many questions that deal with current state of technology and what has been proven to date. It is critical that realistic data be used in the assessment and to highlight the concern, lets consider a person's weight on their drivers license as an example of perception versus reality. Most people (myself included) have a weight on their driver's license that represents what they believe they should weigh or what they aspire to. Unfortunately, that usually conflicts with the blinking digital numbers between their toes when stepping on a scale. In conducting the evaluation, it will only be as valuable as the current state of reality that is used for the process, so this is a polite way of saying to use the numbers on the scale, not the drivers license.



Now, let's move into the details of evaluating the state of technology and readiness for commercialization. As an example for demonstration purposes, let's use the di-methyl glop (DMG) process I have noted in previous series. DMG is an industrial chemical made by fermentation, then separated by centrifugation, purified by crystallization, dried and packaged. We will assume the process is currently operated at a 45,000 pound per year pilot plant and the goal is to build a 2,000,000 pound per year commercial scale facility. A block flow of the process is shown below.



In looking at any advanced biotechnology, there are 5 primary criteria that are used to evaluate readiness for process commercialization as outlined below. None of these criteria individually are a deciding factor, but rather in aggregate are the information needed for the analysis and will be the inputs required for the evaluation tool:

> ***Number of unit operations*** – The top criteria that usually determines the level of complexity in process development is the total number of unit operations (processing steps) involved in the overall production process. The more unit operations, the higher the level of effort required to make a fully integrated process that functions effectively with them. In the DMG example, there are 5 unit operations, which represents the lower end of the range for most advanced biotechnologies. This is primarily because the DMG process has an organism that excretes the final product. In many processes, the product is inter-cellular and requires the cells to be disrupted (homogenized, bead milled, acid/base, etc.) and then isolated (MF, UF, TFF, chromatography, etc.). This often expands the total unit operations in the overall process to 10 or more.
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> ***Scale-up factor*** – This is the growth in size between where the process is currently operating and the proposed production level. In the case of DMG, the commercial scale facility is proposed for 2,000,000 pounds per year and the pilot plant that has been operating has an annual production rate of 45,000 pounds, so dividing the two give a scale-up factor of 44:1. The larger the scale up factor, the more risk involved. It is also possible to look at the scale-up factor of each unit operation and then average them. This approach can show a lower level of risk where scaling up involves multiple pieces of identical equipment (fermenters, centrifuges, etc.)

Status against key process criteria – Every process has a handful of key criteria that are the most important technical milestones needed for the process to be commercially viable. These are typically the items in the techno-economic model that have the most impact on total manufacturing cost when a sensitivity analysis is run. Fermentation titer, product yield per unit feedstock and overall recovery yield of product are some of the most common examples. To determine the overall status against process criteria, divide the the current status of each criteria against its target, then average them. For the DMG example, in the case of titer, the target is 50 grams per liter, but the pilot is currently operating at 35 grams per liter, so the ratio is .70 or 70% of target. Example calculation for each criteria and overall averaging is shown below:

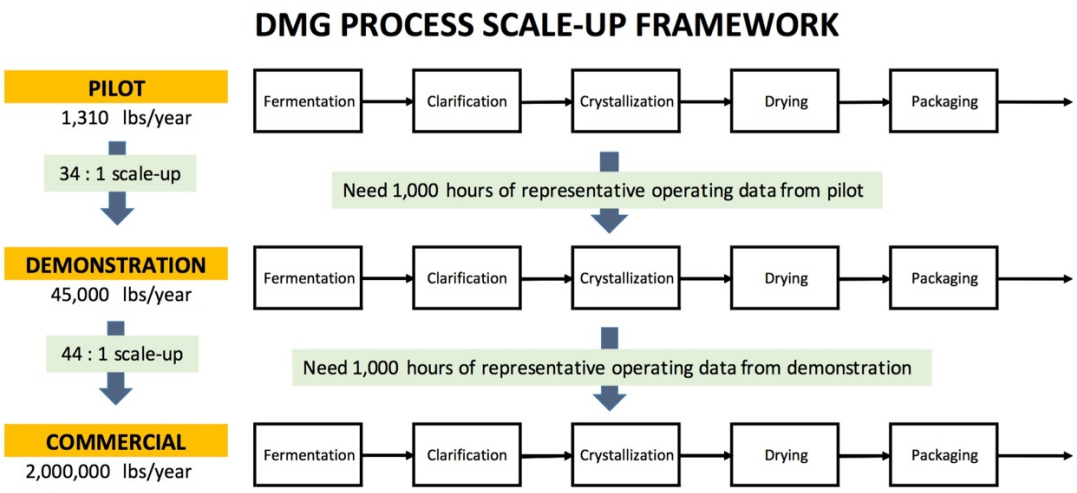
	Pilot	Commercial	Ratio
Titer (g DMG/l)	35	50	0.70
Fermentation yield (g DMG/g glucose)	0.25	0.40	0.63
Recovery yield (g DMG recovered /g DMG produced	76%	93%	0.82
		Overall Process Key Criteria Average	0.71

The risk in key criteria comes both from how far any individual criteria is from the target and also how far the overall average process criteria is from the target. In cases where there is a significant difference of importance between criteria, the individual criteria can be weighted in the calculation, as appropriate.

Fully integrated versus independent operation – It is critical when gathering data at bench or pilot scale for a process, that the process is fully integrated, meaning it is run in a continuous manner in the same location from feedstock to final product. This is the desired standard. In some cases, the process needs be broken into pieces with some portions of it (say fermentation) happening at one site, with broth shipped to another site for downstream recovery. While the second approach does demonstrate the process can produce product, the data generated is of less value than a fully integrated process.

Length of testing at previous stage – The length of time that a process is operated in a continuous manner is very important to determine the quality of data for minimizing risk in scale-up. As contaminants can build up in a process over time, it is common for some problems not to be demonstrated until after weeks of operations. 1,000 hours of continuous operation of the process at the planned conditions is the industry standard. Processes can (and have) been scaled with less operational time, but it does come with higher risk.

When conducting an assessment of process readiness, it is usually helpful to generate a framework diagram showing the block flow of the process at pilot, demonstration scale and commercial, with corresponding production levels. This allows for a more intuitive visual assessment of the magnitude of scale up and highlights if any of the unit operations have changed at the different stages of development.



Commercialization Readiness Scorecard

The excel based scorecard takes the key information discussed in this series and provides feedback on state of readiness. Given the level of information required, it is a high level assessment, but can provide key insight to which areas are of highest risk and where resources are best spent to close technical gaps. For more information or insight on your individual scorecard, contact the author to discuss.

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.