

Process Architecture *in* Biomanufacturing Facility Design

Jeffery Odum
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This book is dedicated to our families, who tolerate and endure the consistently inconsistent nature of our schedules and timeline when developing this type of knowledge tool. Your patience is both appreciated and amazing.

Jeffery Odum and Michael C. Flickinger

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Foreword

Architecture evokes an interaction between fabricated space, form, and human activity. It can be a modest human-scale design or an awe-inspiring monumental work of art. Every architecture has both synergy and limitations. The synergy and limitations can be site, materials, artisanship, climate, government regulations, and certainly resources and budget.

Process Architecture in Biomanufacturing Facility Design is the first volume specifically written for architects, designers, and facility engineers to introduce the unique synergy between bioprocessing–biological medicines–people–facility and the limitations imposed by government regulatory requirements for the safe production of complex human biologics or vaccines by living cells.

Jeffery Odum has carefully assembled contributions into a unique and useful volume that explains the synergy of biopharmaceutical product, a carefully controlled process, equipment, GMPs, and facility design. This work explains how bioprocess architecture—the actual steps in the manufacturing process—affects the design of the manufacturing space and how people operating biological processes within this space produce, purify, formulate, and minimize contamination of potent human medicines.

Training a new generation of architects, designers, and engineers is particularly important now as the types and scale of biological medicines derived from living cells are rapidly expanding. Facilities to manufacture biological medicines for long-term care of chronic or degenerative human diseases are being built today. These new facilities will be capable of producing very large volumes of biologics (10,000 kg of active pharmaceutical ingredient or biologic per year) to meet the anticipated demand for treating hundreds of millions of patients over a long period. Examples of these large-scale biomanufacturing needs are facilities to produce biological medicines for treating diabetes, or Alzheimer's.

These facilities also need to be flexible. Many new facilities will be significantly smaller (reduced footprint, reduced construction costs, reduced utility, water, and solid waste requirements per kg product) to speed construction,

reduce financial risk, and to meet requirements of new sites. Examples are new facilities to rapidly manufacture millions of doses of vaccines and adjuvants to meet global pandemics that have recently been built to improve regional vaccine quality. Vaccines can be complex multicomponent biologics manufactured by multistep processes. However, they must be manufactured as new products each year (often combining new antigens) seasonally. These facilities need to be operated efficiently with standardized automation for biologics to be compliant and cost effective.

In contrast, the emerging field of patient-specific biologics and cell therapy requires a completely different process architecture approach to facility design as each product may be derived from cells from a single patient destined to be immunologically or genetically altered and returned to that same patient. Product isolation and facility design to minimize product bioburden contamination are critical for these types of processes.

Process Architecture in Biomanufacturing Facility Design is an important new work to accelerate the design of a new generation of efficient, flexible, cost-effective, and compliant biomanufacturing facilities to deliver life-changing biologics and vaccines to patients worldwide.

Michael C. Flickinger, Professor, PhD

Preface: Why a Book on Process Architecture?

Process Architecture may not be a term that many people are familiar with in the context of this field. Most people relate this term to computer hardware and software design or business processes such as logistics or enterprise systems. The structure of a process system, or its architecture, is viewed as the hierarchy and relationship of a process system's components. But within the global biopharmaceutical industry, the term has a completely different meaning and holds a key strategic place in the list of activities necessary to develop a drug or biologic manufacturing facility design that meets regulatory compliance requirements.

For biopharmaceutical drug and vaccine manufacturing facilities, the relationship between product, process, and facility requires synergy across architecture and engineering disciplines, which is driven by a set of legally binding guidelines known as current good manufacturing practices, or the cGMPs.¹ These strict regulatory guidelines are the foundation of current drug safety practice related to how these specialized facilities are licensed and operated. The critical first steps in developing concepts for proper operational effectiveness and regulatory compliance involve the execution of *process architecture* as presented for the first time in this book.

Biopharmaceutical process architecture involves the integration of process understanding and facility architecture concepts to create a design that meets the regulatory compliance guidelines for the manufacture of quality, safe drug, and biologic products. Product attributes, process parameters, and operational philosophy are defined and integrated via architectural programming activities that will define the solution(s) to an architectural problem, in this case, how best to provide a regulatory compliant manufacturing facility design.

This book focuses not only on the regulatory considerations driving facility design decisions but also on many of the different aspects of design specific to biomanufacturing pilot and production facilities for both biological therapeutics and vaccines. As the global biotech industry continues to grow

1 Code of Federal Regulations, 21CFR, Part 211.

into its fourth decade, more facility design companies will find themselves in a position to both understand and define facilities in a manner where the architectural program not only addresses function, form, economics, and time but also does so in a manner that will withstand regulatory scrutiny from different global agencies. Operational efficiency, flexibility, high-utilization rates, and a stringent focus on quality will take precedent over image. The practitioner leading the programming effort must not only establish the considerations, limits, and possibilities of the design but must also understand the product–process–facility relationship and be able to apply cGMP in all elements of the conceptual design.

The global biotechnology industry focused on drug and vaccine manufacturing will continue to grow; the execution of sound process architectural programming to define compliant facilities will be an essential part of this growth process. The authors contributing to this book are thought leaders within this industry and bring, along with their skills, a broad depth of experience in process engineering, architectural programming, regulatory compliance, facility operation, and aseptic manufacturing. Their willingness to contribute their time and energy to this project is not only greatly appreciated but is also a valuable and unique contribution to the expansion of the industry's body of knowledge.

Jeffery Odum, CPIP

Chapter 1

Introduction to Biomanufacturing

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1.1 Introduction

While the book covers designing biopharmaceutical and vaccine manufacturing facilities, this chapter is a brief introduction to biopharmaceutical manufacturing covering the essential elements of the overall biomanufacturing enterprise. Biomanufacturing is very complex and challenging. To be successful, the facility must be designed with a basic understanding of the overall manufacturing enterprise and how it functions. To simplify the discussion, vaccines will be combined with protein products for the purposes of this chapter.

The objective of this introduction is to:

- Identify and describe a biopharmaceutical manufacturing enterprise's three basic elements (process, facility, and infrastructure);
- Briefly describe the constituents used in biopharmaceutical manufacturing processes to appreciate the complexity and fundamental issues of operating the process's unit operations (UOs) within the facility;
- Identify the basic process UOs typically used in biopharmaceutical manufacturing;
- Provide a framework for describing, evaluating, and controlling the facility and process UOs, and;
- Provide an understanding of how the overall manufacturing enterprise is operated and controlled.

In order to understand the challenges of biomanufacturing, we begin by looking at the overall manufacturing enterprise that surrounds and operates the manufacturing facility. As shown in Fig. 1.1, the manufacturing enterprise's myriad of components can be divided into three elements. The facility, process, and infrastructure are integrated and operated in concert to produce the product. As will be discussed, the three elements contain a wide variety of components

required to achieve the overall objectives of the enterprise. Although the distribution used here provides structure to this introductory chapter, many variants or alternative distributions are possible.

In older enterprises, the facility and process are interdependent because the two were designed and constructed at the same time, usually for a specific product. In future enterprises, the process and facility will be much less dependent on each other, with the multiproduct facility capable of running a wide variety of different processes. Because the process is not directly integrated with the facility, the processes can be moved in and out of a facility or moved to a different facility depending on manufacturing capacity or logistical requirements [1].

Manufacturing facilities are harder to run than they are to build. For the enterprise to be successful, the facility must be designed to be operated. All three elements must be carefully developed, so they can be integrated to assure the overall enterprise's success. They must work together in order to support and facilitate adequate control of all production activities to assure the efficient production of high quality product over the entire lifecycle of every product produced by the facility. This concept is emphasized by understanding that conformance lots or PPQ (process performance qualification) batches are more than just a test of the process [2]. Conformance lots are a test of the enterprise's ability to operate the process. Many conformance lot issues are encountered because the staff, part of the infrastructure, are not adequately trained and do not have the experience to execute the many tasks and activities required to successfully run the process and facility.

Starting from the beginning, the basic constituents of biopharmaceutical processes are cells, nucleic acids, and proteins.

1.2 The Basic Constituents of Biopharmaceuticals

Biopharmaceutical manufacturing uses relatively simple processes composed of UOs employing relatively simple pieces of equipment as compared to other industries, particularly those in the chemical and petrochemical industries. However, the constituents within the UOs are many orders of magnitude more complex. The purpose of this section is to provide a very brief introduction to the formidable challenges of managing and manipulating these constituents.

A defining element of biopharmaceuticals is the use of cells to produce the product. The product is most frequently a protein, but the product can be the cells themselves used for cellular therapies or in some cases the product can be genetic material manufactured in large quantities to modify or control genetic constructs and control mechanisms within the patient.

The cell is the largest and most complex element. The growth and characteristics of the cells are defined primarily by the genetic information stored in

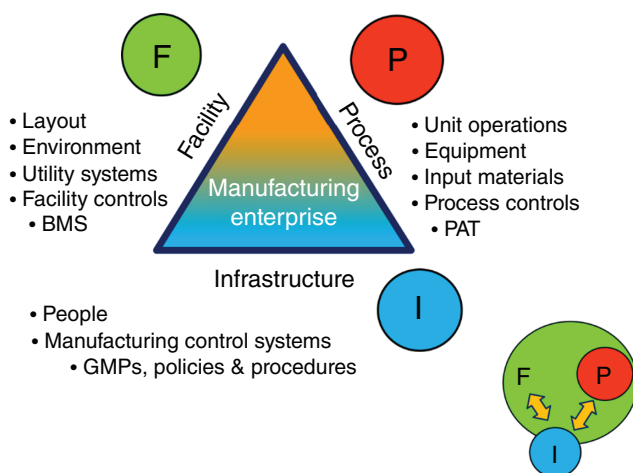


Figure 1.1 The manufacturing enterprise is composed of three elements. Basically, the enterprise operates the process within the facility under the control of the infrastructure. The process and the facility are separate entities that can be run independently with the infrastructure providing the interface between the two. As shown in the side figure, the process is contained within the facility. The infrastructure element resides partially within the facility because the infrastructure is composed of both facility-specific and companywide, multifacility components.

the cell's DNA. The machinery of the cells that use the genetic information is operated by proteins. The discussion will begin by describing the simplest element, proteins. Most pharmaceutical products are proteins manufacturing by the cell under the control of genetic constructs inserted into the cells using recombinant technology.

1.2.1 Proteins

Biopharmaceuticals are proteins. The product is created by cells in a complex environment of many complex biological molecules (carbohydrates, nucleic acids, lipids, and proteins) and cellular processes required for cell growth and product manufacturing. The discussion begins with an overview of proteins and their structure and behavior.

The fundamental structure of proteins is shown in Fig. 1.2. Proteins are polymers of 20 specific amino acids shown in Fig. 1.3 assembled by the cell according to the genetic code contained within the cell.

The sequence of amino acids forms the primary structure of the protein. Depending on many different structural and environmental factors, the amino acid chain is folded into higher order structures. These higher order structures can be defined as follows:

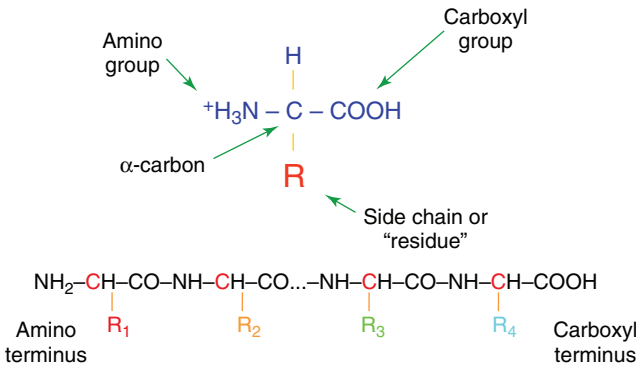


Figure 1.2 Proteins are a polymer of the 20 amino acids listed in Fig. 1.3. They are typically between 100 and 1500 amino acids in length. The term *peptide* refers to amino acid polymers of <25 amino acids.

Amino acid	Abbrev.	Amino acid	Abbrev.
Alanine	Ala (A)	Methionine	Met (M)
Cysteine	Cys (C)	Asparagine	Asn (N)
Aspartic acid	Asp (D)	Proline	Pro (P)
Glutamic acid	Glu (E)	Glutamine	Gln (Q)
Phenylalanine	Phe (F)	Arginine	Arg (R)
Glycine	Gly (G)	Serine	Ser (S)
Histidine	His (H)	Threonine	Thr (T)
Isoleucine	Ile (I)	Valine	Val (V)
Lysine	Lys (K)	Tryptophan	Trp (W)
Leucine	Leu (L)	Tyrosine	Tyr (Y)

Figure 1.3 While the Earth's natural environment contains hundreds of different amino acids, all life forms use only the 20 amino acids shown.

- *Primary*: the linear amino acid sequence of the polypeptide;
- *Secondary*: the localized folding of the primary structure into substructures sometimes called *helices*, *strands*, and *sheets*;
- *Tertiary*: the combining of the secondary spiral and flat elements to form larger three-dimensional structures;
- *Quaternary*: combining of tertiary structures to form a much larger complex three-dimensional structures.

The structures determine the protein's properties, including its safety and efficacy as a therapeutic product.

Additional protein complexity comes from post-translational modifications (PTMs) added to the protein during and after the four structural features

described earlier are formed by the cell. PTMs change the behavior of the protein in solution and affect their therapeutic impact, safety, and efficacy in a wide variety of ways. The four structural features and PTMs along with the various altered product forms resulting from degradation, alternations, misincorporation, and aggregation combine with various impurities and contaminants from the manufacturing processes to determine the complex set of critical quality attributes (CQAs) that define the product's overall quality target product profile (QTPP) as defined in ICH Q8 (R2) [3]. The objective of the manufacturing process is to consistently produce a product described by the product's QTPP defined during development, tested in preclinical testing; and demonstrated to be safe and effective by clinical trials. For more details on the definition of biological products, ICH Q6B and ICH Q5E should be consulted [4,5]. Biochemistry text books can be consulted for more information related to the structure, composition, and behavior of proteins [6–8].

All cells use thousands of proteins, called *enzymes*, to operate the machinery required to perform the myriad of internal maintenance functions, reproduce, and manufacture the product protein [9]. The production of proteins within the cell is carried out by complex metabolic pathways based on the genetic information contained within the cell. The genetic information is stored in the cell's *DNA* (deoxyribonucleic acid) formed by polymers of nucleic acids described later.

1.2.2 Nucleic Acids (DNA and RNA)

DNA provides a stable and efficient mechanism for storing and maintaining genetic information critical to the cell's ability to consistently and efficiently replicate without losing the ability to produce the target protein over many generations. DNA has a complex double helix spiral structure formed by two complimentary sequences of nucleic acids. The shape of the double helix can be found in many text books on the subject.

The management of DNA within the cell is a very complex and poorly understood sequence of internal processes. DNA has six different structural features much like the four structural features of proteins, but much more complex involving other supporting protein molecules to assist with storage, protein expression, and duplication. Further, DNA is subject to additional complex modifications involved in many cellular regulatory functions controlling how the DNA is used for cellular functions [10].

RNA or ribonucleic acid is a second nucleic acid very similar to DNA used by the cell for a variety of functions. The difference between RNA and DNA is the substitution of the nucleotide uracil for thymine in the sequence. While DNA is stable for information storage, RNA is more biologically active, less stable, and used in a number of important biological functions to transfer information and regulate protein production. RNA is also the basis for some biopharmaceuticals

Central dogma:

- **Replication** - DNA \Rightarrow DNA
 - Provides for cell duplication, but retains genetic information
- **Transcription** - DNA \Rightarrow RNA
 - Transfer of information from genetics to protein manufacturing mechanism
- **Translation** - RNA \Rightarrow Protein
 - Proteins from genetic information

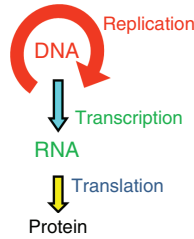


Figure 1.4 The central dogma describes the *replication* of DNA that allows the genetic information to be passed to future generations; *transcription* converts the DNA sequence code for the protein into RNA for transmission to the *translation* mechanism that converts the RNA sequence code into the amino acid sequence that determines the protein's primary structure.

not covered in this introduction. However, the same basic concepts apply to manufacturing biologically active RNA therapeutics.

Nucleic acids and protein expression are connected by the central dogma that describes the three steps required to support cell reproduction and protein production. The central dogma is shown in Fig. 1.4 [11].

Protein expression within the cell is controlled by a wide variety of feedback and feed forward control mechanisms based on the central dogma. Many of these control mechanisms have not yet been identified and much work remains by the scientific community to better understand the myriad of mechanisms used by the cell to control protein expression.

The use of living cells to manufacture the product is the primary distinguishing feature of biopharmaceuticals. While peptides can be manufactured by chemical synthesis, long amino acid sequences and the resulting structural forms and PTMs required for therapeutic safety and efficacy can only be achieved using living cells.

The history of cells goes back more than 3.5 billion years. The evolutionary history of cell development has resulted in extraordinary capabilities and complexity. The following is very brief introduction of the basic features required for the cells to make therapeutic proteins and vaccines.

1.2.3 Cells

In nature, there are virtually an unlimited number of different types of cells that possess a wide variety of capabilities, behaviors, and properties. The field of microbiology is very diverse and covered by many good books [12–14]. Biopharmaceutical manufacturing typically uses and manages one of two types of cells. For the purposes of understanding the fundamental principles associated with biomanufacturing, only two of the myriad of possible cells will be covered here.

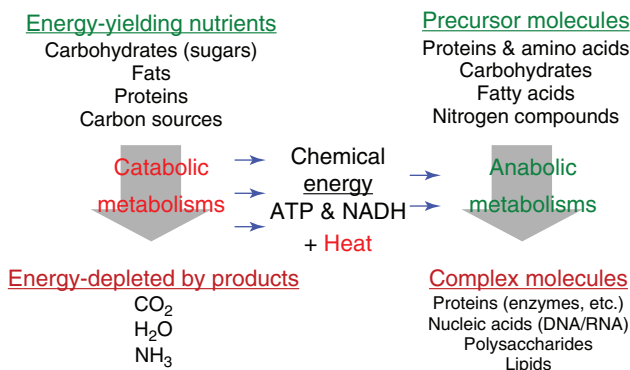


Figure 1.5 All cells operate using catabolic metabolisms that generate energy for the cell by converting energy-containing raw materials into energy-depleted by-products. Anabolic metabolisms use the energy to convert other raw materials into complex molecules required to operate the cells metabolisms and support cell reproduction. The product protein is one of the complex molecules.

The first cell type is prokaryotes, which are relatively simple cells and grow very rapidly. Many prokaryote cells double in number every 30–60 min [15,16]. *Escherichia coli* is one of the types frequently used to make recombinant proteins. Prokaryotes are grown in fermenters designed to meet the requirements for supporting rapid growth.

The second type is eukaryote cells derived from plants, animals, and insects. The most frequently used eukaryote cells are mammalian cells [17]. Of the mammalian cells, Chinese hamster ovary (CHO) cells are frequently used for manufacturing therapeutic proteins. Eukaryotes have roughly a thousand times the internal volume of a prokaryote cell, although the sizes of both types of cells can vary over a wide range. Eukaryote cells are grown in cell culture bioreactors.

Both types of cells operate using metabolisms driven by a large number of specialized protein called *enzymes* necessary to make the myriad of required reactions work efficiently [9]. The metabolisms have evolved over billions of years and are extremely diverse and highly efficient in performing their functions. Taking a simplistic view, the metabolisms can be divided into two categories. Catabolic metabolisms shown in Fig. 1.5 on the left take energy containing raw materials and break them down to provide energy to the anabolic metabolisms on the right. Anabolic metabolisms take complex raw materials and produce the complex molecules required for cell functions and reproduction.

As will be explained, growing the cells and producing the product are determined by the manufacturing process's ability to manage the inputs and outputs of the two metabolisms. Adequate raw materials must be supplied to the cells along with the removal of by-product waste materials. An environment that

supports the cell's metabolic enzymes with the correct operating temperature by removing or adding heat to the cell's environment is required. Thus, the necessary energy and mass transfer conditions and capabilities must be provided by the fermenter or bioreactor.

With the primary constituents identified, the discussion turns to the processes and equipment used to manage the cell's internal processes to grow the cells, produce the target protein, and then purify the product to provide a therapeutic product with the required purity, potency, and activity. The processes and equipment will be described in the context of the manufacturing enterprise are shown in Fig. 1.1.

1.3 Enterprise Element #1—Manufacturing Processes

Expanding Fig. 1.1, the components of the enterprise's process element are shown in Fig. 1.6.

1.3.1 Process—Unit Operations

The distinguishing feature of biomanufacturing is the growing of cells to produce the biopharmaceutical or vaccine. Biopharmaceutical processes or UOs use relatively simple equipment to manage and protect the complex constituents described previously. Some specific requirements of the cells and proteins in the process are poorly understood. The complexity of the cells,

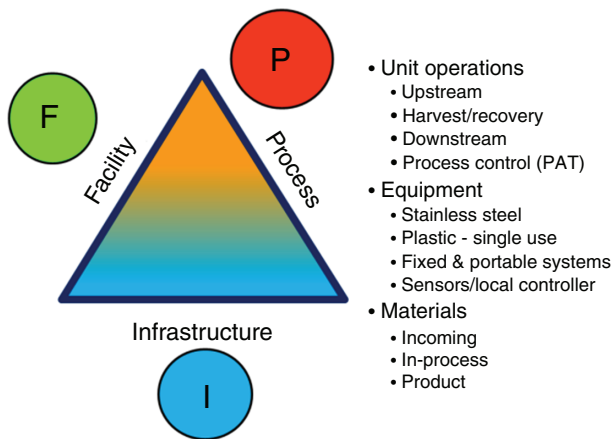


Figure 1.6 The process element of the manufacturing enterprise includes the unit operations required to make the product along with the equipment implementation of the process and the raw and in-process materials required to make the product.