Economics of Fermentation Process

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Factors Affecting Cost

- Relatively high efficiency, coupled with availability and cost of raw materials, allows use of biological systems to produce needed chemical products.
- Prior to commercialization of a fermentation process, extensive economic evaluation is necessary.
- The capital and gross operating cost of a conventional fermentation plant is roughly independent of the product produced.
- The fermentation operating costs per unit volume and per unit time will vary somewhat but will hold generally within a reasonably narrow range.
- Barring use of an exotic raw material, the cost of labor, utilities, and materials would not vary greatly if put on a unit volume and unit cycle time basis.
- Also, processing or extraction can vary in complexity but, by and large, they too will hold to a reasonably narrow cost range.
- Thus, the unit cost of the bulk product is much a function of fermentation yield and fermentation cycle time.
- It is necessary to estimate the size of the present and potential market and the increase in demand for a compound.

Basic objectives of Economically Viable Successful Industrial Process

- The capital investment in the fermenter and ancillary equipment should be confined to a minimum, provided that the equipment is reliable.
- Raw materials should be as cheap as possible and utilized efficiently.
- A search for possible alternative materials might be made, even when a process is operational.
- The highest-yielding strain of micro-organism or animal cell culture should be used.
- There should be a saving in labour whenever possible and automation should be used where it is feasible.
- When a batch process is operated, the growth cycle should be as short as possible to obtain the highest yield of product and allow for maximum utilization of equipment.
- To achieve this objective it may be possible to use fed-batch culture.
- Recovery and purification procedures should be as simple and rapid as possible.
- The effluent discharge should be kept to a minimum.
- Heat and power should be used efficiently.
- Space requirements should be kept to a minimum, but there should be some allowance for potential expansion in production capacity.
- All the above must comply with safety guidelines and regulations.

General Cost Considerations

- In any process, it is important to understand the cost breakdown, to determine where the largest potential savings lie.
- General cost considerations can be grouped as follows:
  - Equipment;
  - maintenance of asepsis;
  - aeration;
  - conversion efficiencies;
  - volumetric productivity;
  - utilities; raw materials and media;
  - and other factors, including temperature, dissolved oxygen tension, foaming, instrument purchase and installation, and microprocessor control of feed-back loops

Preliminary economic evaluation

- The preliminary economic evaluation of a project for manufacturing a biological product usually involves the estimation of:
  - capital investment,
  - estimation of operating costs, and
  - analysis of profitability

Capital Cost Estimation

- The capital investment for a new plant includes three main items:

  1) direct fixed capital (DFC),

  2) working capital, and

  3) startup and validation cost
- The DFC for small biotechnology facilities is usually in the range of $30 to 60 million, whereas for large facilities it is in the range of $100 to 250 million.
- Building costs estimate: the process area required based on the footprint of the equipment and the space required around the equipment for safe and efficient operation and maintenance.
- The area of the various sections (e.g., process, laboratory, office, etc.
- Power requirements of heating, ventilation, and air conditioning (HVAC) systems.

Fixed Capital Cost Estimation.

COST ITEM
TOTAL PLANT DIRECT COST (TPDC)
1. Equipment Purchase Cost (PC)
2. Installation
3. Process Piping
4. Instrumentation
5. Insulation
6. Electrical
7. Buildings
8. Yard Improvement
9. Auxiliary Facilities
TOTAL PLANT INDIRECT COST (TPIC)
10. Engineering
11. Construction
TOTAL PLANT COST (TPC)
12. Contractor's fee
13. Contingency
DIRECT FIXED CAPITAL (DFC)

Operating Cost Estimation

- The operating cost to run a biochemical plant is the sum of all expenses associated with raw materials, labor, utilities, waste disposal, overhead, etc.

Operating cost items and ranges.

COST ITEM	Type Of Cost	Range of values (% of total)
A. Raw Materials	Direct	10-80
B. Labor	Direct	20-50
C. Consumables	Direct	1-50
D. Lab/QC/QA	Direct	2-50
E. Waste Disposal	Direct	1-20
F. Utilities	Direct	1-30
G. Equipment-Dependent	Indirect	10-70
H. Miscellaneous	Indirect	0-20

Raw Materials

- This accounts for the cost of all fermentation media, recovery chemicals, and cleaning materials.
- For commodity biochemicals, such as ethanol, it is mainly the cost of fermentation media.
- For high value products, the buffers used for product recovery and equipment cleaning can be a major part of the materials cost.

Media composition

- The cost of the various components of a production medium can have a profound effect on the overall cost of a fermentation process, since these account for 38 to 73% of the total production cost.
- The organic-carbon source in microbial processes is usually the most expensive component contributing to the cost of the process.
- The price of a natural material may fluctuate due to other competing demands and the annual variation in the quantity harvested.
- Big capital investment may be tied up in natural materials if they are seasonal and require storage. (A particular material may be selected because it is cheap locally, rather than the best substrate).
- A variety of waste materials would seem to be potential cheap carbon sources.
- Unfortunately, it has been shown that their use is very restricted because they cannot compete economically with conventional substrates.
- This may be due to a number of possible reasons including variability of the material, impurities which make downstream processing more difficult, high water content making transport costly, geographical location, quantities produced and limited seasonal availability.
- Problems concerned with the storage, handling and mixing of media should not be neglected.

Labor

- This is estimated based on the total number of operators, which in turn is calculated by summing up the operator requirements of the various operations as a function of time.
- In a single product facility, the number of operators in each shift must be based on maximum demand during that shift.
- In multi-product facilities, each product line can employ a certain number of dedicated operators and utilize floating operators during periods of peak demand.
- In general, smaller facilities tend to utilize a larger number of operators per processing step because they are less automated.
- In general, a typical biotech company that deals with high-value products will allocate at least one operator to each processing step, such as centrifugation, membrane filtration, chromatography, etc. during its operation.
- The setup of a step may require multiple operators for a short period.

Consumables

- This includes the cost of periodically replacing items that may be used up, fouled, or otherwise damaged during processing, such as membranes, chromatography resins, activated carbon, etc.
- The high unit cost of chromatography resins and their frequent replacement can make this item a major component of the operating cost.

Laboratory / QC / QA

- This accounts for the cost of off-line analysis, quality control (QC), and quality assurance (QA) costs.
- Chemical and biochemical analysis and physical property characterization, from raw materials to final product, are a vital part of biochemical operations.
- This cost is usually 10-20% of the operating labor cost.
- However, for certain biopharmaceuticals that require a large number of very expensive assays, this cost can be as high as the operating labor.
- For such cases, it is important to account for the number and frequency of the various assays in detail.

Waste Treatment / Disposal

- Many fermentations have a high daily water usage.
- The waste is incinerated, dumped on waste land, or discharged to sewers, rivers or tidal waters, some expenditure will be necessary for treatment that ensures that minimal harm is done to the environment.
- Treatment of low biological oxygen demand (BOD) wastewater (less than 1,000 mg/L) by a municipal wastewater treatment facility usually costs $0.2-0.5/m3 .
- This is not a major expense for most biotech facilities that deal with high value products.
- Disposal, however, of contaminated solvents (generated by chromatography steps) and other regulated compounds can become a major expense because their unit disposal cost is in the range of $2-20/kg (usually higher that the purchase price of the same chemical).
- Waste disposal may also become a problem if an unwanted by-product is generated as part of the recovery chemistry of a process.

Utilities

- This accounts for heating and cooling utilities as well as electricity.
- Aerobic fermentors are major consumers of electricity but downstream processing equipment generally does not consume much electricity.
- Heat should be conserved and cooling minimized by careful process design.
- A fermentation may include the following heating or cooling stages:
  - Sterilization or boiling of the medium to 100° or above followed by cooling to 35° or below.
  - Heating the fermenter and ancillary equipment to sterilize it, followed by cooling.
  - Heat may be generated during the fermentation. This heat output has to be removed by cooling to maintain the growth temperature of the microorganism within prescribed limits.
  - After harvesting, heat may be required to remove water from the product.
- In downstream processing, clean steam is mainly used for sterilizing equipment as part of equipment cleaning.
- Note that purified water used for buffer preparation and equipment cleaning is often classified as a utility and not as a raw material, thus increasing the cost contribution of utilities.

Equipment-Dependent

- This cost accounts for the depreciation of the fixed capital investment, maintenance of equipment, insurance, local (property) taxes and possibly other overhead-type expenses.
- For preliminary cost estimates, the entire fixed capital investment is usually depreciated linearly over a 10-year period.
- In the real world, the government allows corporations to depreciate equipment in 5-7 years and buildings in 25-30.
- Land is never depreciated.
- The annual equipment maintenance cost can be estimated as a percentage of the equipment's purchase cost (usually 10%).
- A value for insurance in the range of 0.5-1% of DFC is appropriate for most bioprocessing facilities.
- The processing of flammable, explosive, or dangerously toxic materials usually results in higher insurance rates.
- The local (property) tax is usually 2-5% of DFC.
- The factory expense represents overhead cost incurred by the operation of non-process-oriented facilities and organizations, such as accounting, payroll, fire protection, security, cafeteria, etc.
- A value of 5-10% of DFC is appropriate for these costs.

Miscellaneous

- This accounts for on-going R&D, process validation and other overhead type expenses.
- Expenses of this type can be ignored in preliminary cost estimates.
- Other general expenses of a corporation include royalties, advertising, and selling.
- If any part of the process or any equipment used in the process is covered by a patent not assigned to the corporation undertaking the new project, permission to use the teachings of the patent must be negotiated, and some form of royalties is usually required.

Profitability Analysis

- With estimates of capital investment, operating cost, and revenues of a project, one can proceed to assess its profitability and attractiveness from an investment point of view.
- There are various measures for assessing profitability.
- The simplest ones include gross margin, return on investment (ROI), and payback time and they are calculated using the following equations:

$$\text{Gross Margin} = \frac{\text{Gross Profit}}{\text{Revenues}}$$

$$\text{Return on Investment (ROI)} = \frac{\text{Net Profit}}{\text{Total Investment}} \text{ x } 100\ \%$$

$$\text{Payback Time (in years)} = \frac{\text{Total Investment}}{\text{Net Profit}}$$

- Where, gross profit is equal to annual revenues minus the annual operating cost and net profit is equal to gross profit minus income taxes plus depreciation. All variables are averaged over the lifetime of a project.

Recovery Cost

- The costs of product recovery and purification are rarely quoted, though in some processes they are obviously considerable.
- Fermentation: purification cost is 1:1 and with recombinants 1:10.
- This means that the fermentation may only be 10% of the costs, while the recovery accounts for 90%.
- The correct choice of the recovery-purification procedure can be crucial.
- Following factors contributes in cost escalation of the process:
  - Yield losses, even if only modest, are certain to occur at each stage of the recovery process.
  - High energy and maintenance costs associated with running filtration and centrifugation equipment.
  - High costs of solvents and other raw materials used in recovery and refining of products.

Questions

- Discuss economics aspects of any fermentation industry.
- What factors affect the economic status of fermentation processes?
- What are the general cost considerations of fermentation industry? How economics of a fermentation process can be assessed?
- Evaluate the economics of a fermentation process.
- Evaluate the product recovery cost.