Fermentation Economics

A number of basic objectives are commonly used in developing a successful process which will be economically viable.

- The capital investment in the fermenter and ancillary equipment should be confined to a minimum, provided that the equipment is reliable and may be used in a range of fermentation processes.
- 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.

Three key economic objectives in the fermentation stage:

1. **Maximum product yield**
2. **Process productivity**
3. **Substrate utilization**

The demands of subsequent purification stages for high product concentration and high product purity with safety considerations.

Four basic components contributed to the process cost in the following decreasing order:

Raw materials > Fixed costs > Utilities > Labour.

ISOLATION OF MICRO-ORGANISMS OF Potential INDUSTRIAL INTEREST

Important factors which will be of economic significance includes:

1. **Growth on a simple cheap medium.**
2. **Growth at a higher temperature (to reduce cooling costs).**
3. **Better resistance to contamination.(Easy containment)**

The 'designed' isolation media are now being used extensively for the isolation of novel and rare microorganisms.

It has become a common practice to obtain isolates from unusual habitats, which may include extreme environments, to ensure that the greatest microbial diversity is being examined

STRAIN IMPROVEMENT

- Strain improvement using a mutation/selection programme for improving an organism is a potential process which can be very cost effective.

- The mutation programmes significantly increased the penicillin yields from less than 100 units cm^{-3} in the 1940s to over 51,000 units cm^{-3} by 1976 and a four-fold increase in yields between 1970 and 1985.

TABLE 3.5. *Improvement of antibiotic yields during the first 20 years of antibiotic development (Riviere, 1977)*

Antibiotic	Initial yield at time of discovery (units cm^{-3})	Improved yield in France, 1972 (units cm^{-3})
Penicillin	20 (1943)	12,000–15,000
Steptomycin	50 (1945)	12,000–15,000
Chlortetracycline	200 (1948)	12,000–15,000
Erythromycin	100 (1955)	3000

TABLE 12.2. *Criteria for strain improvement* (Schwab, 1988)

Target	Impact on process or product
Improvement of titre and/or specific production rate	General decrease of production costs, improved exploitation of reactor capacity, lower investment costs, increased efficiency in downstream processing steps
Improvement of yield	Lower costs for substrates, decreased production of heat and CO_2, lower cooling costs, less waste and pollution
Change in catabolic capabilities	Use of more favourable substrates (less expensive, better availability, etc.), omission of pretreatment steps (e.g. enzymatic hydrolysis of polysaccharides).
Improvement of technological features of micro-organisms (e.g. flocculation behaviour, structure of mycelium, sporulation, foaming, strain stability, etc.)	Less energy costs for mixing and oxygen transfer, improved separation characteristics, fewer problems in inoculum preparation or scale-up of the process
Improvement of product quality	Decreased production of specific by-products (fewer impurities), prevention of product degradation (e.g. pectinases)
Modification of products	Improvement of solubility in extraction solvents (e.g. addition of specific side chains), increased thermic stability of altered enzymatic properties of proteins
Changing of the locus of product accumulation (e.g. intra cellular to extra-cellular)	Improved product recovery (e.g. omission of cell disruption), correct products (e.g. fully processed proteins).

MARKET POTENTIAL

- The fermentation technologist should be aware of the problem of assessing market potential.

- It is necessary to estimate the size of the present and potential market and the increase in demand for a compound.

- The product which was marketed as an animal protein feed during the 1980s could not compete for price with soya beans in current market and the manufacturing plants were closed down

Four categories of microbial product can be recognized economically and it is important to consider to which category a compound belongs:

1. Low price bulk chemicals, e.g. solvents, biomass, high fructose syrups (US$\$10^2$–$10^3$ tonne^{-1}).
2. Mid price chemicals, e.g. organic acids, amino acids, bipolymers ($\$10^3$–$10^5$ tonne^{-1}).
3. High price microbial and animal-cell products, e.g. enzymes, vitamins, antibiotics, cortico-steroids, vaccines, etc. ($\$10^5$–$10^7$ tonne^{-1}).
4. Very high-price animal-cell products, e.g. mono-clonals, tissue plasminogen activator, etc. ($\$10^7$–$10^9$ tonne^{-1}).

Recombinant Pharmaceutical

- The recombinant protein is produced by a precisely specified process using high quality substrates and processed and purified in an aseptic pharmaceutical facility that has been inspected and licensed by the CBER (Center of Biological Evaluation and Research) of the FDA.

- Steps must also be taken to ensure that there is no cross contamination if more than one product is produced in the same facility.

- Any changes in a process or facilities must be approved by the CBER before implementation. It may take 7 years to obtain approval by the CBER for a production plant.

- In contrast, the requirements for an antibiotic production plant are less stringent and it may be operational in 4 years. The delay in start up to produce the recombinant protein will result in much higher costs.

- It is important to remember that the detailed clinical evaluation of a microbial compound as a drug, plus FDA approval, may take 8-10 years from initial discovery and cost up to $\$150 \text{ X } 10^6$.

Recombinant Therapeutics

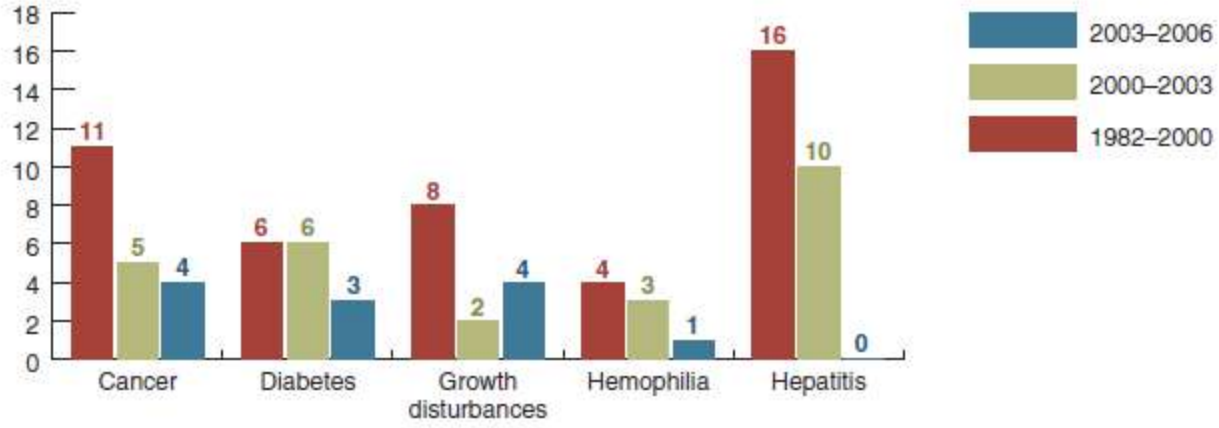

Figure 1 Number of approved biopharmaceuticals in five major markets.

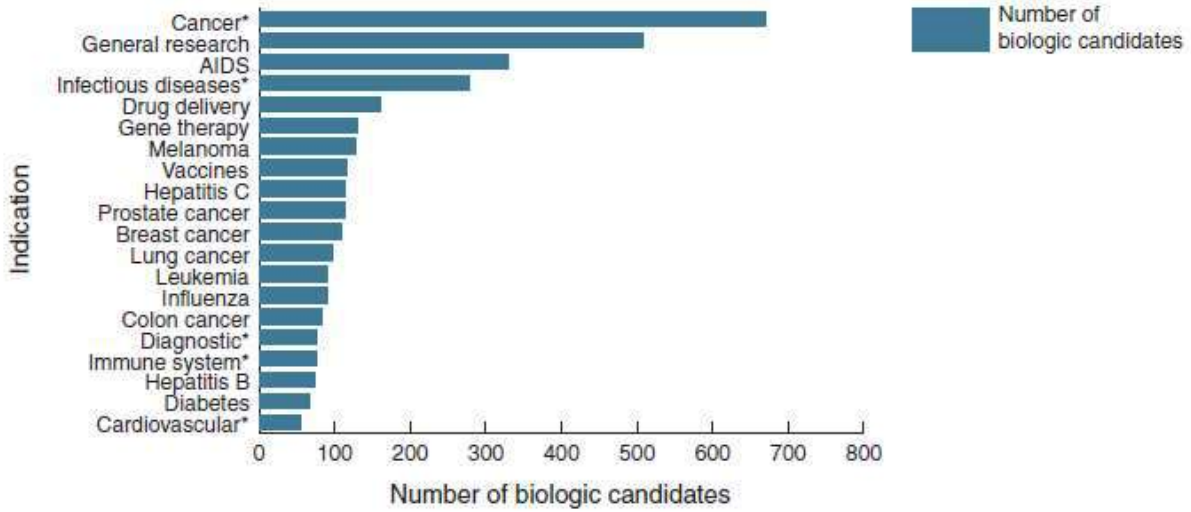

Figure 2 Biopharmaceuticals in the pipeline. (Source: Biopharm Insight, Norwood, MA.)

Future prospects set in 2006

- Annual biopharmaceutical R&D expenditure has stood at $19–$20 billion over the past three or four years and biotech-based products are increasingly dominating the pipeline.

- An estimated 2,500 biotech drugs are in the discovery phase, 900 in preclinical trials and over 1,600 in clinical trials**.**

- **Overall, this represents** 44% of all drugs in the development phase and 27% of all drugs in both preclinical and clinical trials.

- Cancer remains the most common target indication for biopharmaceuticals in development, whereas mAbs and vaccines represent the most significant categories by product number.

- Annual sales of approved biopharmaceuticals were estimated at $33/billion. Sales values of therapeutic mAbs are expected to reach $16.7 billion by 2008.

- The non–mAb-based therapeutic proteins are forecast to reach $52 billion by 2010.

- In total, the total biopharmaceutical market should approach or perhaps exceed $70 billion by the end of the decade.

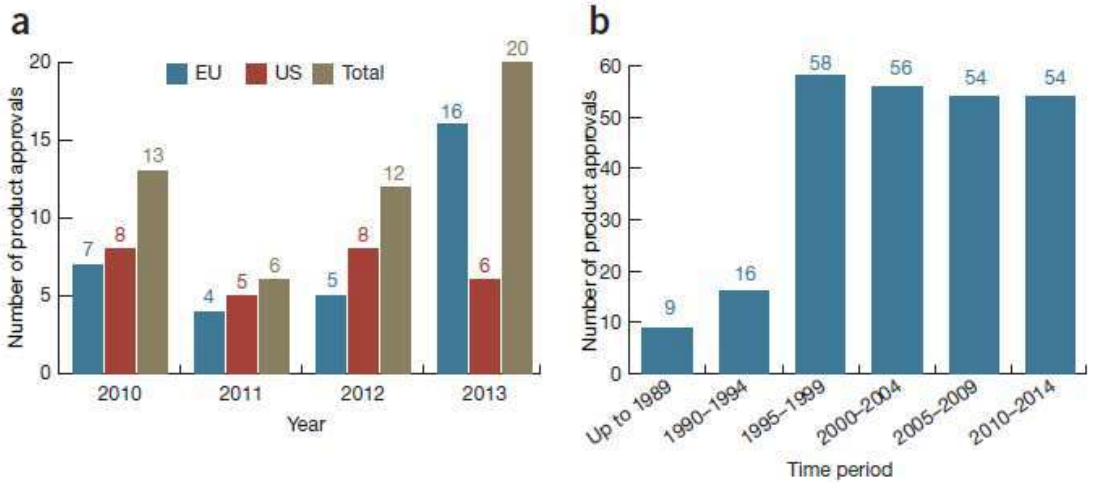

Figure 1 Approvals by region and by date. (**a**) Approvals in US and EU for each of four years in this study period. (**b**) Approval numbers over the indicated periods. Note that both regions experienced a lull in approvals, but in different years. In several instances, the same product has been registered in both regions, but in different years (**Table 1**), hence the yearly totals appear greater than the cumulative number of individual products approved from 2010-2013.

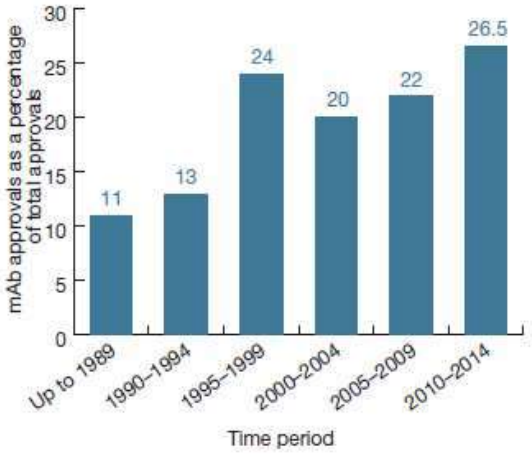

Figure 2 mAbs approved within the indicated periods, expressed as a percentage of total biopharmaceutical product approvals within the same period. Fc-based fusion products are not categorized as mAbs in these data.

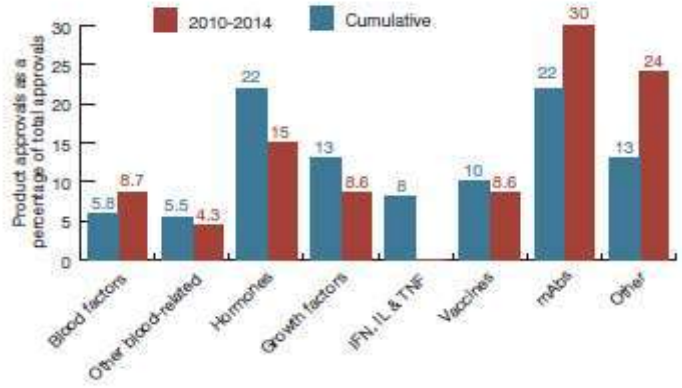

Figure 3 Product approvals, cumulative (1982–2014) and for the current period (2010–July 2014) in the context of product class. Each data set is expressed as a percentage of total biopharmaceutical product approvals for the period in question. IL, interleukin.

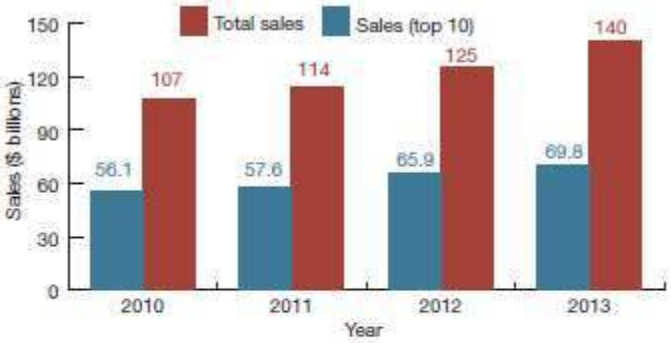

Figure 4 Annual biopharmaceutical sales value (cumulative product sales and sales for the ten top-selling products) for the period 2010 to 2013.

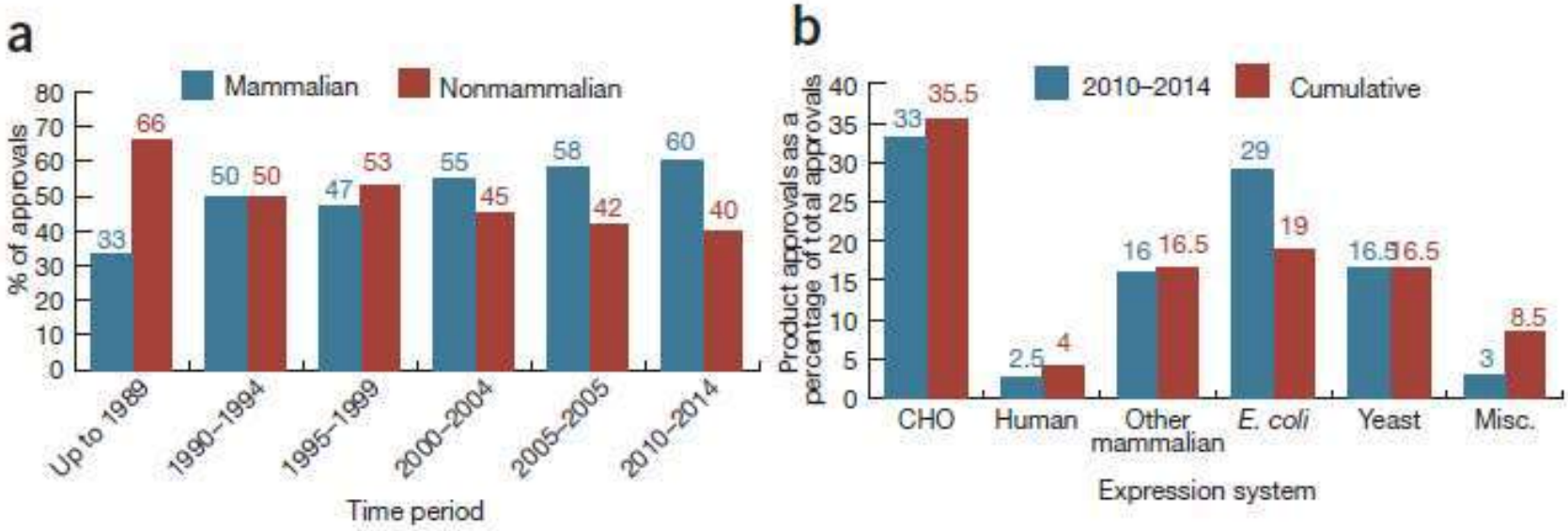

Figure 5 Expression systems used to manufacture biopharmaceutical products. (**a**) Relative application of mammalian versus nonmammalian-based expression systems in the production of biopharmaceuticals approved over the indicated periods. Each data set is expressed as a percentage of total biopharmaceutical product approvals for the period in question. (**b**) Product approvals, cumulative (1982–2014) and for period of this study (2010–July 2014) in the context of expression systems employed. Each data set is expressed as a percentage of total biopharmaceutical product approvals for the period in question.

Table 2 Biopharmaceuticals approved in the United States and/or EU during the current survey period (January 2010–July 2014) by category

Category	Products (by trade name)
Genuinely new biopharmaceuticals	Abthrax, Adcetris, Alprolix, Benlysta, Bexsero, Cyramza, Eloctate, Elonva, Entyvio, Eperzan/Tanzeum, Eylea & Zaltrap, Flublok, Gattex/Revestive, Gazyva/Gazyvaro, Glybera, Jetrea, Kadcyla, Krystexxal, Myalept, NovoEight, Nulojix, Provenge, Ruconest, Tresiba & Ryzodec, Sylvant, Tretten/NovoThirteen, Vimizim, Voraxaze, Xgeva/Prolia and Yervoy
Biosimilars	Grastofil, Inflectra/Remsima, Nivestim and Ovaleap
Reformulated, 'me-too' & related	Afrezza Elelyso, Granix, Hexacima/Hexyon, Lonquex, Lumizyme, Nuwiq, Perjeta, Plegridy, Rixubis, Simponi Aria, Somatropin Biopartners and Vpriv
Previously approved elsewhere	Actemra/Roactemra, Arzerra, Scintium and Victoza

Table 3 The 20 top-selling biopharmaceutical products in 2013

Ranking	Product	Sales ($ billions)[a]	Year first approved	Company	Patent expiry (EU)	Patent expiry (US)
1	Humira (adalimumab; anti-TNF)	11.00	2002	AbbVie & Eisai	2018	2016
2	Enbrel (etanercept; anti-TNF)	8.76	1998	Amgen, Pfizer, Takeda Pharmaceuticals	2015	2028
3	Remicade (infliximab; anti-TNF)	8.37	1998	J&J, Merck & Mitsubishi Tanabe Pharma	2015	2018
4	Lantus (insulin glargine)	7.95	2000	Sanofi	2014	2014
5	Rituxan/MabThera (rituximab; anti CD20)	7.91	1997	Biogen-IDEC, Roche	2013	2016
6	Avastin (bevacizumab; anti-VEGF)	6.97	2004	Roche/Genentech	2019	2017
7	Herceptin (anti-HER2)	6.91	1998	Roche/Genentech	2014	2019
8	Neulasta (pegfilgrastim)	4.39	2002	Amgen	2015	2014
9	Lucentis (ranibizumab; anti-VEGF)	4.27	2006	Roche/Genentech, Novartis	2016	2016
10	Epogen/Procrit/Eprex/ESPO (epoetin alfa)	3.35	1989	Amgen, J&J, KHK	Expired	2013
11	Novolog/Novorapid (insulin aspart)	3.13	1999	Novo	2015	2015
12	Avonex (IFN-β-1a)	3.00	1996	Biogen Idec	2015	2015
13	Humalog mix 50:50 (insulin lispro)	2.61	1996	Lilly	2015	2014
14	Rebif (IFN-β-1a)	2.59	1998	Merck Serono	2015	2013
15	Aranesp/Nesp (darbepoetin α)	2.42	2001	Amgen, KHK	2016	2024
16	Advate/Recombinate (Octocog α)	2.37	1992	Baxter		
17	Levemir (insulin detemir)	2.15	2004	Novo	[Levemir]	2014
18	Actrapid/Novolin (insulin)	2.02	1991	Novo	2017	
19	Erbitux (cetuximab; anti-EGF)	1.92	2004	Bristol-Myers Squibb, Merck Serono	2014	2016
20	Eylea (aflibercept; anti-VEGF)	1.88	2011	Regeneron, Bayer	2020	2021

[a]Financial data from LaMerie Business Intelligence. J&J, Johnson & Johnson

Table 4 Biosimilar products that have gained European Marketing Authorization within the EU.

Product type	Biosimilar brand	Reference product	Year approved	Marketing authorization sponsor	Manufacturer of active substance
Somatropin (hGH)	Omnitrope	Genotropin	2006	Sandoz (Kundl, Austria)	Sandoz (Kundl, Austria)
	Valtropin	Humatrope	2006 (withdrawn 2012)	Biopartners (Reutlingen, Germany)	LG Life Sciences (Jeonbuk-do, South Korea)
Epoetin alfa (EPO)	Binocrit	Eprex/Erypo	2007	Sandoz (Kundl, Austria)	Rentschler (Laupheim, Germany) & Lek (Menges, Slovenia)
	Epoetin alfa hexal		2007	Hexal (Holzkirchen, Germany)	
	Abseamed		2007	Medice Arzneimittel (Iserlohn, Germany)	
Epoetin zeta (EPO)	Retacrit		2007	Hospira (Warwickshire, UK)	Norbitec (Uetersen, Germany)
	Silapo		2007	Stada (Vilbel, Germany)	
Filgrastim (G-CSF)	Ratiograstim	Neupogen	2008	Ratiopharm (Ulm, Germany)	Sicor (Vilnius, Lithuania)
	Filgrastim ratiopharm		2008 (withdrawn 2011)	Ratiopharm (Ulm, Germany)	
	Biograstim		2008	AbZ pharma (Ulm, Germany)	
	Tevagrastim		2008	Teva (Radebeul, Germany)	
	Zarzio		2009	Sandoz (Kundl, Austria)	Sandoz (Kundl, Austria)
	Filgrastim hexal		2009	Hexal (Holzkirchen, Germany)	
	Nivestim		2010	Hospira (Warwickshire, UK)	Hospira (Zagreb, Croatia)
	Grastofil		2013	Apotex (Leiden, the Netherlands)	Intas Biopharmaceuticals (Gujarat, India)
Follitropin alfa (FSH)	Ovaleap	Gonal F	2013	Teva (Utrecht, the Netherlands)	Merckle Biotech, (Ulm, Germany)
	Bemfola		2014	Finox Biotech (Balzers, Liechtenstein)	Polymun Scientific Immunbiologische Forschung (Klosterneuburg, Austria)
mAb	Remsima	Remicade	2013	Celltrion Hungary Budapest, Hungary	Celltrion (Incheon, Korea)
	Inflectra		2013	Hospira (Warwickshire, UK)	

hGH, human growth hormone

What determines the cost in industrial production

- Raw materials
- Utilities
- Labour and supervision
- Fixed charges
- Maintenance
- Operating supplies
- Waste
- Materials
- Recovery
- Other/contingent plan cost

Plant and equipments (Bioprocess Development)

- The operational vessel volume is a critical factor when considering high volume-low cost products.

- Cooling and aeration requirements and the method of fermentation vessel construction also very critical.

TABLE 7.1. *Service provisions for a fermentation plant*

Compressed air
Sterile compressed air (at 1.5 to 3.0 atmospheres)
Chilled water (12 to 15°)
Cold water (4°)
Hot water
Steam (high pressure)
Steam condensate
Electricity
Stand-by generator
Drainage of effluents
Motors
Storage facilities for media components
Control and monitoring equipment for fermenters
Maintenance facilities
Extraction and recovery equipment
Accessibility for delivery of materials
Appropriate containment facilities

TABLE 12.5. *Capital cost breakdown for fermentation plant*

Item	% of total
(a) *Penicillin plant,* estimated for five 225,000 dm^3 fermenters with ancillary equipment (Swartz, 1979)	
Process equipment	23.6
Installation	5.2
Insulation	1.9
Instruments	2.7
Piping	11.8
Electrical	15.8
Building	11.3
Utilities	21.3
Site	2.4
Laboratory equipment	3.8
Spare parts	0.5
(b) *Norprotein plant* (Mogren, 1979)	
Raw materials storage	10
Media preparation and utilities	17
Fermentation	41
Cell recovery and drying	22
Product storage	10
(c) *ICI plc. Single-cell protein plant* (Smith, 1980)	
Raw materials	3
Storage and packing	12
Off-site services	16
On-site services	11
Fermentation	14
Compression	9
Dewatering	19
Drying	12
Effluent treatment	4

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.

- Powders must be kept in dry conditions because of the possibility of substances becoming rock-like or glutinous.

AIR STERILIZATION

- The problems associated with producing large volumes of sterile air for aerobic fermentations are unique.

- Sterilization by heating is technically possible,

- Absolute fixed-pore membrane systems using pleated membranes of Poly-tetra-fluoro-ethylene PTFE are now widely used in the fermentation Industry.

- Factors to consider include the cost of replacement filters or filter materials, servicing and Labour.

- The treatment of fermenter exhaust gases to satisfy containment requirements is also important.

- Treatment is normally by filtration with 0.2 mm microfilters, but in-line incinerators may be an alternative approach.

HEATING AND COOLING

Ideally there should be no heating or cooling at any stage in a fermentation process, but because this is virtually impossible, heat should be conserved and cooling minimized by careful process design.

A fermentation may include the following heating or cooling stages:

1. Sterilization or boiling of the medium to 100° or above followed by cooling to 35° or below.
2. Heating the fermenter and ancillary equipment to sterilize it, followed by cooling.
3. 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.
4. After harvesting, heat may be required to remove water from the product.

- Cooling requirements will be influenced by the size and type of an individual process
- Another way to minimize cooling costs is to use microorganisms with higher optimum growth temperature
- The selection and use of thermophiles and thermotolerant organisms would have obvious advantages to reduce cooling demands

AERATION AND AGITATION

Nearly all fermentations require some form of mixing to maintain a constant environment, and many also need aerating. Fermentations may be broadly classified into:

1. Fermentations which are anaerobic where oxygen is undesirable, e.g. acetone-butanol.

2. Fermentations which have a minimal oxygen demand, e.g. ethanol.

3. Fermentations which have a high oxygen demand, e.g. antibiotics, acetic acid, single-cell protein.

TABLE 12.6. *Effect of substrate and yield coefficients on SCP operating costs* (Abbott and Clamen, 1973)

Substrate	Substrate costs		O_2 transfer costs	Heat removal costs	Combined costs
	(¢ lb^{-1} substrate)	(¢ lb^{-1} cells)	(¢ lb^{-1} cells)	(¢ lb^{-1} cells)	(¢ lb^{-1} cells)
Maleate (waste)	0	0	0.46	0.75	1.2
Glucose (molasses)	2.0	3.9	0.23	0.54	4.7
n-Paraffins	4.0	4.0	0.97	1.4	6.4
Methanol	2.0	5.0	1.2	1.9	8.1
Ethanol	6.0	8.8	0.75	1.3	10.9
Acetate	6.0	16.7	0.62	1.1	18.4

RECOVERY COSTS

The costs of product recovery and purification are rarely quoted, though in some processes they are obviously considerable.

Fermentation: purification cost :: 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

1. Yield losses, even if only modest, are certain to occur at each stage of the recovery process.

2. High energy and maintenance costs associated with running filtration and centrifugation equipment.

3. High costs of solvents and other raw materials used in recovery and refining of products.

WATER USAGE AND EFFLUENT TREATMENT

Many fermentations have a high daily water usage

TABLE 12.8. *Daily water usage in fermentation processes*

Industry	m^3 of water used day^{-1}	Reference
Maltings	230	Askew (1975)
Brewing	10,000	
Distilling	320	
Antibiotics	245	
Antibiotics	5,200	Hastings and Jackson (1965)
Acetic acid	700	Pape (1977)
Single cell protein (methanol substrate)	4,000 to 12,000	Taylor and Senior (1978)
Yeast (alkane substrate)	18,200	Ratledge (1975)
Bacteria (methanol substrate)	45,500	
Bacteria (methane substrate)	18,200	

- In the majority of fermentation processes it is impossible to dispose of effluents at zero cost.

- 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.