FERMENTATION 3.0

Scale-up from Pilot to Commercial

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About Myself

30 years in advanced biotechnology and chemicals, focus on commercializing first of a kind technology

→ ***Currently*** – independent consultant assisting companies in commercializing advanced biotechnologies

→ ***Worked for leaders in the industry*** – Impossible Foods, Solazyme and Harris Group

→ ***Commercialized broad range of fermentation technologies*** - Aseptic, syngas and methane to fuels, foods and chemicals.

→ ***Based in Sacramento, CA***

Scale-up of Industrial Fermentation

There is no substitute for a fully integrated pilot process

→ Modeling is a good screening tool, but not a substitute for running fermentation in the selected equipment.

→ Commercial fermenters cannot be selected out of a catalog, they need to be designed ground-up for your organism.

→ Analyze pilot “failures” and understand them. You can learn faster and cheaper during scale-up from what doesn’t work.

→ Fermentation is not a static unit operation with consistent parameters, it is important to understand how they change during a run and the impact it has on facility design.

Facility Design

Understanding ***fit for purpose***

→ Pharmaceutical

High sterility fermentation, expectation of "clean batches". Represents high finish materials and significant capital cost.

→ Industrial Biotech

Uses pharmaceutical as a guide, but makes risk-based adjustment to fit the proposed purpose. Significantly lower cost than pharma approach.

→ Food

Focus on how to clean equipment and control certain "bad" organisms, not all organisms. Often very different than traditional biotech.

→ Traditional Ethanol

Very large fermenters with limited sterility considerations. Target organism out-competes most other organisms, gold standard for low cost fermentation.

Fermentation Scale-up Example

→ **Lab Fermenter** – purchased as package

→ **Commercial scale**, must determine:

- → Fermenter vessel (agitated, air-lift or bubble column)
- → Oxygen Transfer Rate (high OTR limits options)
- → Agitation (mechanical mixing or gas dispersion)
- → Cooling system (coil or jacket, dead zones, chilled)
- → Robust sterile design (polish, weld quality)
- → Clean in place approach (steam, chemicals, etc)
- → Organism control strategy (assuming GMO)

Ability to prove out alternate options at pilot scale is a challenge

Key Strategic Considerations

→ ***Start at the end and work backwards*** – determine a concept for a commercial plant and configure pilot to provide representative data.

→ ***Understand your feedstock*** – purity can vary dramatically and impact downstream processes. Trace contaminants can cause significant issues, especially downstream.

→ **Know what success looks like** – important to understand what final product specifications need to be met up front. Will save time, money and heartaches!

Understand Fermentation Key Criteria

→ Required oxygen transfer rate will often dictate the type of fermenter required.

→ Fermentation temperature may required chilled water, significant cost to consider in selecting organism.

→ Impurities are not generally inert. They need to be quantified and disposition known.

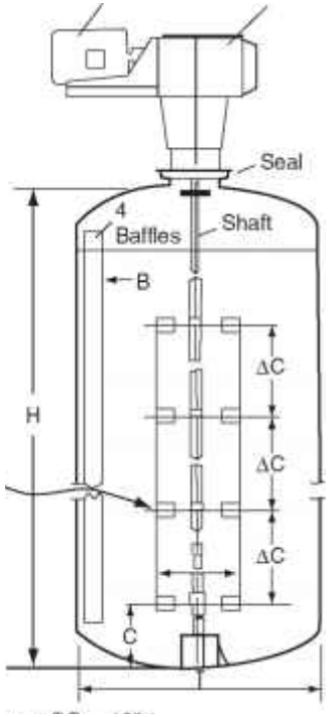
→ Inherent sterility of process – is it favorable towards contamination and what are your product requirements?

At commercial scale, you will be forced to cut your list of wants down to only must have items

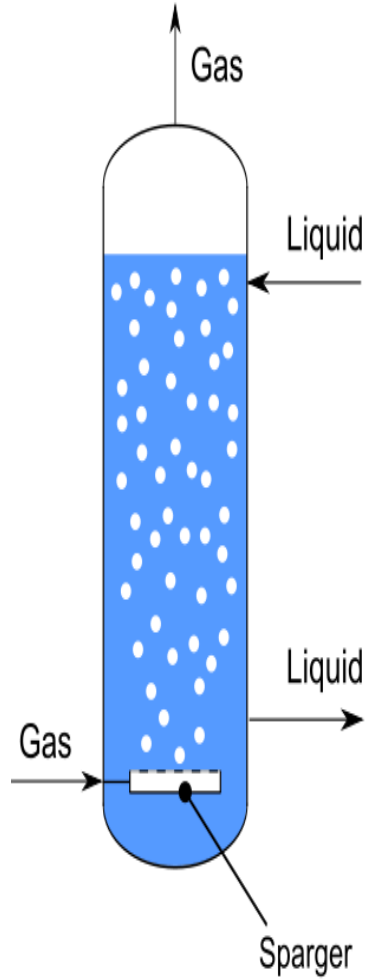
So, What is Really the Difference?

Criteria	Aseptic Fermentation	Corn Ethanol
Fermenter Pressure	30 – 50 PSI	Atmospheric
Typical Commercial Size	500,000 liters	1,000,000 gallons
Cooling Configuration	Internal Coils/External Exch.	External Heat Exchanger
Air Requirement	Sterile Air	None (anaerobic)
Mixing	High Shear Agitation	Low Shear Mixing
Surface Finish	Mid to High Polish	Standard Mill Finish
Sterile Boundary	Robust, Heat and Filtration	Limited
Cleaning/Sterility	Clean then Steam in Place	Clean in Place
Typical System Cost	$6M - $10M	$5M - $7M
Typical Cost per Installed Liter	$16	$1.6

Fermenter Configuration



AGITATED	PARAMETER	BUBBLE COLUMN
~3:1	**Aspect ratio**	~7:1
Mechanical agitation	**Mixing**	Bubble lift and/or pump around
• Higher OTR and/or viscosity • Liquid based carbon sources • High cell conc.	**Best Fit**	• Lower OTR and/or viscosity • Better for gas-based processes • Lower cell conc.
• Higher capital cost • Smaller max. size • Onsite fermentation	**Key Notes**	• Lower capital cost • Larger fermenters • Offsite fabrication



Agitation and Mechanical Power

→ OTR is more than mixing power, influenced by viscosity, cell density, pressure, heat removal, etc.

→ Benchmark used to compare mixing options is horsepower per unit of fermentation volume, from all sources.

→ Mixing configuration can be quite complex and more than just power, blade design and configuration (Rushton vs propeller).

→ Mechanical agitation has significant impact on fermenter design, needs to be understood up front.

Can it really use that much power?

→ **YES!**

→ Often a surprise with aerobic fermentation and key consideration for plant location.

→ Major uses are in fermentation (agitation, air compressors, chillers, etc.)

→ Agitated fermenter and bubble columns use lots of power, just in different areas.

Flammable Gas Feedstocks

→ Syngas and methane are common feedstocks that present different challenges than typical aseptic fermentation

→ Safety is a key driver, exponentially more significant if it is an aerobic fermentation

→ Sterility concerns are typically less for gasses

→ Methane fermentation has very high heat removal rates, major design consideration

→ Syngas supply consistency and CO/H_2 ratio important

Sterile Design Considerations

→ Meeting required process sterility is critical, but comes at a capital and operating cost, needs to be optimized

→ Need for steam in place (SIP) can impact fermenter design, but come “free” if pressure rating is in the 50 psi range

→ External pump around cooling is more cost effective, but can presents a challenge for high sterility if not properly designed

→ Surface finish can be hard to determine and costly for high polish on commercial size fermenters

Scale-Up Considerations…

- → Pilot and demo facilities are not just for gathering data to scale-up the process, they fill the need for generating samples.
- → Ability to produce “real” quantities of your product is important to developing markets, often ends up being highest need.
- → Inherent conflict between using a pilot plant for process development and making representative samples.
  - → When developing your process, making change is necessary and failure at times is an expected outcome.
  - → If you have a requirement for product, you want to operate at proven conditions with predictable outcomes.

Relevant Articles in the Digest

→ *Scaling-up Through Contract Manufacturing*

→ *Take the Test – Evaluating Commercial Readiness*

→ *Strategic Approach to Scale-up*

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