Fundamentals of BioProcess Scale-Up

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LEE ENTERPRISES CONSULTING, INC.

About Lee Enterprises Consulting

◆ *SEASONED, INDEPENDENT, PROFESSIONAL EXPERTISE* ◆

- **OUR TEAM:** We are the world's largest bio consulting group with over 100 subject matter experts.
- **OUR PROJECTS:** Our members have completed thousands of projects in anaerobic digestion, biofuels, biomaterials, chemicals, DSP, feedstocks, fermentation, gasification, pyrolysis, synthetic biology, and water/ wastewater treatment.
- **OUR ADVANTAGE:** We provide independent third party expertise that provides cost-effective, interdisciplinary teams with a single point of client contact without hiring additional full-time employees.
- **OUR CLIENTS:** Our clients include biofuels companies, biochemical companies, investors, banks, entrepreneurs, plant owners, law firms, biotechnology providers, energy companies, and engineering firms.

Gulf Oil Corporation
Jayhawk Works, KS - 1976

Scale-Up is a Complex Process

If its thicker than ketchup –

- It might not mix too well.

The Challenge of BioProcess Scale-Up

- Scale-Up is the practice of increasing the size and scope of a specific process
  - Fermentation is often the focus in a bioprocess, but scale-up involves all process unit operations
- It is Different
- It Requires a Different Set of Expertise
- It is Larger Scale
  - Don't Ignore Standard Scaling Rules to the Small Side
  - Size Has Its Advantages, BUT It Also Has Its Challenges
- It is Expensive
  - So Is Failure

Why Do Scale-Up Do?

- Defines Known Risks
- Identifies Potential Risks and Impact
- Defines/Recommends Risk Mitigation Options
- Creates Dialogue of Shared Goals of Stakeholders
- Validates Project Readiness Level and Risk
- Satisfies Investor/Lender Requirements

Risk Mitigation

- **Determine your greatest risks**
  - Product Market?
  - Product Efficacy?
  - Process Scale?
  - Equipment Scale?
  - IP Strategy?
  - Regulatory Approval?
  - Financing?
- **Get Good Advice**
  - Internal
  - External
- **Prepare**
  - Expect the Unexpected
  - Make Contingency Plans
  - It will take longer than you think
  - It will cost more than you think

What Is Scale-Up Risk?
The 1,000:1 Cost Rule

- Assume the cost of correcting a mistake at **Conceptual Design** is **$10,000**
- Then expect the cost of correction will be:
  - **$100,000** if corrected during **Detailed Design**
  - **$1,000,000** if corrected during **Construction**
  - **$10,000,000** if corrected after **Operation has begun**
  - **$???????** if it **Fails to Operate**

Catch Problems EARLY!

Why Scale-Up a Process?

- Demonstrate technical operations
  - Production
  - Recycle
  - Waste
  - Logistics
- Demonstrate environmental compliance
- Demonstrate production targets and specifications
- Develop equipment specification data
- Solidify intellectual property
- Confirm financial projections
- Reduce technical risk for future commercial scale operations
  - ***This is not an exercise that is done for fun***

What Are You Trying to Achieve?

- Prove (Predict) That Your Process Can Run As Expected At Commercial Scale
- Assess The Risks For Full Commercial Scale Operations

The Technology Development Pipeline

- Basic Research
- Applied Research
- Technology Development
  - Piloting – Scale Up
  - Integrated Operations
- Commercial Development
- Commercial Operations

Fermentation Scale Definitions

- Definitions are not used consistently within a specific industry, or even more so, across different industries
  - Bench scale: Less than 10L
  - Pilot Development Unit (PDU): 200 – 300 Gallons
  - Integrated Pilot: Thousands of Gallons
  - Demonstration: Tens of Thousands of Gallons
  - Integrated Demonstration: 1/10 Commercial Scale
- Volume, Throughput, Types of Equipment, etc. are all used to differentiate needs

Technology Readiness Level

- **9 Levels of Technology Readiness** (Humbird)
  - Basic Research/Elevator Pitch
  - Applied Research/Business Plan
  - Proof of Concept/Value Proposition
  - Minimum Viable Process (MVP)
  - Integrated Validation of MVP
  - Integrated Pilot Operations
  - Fully Integrated Continuous Pilot Operations
  - Precommercial Demonstration Operations
  - Full Scale Commercial Operations
- ***Where are you?***

"Begin with the End in Mind"

Stephen Covey: 7 Habits of Highly Effective People

- What does the commercial scale look like?
  - What are the unit operations?
  - What commercial type equipment is needed?
    - Feedstock Handling
    - Pumps/Valves/Conveyors
    - Reactors
    - Separation/Purification
    - Dewatering/Drying/Packaging
    - Waste Handling/Disposal
    - Automation
    - Environmental/Safety Features
- What Regulatory/Environmental Permits are Required?
- What Safety Features and Training are Needed?
- What commercial type inputs are required and available?
  - Water Quality
  - Feedstock Quality
  - Chemicals

What Are You Trying to Achieve?

- Do your homework
- Develop a Commercially Compatible Process
  - As Early as Possible
  - Basic and Applied Research Level
- What does that mean?
- Define what a successful commercial process looks like
  - Not what you think it looks like . . . .
  - What do successful existing commercial processes look like
  - Don’t guess – this is important!

Get Good Advice

- Get Advice Early
- Internal Advice
  - Large vs Small vs Start-Up Company
  - Do you ***really*** have the full range of experiential expertise?
    - Theory is nice, but does it match with real world operations?
    - Successful Scale-Up/Commercial Experience
  - What are your weaknesses?
- External Advice
  - Fill Knowledge Gaps
  - Fill Experience Gaps
  - Provide an Alternative/Independent Perspective
    - Have you missed the forest for the trees?
    - Is there a different approach?
  - May provide synergistic value

Ask Some Basic Questions

- What is the Commercial Scale for Your Fermentation Technology?
  - 100 gallons
  - 1,000 gallons
  - 30,000 gallons
  - 500,000 gallons
- Is Your Fermentation Aerobic or Anaerobic?
  - What Kind of Agitation Strategy Do You Need?
  - What Degree of Aeration Do You Need?
    - What can you afford?
- What Is Your Down Stream Process?
  - Distillation
  - Filtration
  - Centrifugation

How Should I Prepare?

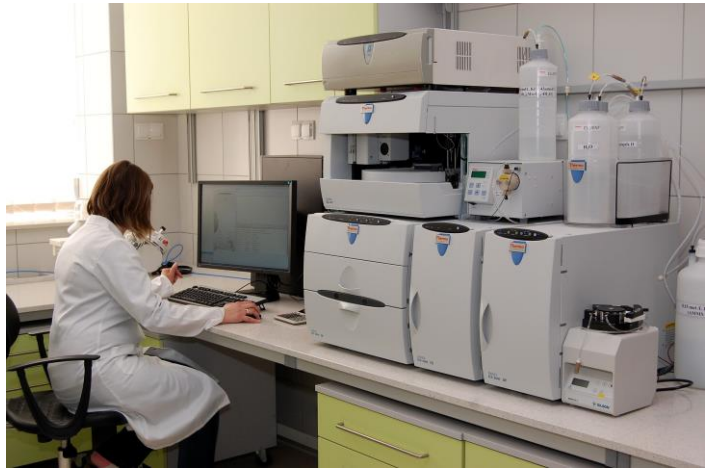
- Determine what requires piloting and what scale of operation is relevant?
- Are integrated operations necessary?
- Develop and Understand your TechnoEconomic Assessment (TEA) Model
- Conduct sensitivity analyses of key operations
- Prepare a technology transfer package
  - Defining what you don't know is as important as what you do know
- Understand and reflect risk in the budget
  - Contingency planning
- Identify the changes needed to achieve scale-up
- Pick a suitable location for piloting
  - Internal vs External
- Be diligent in training and documentation

How Do These Factors Impact Scale-Up?

- What are my Greatest Barriers to Successful Commercialization?
- What Scale of Operations Will Answer my Key Questions to Reduce Risk?
  - Large Enough to Use All Commercial Type Equipment for your Process
  - Large Enough to Generate Key Experimental Samples and Data
- Find Experienced Personnel
- Get Extensive Data
- This is EXPENSIVE
- Don’t Repeat Unnecessarily

Develop Key Data

- Get the Right Data
  - Technical Data
  - Financial Data
- Get Data, Get Lots of Data
  - Over Sample
  - Over Instrument
  - Analyze
  - Make Data-Driven Decisions
- Fill Gaps
- Confirm Results At All Scales
  - Is the process repeatably reliable?
  - How robust is the process?
    - Can it survive process upsets?

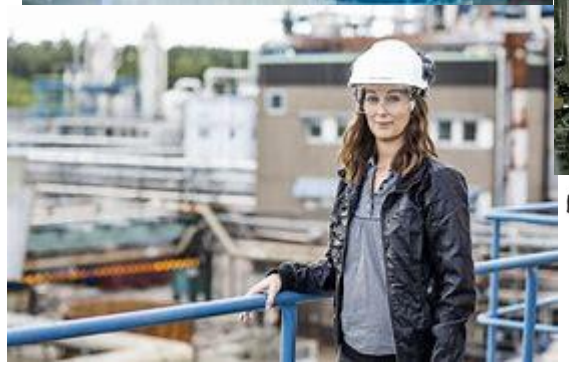


Make Data Driven Decisions

- Ask/Answer the Right Questions Early
  - Technical
  - Financial
- Identify Minimum Performance Targets
- Establish Preliminary TEA Model
- Establish Realistic Timeline – Avoid Shortcuts
- Establish Fully Integrated Performance Runs
- Conduct Mandatory Stage-Gate Reviews
- Avoid Emotional Decisions

Who Is On Your Team?

- **Experienced: Been There, Done That**
  - Most have conducted Discovery and Early Applied R&D
  - Fewer have conducted Commercially-Focused PDU scale development
  - Fewer yet have conducted large fully integrated pilot/demo development
  - Even fewer have run commercial operations
- **Internal**
  - Technical
  - Business
- **External**
  - Fill the Gaps
  - Independent Third Parties



The Integrated Pilot Plant

- How Big is Big Enough?
  - Integrate ALL Unit Operations
- Avoid Shortcuts
- Build/Operate
  - Self-Perform
  - Do you have proven expertise?
    - Design
    - Procurement
    - Construction
    - Operation
- Pilot Plant Service Provider
  - What Unit Operations are Missing?
    - Can they be added at the needed scale?
  - Do they have the proven expertise?
    - Yes/No
    - Do you have the missing expertise?
- Complete 1,000-Hour Integrated Campaigns
  - Did They Meet Expectations?
  - Why/Why Not?
  - Were There Operational Hiccups?
  - Are They Show Stoppers?

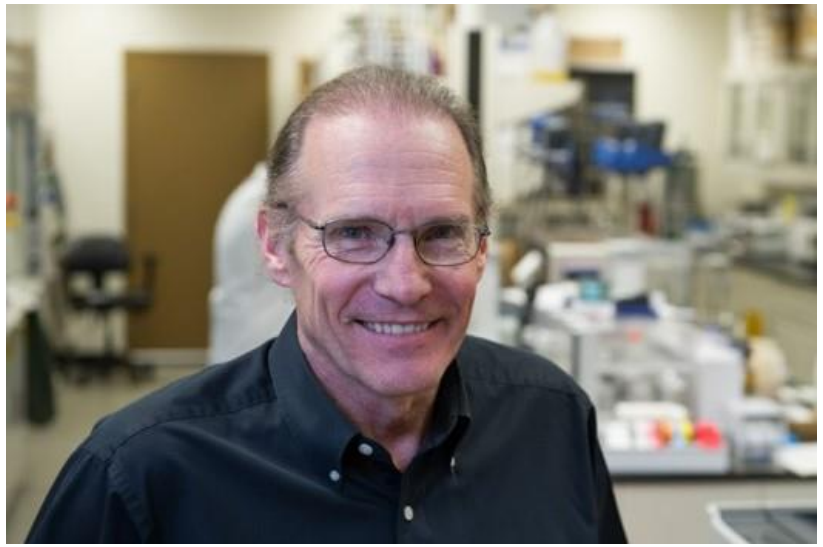
Do You Need a Demonstration Plant?

- What is the scale ratio from integrated pilot plant to commercial?
- What Unit Operations are Unproven at 1/10 Commercial Scale?
- Can a Demo Plant Have Commercial Applications?
- What is your tolerance for risk?

Conclusions

- “Begin with the End in Mind”
- Get Good Advice – Internal and External
- Expect and Prepare for the Unexpected
- Make Data-Driven, NOT Emotional Decisions
- Establish a Fully Integrated Pilot Plant with Commercial Size Components
- Scale-Up Shortcuts are often Illusions of the Solutions They Pretend To Be
- Conduct Successful, 1,000-Hour (minimum), Fully Integrated Performance Runs
- Demonstrate Unproven Unit Operations at 1/10 Scale of Minimum Commercial Scale

Thank You!



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Accredited Member

LEE ENTERPRISES CONSULTING, INC.

Background: 40+ years senior/executive experience in fermentation, bioprocess technology development, scale-up, and commercialization, technology due diligence, business development, and expert witness services

Consulting/advisory services to developers, companies, and investors in the US and internationally