CHAPTER 1

Introduction

1.1 Overview

Bio-pharmaceuticals has emerged as one of the most critical industries in the twenty-first century. Advances in science and medicine have led to new techniques, new medicines and vaccines with far-reaching impact on the health of the global population.

Most biological processes have complex and precise requirements for optimal quality, yield, and production. These requirements may be technical or regulatory in nature. Both are equally important in ensuring a safe, effective, and proven process. Proper design and implementation of automation systems help to ensure a safe, predictable, high quality, and low-cost supply of the world's vaccines and medications.

This book provides guidance to the engineer who is attempting to apply automation to bio-pharmaceutical processes. Technical, biological, and regulatory requirements are addressed. The primary focus is the effect of these requirements on automation system design and implementation.

1.2 Factors Affecting Automation in Bio-pharmaceuticals

Many factors affect the application of automation in the field of bio-pharmaceuticals. Some of these factors are driven by the unique nature of biological processes, and others are driven by regulatory requirements. This section outlines some of the key factors that will influence automation system design discussions throughout this book.

Biological Processes

Biological processes, by their very nature, are extremely complex. Consider the fact that a single cell may complete over 10,000 chemical reactions in one second [1.1]! Each of these reactions is dependent not only on the environment around the cell, but also upon the "history" of that particular cell, as determined by the concentrations of various proteins, enzymes, food and waste products present within the cell.

In most cases, the desired end product may be only one of the thousands of chemical compounds produced by that cell. These compounds are so complex that they may have molecular weights measured in the hundreds of thousands [1.2]. In some cases, the cells themselves are the product.

Figure 1–1 shows that, in a sense, each biological cell is a factory with raw materials, processes, controls, and waste processing capability.

Designing the process to effectively grow and purify a single compound requires great attention to detail. Product yields may vary by order of magnitude, due to minor changes in pH, temperature, or concentration of trace elements. The automation system must similarly be designed with great attention paid to the control of the key process variables.

Dynamic models can be used to provide insight into the process at design time. They may also be used to optimize operations for yield, throughput, and quality. Chapter 7 discusses the modeling of key unit operations.

Keep in mind that some bio-pharmaceutical processes are very small bench-scale operations, while others may involve a million liters or more. The scale of the operation or the value of the product may drive the engineer to more complex automation solutions.

Precise, repeatable control is certainly a goal of automation in any industry. However, in bio-pharmaceuticals, the entire production run may be completely scrapped if you cannot prove that you have succeeded. Products from a "bad" run can not be slowly blended in with the next batch—as is often done, for example, in the chemical, oil, or pulp and paper industries. The applications, detailed in Chapter 3 of this book, are targeted at design and implementation considerations to ensure precise and repeatable control of the most common bio-pharmaceutical processes.

Advanced control methods are often used in this industry. On-line property estimators may be used where a direct measurement is impossible or impractical. Adaptive and Model predictive controls may be used to help compensate for the non-linearities and interactions, respectively, that

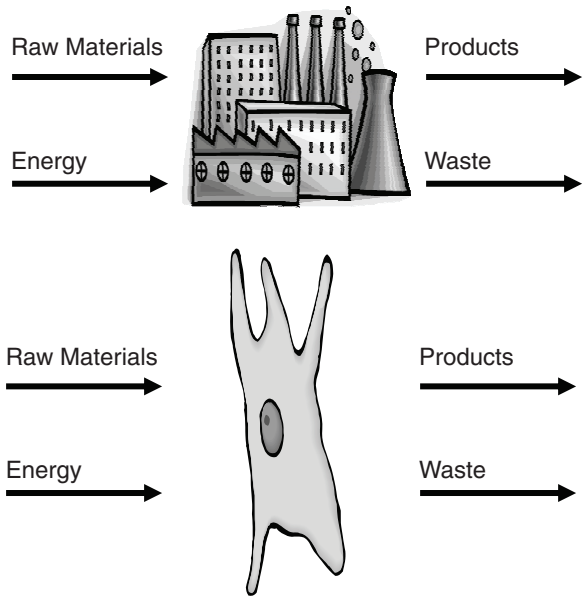

Figure 1–1 The Cell as a Factory

often occur in biological systems. Advanced Batch Control methods may also be used to supervise and coordinate the actions of several unit operations, or to orchestrate the production of multiple products using some of the same equipment. Chapter 7 focuses on all of these aspects of advanced control applications.

Government Regulations

A variety of government agencies worldwide are responsible for ensuring a safe, pure, and efficacious supply of medicines to the world's population. Each agency has its own set of regulations and interpretations, designed to ensure that these criteria are met. Throughout the pharmaceutical industry, these regulations directly affect the product being produced. Regulations also govern the engineering design, engineering, construction, commissioning, and qualification of the production facilities themselves.

Most agencies expect regulations to be something of a moving target, continuously improving over time. As such, it would be nearly impossible to cover the specific expectations of every regulatory agency in this book. Rather, we will highlight the key design principles and regulatory factors, directing the design engineer toward an effective design, and referring the

engineer to the most current regulatory guidance for the most current practices.

U.S. FDA 21 CFR Part 11

In 1997, the United States FDA issued a regulatory code update known as 21 CFR Part 11, which focuses on "Electronic Records and Signatures." This regulation directly impacts almost all automation systems. The focus of the regulation is to ensure the integrity of data and authorizations within electronic systems [1.3].

In 2004, the FDA issued a new "Guidance" document on the enforcement of 21 CFR Part 11. This guidance provides additional interpretation of the regulation [1.4].

While this book can not be a thorough reference on 21 CFR Part 11, it will provide practical insight and guidance into the incorporation of Part 11 requirements in your automation application. Chapter 5 discusses the implications of 21 CFR 11 in more detail.

Good Engineering Practices

Good Engineering Practices (GEP) are used to ensure that the engineering process follows a logical, well-documented, and structured plan. GEPs include:

- Clear design specifications
- Structured reviews such as Enhanced Design Review (EDR)
- Clear approval processes for all design documents [1.5, 1.6].

For automation applications, it is imperative that Good Engineering Practices be applied. This is particularly true for the key design documents, such as P&IDs, Network Diagrams, and IO Lists. The "Managing Automation Projects" section of Chapter 4 provides some guidance on specific GEPs to be used when designing automation applications.

The Good Automated Manufacturing Practice guides, or "GAMP" guides, published by ISPE, contain extensive suggestions for proper documentation of the automated systems. This book will not duplicate the GAMP guides, but will provide guidance in developing the application, while deferring to the GAMP guides for documentation practices [1.5, 1.6].

Validation and Qualification Requirements

The procedure for validating or qualifying a process involves a systematic, documented review of the final system against the design specifications. The qualification process is most often conceptually modeled using the GAMP-developed V-Model illustrated in Figure 1–2. The V-Model shows the typical steps and deliverables in an automation project, starting from top left, following down to the bottom of the chart, and then continuing up to the top right. Each activity or deliverable on the right-hand side of the "V" is used to validate the deliverable or activity on the left-hand side.

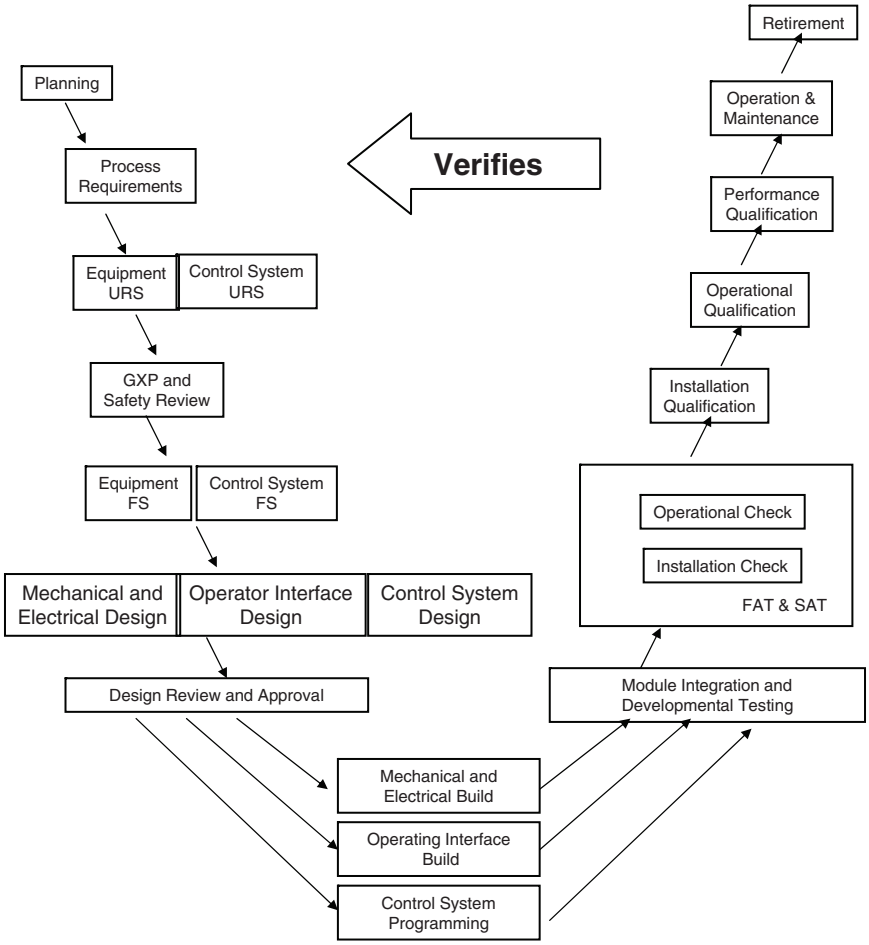

Figure 1–2 The V-Model for System Qualification (Source: ISPE GAMP)

The key components of any validation or qualification activity are the documentation of design requirements followed by the verification that the finished system complies with those specifications. The GAMP Forum has developed widely accepted guidelines for the commissioning and qualification of automated systems [1.3, 1.4]. The guidelines are fairly generic. This text will attempt to fill in some specific information for process control automation applications in the bio-pharmaceutical field.

Maintaining and controlling documents is an absolute "must." Keep in mind the auditor's motto: "Not Documented, Not Done." This means that if you have completed an activity, but not documented that activity, the inspector cannot accept that the work was done. For example, if you held a design review, but didn't publish notes...how could you confirm the review was successfully completed?

For the most part, the documentation required is not much different than what is supplied for any automation system designed using Good Engineering Practices (GEP). However, it is important that strict document control procedures are followed.

In addition, qualification activities must follow an organized, pre-approved plan, and usually conclude with a formal report. Other organizations, such as the Quality Assurance Department, may need to review or approve the reports and other documents.

Sanitary Design, CIP and SIP

Microbial life is extremely robust. Microbes will find a way of surviving, even thriving, in the most restrictive of environments. In fact, most microbial life requires only warm water and a tiny bit of food. Great attention must be paid to the details of piping and instrumentation "fit and finish" to ensure that your production system does not harbor potentially harmful microbes.

This directly affects automation systems because instruments and valves are subject to sanitary design requirements. This includes ensuring that surface finishes are extremely smooth, and ensuring that sharp inside corners and "dead legs" do not exist. Piping must be designed to ensure "drainability" of all piping, instruments, and valves. Sanitary design considerations are addressed in some detail in the "Hardware" section of Chapter 2.

To ensure purity of product, and to reduce or eliminate the risk of exposing personnel to harmful materials, Clean-In-Place (CIP) and Steam-In-Place (SIP) procedures are used. These procedures will subject the process equipment and instrumentation to chemical cleaning fluids, and extreme temperature conditions.

The CIP and SIP operations themselves are typically automated sequences of process operation. They will need to sequence valves to ensure that all possible flow paths have been cleaned or steamed. Chapter 3 describes design considerations for the automation of CIP and SIP systems.

Containment

Many biological systems used in manufacturing contain pathogens: organisms which are harmful to humans. These pathogens must be contained to prevent exposing workers or the general public to life-threatening organisms. Most biological systems are subject to contamination from other opportunistic organisms, competing for the food source, or even attacking the desired organism and/or products. For these reasons, many bio-pharmaceutical processes must be "closed" or "contained."

Closed systems present certain instrumentation and control challenges. For example, the engineer must consider how to clean, maintain, and calibrate instruments in this environment. Access to the instrumentation during installation and maintenance may provide some difficult design challenges. These are discussed in the "Maintenance" section in Chapter 4.

Also, control tolerances for HVAC system may be tightly regulated, leading to specific controller, alarming, and interlock requirements. Room pressures are often tightly controlled to ensure that airflow between rooms is carefully managed.

In bio-pharmaceuticals, unlike other industries, HVAC is considered a part of the process. As such, the automation engineer will need to be knowledgeable in the HVAC process in addition to the more traditional parts of the process.

Quality

Quality is a very broad, yet very simple topic. Consider that most bio-pharmaceutical products are intended to be used to improve health. Vaccines, for example, are injected directly into the bloodstreams of babies and the elderly. Ensuring that the product repeatably meets exacting

standards seems obvious. Paying attention to all of the details to ensure that this happens is vital...literally.

Ensuring the quality of the automation application requires that attention be paid to Good Engineering Practices (GEPs), Good Automated Manufacturing Practices (GAMP), and Commissioning and Qualification (C&Q). One of the primary goals of this book is to ensure that the engineer has an understanding of the quality impact of design decisions.

Manufacturers must maintain independent Quality Departments, which provide internal oversight to design, qualification, operation, and maintenance. Chapter 4, "People, Projects, and Profitability," discusses some of the key systems that must be in place to ensure a quality result for your automation system.

Procedures

Procedures affecting automation system design may include specific measures for, among others:

- Documentation
- Design Review
- Commissioning and Qualification
- Instrument Calibration
- Change Control
- Maintenance

Because each company's procedures may vary, it is important that the engineer has a good understanding of company-specific procedures. Chapter 4, "People, Projects, and Profitability," provides some guidance on procedures.

Also, the *GAMP Good Practice Guide* [1.4] is an excellent reference on this topic.

Personnel

In this highly regulated industry, companies must employ properly trained and qualified (documented) personnel, both internal and contracted.

Manufacturers must be able to document that personnel were trained in all appropriate procedures.

It is important to note that training and qualification must address both external and internal competencies. External competencies include such things as PLC programming capability; computer and network understanding; and the abilities to read, write, and review engineering drawings. Internal competencies include understanding of the particular process being controlled, as well as training in company-specific or site-specific procedures. Both internal and external competencies must be addressed and documented.

Industry groups are a valuable resource for establishing documentation of external competencies. For example, the ISA "Certified Automation Professional" program and the "Certified Control System Technician" program provide a solid measure of assurance and documentation that personnel are qualified. ISPE also offers courses in the application of GAMP. [1.7, 1.8]

Chapter 4, "People, Projects, and Profitability," addresses key issues in the selection and qualification of personnel for automation work.

Vendor Management

It is very typical for an automation project to employ many different vendors to handle design, construction, commissioning, qualification, and maintenance of the automation system.

To ensure the quality of the automation system design, companies must employ qualified vendors. A proper vendor evaluation program, coupled with direct oversight of all contracted deliverables and services, is vital to a high-quality outcome.

The first step in ensuring a quality result with any vendor is to have a clearly-defined scope. Scope definition is addressed in the "Managing Automation Projects" section in Chapter 4.

1.3 How this Book Is Organized

Chapter 2—Hardware and Software

Chapter 2 focuses on design criteria for hardware and software in the bio-pharmaceutical industry. The focus is on the most commonly used systems in bio-pharmaceuticals.

The first part of the chapter focuses on hardware, including valves, instrumentation, and transfer panels. We discuss the key design and implementation considerations for each of these devices.

The second half of this chapter discusses software design considerations, including Good Automated Manufacturing Practices (GAMP), Modular Design, Skid Integration, and System Security.

Chapter 3—Applications

Chapter 3 provides a great deal of information on the design of automation systems for the most common processes. For each process, we describe:

- Process Description and Challenges
- Instrumentation
- Control Strategies

The engineer must develop a solid understanding of the process being controlled to effectively design the automation system. The goal of this chapter is to provide a basis for understanding some of the most common processes in bio-pharmaceuticals.

Chapter 4—People, Projects, and Profitability

Chapter 4 provides guidance on some of the "soft" issues affecting automation system implementation. It is crucial for the engineer to understand that an excellent design, if poorly implemented, will result in failure. To ensure success, we must consider the critical "soft" issues. The chapter is divided into three sections: People, Projects, and Profitability.

In the "People" section we discuss the impact of process automation:

- Roles and Responsibilities
- Training
- Qualifications

In the "Projects" section we discuss the most important procedural issues for automation, including:

- Scope Definition and Scope Control
- Change Control
- Vendor Selection and Commercial Issues

In the "Profitability" section we discuss some of the financial considerations of automation system design. This includes discussion of the following topics:

- Project Management
- Vendor Management
- Balancing Quality, Cost, and Schedule
- Value Engineering for Automation

Automation may be a relatively new technology in some plants. The goal of Chapter 4 is to identify key adaptations that may be required for the organization to implement and support automation.

Chapter 5—Computer System Validation

Processes used in the manufacture of pharmaceuticals for human consumption must be validated. The scope of validation includes not only the chemical processing unit operations themselves but also supporting aspects of manufacturing operations such as assay validation, cleaning validation, utility validation (e.g., use of purified water), and computer validation. Chapter 5 summarizes validation requirements for computer systems.

Chapter 6—Batch Control

Many bioprocesses are batch in nature, rather than continuous processes. Automation of batch systems brings some special challenges. Chapter 6 identifies key aspects of automation design for bio-pharmaceutical batch processes.

Chapter 7—Advanced Automation Techniques

Advanced control methods are often used in the bio-pharmaceutical industry. Online property estimators, some based on artificial neural networks, are used where direct measurement is impossible or impractical. Adaptive control, event tracking control, and fault diagnostics are becoming more common at the production scale.

Modern control computers are moving beyond the integration of monitoring, control and diagnostic functions to incorporate dynamic process simulations. Online process and recipe simulations can reduce time to market by identifying production problems and supporting scale-up during process development.

Chapter 7 explores advanced techniques and emerging methods for automation of bio-pharmaceutical processes.

Appendices

The Appendices contain valuable reference information, including:

- A list of Supplemental References
- Glossary of Terms

What is NOT Covered in this Book

The focus of this book is on the *application* of automation. We do, of course, consider the regulatory and procedural issues, but will not seek to be an arbitrator of regulatory interpretation. Every application is different, and the responsible engineer must interpret the regulatory codes as applied to their specific application.

At the practical level, the authors have strived to remain vendor-neutral, and do not endorse any particular supplier of equipment, software, or services throughout this text.

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