Economic Analysis of Fermentation Processes

Harold B. Reisman, Ph.D.
Director of Manufacturing
Formulated Foods Group
Stauffer Chemical Company
Westport, Connecticut

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INTRODUCTION

The last decade has been marked by enormous change in the life sciences. New bioactive entities have been made and novel techniques have opened new vistas in molecular biology. Monoclonal antibodies offer a reasonable hope for targeted drug missiles to cure disease; many new diagnostic methods are based on this advance. New vaccines are being prepared from specific protein moieties offering disease prevention without side effects. In microbiology, classic mutation methods have been superceded by protoplast fusion and recombinant DNA technology. A host of new compounds arises monthly and new processes are presented which offer potential for mass production of well-known biodynamic molecules as well as the ever-growing list of newer ones.

The more mundane area of economics (as applied to what is called, for simplicity, biotechnology) has only recently received more serious attention in the business community. Sooner or later, one must move from concept, discovery, or laboratory preparation to sale of a desired material. This simple fact is true regardless of the material's nature or its derivation. The many new biotechnology companies are finding that issuance of stock and even a patentable discovery are not sufficient to maintain long-term corporate viability. Many of these companies may find themselves in the position of creators, holders, or purveyors of technology while they are, or may become, totally dependent upon larger competitors (major pharmaceutical companies) to do actual production, marketing, and sale of resultant products.

It is the purpose of this book to outline and detail the many steps which are involved in bringing a fermentation product to market. Ultimately, investment must result in a monetary return (unless there is some other overarching goal). Many of the steps are applicable to the production of vaccines, antibodies, bioactive peptides, and so forth, but the basic orientation is that of a fermentation product. No single text can cover in depth all necessary planning, scheduling, construction, costing and marketing operations that must occur; however, there is enough detail given so that anyone with a reasonable technical background will be aware both of the actual steps needed and the methodology used to complete each step effectively and efficiently (see Figure 1). Finally, return on investment and sensitivity analyses are reviewed to bring the economic picture into focus.

The potential of the microorganism is legion. A few examples suffice. Solvents and precursors (acetone, butanol) can be made by anaerobic fermentation. Microbial polysaccharides can be used as food additives and in enhanced oil recovery. The potential for food, feed, and ethanol production from waste cellulosic materials via microbes exists. Textured mycelial food products that simulate veal and chicken have been produced. Psychoactive and immunoactive compounds can be produced microbially. Microbial synthesis of interferons, rennet, and growth promoters is now possible. It must be noted that only some of the above processes are, or will be, commercial. Some may move to commercial scale in the future. The major determinant, at least in the West, will not be technical feasibility, but economics.

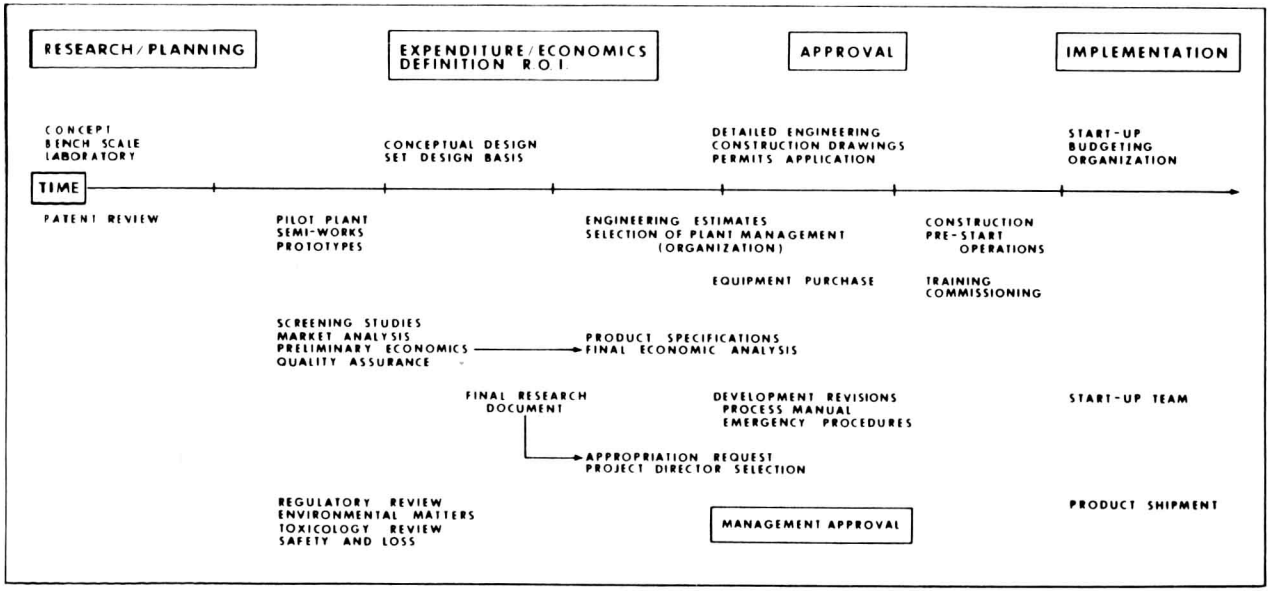

FIGURE 1. The project cycle.

THE AUTHOR

Harold B. Reisman is Director of Manufacturing for the Formulated Foods Group of Stauffer Chemical Company. He has over 25 years of industrial experience in fermentation design, product isolation, scale-up, pilot plant operations, fermentation plant construction, start-up, and operations. Products include antibiotics, vitamins (riboflavin and B_{12}), amino acids (lysine, monosodium glutamate), therapeutic enzymes, interferon inducers, as well as novel food ingredients. Current responsibilities include manufacturing operations, research, development and applications support for the Food Group, quality assurance and control, and regulatory and environmental affairs.

He received his undergraduate degree in chemical engineering from Columbia University, New York, and a Master's degree working with Prof. R. K. Finn at Cornell University, Ithaca, N. Y. He returned to Columbia for his doctorate in chemical engineering working with Prof. E. Gaden on optimization and kinetic analysis of penicillin fermentation. A Fulbright Grant supported a year's postdoctoral research at the Istituto Superiore di Sanita in Rome working in a group headed by Prof. E. Chain. Dr. Reisman was then employed as Section Manager in the Merck, Sharp and Dohme Research Laboratories in biotechnology and fermentation development. A number of papers were published and a patent on continuous fermentation ensued.

He joined Stauffer in 1973 and was Bioengineering Laboratory Director, Plant Manager, and Business Group Director prior to assuming his current position. He has visited Japan more than half a dozen times and has been involved in technical and commercial exchanges with three major biotechnology firms there.

He is a member of the American Institute of Chemical Engineers, the American Chemical Society, and the Institute of Food Technologists. He has authored chapters in *Microbial Technology* and the *Encyclopedia of Chemical Processing and Design*.

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RESEARCH AND DEVELOPMENT

I. RESEARCH ORGANIZATION

The research organization is a critical determinant in the economic success of most companies. This is all the more so in a high technology business. Successful development of new biological products depends upon integration of the research organization at all levels in the company. The person in charge of the research organization should be included in the highest policy-making level of the company. Research interfacing with all staff groups, manufacturing, and especially marketing is imperative to smooth and accelerate product introduction.

Characteristics of a smoothly functioning and productive organization are

1. Responsive to changes in market need (including means of delivery); marketing and sales information flows constantly to research managers; program corrections are made so that solutions match real problems.
2. Selectivity is exerted so that available resources (manpower, money, materials) are not dissipated, but applied and focused on strategic programs.
3. There is an ongoing search for novel, but related product concepts, while reexamination leads to dissolution of programs which show little promise or progress.
4. Functional levels are kept to a minimum. There is movement of people to match needs whether they arise in the research laboratory, the pilot plant, the operating plant, or the marketplace. Structure is fluid.
5. Innovation is fostered and rewarded. There is a climate of creativity that is recognized within and without the company.
6. Research results are reported (not overreported) in a timely fashion. A sense of enthusiasm pervades the research group and members are anxious to resolve issues and let others know of that resolution. Progress is made (translation to production scale, for example) without all possible design data in hand. Risks are mutually understood and accepted.
7. Corporate objectives are clear and there is an agreed-upon balance between short- and long-term projects. Strategic decisions are made or changed with intimate involvement of key research personnel.
8. Research personnel have, or are taught, a financial understanding of the company (and industry) and so can understand and explain business implications of various modes of action.

Why spend this effort on research and development when the subject is "economics"? The answer is clear. The commercial success of a venture or a fermentation company is tied to research success; furthermore, the cost of research is very high and going higher. The difference between success and failure can easily be measured in tens of millions of dollars; it is not unusual to involve swings in the hundreds of millions. Clearly, the costs of numerous failures will mean shrinkage or dissolution of the company. Some 15 years ago, cost per professional research staff member was $50,000 annually. Even at an inflation rate of 5%, the annual cost now would be slightly over $100,000/year. Indeed, published information supports the rough estimate.[1] A survey of 157 industrial research organizations indicates that operating cost per professional was $119,000 in 1985 compared to $113,000 in 1984. Fifteen pharmaceutical companies were included in the survey; for that set, cost

per professional was $84,000 in 1984 and $91,000 in 1985. For the pharmaceutical group, R & D expenses as a percent of sales averaged 7.5 in 1984 and 7.3 in 1985.

Data for four large companies (full year 1984) are shown below:[2]

	Sales ($million)	Earnings ($million)	R & D expenditures ($million)	R & D as % of sales
Eli Lilly	3109	490.2	341	11.0
Pfizer	3855	507.9	252	6.5
Merck	3560	493.0	393	11.0
G.D. Searle	1246	161.6	120	9.6

Earnings exclude extraordinary and nonrecurring items. R & D expenditures are a very high percentage of net income; values of 50 to 80% are common. For start-up firms, R & D costs may be many times net earnings, if there are earnings at all. For 30 pharmaceutical firms, R & D expense was 6.7% of sales (on the average) and accounted for 40% of pretax income (also an average value).[3] The average R & D cost per company employee was $5704. To compare to other research-oriented groups, average R & D expense as a fraction of sales for the chemical industry was 3.0% and for the electronics industry, 4.3%. Even with these levels of R & D expenditures (some might conclude *because* of these levels of expenditure), Lilly, Merck, and Pfizer can be found among the top 100 U.S. firms when ranked in order of corporate cash flow.[4] Their respective returns on equity were 22.1, 19.4, and 20.7%; these are very respectable figures.

There are about 400 firms that can be called biotechnology oriented. It is a matter of conjecture as to how much of the orientation is real and how much is capitalization on an area of great interest. Among the so-called start-up companies, R & D expenditures (1984) range from less than $1 million (Ribi) to about $55 million (Genentech). What is consistent is the high ratio of R & D expense to total expense. Table 1 is a compilation of data for selected biotech companies of differing sizes. Expenditures for R & D are often equal to, or greater than, annual sales figures.

A ten-person team (with necessary support structure) is not very large even for a start-up company. Cost is in excess of a $1 million/year. Ten man-years (or in more conventional terminology 120 man-months) pass very rapidly; most often, multiyear commitments are essential. The reason for inclusion of this subject is clear, as is the need for careful research planning.

While much of the interest in biotechnology is focused on the smaller, start-up firms, major changes have occurred in very large organizations as well. In the early 1970s, Monsanto spent less than 3% of sales on R & D. The figure has moved to greater than 5% of sales a decade later, with dollar spending on R & D approaching 400 million. Much of this transformation is related to a shift to biotechnology, agricultural chemicals, and health care. This is a major restructuring of a very large chemical company. Many aspects of the strategic change and the company's research and development structure are detailed in a very useful article on Monsanto, including an interview with H. A. Schneiderman (senior vice-president of R & D).[5] In 1985, Monsanto purchased G. D. Searle, thus, making a further and major commitment to pharmaceuticals and biotechnology. The cost to Monsanto was $2.7 billion. Not only is a massive change for a corporation involved, but there is a directed effort into new business and technical areas. Cultural changes are involved, a new regulatory outlook has been introduced, and a new time frame for development is in place. Technical-marketing interactions and needs are explained. It will be instructive to read this article and monitor the company in the next decade. The picture that emerges after expenditure of hundreds of

Table 1
R & D EXPENDITURES AND SALES FOR SELECTED START-UP COMPANIES: 1984[a]

	Revenues		Expenses		Net gain or (loss)
	Sales	Interest	R & D	Total	
Amgen	2.78	3.33	8.76	11.06	(4.94)
California Biotech	6.71	1.56	7.26	8.34	(0.13)
Centocor	10.88[b]	1.96	6.72	12.14	0.70
Cetus	35.85[b]	10.37[c]	31.41	45.16	0.99
Damon Biotech	2.39	2.66	3.82	8.55	(3.51)
Genentech	65.63[b]	4.16	54.98	66.78	2.72
Hybritech	14.60 16.23[d]	3.11	13.70	32.66	(1.83)
Molecular Genetics	6.37[b]	2.85	4.81	9.86	(0.64)
Monoclonal Antibodies	1.62[b]	0.59	1.39	5.83	(3.62)
Ribi Immunochem	0.52	0.40	0.43	1.20	(0.29)

[a] Dollars in millions.
[b] Includes "sponsored research" or "contract revenue".
[c] Includes "other income" of $0.73 MM.
[d] Listed as "contract revenues"; total operating revenue $30.83 MM.

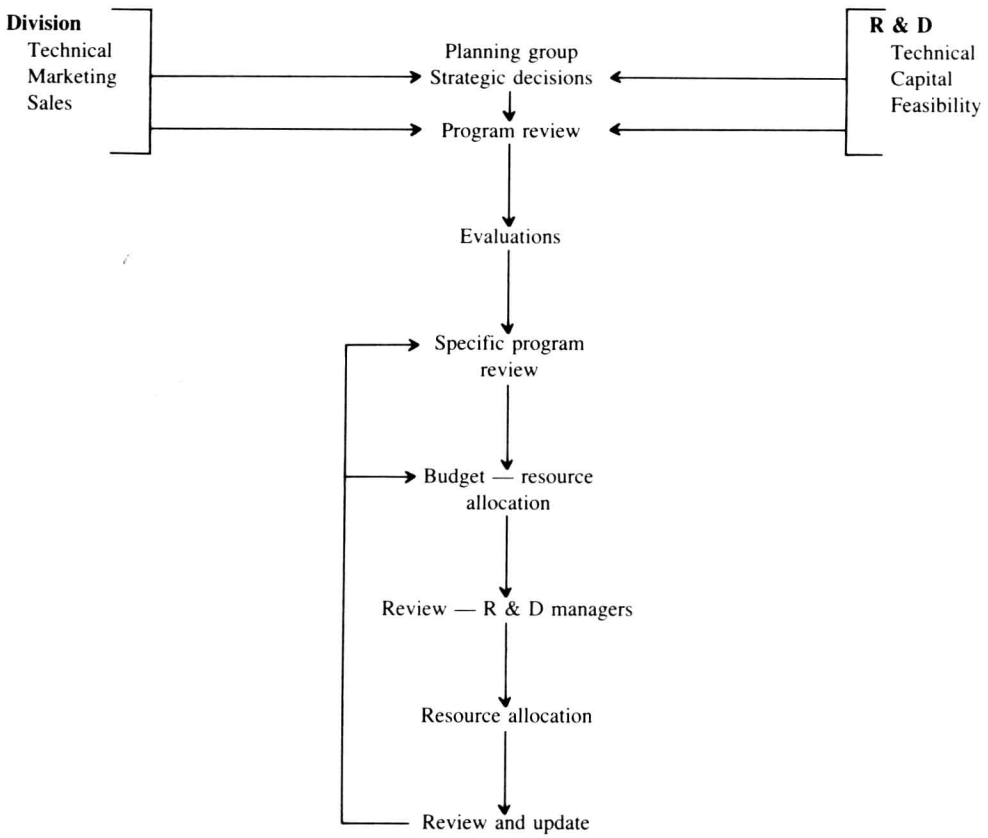
millions of dollars in capital and equal or greater sums in R & D expense will present a classic case study whatever the economic outcome.

Setting of product objectives is a management decision. It is imperative that once these objectives are communicated, two important summaries be detailed and recorded. One concerns allocation or development of capabilities and resources. The second involves total resource allocation, including funds needed for research and development, regulatory affairs and clearance, capital (or lease/rental), and marketing. Both summaries must be updated on a routine basis. It is obvious that the early summaries are merely best estimates and may have a large margin of error. It should be equally obvious that even 3 months of lab work, legal and regulatory review, and marketing analysis will stimulate major revisions in the "first pass" summaries. The changing resource needs and resource (cash) flows must be updated and communicated to those responsible for setting the product or process objectives. While the first steps — resource allocation and flow of funds — are often taken, due regard to follow-up may be lacking. The seeds of discord or failure are often sown as revision is cursory or disregarded altogether.

The *planning* phase (Table 2) involves, first, defining and communicating the objective. In order to achieve the objective, a list of activities is required. Not only are certain activities to be done, they must be completed in a logical sequence in an approved time frame. The establishment of a logic sequence in time may involve various bar charts, PERT charts, networking, scheduling, or computer-generated sequences. The planning sequence may involve none of these, but some sequence (even if a mental image) must be mutually agreed upon and should be followed. However, the hazards of following an abstract mental image should be understood.

Once the planning phase is complete, the *allocation* procedure must be followed. New and available resources are compiled. The work schedule is set and budgeting requirements are detailed. All overheads are included whether by factor or by line account. Necessary interfacing with legal and regulatory personnel (in-house or out) should be programmed. If

Table 2
THE PLANNING SEQUENCE



After *Innovation*, No. 19, 51, 1971.

the product is to be marketed at a known future time, critical points in the logic sequence must be established. Clearances are a fact of life and the sooner the requirements and their fulfillment are programmed in, the better the hope for project completion. A cash flow forecast should be included in the allocation phase. While not absolutely essential at this point, certain problems that seem likely can be identified and contingency plans made. In the subsequent *update* phases (which will probably result in plan modification, timing changes, and reallocation of resources), it is essential that problems be identified and multiple contingency plans be prepared.

The pharmaceutical industry is highly innovative, but it must be considered market driven. A commercial enterprise would not seek a specific antibiotic against an ubiquitous and harmless microorganism unless there were some ulterior motivation; similarly, for a monoclonal antibody against a circulating protein that signaled nothing in a physiologic sense. In general (and as compared to a "heavy" industry), the industry is characterized by relatively modest capital investment relative to the value of the product. Investment is high relative to quantitites produced. The industry norm is to have a multiplicity of products and a reasonable new product flow to compensate for product obsolescence. The term "obsolete" refers more properly to displacement by more active materials having fewer side effects. The objectives of research in the fermentation industry are

1. Screening for, and selection of, novel bioactive moieties and the means for their synthesis and purification

2. Improved functional performance of a precursor, a novel compound, or a derivatized natural or synthesized product
3. Cost reduction for novel or existing product formation by applying microbial, chemical, biochemical, and engineering techniques
4. Scale-up and commercialization of any and all of the above

A short summary of the many steps needed to bring a discovery to mass production has been published; product requirements for clinical or field trials are given.[6] Interrelationships between strain improvement, medium development, and process optimization are shown. Examples of successful development are described.

Understanding the value of R & D in a qualitative way is simple when a number of new products have been developed in a short time interval. Putting this understanding in a quantitative form is far more difficult. Even when accomplished, heated discussion often ensues. Normal accounting indicators, such as profit from operations (PFO), return on investment (ROI), and profit-to-sales ratio, are not adequate if applied directly and indiscriminately to annual research expenditures. Some assumptions and weighing are needed to quantify research productivity.

The quantitative evaluation of research and development is essential (if only for proper research planning) and it is possible. Both tangible and intangible factors can be listed and weighted. Not least of these factors is how much a product or process contributed to corporate goals by being translated into dollars. All aspects of research (fundamental, applied, engineering, start-up, competitive evaluation) can be judged by how much has been generated in dollars by year over a reasonable time — compared to the expenditure. The simplest format is to first divide the corporation into manageable "categories". (For a start-up company, the number may be one or two.) Each business category should have a percentage of the total research effort "assigned" to it. Ideally, a 5-year history can be used. The successful projects (criteria must be established for "success" — monetary return is not a bad starting point) should be listed. The gross profit contributed by these successful projects can be summed. Once again, a sufficiently long history is needed. Five years seems like a minimal period. A very coarse ROI can be calculated by summing the profit contribution for each business and dividing by the cost of R & D in that same business. It may be necessary to project future earnings in some cases. One can, of course, use this simple model in the planning cycle, that is, determine a minimum acceptable return on research investment and fund the necessary projects so that a reasonable success rate gives the desired return. It is rather more complex than given here, since the number of variables and degree of uncertainty are very high at the initiation of a program.

Decision analysis has been used in evaluation of R & D projects. Thomas[7] discussed strategic management of R & D in two detailed cases — one in the electronics industry and one in the ethical pharmaceutical industry. He notes that in recent years pharmaceutical companies have limited research areas, so that expertise and an understanding of the market can be built up leading to success in closely related, integrated product areas. One not insignificant reason for focusing is the fact that new drug development and clearance might involve "investments in excess of $50 to 75 million". The specific study involves licensing and a joint venture strategy with significant up-front investment. Decision analysis with decision trees (toxicological trials and clinical trials with different scenarios) is reviewed. Risks were rated as was reward (present values analyses at high to low probability). The findings, which seem to apply to most research management situations, can be detailed under the headings of assessment problems, discounting processes, flexible decision criteria, and the process of policy dialogue. A few of the conclusions are

1. Balancing risk preference and time preference is very important in R & D management.

2. Managers want multiple performance measures for portfolios and individual projects.
3. The role of decision analysis was to provide output as a function of numerous variables and express results in terms of dynamic interactions. One criterion of utility was not adequate.
4. Profiles of cost, revenue, cash flow, and capacity encourage awareness of risk and uncertainty on an individual project and a portfolio of projects.

Schmitt presents an overview of corporate R & D and, also, discusses overall corporate R & D strategy.[8] The key points of emphasis are similar to those noted above — synergy, interdisciplinary focus, and lead time. A pragmatic or a "trying" approach between the technology and marketing sectors is needed to progress at a sufficiently rapid pace. Once more the point is made that ROI does not tell it all.

An important survey and analysis of research and development productivity is available in a two-part series.[9] It is possible to construct a framework which not only identifies key productivity factors, but also selects methods which will measure and improve economic return. Out of the many possible activities, 13 were identified and ranked by many research directors as having the greatest impact on R & D return. These high return activities are listed below, in order of importance, and many suggestions are given that relate to these efforts.

Rank	
1	Identify customer needs
2	Professional personnel quality
3	Coupling to technical efforts — marketing
4	Identifying projects
5	Identifying technical possibilities
6	Demand outlook
7	Project staffing
8	Strategies of competitors
9	Coupling to technical efforts — manufacturing
10	Project planning
11	Identifying limits
12	Project termination
13	Characterizing technology

The R & D yield is defined as the profit made from improvement in technical performance. The first and third rankings relate to "yield" in that both must be successful to maximize economic return.

There are certain other major interrelationship problems that must be overcome. These refer to research interactions with other parts of the company. Even if overcome in one time period or in one project, these problems seem to reappear in a cyclic fashion. The first concerns monitoring of a project. Not only does research management have an interest in focused effort to achieve timely results, there are other corporate functions — manufacturing and marketing are merely two obvious ones — that are deeply involved in research expenditures, process details, product configuration, and, most of all, timeliness. The subject of how to keep projects on track is discussed in a clear and organized fashion by Szakonyi.[10] (He discusses four general "needs" or "processes" that must be satisfied whether the project reviewer is within the research organization or elsewhere in the company.)

1. Tangible results. Some progress must be visible as time passes. Milestones must be met. Stepwise progress must be obvious even to the untrained eye. The sense of what

might be called "partial accomplishment" will be an ongoing positive reinforcement of research personnel and those in other groups.

2. Compare technical progress with costs. It is probably true that given unlimited funds and unlimited time, any goal can be reached. Given constraints of money and time, it is imperative that progress must be related to expenditure. Costs must be viewed retrospectively and prospectively. If so much has been spent to get to 30% of where we thought we would be, how much more will be realistically needed to complete phase I of the project? Hard decisions must be made when costs incurred and progress attained show serious discrepancies.
3. System of progress reports. While voluminous or tedious documentation is invariably a waste of time, no documentation will result in the same, or greater, waste of time and money. Generation of paper is to be avoided, but a routine and periodic release of progress reports is necessary. This is a good idea even if there is nothing positive to report; some might add that in such a case, it is even more important that a report be issued. All interested personnel, whether line or staff, must be informed on status of effort.

Szakonyi[10] has a terse human relations summary on research interactions with others in the company:

> "Rather they will be based on conditional agreements that both sides will continue to cooperate as long as they both continue to gain something from their cooperation. The trick to keeping R & D projects on track, therefore, involves keeping these conditional agreements viable by making sure that the objectives of the R & D project coincide as closely as possible to the diverse and specific objectives of the people involved."

The second major interaction problem (or opportunity) occurs on translation of a process to manufacturing. There are a host of factors (mainly economic) which come into play and this situation will be discussed in a subsequent section on start-up.

II. PROCESS DEVELOPMENT AND SCALE-UP INFORMATION

The aim of process development is quantitative delineation of all key factors which will permit timely and economic design and construction of an operating plant (or part of a plant) which will then perform in a stable, predictable, and cost-effective manner to produce a desired product of known quality at a determined rate. There are many factors that will impact cost and each must be considered. The degree to which quantitative definition (involving prediction equations, mean values, standard deviation, sensitivity analyses) is needed depends upon the specific process and product, and the very determination of emphasis sets the tone for later success or failure. Great precision and detail covering a weak interaction or tertiary variable not only does little to aid process design or operation, but the effort detracts from an understanding of primary variables.

Key factors in process development include:

Raw materials	Material balance
Strain selection	Component balance
Strain maintenance	Type/extent of recycle
Media development	Energy requirements
Process optima	Aeration-agitation needs
Waste streams	Sensitivity to upsets
Quality control	Downstream recovery
Equipment design	Stability (in-process, product)

A simple outline should be prepared so that available laboratory or published information is listed and unknowns are highlighted. Modifications can be readily made as development proceeds. Such a simple outline is given below for a well-known fermentation, that for citric acid:

Carbohydrate	Beet molasses
	Glucose syrups
Nitrogen source	No other additive if molasses used/salts
Process	Submerged or tray
Efficiency	
Fermentation	90 + %
Isolation	90%
Microorganism	*Aspergillus niger* (with identification)
Sugar, initial	15—18%
Cycle time	
Submerged	3—5 days
Tray	10 days
Turnaround	10 hr
Temperature	25—30°C (may be staged)
pH	2.5—3.5 (controlled)
Airflow	0.5—1.0 vol/vol/min
Pressure	1.5 atm
By-products	Mycelium, oxalic acid
Pretreatment/additives	Methanol (2% to fermentation)
	Cation/ash levels critical
Isolation	Settle/filter mycelium
	Precipitate as calcium salt
	Redissolve with H_2SO_4
	Demineralize/decolorize
	Crystallize and dry

Reviews on process design and scale-up have been written. A review by Lilly[11] is useful, especially since he notes that one " . . . may feel that it is a wonder that anything has been scaled up". A history of fermentation development and background information on fermentation design and operations is given by Bjurstrom.[12] There are a number of books which give a good theoretical background to various aspects of development and scale-up while containing many examples involving industry practice. An academically oriented text by Bailey and Ollis[13] is worth consulting. Transport phenomena are well described and design examples (sterilization, reactors) are given. Blakebrough[14] edited two volumes that combine theory and practice. The second volume contains chapters that cover some aspects of downstream processing (such as evaporation, drying, heating, cooling, use of radiation). There is some extension into the foods area, but many examples of industrial equipment are given. Perlman[15] discusses products and producers (commercialized through 1977) and covers raw materials, fermentor design, and an overview of recovery.

During laboratory and pilot plant development, alterations in key process variables will have been studied. Some of the variables were purposefully changed in optimization studies and some resulted from process upset, mischarge of nutrients, or "unknown" factors. The overall picture that emerges should point to those parameters which must be controlled within a narrow band and those variables that might be permitted to range somewhat more widely. The next step concerns creation of a micro- and macroenvironment, on a large scale, that will allow maximal rate and yield to be obtained *within economic constraints*. The last point is sometimes neglected at costs which become apparent at a later time.

Some simple examples will suffice for now:

1. Very often, use of any reasonably effective defoamer depresses yield by 5 to 10% regardless of other changes. Scale-up fixes operating volume at 65% of nominal production fermentor volume to ensure no foam loss under highly aerated conditions. However, if defoamer use is "permitted" and a 7 1/2% yield loss assumed, operating volume could be 75% of nominal volume and overall recovery would be improved by 6.7%. Even a 10% yield loss means enhanced overall product formation with use of defoamer.
2. Optimum productivity is achieved at a specific oxygen transfer rate (OTR) and dissolved oxygen (DO_2) level. At the desired operating volume, a specific power input and turnover time is required to satisfy the OTR and DO_2 constraints. The drive, motor, seal, and shaft assembly require a step change in duty/diameter/mechanical support. No balance is made between the major increment in capital investment (plus maintenance and on-going energy cost) and the modest yield or rate reduction corresponding to somewhat less stringent agitation-aeration requirements.
3. A pilot extraction operation involves multistage solvent extraction and carbon purification. Recoveries of solvent are 98% and product recovery is 96%. These extraction stages are scaled to a production facility. No calculation is made of recovery and total operating cost (including changes in labor, materials, maintenance, energy, depreciation, taxes, insurance) if solvent recovery is only 96% and product recovery is 93%. Just as in heat recovery, the maximum in recovery most often does not correspond to the economic optimum or least cost point.

While there is no intent to give an in-depth review of critical parameters, certain points will be covered that are of major significance. Reviews are available for more detail and analysis.

III. MIXING AND OXYGEN TRANSFER

The first and foremost scale-up parameter in fermentation design is mixing. It is rather remarkable that the earliest fermentors for antibiotic production (constructed in the late 1940s and early 1950s) remain usable today for many new generations of microbial product. The use of a stirred tank gas-liquid contactor has endured for four decades; there is no indication that the design will soon be retired. In the interim, there have been reports on aerated columns (tower fermenters), oxygen supplemented fermentation, draft tube vessels, disk or rod agitators, vibrating mixers, external circulation systems with pumps, and gas lift fermenters. At best, some of these designs have found selected niches; others are laboratory curiosities. Clearly, the sparged agitated contactor performs in a manner that satisfies physiologic requirements of many microorganisms.

Not only must a unit volume be satisfied (temperature, dissolved oxygen, nutrients, pH, redox potential, pCO_2), but vessel turnover must maintain quasi-homogeneity. In a shake flask or laboratory fermenter, turnover time is minimal; it can be measured in seconds. Gradients are minor or nonexistent. Any material added — whether it is substrate, acid, or base — is mixed into the bulk of the fluid with negligible delay; that is, every unit volume "sees" predetermined optima with little or no delay. At most, some seconds pass before recirculation occurs. For oxygen transfer, the critical region is the impeller zone where initial shear on the gas bubble occurs. This is the region of maximum DO_2; recirculation time to this region determines whether or not oxygen deprivation occurs.