



Scale-Up of Industrial Fermentation Processes

There are several reasons to scale-up a process and companies need to be focused on why and how in order to successfully complete a campaign and within budget

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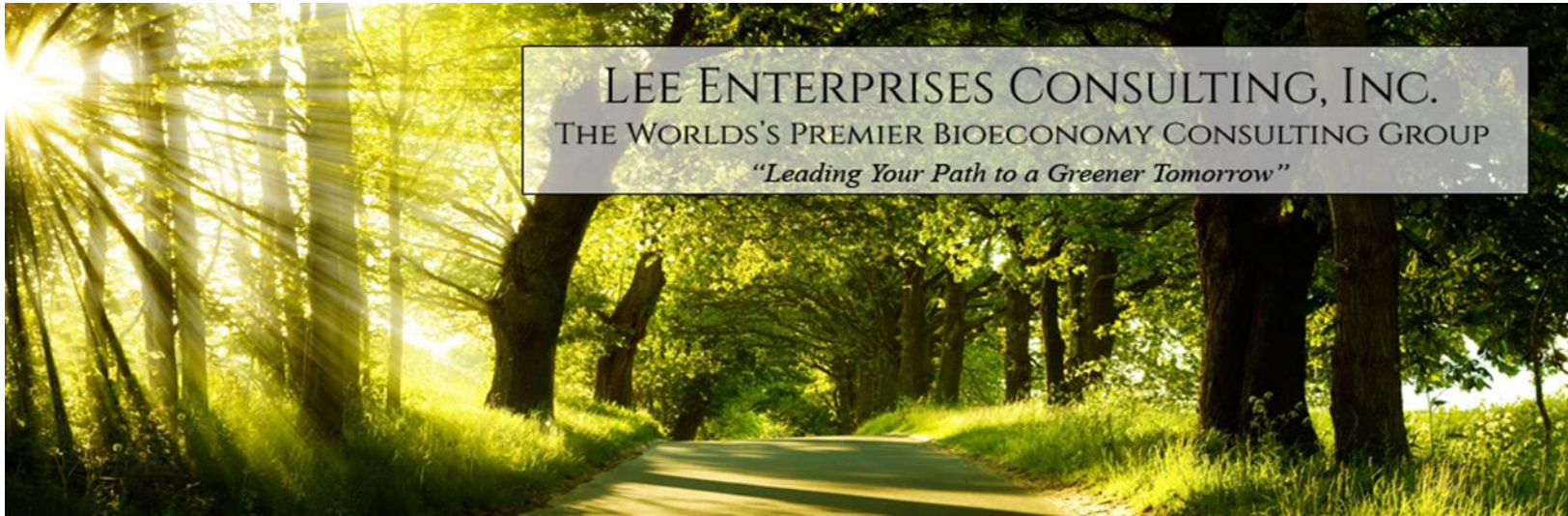
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Brett Schreyer is a PhD chemical engineer with nearly 20 years of experience in optimizing and successfully scaling up industrial biotech fermentation processes, managing piloting and production campaigns, modeling processes to design equipment and production facilities, and perform techno-economic analysis to drive decision making. Brett is an independent consultant and an accredited member of Lee Enterprises Consulting, a world leader in bioeconomy consulting services.



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Reasons to Scale-Up a Process

1. Demonstration: to prove the process runs nearly identical at a larger scale vs. what's been shown at lab scale
 - *Show your process works*
2. Piloting: to generate the data necessary to design a production facility
 - *Get the data to build your own plant*
3. Material: to generate material that meets product specifications
 - *Make product and sell it*



In Preparation for Scale-Up

- Prior to scaling up, test for scale sensitivities at bench scale, such as non-homogeneity (e.g. variations in pH, D.O., pCO₂, substrate concentration, etc.)
 - Time at scale is expensive, want to minimize surprises, trouble shooting, and lost batches
- Adjust media prep to make it amendable to large scale formulation and test in lab
- Prepare detailed tech transfer document that includes:
 - Description of entire process (seed train, when to harvest, purification, etc.)
 - Analytical protocols to measure product and key metabolites
 - Fermentation media recipe and how to prepare
 - Control setpoints, control bands (e.g. $T = 35.0^{\circ}\text{C} \pm 1.0^{\circ}\text{C}$), and preferred method of control
 - Average run data of best condition, include error bars to show variance ($n \geq 5$ replicates)
 - Data and information on process sensitivities (e.g. pH, D.O., temperature, feed rate, etc.) in case process varies from setpoint
 - Advice on how to respond to process excursions- where are the cliffs?
- Contract facilities need enough information to generate their own batch record/run sheet to replicate your process in their facility
 - Remember: you are the expert on your process, they are experts on their equipment

Scaling Up for Demonstration Purposes

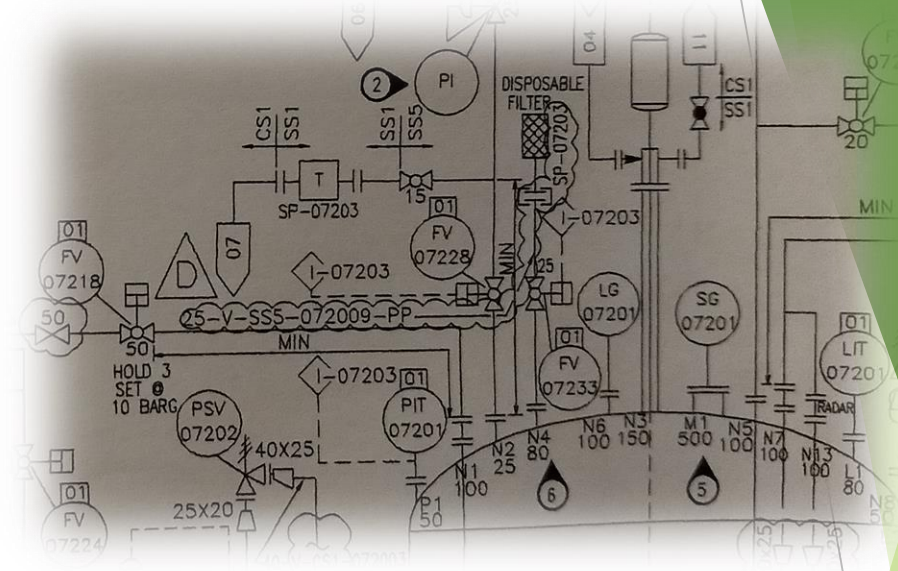
- Usually performed when a significant fermentation milestone is achieved in lab, but well before final production target is achieved (e.g. 50 - 75% of target fermentation titer or yield)
- For small companies with limited equipment resources (i.e. no access to pilot equipment), this is often the first time operating process at scale larger than 5 - 30L
- Importance of demonstration scale-up
 - Prove process works at larger scale, usually around 100x of lab scale (200 - 2000L fermenters)
 - Identify sensitivities to scale
 - For start-up companies, often a requirement of investors or used to solicit investor interest
- Fermentation
 - Test large-scale media prep process (prevent precipitation, add heat sensitive components, etc.)
 - Test and optimize seed train
 - What does success look like? For example, replication of titer and yield within $\pm 10\%$ of companies average results
- Downstream Processing
 - May only have limited proof of concept data from bench scale development
 - Wise to confirm purification process or test competing strategies at a pilot scale, e.g. use fermentation broth as test material for preliminary process development studies

Scaling Up for Demonstration Purposes (cont'd)

- At end of successful Demonstration campaign, have:
 - Data that shows nearly identical performance at bench and pilot scale and good reproducibility between at least 3 runs
 - Proof that fermentation process can be transferred to second party, replicated, and scaled up (which is not trivial!); independent verification is a big win
 - Information to drive further process development and scale-down studies for both fermentation and downstream processing
- Important to stay focused on demonstration goals
 - Do not assume you'll have large quantities of in-spec product at end of campaign (that is a different goal), especially if downstream process has never been run at a large scale
 - Do not use data to finalize process design decisions; at best it can point you in a reasonable direction
- Costs:
 - If using contract facility, costs dependent on fermenter size, type of facility, and length of campaign
 - For just fermentation in a 200 - 500L fermenter, a 3 run campaign can be in the \$40k - 100k range (costs increase with increase in fermenter size)
 - Including tech transfer and downstream process development, costs likely to be in the \$100k - 200k range or more (always get quotes for accurate budgeting)

Scaling Up for Piloting Process

- For a company that plans to build and operate its own fermentation facility to produce its bio-based product, then piloting is a necessity
- Goal of piloting: to generate data and answer design questions to accurately design and build a production facility; the product of piloting is data and information
- Prior to piloting need:
 - Flow sheet for production facility with all unit operations
 - Equipment identified for each unit operation, or at least narrowed down to a couple of options to be tested at pilot scale
 - Tech transfer document
 - List of questions to answer during piloting; for example:
 - How robust is fermentation at large scale? Are there process sensitivities in large fermenters?
 - What are the design and operating parameters for a micro-filtration system?
 - How does recycling influence unit operations, such as ion exchange or crystallization?
 - Which operation has the greatest influence on product recovery? On product quality?



Scaling Up for Piloting Process (cont'd)

- If a company is not going to build its own pilot facility, then it needs to find and evaluate contract piloting facilities
- Things to consider when evaluating pilot facilities
 - Rank facilities based on closest match to your process flow diagram: do they have most to all of the equipment you need? May have to rent or purchase equipment to fill in any gaps
 - How well can they simulate recycle streams?
 - Have they done this before? How experienced is the staff?
 - Can they commit to a long piloting campaign (at least several months)?
 - What will it cost?
 - Where are they located (closer is better)?
- Avoid distractions and stay focused on piloting goals
 - This is not a production campaign- do not assume you can sell product from a piloting campaign as much of it may be out of spec
 - At best any in-spec product from a piloting campaign can be given as samples to potential customers to garner interest (e.g. off-take agreements) for the production facility
 - Commandeering a pilot campaign to make significant quantities of in-spec material will either extend the time and cost of campaign or force engineering team to make design risks due to incomplete data from piloting

Scaling Up for Piloting Process (cont'd)

- At the end of a piloting campaign, you should have:
 - Complete mass and energy balance of entire process
 - Data and process information package for FEL-2 and FEL-3
 - Valuable experience to start-up and run new facility
- Costs for a piloting campaign
 - For a novel, 1st generation facility, costs can range from several hundred thousand to several million dollars to pilot a process (always get quotes for accurate budgeting)
 - Investing more time and money at lab and pilot scale will reduce costs and time during facility start-up where expenses will be much greater (don't be penny wise, pound foolish)
- Cost saving measures
 - Learn as much as you can from similar processes, focus on differences in piloting
 - *Don't assume purification will be nearly identical to that of a chemical process; a fermentation process generates unique impurities that need to be dealt with*
 - Experiment as much as you can in-house at lab scale to better focus efforts at pilot scale
 - *An in-house mini-plant (30-50L fermenter with matching DSP) can answer many process and design questions, shortening time at a larger pilot facility (but does NOT replace a piloting campaign)*
 - Prioritize piloting tasks (risk analysis)
 - What info is absolutely needed vs. nice to have
 - Everyone needs to agree on risks, accept them, and how to manage them

Scaling-Up to Make Product

- Two typical reasons for large scale production
 1. Seed the market: sell (or give samples) to interested customers and generate interest or off-take agreements to support building a fermentation production facility
 2. Make product and sell it for a profit: if product has relatively high value, small market, then may make economic sense to hire a CMO to produce your material
- Goal of production campaign is to make in-spec product for customers: you want to convince customers your product is equal to if not better than competitors
- Need tech transfer document with clear product specifications (don't forget packaging)
- Best to have previously scaled-up or piloted process, otherwise will have to spend longer time at CMO during tech transfer to dial in process
- CMO facility unlikely to be a perfect match to process (e.g. lower yield or recovery), but priority should be placed on facility being able to produce in-spec material for a reasonable cost
- Again, stay focused on goal of campaign- to make quality product
 - Some data may be applicable in designing production equipment and facility, but it does not substitute for a piloting campaign
 - Production campaign at CMO likely to be batch processing while 'build-to-design' facility will use more cost effective continuous processing, so piloting needs to match process

Scaling-Up to Make Product (cont'd)

- At the end of a production campaign, you should have:
 - In-spec product that meets or exceeds customer's expectations
 - Batch run data that can be used to improve the process, explain outliers, decrease lot variability, etc.
- Costs of a production campaign
 - Depends on size of fermenters/equipment, length of campaign, and type of facility
 - Price per batch increases with fermenter size, but production cost per unit mass product (\$/kg) decreases with fermenter size (economies of scale)
 - The more regulated the product, the more expensive the campaign (e.g. facility fees): food and nutraceuticals more expensive to produce than biofuels and commodity chemicals
 - Price per batch can start at around \$100,000 and quickly go up from there; always get quotes for accurate budgeting
- There is a product price point where a company breaks even when producing at a CMO
 - Above that point the company makes a profit, such as with high value, low volume chemicals (specialty chemicals, nutraceuticals, etc.)
 - *Company will have to decide if/when it makes sense to use CMOs or move to build, own, operate*
 - Below that point the company operates at a loss with a CMO, such as with low value, high volume chemicals (biofuels, commodity chemicals, etc.)
 - *Any production campaigns are usually used to seed market or fill a gap before a build, own, operate facility is up and running*

Expertise Required to Plan and Execute a Scale-Up Campaign

Need personnel with both technical and management experience

Technical

- Well versed in fermentation and purification operations and process development
- Know how to scale-up and scale-down
- Experience with large scale equipment and utilities
- Write/edit a thorough yet concise tech transfer document
- Review and edit CMO batch records/run sheets
- Evaluate contract facilities, how well they match process, determine if additional equipment will need to be rented or purchased, and gauge facility personnel expertise
- Examine and summarize data, troubleshoot/problem solve

Management

- Serve as technical representative when negotiating services contract
- Prepare budget for campaign
- Project management skills: plan logistics (purchasing and shipping of raw materials, product), scheduling, resource management, etc.
- Manage relationship and serve as conduit of information between company and CMO
- Actively manage and lead campaign and be first to respond to questions

To Successfully Scale-Up a Fermentation Process....

- Clearly define purpose of campaign and stay focused: campaign goal determines scale (fermenter size), type of facility, length of campaign, and costs
Avoid 2 for 1: trying to achieve two goals in one campaign can lead to competing interests, lack of quality in product and/or data, and not achieving goals
- Budget for the campaign as company expenses will increase significantly during scale-up activities
Be smart and prioritize scale-up tasks when deciding how to keep costs under control; use risk management when prioritizing, own the risks and plan for potential consequences
- Have expertise to lead campaigns so project is partnership with CMO and company is driving decisions vs. having a client/CMO relationship turn sour or having CMO making decisions
Don't want finger pointing between company and CMO; strong collaboration with CMO leads to success



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