Successful Scale-up of Industrial Fermentations: Process Development, Engineering and Economics

by

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Key Factors for Bioprocess Technology Selection, Scale-up and Engineering of New Facilities

- Biocatalyst
- Raw Materials
- Process Technologies
- Products
- Scale
- Economics

Success is through
Early Integration of
Process Development, Engineering & Economics
From R&D to Commercial Manufacturing Facility
Key Project Phases – Operations & Engineering perspectives

R&D

Technology Transfer (Scale-up)

Conceptual Design

Detailed Engineering

Marketing Study

Feasibility Study

Construction

Qualification Masterplan, Commissioning

Start-up

• Cost estimate
• Decision on project

Commercial Mfg.

Cost Impact of Key Engineering Project Phases

Key Success Factor:

Typical BioProcess Block Flow Diagram
Basis for Facility Concept Design

Media Prep / Sterilization Solutions Prep/Storage

Fermentation or Bioconversion

Recovery & Purification

Bio / Microbial Labs.

Utilities:
- Process Water
- Steam
- Cooling Water
- Chilled Water
- Compressed Air
- Electrical
- HVAC
- Waste Systems

Warehouse:
- Raw Materials
- Product

Finishing

BioProcess Design Basis & Scale-up - Upstream
Fermentation & Bioreactor Critical Design Parameters

**Biological & Chemical**
- Culture type
- Containment
- Operating and Optimal ranges for:
  - pH, Temperature
  - Foam type & control
  - Shear, Viscosity
  - DO₂, CO₂, Pressure

**Process Engineering**
- Process type (batch, continuous, fed-batch)
- Oxygen Transfer Rate (OTR)
- Heat Transfer
- Bioreactor type & Scale-up
- Instrumentation & Controls
- Sterile/ rDNA Design, MOC
- Media Prep./ Sterilization
- CIP & Waste systems
Typical Bioreactor Designs

- STRs
- JLR
- BC
- Bioconversion reactors

Microbial Cultures in Submerged Fermentation Systems

Cultures or Biocatalysts in Immobilized Systems

Bioreactor Design Selection – Industrial Realities

Biocatalyst, Process KPI & Scale: All Inter-related

Industrial-scale Limitations

Microbial Cultures
- Bacteria
- Yeast
- Fungal

Maximum Fermentor Size vs. Major KPI: OURmax

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### Commercial Fermentation Scale-up Challenges & Options

#### Case study of BC

- **Scale-up Challenges**
  - Mixing effects on Metabolism & Productivity:
    - Pressure
    - Gradients/oscillations-Gas: \(O_2, CO_2\)
    - Grad/oscil- Liq: Glucose, NH3, pH
  - Temperature Control

- **Risk Management & Solutions**
  - Scaled-Down tests at Lab/Pilot
  - Simulate Micro/biology & Macro/Eng’ng.
  - FMEA, 6-Sigma approaches

#### Fermentation Facility Definition: Risks & Economics

##### Selection of Bioreactor Design, Size & Quantities

<table>
<thead>
<tr>
<th>Design &amp; Economic Selection between:</th>
<th>Industrial-scale Limitations</th>
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<tbody>
<tr>
<td>• 1 X 400 m³ ……. $</td>
<td>OURmax (mM/l.hr) vs. Major KPI: OURmax</td>
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<tr>
<td>• 2 x 200 m³ ……. $$</td>
<td>Maximum Fermentor Size</td>
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<td>Risks (KPI, $)</td>
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<td>Vm (m³)</td>
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- **Technology Risks (BRX)**
  - Scale-up risks
  - Operational flexibility, utilities
  - Costs: CAPEX, OPEX

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### BioPrizM
Which Key Performance Indicators (KPI’s) to select?

- High Cell Density, Maximum Fermentation Titer?
  .... *Not Always! Don’t disregard industrial limitations!*

- Yield of Feedstock Bioconversion can be a major KPI for Cost of Goods Sold (COGs), but impact can change with Product, Technology & Scale
BioProcess Modeling is Key for Economic Optimizations

- Modeling and Cost Sensitivity Analysis:
  Need Simulation by Professionals Experienced in Real Commercial Scenarios for Reliable Estimation of Facility CAPEX & OPEX

- Industrial Process Modeling is a major Guide for R&D and Project Objectives... i.e. What to Focus on?
Process & Project Engineering, Economics and Strategy

**COGS vs. Capacity, Media Costs, Titer**

- **COGS vs. Capacity at Various Titers & Media Costs**
- **COGS vs. Titers at Various Capacities**

- Economic analysis defines “Critical” or Minimum **Capacity** or **Titer** for Optimum COGS

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**Process & Project Engineering, Economics and Strategy**

**Costs vs. Scale. Product impact on COGS Distribution**

- COGS decreases with increased Capacity or Scale.
- **CAPEX** % of COGS changes with Scale, Technology & Product

**Product-type impact**

- **Raw Materials** cost % of COGS in Industrial Biotech is **More** than for BioPharma
- **CAPEX** % of COGS in Industrial Biotech is **Less** than BioPharma.
Conclusions
BioProcess Commercialization: Success factors

- **Integrate, early on**, R&D, Engineering and Manufacturing **Teams**
- Assess each Bioprocess option from an **Integrated industrial** view
- Select optimal option based on **Scale-up** reliability & economics
- Use **Modeling** to evaluate each Bioprocess impact on **Facility** Design, Utilities & Costs
- Perform a **Conceptual Design** with preliminary CAPEX and OPEX

THANK YOU!

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