BIOPROCESS ENGINEERING: SYSTEMS, EQUIPMENT AND FACILITIES

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PREFACE

The development of genetic engineering and monoclonal antibody technology, which started in the 1970s, has led to the introduction of a large number of new products with application in many different areas. The most highly visible applications have been in the area of human health care, with products such as human insulin, interferon, tissue plasminogen activator, erythropoietin, colony-stimulating factors, and monoclonal-antibody–based products. In addition, significant new products for agriculture, the food industry, fine chemicals, and the environment are also under intense development. Although products analogous to these new biotechnology products had been made previously, the number and diversity of products, and the number of companies involved, has grown tremendously. Experience in the manufacture of these "biotech" products was very limited, and the technology needed was seen by many as a limiting factor in the successful application of biotechnology. Improvements in production technology were required, as well as a rapid increase in the number of people involved in all of the different aspects of production. The field of *bioprocessing* became a very important part of biotechnology.

Bioprocessing encompasses the many steps required to synthesize, isolate, and formulate the products. There is a great deal of diversity in methods, and in the equipment and facilities required. However, several key processes and types of equipment are utilized in the production of most biotech products. The synthesis of biotech products by microbes or by cells from higher organisms is generally carried out in fermentors, although some new products are being synthesized in "bioreactors", or in animals. Alternatively, the synthesis of relatively small molecules can be carried out directly by chemical methods, without the need for biological cells. The isolation of the product from the fermentor broth or animal fluid generally involves initial steps of clarification or concentration of the fraction containing the product; centrifugation, precipitation, and filtration are the most common ways to accomplish this. Subsequent purification and formulation steps are highly dependent on the nature of the product and its application. Chromatographic procedures are used almost without exception to separate pharmaceutical products from the remaining contaminants. For products outside the pharmaceutical area, the final steps in manufacturing vary widely with the type of product.

The field of bioprocessing involves many areas of expertise, and requires the fulfillment of several sometimes conflicting criteria for success. Biological and biochemical expertise are required to develop and conduct the processes for the synthesis and purification of the products. A broad range of engineering expertise is required to design and construct the many aspects of the manufacturing facility. This includes the process equipment, the support systems that, for example, provide pure water, clean steam, and waste handling, and the facilities that house the equipment. Furthermore, an understanding of regulatory requirements from the viewpoints of pharmaceutical standards (for example, Good Manufacturing Practices), environmental concerns, and worker safety is also essential. Success is measured in terms of reliability of the overall process, time from conception to routine operation, cost of production, and satisfaction of regulatory requirements.

The limited past experience with bioprocessing and the need to rapidly develop manufacturing capacity, especially in the new biotech companies, have given rise to a need for information that will allow the many individuals entering this field to develop and operate the production facilities. This book was conceived to assist those people with acquiring or expanding their knowledge of the bioprocessing field.

The book is subdivided into four sections, covering *Process Systems*, *System Components*, *Support Systems*, and *Facility Design*. The first and third of these sections reflect the fact that there are two types of equipment required in the plant: the equipment in which the actual product is synthesized or processed (such as the fermentor, centrifuge, and chromatographic columns) and the equipment that supplies support for the process or the facility (such as the water system, steam generator, waste system, and air conditioning). In the second section, System Components, are described such components as pumps, filters, and valves, which are ubiquitous and not limited to a certain type of equipment. The final section, Facility Design, covers planning and designing the entire facility, including the requirements for containment and validation of the process. There is some overlap in the topics covered, but this is seen as useful because different perspectives and in some cases different points of view are brought out.

Although this book has a wider scope than do most books on bioprocessing, it cannot cover every aspect of bioprocess engineering completely. Where there is ample literature already covering certain specialized fields, such as mammalian cell bioreactors, the authors have been encouraged to refer to existing works, rather than discuss those fields in detail. The emphasis has been on examining the systems and components that are common to most or all biotechnology production processes, instead of going into the particulars of all of the alternatives for each specific step in bioprocessing.

The authors for each of the chapters in this book were requested to provide information that would be of practical use in the design or operation of a bioprocessing facility. The authors have relied heavily on the experience they have gained in the performance of their jobs, and through interactions with their colleagues. In many cases, we found differences of opinion as to the best tactic for solving the problems encountered in bioprocessing. The authors were encouraged to explore the options available, and to give their opinions on what they felt was the best approach. Their differences in opinion demonstrate that the field of bioprocessing is still developing rapidly, which makes it both difficult and challenging. We hope this book will assist the participants in the field to make progress more rapidly.

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PROCESS SYSTEMS

Fermentor Design

Marvin Charles and Jack Wilson

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In this chapter we consider only agitated vessels for aerated, aseptic fermentations. Many other vessel types with distinct advantages for specific applications have been proposed, and a few of these have been used for limited commercial applications. In most cases, however, their advantages do not outweigh those of the agitated tank (namely, that it is better understood, offers more reliable scale-up, and is easier to adapt to multiple products), which is likely to remain the dominant fermentor type for the foreseeable future. Information about other fermentor types is given in the references [1, 2a, 3a].

We address the basics of sizing and designing fermentor vessels and their agitation and aeration systems. We also discuss popular misconceptions and design pitfalls. We work through a somewhat detailed design example at the end of the chapter.

Finally, this chapter is not a complete design manual. Rather, it is a guide that illustrates how a good design engineer thinks, some of the methods he (or she, understood throughout) employs, and the kinds of information and resources he needs to do his job best. It should benefit not only those beginning to study the basics of fermentor design (students and practicing engineers), but also those interested in buying fermentors and complete systems.

1.1 Design Philosophy

The objective of rational design is to produce the plans necessary to build economical systems that satisfy well-considered performance criteria. Two generalizations worth noting are:

(a) The purpose of a fermentor is to provide a contained (protected), controlled, homogeneous environment, in which a fermentation can be performed safely and practically to achieve particular objectives.

(b) Objectives usually are defined rather loosely for lab applications, and tend to become tighter with increasing scale. A high degree of flexibility usually is a major objective in the lab. Reliability, safety, cost, and compliance with regulatory requirements usually are primary factors for production equipment. These transcendent criteria are touchstones for ordering the priorities of more specific performance criteria, such as mixing quality, oxygen transfer, and heat transfer.

The realization of process objectives depends on reliable operation of an entire system, of which the fermentor is only one part; therefore, rational design of the fermentor requires careful consideration of how it is integrated into the process. The designer should, therefore, consider from the outset factors such as plant scheduling, space constraints, relationships between fermentor productivity and throughput rates of downstream equipment, containment and validation requirements, utilities requirements, potential interruptions in normal plant operation, overall labor requirements, and operating versus capital costs. Monitoring/control, sterilization

methods, and the number and types of addition vessels also must be considered as early in the design process as possible, particularly with regard to how they affect overall process requirements.

The designer usually must use information obtained at a scale much smaller than the one for which he is designing. Very frequently, he must start while the fermentation still is being developed at lab scale. And so he enters the mystical world of fermentation scale-up. Much has been written about scale-up criteria, but what has not been written usually is more important than what has been written. Published scale-up criteria usually fall into one or more of the following types:

(a) primarily theoretical, and based on assumptions and gross simplifications that are not valid for most fermentations;
(b) single-parameter objectives (such as maintenance of oxygen-transfer level);
(c) experiments in which observations are limited to those required to study single-parameter objectives;
(d) experiments involving scale-up from very small to small;
(e) experiments done under very idealized conditions, which are impractical for commercial applications.

Some of the popular scale-up methods (so-called) come in the form of correlations, which either are implied or are inferred to be scale-independent and to have a wide range of applicability. Unfortunately, most are not. Others are cast as rules of thumb, subject to similar implications or inferences. Most of these are based on very limited observations of specific fermentations.

The critical factors missing in all of the methods are integration and the recognition that what is important at one scale may not be important at another. These missing factors can lead to very significant problems, since just about every aspect of a fermentation influences most other aspects. The reality is that sound design requires a great deal of compromise, based on a wide range of real experience doing real fermentations at meaningful scale. Rational scale-up is not a simple textbook exercise.

The various methods and rules alluded to above are presented in many references [4, 5a, 6], and are not repeated here. But you are cautioned to bring to such readings all the critical thinking you can muster, and to seek experienced counsel.

Design is an applied art, not a science. It requires the consideration of a host of interrelated factors, many of which are risk assessments and value judgments; therefore, the design engineer must apply experience and judgment in reaching reasonable compromises without attempting to violate the laws of physics. In general, there is no such thing as the ideal fermentor. The engineer who forgets the basic principle that "good enough is better than perfect", and attempts to optimize a satisfactory design, probably won't see the system built in his lifetime, and probably should be in some other line of work.

The designer must balance theory with the application of quantitative, empirical correlations and various rules of thumb. Lest the novice be led astray, it is important to note right away that many of the so-called quantitative methods leave a great deal