*Chapter 7*

# Quality Assurance

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## Objectives

This chapter provides an overview of Quality Assurance (QA) efforts in a biomanufacturing facility.

After completing this chapter the student will be able to:

- define the term *quality* as it relates to the biopharmaceutical manufacturing industry.
- define and distinguish between the terms *Quality Assurance* and *Quality Control* and explain how they both fit within a Quality System in the industry.
- define the roles of the organizational groups Quality Assurance, Quality Control, and Regulatory Affairs.
- describe the specific functions of the QA organizational group.
- describe the basis of the key regulations and the key global regulatory agencies (FDA and EMA) overseeing operations.
- define the terms *GMP* and *cGMP* and their place in a QA system.
- analyze a situation where a QA failure in the pharmaceutical industry resulted in significant public impact.

## Terms

**Change Control:** a formal, documented process used to ensure that changes to a product or system are introduced in a controlled and coordinated manner, thereby reducing the possibility that unnecessary and potentially harmful changes will be introduced; also provides a documentary record of the evolution of the product or system.

**Continuous Improvement (CI):** recognizing that all products, processes, and systems can be improved, CI describes methodologies and management systems designed to enable ongoing improvement.

**current Good Clinical Practice (cGCP):** a guideline that describes a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected.

**current Good Laboratory Practice (cGLP):** a set of guidelines published by various governments which describes general principles that must be complied with when planning, performing, monitoring, recording, reporting, and archiving preclinical laboratory studies; these studies generate data by which the hazards and risks to users, consumers, third parties, and the environment can be assessed for pharmaceuticals and other products.

**current Good Manufacturing Practice (cGMP):** a set of guidelines published in the United States Code of Federal Regulations (CFR) that describes general principles that must be complied with in the manufacture of effective pharmaceutical products in order for the product to be safe; the term *current* indicates these are not static but evolve over time.

**Drug product:** also known as a medicinal product; a formulated dosage form that contains the drug substance, normally (but not always) in combination with one or more inactive ingredients (excipients), that is ultimately used by the patient via a tablet, injection, ointment, etc.

**Drug substance:** also known as an API (Active Pharmaceutical Ingredient); a material that is intended to be used in the manufacture of a drug product and when so used becomes an active ingredient of the drug product; provides the therapeutic effect of the drug product used by the patient; most biopharmaceutical drug substances are protein in nature.

**Electronic record:** any combination of text, graphic, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

**Electronic signature:** an electronic symbol attached to a record for the purpose of signing the record; electronic signatures are conceptually the computerized equivalent of handwritten signatures; an electronic signature provides a unique basis for confirming the identity of the person who made the signature.

**European Medicines Agency (EMA):** the legal agency in the European Community that administers the regulation of medicines in the community and associated nations.

**Expiry period:** the period of time from the date of manufacture that the product or substance is considered to be fit for use.

**Food and Drug Administration (FDA):** the governmental agency in the United States responsible for oversight of the foods and drugs made available to consumers.

**Good Manufacturing Practice (GMP):** a set of guidelines published by various governments which describes general principles that must be complied with in the manufacture of safe and effective pharmaceuticals.

**Pharmacopeia:** a pharmaceutical reference that contains directions for the identification of samples and the preparation of medicines and functions; pharmacopeias are typically published under the authority of a government or a medical/pharmaceutical society.

**Quality Assurance (QA):** all aspects of the systematic monitoring and evaluation of the various activities being performed during pharmaceutical manufacture to verify that appropriate standards of quality are attained and to assure that the products are of the required quality for their intended use.

**Quality by Design (QbD):** a systematic approach to development that begins with predefined objectives and emphasizes product/process understanding and process control based on sound science and quality risk management.

**Quality Control (QC):** all testing that is performed during pharmaceutical manufacture on the associated products and intermediates in order to verify that appropriate standards of quality are attained.

**Quality Risk Management (QRM):** a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

**Quality System (QS):** management system to direct and control a pharmaceutical company with regard to quality.

## Introduction to the Quality Assurance of Biopharmaceuticals

In the manufacture of biopharmaceuticals, both drug substances and drug products are produced, and it is the quality assurance of each of these that is the focus of this chapter. A working definition and brief differentiation of each, however, is beneficial to understanding how each are affected by quality assurance procedures.

A **drug substance** is any substance or mixture of substances intended for use in the manufacture of a drug product and when used so becomes an active ingredient of the drug product—provides the therapeutic effect in the product. Drug substances are intended to produce pharmacological activities, immunological impacts, or other direct effects in the diagnosis, cure, mitigation, treatment, or prevention of disease. Most biopharmaceutical drug substances are proteins. A **drug product**, on the other hand, is a formulated dosage form that contains the drug substance, normally (but not always) in combination with one or more inactive ingredients (excipients), that is ultimately used by the patient. Most biopharmaceutical drug products are injectable solutions.

Relative to production of small chemically-synthesized drug molecules, the quality requirements for safety, efficacy, and purity of biopharmaceutical products pose novel challenges for product manufacture and supply. These challenges arise from the greater complexity of the manufacturing processes necessary for biopharmaceutical production and the products themselves (e.g., molecular size, fragility, heterogeneity, etc.). Other challenges regard potential unique impurities such as DNA, host cell proteins, and various post-translationally modified forms of the desired protein as well as the potential for transmission of infectious agents that might be carried by or produced by the cell line used in the production process.

There are many examples that demonstrate that the quality of a biopharmaceutical product cannot be "tested" into such products but rather must be "built" into all aspects of the biopharmaceutical production process (Figure 7-1).

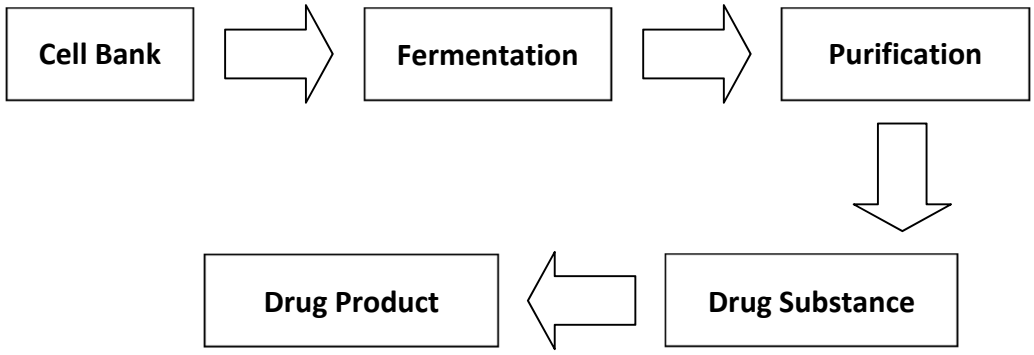


**Figure 7-1. Biopharmaceutical production process**

Maintaining quality is required throughout the product lifecycle. For biologic and biopharmaceutical products the life of the product begins with the establishment of the cell bank. This is a freezer stock of cells that are either naturally capable (or capable through the process of genetic engineering) of producing the product of interest. The cycle continues through the development of cell culture/fermentation processes, through harvest and purification of the commercial active drug substance, to drug product manufacture, and finally through to the expiry period of the product.

Full compliance with the requirements of the applicable current **Good Manufacturing Practice (cGMP)** is expected beginning with the cell bank phase, including all associated facilities, raw materials, and components necessary for the establishment of the cell bank. **Current Good Manufacturing Practice** is a set of guidelines published in the United States Code of Federal Regulations (CFR) that describes general principles that must be complied with in the manufacture of effective pharmaceutical products in order for the product to be safe. The term *current* indicates these are not static but evolve over time. They include, for example, management, people, facilities, materials, controls, records, and self audit. Most countries around the world have enacted laws that require companies that manufacture medicines to conform to GMPs. In some cases this is through the creation of their own GMP guidelines that correspond to their national legislative regulatory framework.

Assuring the quality of a biopharmaceutical product involves the consideration of a number of overlapping aspects, including facility and equipment design, validation, training, documentation, auditing, investigations, and testing and specifications. Though each of these plays a vital role in overall quality assurance, only some are addressed in detail in this chapter; others are addressed elsewhere in the text or have entire chapters devoted to them. A brief description of each, however, will aid in understanding the overall quality assurance concept.

The importance of facility and equipment design is addressed by reference to the system utilized for aseptic control of manipulation of the Working Cell Bank (WCB) vial and fermenter inoculation. This is discussed in the *Facilities* and *Microbiological Control* chapters.

Validation is of particular importance in biopharmaceutical manufacturing. *Chapter 5-Validation* addresses various aspects of validation, ranging from the requirements for culture through the main processing stages (purification, fermentation, and aseptic processing), and associated ancillary items such as cleaning, validation, and analytical validation.

Training in biopharmaceutical operations must ensure that individuals with varying levels of expertise and scientific training from the operator to the Ph.D. scientist receive appropriate training in GMP, job-specific skills, and safety.

Documentation is critically important in pharmaceutical manufacturing as it not only ensures that tasks and duties are standardized and adequately understood by all applicable personnel but also provides a record of all tasks, duties, and activities performed at any given time. These records not only enable organizations to review information when researching or investigating complaints or other such issues but also aid regulatory agency inspectors in reconstructing specific activities and arriving at solutions for rectifying shortcomings.

Auditing is a standard aspect of all quality systems and in this context refers to the audit an organization performs internally as opposed to the external audit performed by regulatory agencies. Typically in such audits either the Quality Unit (QU) or the operational group itself will devote some of its time to checking and verifying ongoing operations and documentation to ensure all is being performed properly. Investigations are required when issues/events occur and something does not proceed according to plan. The root cause must be determined and corrective actions implemented to prevent recurrence.

Testing and validation required during the manufacture of biopharmaceutical products is much more extensive than the requirements for the manufacture of small molecule drugs. The various types of tests that are performed (in-process, environmental monitoring, raw materials, components, drug substance, and drug product) are described in the *Upstream Processing* and *Downstream Processing* chapters In all cases, testing is implemented to ensure that the final dosage form, the active drug substance, and all other materials involved in the manufacturing process (e.g., excipients, packaging materials, product contact materials, etc.) conform to required standards or specifications.

To ensure the quality of each batch of drug product, all of the materials and processing steps from the establishment of the cell bank through cell culture/fermentation, purification, and final drug product manufacture, must be shown to be in compliance with expected standards and specifications (Figure 7-2). The types of specifications will be described later in this chapter.

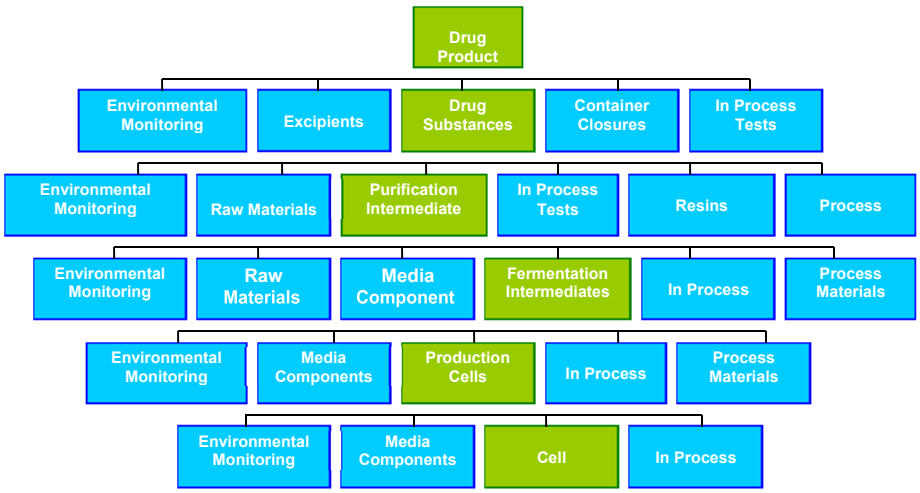


**Figure 7-2. Biopharmaceutical QC testing scheme**

Ultimately the assurance of quality depends on experienced, trained, and committed personnel operating in accordance with well planned, rigorous, and comprehensive policies and procedures that comprise the plant quality systems.

## Quality Assurance (QA), Quality Control (QC), and Quality Systems

In its most general sense, **Quality Assurance** refers to the activities undertaken to guarantee that an organization produces a product of expected and stated quality. Within organizations that produce pharmaceutical and/or biopharmaceutical products, QA is also used to refer to a particular organizational group. This group, required by law, oversees operations and procedures to guarantee that components used in the manufacture of products and the final products themselves meet the required quality standard.

**Quality Control** is often used in two contexts:

- efforts taken to test both the components that go into making a product and the final product itself to ensure that requisite standards are met
- an organizational group that is often under the direction of the QA group; the QC group is responsible for performing actual tests and/or measurements on product samples and drawing conclusions about the properties of the entire batch of product from which the sample was taken.

One of the most common ways to control quality is through testing the product to demonstrate that it complies with certain standards (pharmacopeial standards). A pharmacopeia is a publication that describes the standards for medicines and their active substances. Though the earliest known pharmacopeia is from China and dates back to 4000 B.C.E., there are various pharmacopeias available today, such as the United States Pharmacopeia (USP), the European Pharmacopeia (PhEur), and the Japanese Pharmacopeia (JP). Each is regularly updated to take account of scientific advances, and each has a change process that includes regulators, industry, and academic involvement. The USP is the commonly used reference within the United States.

While QC activities are essential for ensuring a quality product, they are not sufficient to guarantee that each unit in a lot or batch meets the required quality standard. Consider a batch of one million tablets and a requirement that each tablet contain $1.0 \pm 0.1$ mg of the medicinally active substance. Testing that any particular tablet contains this amount of active substance, the tablet becomes destroyed in the process. Thus the only way one could "guarantee" through QC that each and every tablet contains this amount of substance would be to test (and thereby destroy) all the tablets. Since this is not a reasonable process, a sample of the tablets is taken from the batch and the test result of this sample is extrapolated to the properties of the batch as a whole. Though this procedure is often satisfactory, there are times when the adverse is true. For example, if a facility is producing sterile medicines, each individual unit must be free of extraneous microbes. This means the facility must test for the absence of something. It is unsafe to assume that if one unit tested negative for microbial contamination, however, that all other units within that lot would test negative as well. Although extraneous microbes may prove to be absent in 200 tested units from a lot or batch of one million (and indeed extraneous microbes may be absent from 999,999 units of the million), it is little consolation to the one person who receives a contaminated unit and consequently becomes ill.

As a result of examples such as the aforementioned, an industry approach has developed that assumes that quality cannot be "tested" into a product but can be designed in. While QC is an essential and valuable activity in today's biomanufacturing industry, it is not seen as sufficient

in assuring the quality and safety of products. Consequently, the industry relies upon the assurance and guarantees that stem from QA activities.

The thinking about quality in the pharmaceutical industry, especially in manufacturing operations, is not static but rather evolves continuously as new concepts are introduced that are particularly useful and successful. Today QC and QA are seen as parts within a Quality System (QS); those who work in QC typically report to a manager who in turn reports to a QA leader. This is a fairly common relationship, but it evolves as well, much like quality as a whole.

A **Quality System** is defined as "a management system to direct and control a pharmaceutical company with regard to quality." It is not only a way of thinking about quality issues but also a "management system" that defines how management expends its time and energies in the QS arena.

Much of today's Quality Systems Thinking has been guided by the realization that increases in efficiency in pharmaceutical manufacturing have historically lagged behind those of other modern, high-tech products; while reasonable product quality could be achieved in the past, it sometimes required excessive effort and cost. This was due in part to organizations paying less attention to the efficiency of manufacturing practices and processes and focusing instead on the efficiency of the preceding Product Development operations (even though manufacturing costs generally account for approximately 25 percent of the overall expense of producing a pharmaceutical product). Even today, as some pharmaceutical product waste (manufacturing loss) can be as high as 50 percent, some organizations still find it difficult to analyze or understand the reasons for manufacturing failures. Implementation of prudent process improvements and new technologies that could reduce manufacturing cycle times and costs are often slowly adopted. The resulting manufacturing inefficiencies and long cycle times result in biopharmaceutical products that are typically very costly. Further, shortages of essential medicines are not uncommon and are often attributed to inadequate manufacturing protocols, procedures, and testing.

Factors such as these stimulated organizations to perform extensive self-evaluation in the 1990s, prompting Dr. Janet Woodcock, a senior figure in the FDA, to articulate in the early 2000s the need to move to what she termed "the desired state of pharmaceutical manufacturing." In Dr. Woodcock's words this would be

> "…a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight."

The adoption of Quality System Thinking is still in its infantile stages, and while it is too soon to see dramatic improvements across the industry in product quality and related matters, the new tools of Quality Risk Management and Quality by Design are making an overall practical impact on operational efficiency. It is important that all those involved in pharmaceutical manufacturing understand how the traditional concepts of QA, along with Good Manufacturing Practices (GMP), fit into current Quality System Thinking and that QA and GMPs are vital components of the day-to-day activities of technical personnel.

The Quality System definition used in this text is from a document entitled *ICH Q10: Pharmaceutical Quality System* and is based on concepts from the ISO, specifically ISO 9000

Quality Management. In the ICH Q10 way of thinking, the QS focuses on quality achievement throughout the lifecycle of the product from conception to retirement, so quality must be designed into the product. Management commitment and support are required, with efforts focused on continuous improvement of processes, products, and systems.

ICH Q10 does not mention QA specifically but alludes to it. It is defined in ISO 9000, however, as that part of quality management that is "focused on providing confidence that quality requirements will be fulfilled." QA then is an umbrella term for all those activities that enable organizations to assure the quality of the item in question as well as a set of technical activities to help provide this confidence.

## Good Manufacturing Practices (GMPs)

It is a common goal in all manufacturing settings to perform consistently from day to day in order to repeat expected favorable results. To aid in successfully accomplishing this goal, however, organizations must document procedures in detail, including the procedure itself, the time or date the procedure was performed, and the person or persons involved. These common-sense ideas are the underlying principles of **Good Manufacturing Practice (GMP**), considered a set of standards that captures the best practices for manufacturing work.

In a basic sense GMP can be envisioned as a guideline for

- clarifying the work that needs to be performed
- ensuring that knowledge and training are adequate to enable work to be performed as needed
- preparing records of the actual activities and times

A government-mandated standard set of GMPs was issued in the early 1960s in the United States. Today there are GMPs in effect in over 100 countries, either through that country's own national GMP or via the adoption of global codes such as the World Health Organization (WHO) GMP. In nearly all cases, however, GMPs are legal requirements, and the failure of an organization to comply may result in litigation and penalties.

There are two widely referenced sets of GMPs that are used globally: 1) the United States cGMP, which is enforced by the **FDA** and applies to all products produced within the United States (including Puerto Rico) as well as all imported products and 2) the European Union (EU) GMP. The FDA cGMP is described in Title 21 of the Code of Federal Regulations parts 210 and 211 and in parts 600 to 680 for biological medicines (Figure 7-3). The European Union GMP, on the other hand, is enforced by the various agencies of the 27 member countries of the European Union and is described in Volume 4 Pharmaceutical Legislation Medicinal products for Human and Veterinary Use Good Manufacturing Practices.

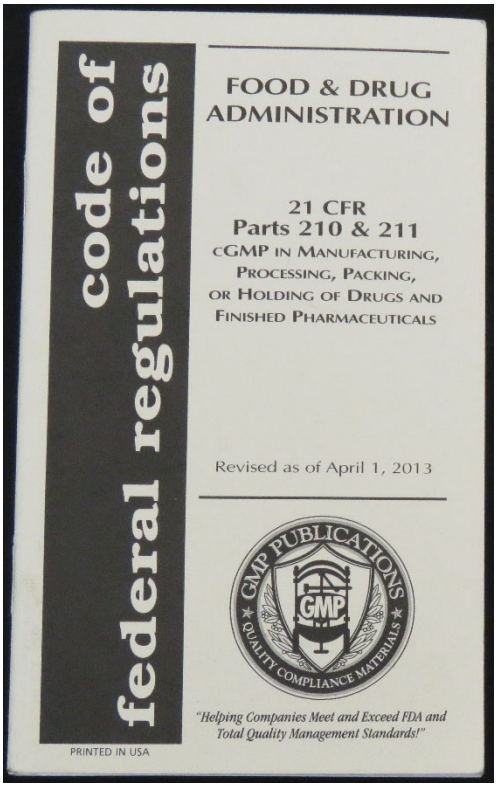


**Figure 7-3. CFR 21 and Volume 4 GMP**

These two sets of GMPs are superficially different in the language (Table 7-1); however, they are fundamentally similar in that they each describe minimum standards and consist of the following requirements:

- manufacturing processes and associated controls are defined clearly and all critical processes are validated
- all changes to manufacturing processes are subjected to a strict system of control
- work instructions and procedures are documented, controlled, and clear
- operators, technicians, etc., are trained to perform and document their work activities as they occur
- records are kept during manufacturing that demonstrate that all required steps are properly taken and that all deviations are investigated and documented
- records of manufacture (including distribution) are retained, readily accessible, and allow the complete history of a batch to be traced
- control of distribution is in place to minimize risk to the quality of the medicine
- a recall system is in place
- all complaints regarding the medicines are investigated adequately and appropriately

and corrective actions are taken to prevent recurrence

**Table 7-1. Comparison between some main features of United States cGMP and European Union GMP**

| CFR Sub Part # | Topic | EU Vol. 4 Chapter | Topic |
|---|---|---|---|
| A | General Provisions | 1 | Quality Management |
| B | Organization and Personnel | 2 | Personnel |
| C | Buildings and Facilities | 3 | Premises and Equipment |
| F | Production and Process Controls | 5 | Production |
| I | Laboratory Controls | 6 | QC |
| J | Records and Reports | 4 | Documentation |
| K | Returned and Salvaged Drug Products | 8 | Complaints & Product Recall |

It is worth noting that the preamble to the cGMP set in the Code of Federal Regulations states the following in section 210.1(a):

> "The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum current Good Manufacturing Practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess."

Thus in the view of the FDA these are minimum standards that are required in manufacturing pharmaceuticals to ensure that the product produced will be of the required quality. If cGMP is not followed, the product may not be of the required quality.

A similar sentiment is expressed in the European Union GMP:

> "To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice, Quality Control, and Quality Risk Management."

It is clear from this statement that in Europe it is envisaged that GMP is a component of QA and that GMP, QC testing, and Quality Risk Management are all necessary to make medicines of an appropriate quality.

Implementation of a standardized set of GMPs for guiding manufacturing practices within the pharmaceutical industry has greatly improved the reliability of pharmaceutical manufacturing. Not surprisingly, other types of GMP have evolved for use in other areas related to the pharmaceutical industry. Examples include GCP (Good Clinical Practice), which captures the best practices to be used in clinical trials, and GLP (Good Laboratory Practice), which captures the best practices to be used in pre-clinical laboratory testing.

## Elements of a Pharmaceutical Quality System

Figure 7-4 illustrates the evolution of the pharmaceutical quality system's key quality processes. Today's Quality System includes a few newer concepts in addition to the traditional QA, QC, and GMP. These newer concepts include:

**Quality by Design (QbD)**: QbD is the subject of the International Conference on Harmonization (ICH) Q8 Guidance. It is defined in ICH Q8 as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science and quality risk management. QbD is concerned with the product being designed with the ultimate quality/performance characteristics in mind from the outset.

**Quality Risk Management (QRM)**: QRM is the subject of the ICH Q9 Guidance. It is defined in ICH Q9 as a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle. Q9 essentially recognizes that there risks associated with the use of medicines. Furthermore, it recognizes that these risks can never be fully eliminated but can be understood, controlled,

and managed to an acceptable level at which the benefit to the patient clearly outweighs all associated risks. QRM describes methodologies to deal with risk management.

**Continuous Improvement (CI)**: Recognizing that all products, processes, and systems can be improved, CI describes methodologies and management systems to enable ongoing improvement. There is no specific ICH Guidance on CI, but CI is a central part of the thinking behind ICH Q10 and its predecessor, ISO9000.

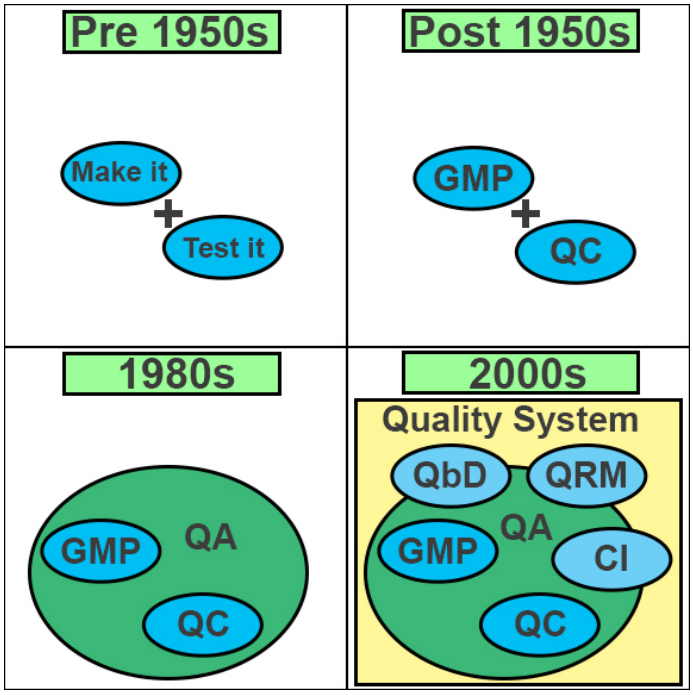


**Figure 7-4. The evolution of the pharmaceutical quality system's key quality processes**

A key responsibility of the quality system is the assurance that facilities, materials, and processes meet expectations. This is largely accomplished through testing performed in the QC labs. The testing is performed to demonstrate that the process and the safety, quality, purity, and identity characteristics of the material make them fit for use in the manufacture of a biopharmaceutical. Specifications are applied to raw materials, components and process material excipients, containers, closures, cell banks, process performance, intermediates, drug substances, and drug/finished products. The manufacturing facility's daily performance must meet the design criteria for the operations that are being performed. This is typically addressed through the monitoring of air quality, including air exchanges, air flow and pressure, humidity, and environmental non-viable and viable microbial particulate levels. Water quality requirements to be monitored include chemical/microbiological characteristics and process controls (temperature, flow rates, etc.). Supplied gas must be checked to ensure that it meets chemical/microbiological characteristics as well as process control criteria.

The criteria or specifications have three sources: Standard Specifications, Internal Specifications (or fit for use at time of use), and Expiry Specifications.

- Standard Specifications are those requirements that are typically established by recognized standard-setting bodies. These may include American Society for Testing and Materials (ASTM), engineering, and various pharmacopoeias.
- Internal Specifications (fit for use) are determined internally as part of the specific requirements of the facility, process, or product.
- **Expiry specifications** are those that define acceptable limits throughout a product's intended use period.

The product testing characteristics that are typical to a biopharmaceutical include potency, purity, identity, and safety. Table 7-2 categorizes typical tests according to these characteristics.

**Table 7-2. Testing characteristics Table**

| Characteristic | Function | Test Performed |
|---|---|---|
| **potency** | biological activity<br>immunological activity<br>chemical activity | bioassay<br>ELISA<br>HPLC |
| **purity** | chemical<br>biochemical<br>process materials | residual DNA |
| **identity** | characterization methods | chromatography<br>electrophoresis |
| **safety** | microbiological | sterility<br>endotoxin<br>bioburden<br>viral tests |

## The Responsibilities of the Quality Unit

Within all medicine regulatory frameworks it is a requirement for each organization to maintain a functional group responsible for overseeing the execution of activities in compliance with cGMP. This functional group is often known as the Quality Unit.

As mentioned earlier, the responsibilities of the QU are defined in the relevant country's regulations. These regulations include the responsibility and authority for the disposition (i.e., approval or rejection) of all production materials (e.g., filters, tubing sample containers, etc.), the review and approval of all procedures and specifications (e.g., Standard Operations

Procedures, Production Document, In-process pH specifications during fermentation), Validation/Qualification documents, change controls, and regulatory submissions. It is essential to ensure systems/programs are established and maintained for:

- adequate inspection
- sampling
- testing and identification of deviations
- investigations
- corrective actions/preventive actions

The QU is expected to act independently of production/manufacturing in executing its responsibilities. A typical QU includes Quality Control and Quality Assurance functions. Quality Control involves inspection and testing, whereas Quality Assurance assures product integrity, potency, purity, and stability of all aspects that influence product quality throughout the lifecycle of the product.

## Primary QA Activities

QA's key responsibilities are to provide confidence that quality requirements are fulfilled. This is achieved through assuring that facilities, materials, and processes are as expected. There are several key QA activities required to ensure that a product will be safe, effective, and of the appropriate purity. These include documentation review (production documentation, test records), investigations of unusual findings, change control , and review of Market authorization

### Documentation review

Documentation plays a vital role in pharmaceutical manufacturing; and though document review is a key aspect of the QA team's responsibility, in order to be successful the team must also be available to the other members of the manufacturing team to coach them and develop their understanding of the process. There are certain key documents that the QA group is required to review and approve before the manufactured batch can be dispositioned. These are described in the following sections.

#### Production document

During production the technicians are essentially following a recipe. It is important to have a well-defined production document in order to ensure that the product is consistently manufactured as intended. During production, data are collected, which is a necessary part of the consistency of the process. Data collection may range from set-up parameters for equipment to in-process tests that are completed to ensure the production line operates within certain specifications. After a batch has been completed, the QA staff member is responsible for reviewing the production document to ensure that each step was completed properly; the recorded information has met the specifications; and the production yields are within limits. Any deviations are examined carefully, as they could impact the quality of the production.

Typically the QA staff member reviews calculations for correctness; inputted materials to ensure the right starting materials are utilized; and that in-process data (such as tablet hardness and weight for a pharmaceutical product or volume of fill for a liquid biological product) are within specifications. QA assures that all deviations are appropriately investigated for potential product impact (Table 7-3).

**Table 7-3. Types of errors that result in poor quality**

| Types of errors | Potential result |
|---|---|
| transcription errors | incorrect use of data in downstream processing |
| omission of data, such as weights | loss of the production batch for missing critical parameters |
| omission of details, such as conditions during deviations | loss of the production batch for missing critical details to support the quality of the batch |
| omission of verification, such as forgetting to document the witness of a critical step | loss of the production batch for critical processing steps |
| mix-up of labeling, such as the wrong label used | cross contamination of the batch with incorrect materials |
| skipping of processing steps, such as not paying attention to each step of the process | loss of the production batch or possible contamination of the batch |

## Test record

Once a product has been manufactured it must be tested to ensure it meets the specifications for safety, purity, efficacy, and quality. The laboratory should receive samples representative of the batch; those samples must be tested against pre-determined criteria. Once the testing has been completed, the results in total are reviewed against the specifications. This test record review ensures that the product has met parameters that are important relative to the product quality. Any results that are outside of the specification or trending negatively (away from a specification) must be investigated. This review and investigation are important in maintaining a consistent production and a high quality product. Table 7-4 is an example of a Certificate of Analysis (or COA) for a drug product and drug substance. This highlights the tests, required specifications, and results from necessary QC testing.

**Table 7-4. Sample Certificate of Analysis (test records for a drug product and drug substance are shown)**

| **Drug Product - Insulin for Human Injection – USP** | | |
|---|---|---|
| **Test** | **Specification** | **Results** |
| identification | part A – clear colorless solution<br>part B – HPLC retention time matches the reference standard | clear colorless solution – Pass<br>Pass |
| bacterial endotoxins | < 80 USP endotoxin units/100 insulin units | < 5 EU/100 insulin units – Pass |
| sterility | meets USP <71> sterility requirements | Pass |
| pH | between 7.0 – 7.8 | 7.6 – Pass |
| assay | 95.0 – 105.0 % label claim | 101.3% - Pass |
| **Drug Substance - Insulin lispro DS – USP** | | |
| **Test** | **Specification** | **Results** |
| identification | part A – chromatogram<br>part B – peptide fragments | Pass<br>Pass |
| loss on drying | not more than 10.0% @105$^{o}$C for 16 hrs | 5% – Pass |
| limit of high molecular weight proteins | not more than 0.25% | 0.1% – Pass |
| zinc content | between 0.30 and 0.60% found | 0.40% – Pass |
| assay | TBD | |

## Investigation reports

Unusual findings in the production, documentation, or test records must be fully investigated. The important components of the investigation should include: the event (or deviation), background into the event, a determination as to the root cause for the event, any negative trends, any indicated Corrective Actions and Preventative Actions (CAPA), and a conclusion

regarding the event. The investigation is meant to ascertain why the event occurred, with the ultimate goal of preventing future occurrences. Preventing future deviations will ensure a consistent supply of high quality product, save time and resources dedicated to investigations, and reduce rejected product (i.e., product that failed to meet requirements).

The role of the QA staff member should not be to conduct the investigation but rather to review the final investigation report and ensure it is adequate and proportionate to the seriousness of the deviation. This can often be a source of conflict between the investigation team, who generally consider they have done an acceptable job, and the QA staff member, who "picks holes" in the work of the investigation team. Thus this provides a good opportunity for all involved to practice diplomatic skills and appreciate diverse views, as everyone's goal is to produce a safe, effective, and pure product.

There are several common techniques used to perform investigations depending on the complexity. One is the "5 Whys" method for simple investigations, which utilizes a deductive reasoning model (discussed in ***Chapter 6 Environmental, Health, and Safety***). Alternatively, more complex investigations require tools like the Ishakawa (Fishbone) or Kepner-Tregoe (KT) models. Refer to ***Chapter 2 Operational Excellence*** for more details on these and other techniques. Table 7-5 provides examples of when these various techniques can be utilized.

**Table 7-5. Investigation types**

| **Investigation Type** | **5 Whys[1]** | **Fishbone diagram[2]** | **KT Table[3]** |
|---|---|---|---|
| | drill down to true root cause | brainstorming for causes | problem analysis, troubleshooting |
| minor | useful | useful | not useful |
| major/critical<br>low complexity | useful | useful | Maybe |
| major/critical<br>medium to high complexity | useful | useful | Useful |

1 A simple use of using two to five questions to drill down to the root cause. For example: Why did my car not start, causing me to be late for class? (It ran out of gas). Why did it run out of gas? (I forgot to stop on the way to school to get gas). The solution: Get gas the night before to avoid the problem in the future.

2 The Ishikawa (Fishbone) diagram is used to brainstorm for causes using a process map, identifying possible causes under each category and asking "What has changed?" This is also the approach of the Cause and Effect method of analysis.

3 Kepner-Tregoe (KT) is a method of asking "What is?" or "What is not?" as part of the investigation. For example, asking what is working or what is not working either eliminates or highlights areas on which to focus for troubleshooting.

## Change control

**Change control** is the formal process by which an organization documents changes to a process, procedure, or other element of operations. All elements that might conceivably impact the product quality (whether directly or indirectly) should be subject to change control. This system ensures changes are introduced in a controlled and coordinated manner, thereby both reducing the possibility that unnecessary and potentially harmful changes will be introduced and providing a documentary record of the evolution of the product or system. The various types of change control include automation, process, procedural, analytical, and facility.

The reasoning behind documenting the changes in a system is clear from a historical perspective; in addition it provides a mechanism to document all of the necessary steps that are required to actually perform these changes. In a change control system an individual can prospectively identify a checklist of actions that are necessary to make changes. Along with end-product testing, these actions could include validation, stability, and characterization studies. Depending on the extent of the change and the potential to impact product quality, changes fall into several categories with respect to notifying various regulatory agencies. For example, the FDA categorizes the types as Changes Being Effected (CBE), Changes Being Effected in 30 Days (CBE 30), Annual Report, and preapproval. It is important to note that significant changes require FDA approval.

## Marketing Authorization

In order for a company to market and sell a new drug product, it must submit and obtain approval for a New Drug Application (NDA) from the FDA. Documentation in the NDA includes data from preclinical and clinical testing and manufacturing processes. Marketing Authorization Application (MAA) is the European equivalent of the NDA and it allows a company to market a medicine in either some or all of the countries in the European Union. The term is also used to refer to the set of documents that is submitted to the regulatory agency to obtain that license. The QA team must ensure that individual batches of the product are manufactured in the manner that is described in the NDA or MAA.

## Deviations

If a deviation occurs and there is a potential to impact product that has already been released to the market, there are several actions that must be considered. In the most significant cases products are recalled from the market, often at great expense and to the dismay of executives, partnering companies, stockholders, and investors. Table 7-6 lists recall types and severity.

**Table 7-6. Recall types and severity**

| Recall Classifications |
| --- |
| **Class I:** dangerous or defective products that predictably could cause serious health problems or death (e.g., an injectable drug determined to be contaminated, a label mix-up on a lifesaving drug, etc.) |
| **Class II:** products that might cause a temporary health problem or pose only a slight threat of a serious nature (e.g., a drug that is under-strength but is not used to treat life-threatening situations) |
| **Class III:** products that are unlikely to cause any adverse health reaction but violate FDA labeling or manufacturing laws (e.g., a minor container defect, lack of labeling on the product container, etc.) |

In advance of any product recall, though not exclusively, a notice is provided to the responsible regulator by the corporate organization. In the United States notification is required for any incident that may impact product quality or safety for a pharmaceutical product. Additionally, a Field Report must be filed with the government within three days—for a biological product, a Biological Deviation Report must be submitted within 45 days. In the European Union, notification to the supervisory authority is typically performed within three days.

## Documentation in Pharmaceutical Manufacturing

It is often stated that the pharmaceutical industry produces both medicines AND documentation. The latter is an essential aspect of biomanufacturing, and it is important that all those engaged in the process fully understand his or her respective responsibilities in ensuring proper documentation practices and procedures are followed.

Essentially there are two main reasons why proper documentation is so vital to the industry: 1) good documentation prevents the errors and misunderstandings that arise with spoken communication and 2) good documentation provides a definitive record of occurrences at a particular time during the manufacture of a particular batch of product. Furthermore, the patient using such medicines needs to be confident that confusion about the medicines' manufacture has been eliminated—and this is also achieved through proper documentation.

The essence of proper documentation is that it is prepared at the time the actions occur, as there is little value in attempting to recall what was previously performed. These actions must be recorded using permanent means (e.g., indelible ink) rather than something that can easily be erased (e.g., pencil) or destroyed. The appropriate parties must sign off on initial documentation, and for critical steps an independent person must verify what is being documented (also performed at the time of occurrence).

Documentation can involve numerous aspects of the manufacturing process, including a manufacturing step, an in-process manufacturing test, or a training session. By not physically

documenting an activity, there is no record of the event taking place—in the eyes of a skeptic the event did not occur. Thus documentation that accompanies the product is as equally important as the product itself.

Documentation can take many forms, such as the:

- production document (steps of the manufacturing operation)
- operational log books (documentation of cleaning or other critical steps)
- training documents

Documents can be in written or electronic format. An **electronic record** can include any combination of text, graphic, data, audio, pictorial, or other information represented in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system. While the two formats may provide the same information, electronic documents require additional controls. These controls prevent the documents from being changed or altered. For data collection or documentation review purposes, an electronic signature may be required. **Electronic signatures** are conceptually the computerized equivalent of handwritten signatures. An electronic signature provides a unique basis for confirming or authenticating the identity of the person who made the signature.

## Regulations and Regulatory Agencies

It is apparent that organizations must strictly adhere to cGMP, but how can the general public feel confident that this is actually occurring? Who has oversight of the manufacturer? This is the purpose of government regulations and the job of regulatory agencies. As mentioned earlier, the regulations for biologicals have paralleled the development of the cGMP and are defined in CFR (21 CFR 600-800).

Many of the regulations and laws concerning medicines were established in response to issues with products that were already on the market. When these issues were analyzed, relevant laws were deemed inadequate and tightened. Until the mid-20th century, for example, snake oils and "magic" elixirs that contained carcinogenic petroleum products and strong acids were peddled to cure ailments ranging from hair loss to consumption (now known as tuberculosis). Even today home remedies are commonly sold based on a myriad of unsubstantiated claims. With an effective regulatory system, however, many of these products have been proven ineffective at best, with some being classified as dangerous. Had the FDA and current regulations existed 100 years ago, it would have prevented these products from making it to market. Unfortunately there have been a number of cases of ineffective, dangerous, or even life-threatening prescription and Over the Counter (OTC) drugs in the history of the global pharmaceutical industry.

Even reputable, conscientious manufacturers can err. For example, a national scandal erupted in 1937 when the S. E. Massengill Company in Tennessee marketed a product called sulfanilamide, a liquid dosage form of what was an effective medicine for the treatment of streptococcal infections. The company, however, was unaware that the solvent used, diethylene glycol, was poisonous. Before the FDA could track down this "Elixir Sulfanilamide,"

107 persons had died. In a powerful and poignant letter to a friend, a doctor who had prescribed the medicine wrote about it:

> "Nobody but Almighty God and I can know what I have been through these past few days. I have been familiar with death in the years since I received my M.D. from Tulane University School of Medicine with the rest of my class of 1911. Covington County has been my home. I have practiced here for years. Any doctor who has practiced more than a quarter of a century has seen his share of death.
> But to realize that six human beings, all of them my patients, one of them my best friend, are dead because they took medicine that I prescribed for them innocently, and to realize that that medicine which I had used for years in such cases suddenly had become a deadly poison in its newest and most modern form, as recommended by a great and reputable pharmaceutical firm in Tennessee; well, that realization has given me such days and nights of mental and spiritual agony as I did not believe a human being could undergo and survive. I have known hours when death for me would be a welcome relief from this agony."
>
> (Dr. A.S. Calhoun, October 22, 1937)

As a result, the manufacturer was assessed the largest fine ever levied under the Food and Drugs Act of 1906 and Congress enacted the Food, Drug, and Cosmetic Act, creating a strengthened Food and Drug Administration. The act prohibited the use of any new drug without prior filing and approval of a New Drug Application (NDA) and further required that the drug must be safe when used as directed on the label.

Other similar, notable regulatory changes in the United States include the following:

- 1901: Diphtheria patients were routinely treated with antitoxin derived from horse serum. The lack of controls used in the product manufacture resulted in the deaths of 13 children. Congress enacted the Biologics Control Act of 1902 that required the annual licensing of vaccine manufacturers. It further required annual inspections of facilities and oversight by qualified scientists. This act was later replaced by the 1938 Food, Drug, and Cosmetic Act.
- 1962: In response to thalidomide and its link to birth defects, an amendment was made to the Food, Drug, and Cosmetic Act of 1938 that required the demonstration of drug effectiveness prior to the FDA granting approval.
- 1976: The FDA and the pharmaceutical industry proposed extensive revisions and expansions to requirements for controls in the manufacture of pharmaceutical products. The cGMP defined the requirements that assured drug products were produced under safe conditions. They also defined the failure of a manufacturer to conform to these requirements, in which case the product would be deemed adulterated.
- 1977: The NDA was updated, requiring system and process validation.

- 1982: In response to the cyanide tampering of Tylenol, the FDA required tamper-evident packaging for all OTC drugs.
- 1992: During the late 1980s, some organizations that produced generic brand products were found to be following unethical practices, including non-adherence to the cGMP. This lead to the Generic Drug Enforcement Act and prosecution of the manufacturers by the FDA. The repercussions of the 1993 Barr case are still being felt within the industry today. As a result of the case, a federal court, in landmark regulatory action by the FDA, ordered the generic drug manufacturer Barr Laboratories to recall millions of its analgesic and antibiotic tablets for failing to meet quality requirements.

Many incidents have occurred over the years that have impacted the development of specific requirements for biological products. As discussed in ***Chapter 5 Validation***, a vaccination against polio, which was later found to inadvertently contain a live virus, infected several hundred people with polio. This event lead to the requirement that procedures used in testing vaccine safety be thoroughly reviewed and manufacturing facilities be adequately inspected. In the 1980s another case involved the contamination of a blood supply by Hepatitis and HIV. This resulted in significant requirements on the controls of incoming materials to ensure they were free from potential contamination, along with process concerns related to viral removal.

One of the results of events such as the ones above is that all modern countries today have strict laws to regulate all aspects of the development, marketing, and manufacture of medicines. These laws are generally administered by Medicines Regulatory Agencies that oversee production and distribution of pharmaceutical products, with the primary purpose of protecting public health and safety. Such bodies (e.g., FDA, EMA, etc.) are often referred to as Boards of Health (BoH) and set the standards for the safety, efficacy, and control of medicines. Other national agencies include the MHRA (Medicines and Healthcare Products Regulatory Agency) in the UK, IMB (Irish Medicines Board) in Ireland, and ANVISA (Agência Nacional de Vigilância Sanitária) in Brazil. All of these agencies work to ensure medicines sold and/or supplied in their country, as well as exported from their country, are safe, efficacious, and meet required quality standards. These agencies generally license companies before their pharmaceutical or biopharmaceutical products are even commercially sold (marketed) or tested in clinical trials. These licenses are typically required for both the manufacture of the product as well as its distribution. Each manufacturer must register the product with the relevant Board of Health in the applicable country and obtain approval/licensing prior to marketing in that country. The requirements for approval/licensing are published in accordance with the relevant country's practices. In the United States these requirements are published in the Code of Federal Regulations. Documentation requirements include information on clinical and product development as well as product manufacturing information such as:

- facilities
- materials
- methods
- procedures

- processes
- controls

A regulatory submission and approval of this information is required for every product prior to distribution and commercial marketing. The filing constitutes a binding commitment of adherence by the manufacturer with each regulatory agency until the dossier is amended.

For the execution of regulatory conformance, two groups in an organization are typically involved—Regulatory Affairs and Quality Assurance. The Regulatory Affairs group is typically the interface between the organization and the Boards of Health. It is responsible with assuring that the preparation and submission of the dossier meets the particular BoH's requirements. The Quality Assurance group is responsible for ensuring that the daily operations of product manufacturing and supply comply with the BoH requirements—those filed in the dossier as well as the relevant GMP expectations.

## Regulatory Inspections

One of the most important ways for regulatory agencies to carry out their mandate of protecting public health is by inspecting activities at pharmaceutical companies. The purpose of these inspections is to verify that activities are being performed in accordance with cGMP requirements and with the requirements of the dossier(s) that the organization submitted to the relevant agency.

Manufacturing facilities are assessed against standards on a frequency that is risk-based. The risk-based approach considers whether the facility produces a sole-sourced product, a vaccine, a sterile product, or a medically-significant product. The potential risk and its impact are used to determine frequency of inspections. International regulatory agencies complete inspections either on a frequency that is tied to new products or biannually for regular GMP or cGMP (FDA) inspections as applicable.

Regulatory agency inspections fall into one of the three following categories (Table 7-7 lists these types and their frequencies):

- pre-approval inspection: performed at the time the dossier is under review for licensing; during this inspection the focus is on two areas: 1) verification of development data and 2) confirmation of the ability to manufacture in accordance with the dossier and cGMP.
- routine inspection: performed as surveillance of ongoing compliance with cGMP using a prescribed schedule based on the regulatory agency's requirements
- for cause inspection: can be performed when the regulatory agency has concerns over the manufacturing and control of a product/products; triggers for these include, but are not limited to, significant product complaints, market recall of a product, and notification of product quality issues.

**Table 7-7. Types of inspections and frequencies**

| Inspection Type | Frequency | Special notes |
|---|---|---|
| Pre-Approval inspections | each Biological License Application (BLA), potentially each major supplement | new products, new facilities, or major renovations, product specialists |
| Routine inspection | biennially; could also be performed either annually or less frequently than every two years | risk based, more frequent for sole supply, vaccines, or parenteral products; usually unannounced |
| For Cause inspection | as the event dictates | unannounced, compliance experts |

Quality Systems recommend a set of evaluation activities that routinely check how well an organization is doing in achieving its quality objectives. A key evaluative activity is self inspection, or the internal audit. Organizations that follow recommended Quality Systems practices will find that a regulatory inspection serves to confirm what internal audits have already shown. In other words, there should be no surprises when the regulatory agency visits the facility. Unfortunately, however, this is not always the case. Oftentimes organizations convince themselves of the correctness of a particular point of view only to find that the regulatory agency inspector disagrees. This is not surprising, as many regulations are necessarily top level (i.e., general in nature) and oftentimes vague and can require extensive discussion and interpretation before precise requirements can be derived and turned into actual practices. Furthermore, requirements can change over time, as the industry as a whole is constantly dealing with "current" manufacturing practices. Consequently, it is important in the pharmaceutical manufacturing arena that the views of any one individual do not dominate or supersede all others—diverse views and input should be valued and factored into the decision-making process. This type of approach helps to minimize the number of surprises and maximize the ability to meet the requirements of cGMP.

The typical regulatory agency inspection can last for approximately a week or more, with typically 2–3 inspectors visiting the site. The inspection will generally commence with a presentation of the site and its activities, key products, etc., to the inspection team by the senior management, thereby orienting the inspectors. Typically the inspection team will then tour the facility and observe events as they occur in routine operations. It is increasingly common during such tours for inspectors to approach individuals and question him or her concerning the specifics of the process, the reasoning behind the process, etc. The implication is that all those working in the industry should fully comprehend the process and his or her related responsibilities. Such questioning can seem challenging or intimidating to some individuals. It is essential, however, that anyone faced with such a situation answer truthfully, concisely, and clearly and discuss specific SOPs or production batch records as required. After

providing the required information, one should ensure that the inspector is satisfied and that he or she has permission to return to work. The interviewee should be prepared to document the meeting, reporting the information to a supervisor.

Following the tour the inspectors typically meet in a conference room at the facility. During the meeting they allot the majority of their time to reviewing documents. With this information they aim to assess the facility's state of cGMP compliance. Below is a partial list of the documents the inspectors might review; however, any types of record or other documentation that the inspectors feel will provide them with an understanding of the state of compliance may be reviewed as well.

- facility and system drawings
- validation and qualification reports and data
- laboratory data
- SOPs
- production batch records
- engineering and maintenance records
- training records
- investigation reports
- change controls
- organizational charts

At the end of the inspection the team will typically provide the site management with an indication of the deficiencies observed during their inspection in a close-out meeting. (For the FDA this list of deficiencies is provided as an official FDA form, FD 483 [often referred to as a 483]). The general focus of the close-out meeting is usually on issues that need improvement, with only a rare reference to those that do not. The inspection is not considered complete until the inspection team has left the facility. The organization then begins the process of responding to the team’s findings with appropriate actions. These actions are later submitted to the regulatory agency, and the agency can either accept them or require further action and/or dialog. It is important to note that repetitive 483s have the potential to result in substantial economic losses and in some cases corporate failure.

The results of an inspection and the subsequent follow-up are vital to an organization. It is possible for poor results and/or inadequate follow-up to prevent an organization from supplying a market. Furthermore, a Board of Health may not license the organization for a particular product or may withdraw an existing license. If the deficiencies found during the inspection were significant, a regulatory agency has levels of escalation based on a deficiency's significance. If the findings are minor or the organization addressed them appropriately, the FDA then considers the site as Voluntary Actions Indicated (VAI). If the site has not made the appropriate corrections or if systemic issues continue over successive inspections, the facility may be considered Official Actions Indicated (OAI).

In the case of OAI, there are a number of options the agency can take. It can issue a warning letter, which is considered a serious communication and indicates the site remains deficient—this can result in sanctions. Other actions can include seizure of products, issuance of a Consent Decree, or closure of a facility (in 2010 Genzyme Corp. signed a Consent Decree to correct violations at the Allston, MA manufacturing plant, resulting in a $175 million loss). A Consent Decree is a legal action that forces a firm to stop production and enables the FDA to seize all records; it may ultimately result in prosecution of the company, its representatives, or its employees and/or the closure of operations. A Consent Decree can also force a facility to employ a third party to monitor their activities (or act as an independent check on the Quality Unit as part of on-going operations). These types of injunctions can be costly for an organization and can at times lead to a business's demise. Fortunately for Genzyme, the company was able to correct its manufacturing problems.

In all cases there are usually significant costs in correcting the issues identified by a regulatory inspection team. In the worst situations remedial actions can take years and cost millions of dollars. International regulatory agencies, while not having legal jurisdiction in the United States, can prohibit an organization's products from entering that particular country if quality issues are not addressed.

## Check Your Knowledge

1. Describe the difference between Quality Control and Quality Assurance.
2. List three activities for each of the functions of Quality Control and Quality Assurance associates.
3. Does checking the pH and temperature during product manufacturing fall under QA or QC?
4. Why must quality be built into a manufacturing process and not merely tested for at the end of the process?
5. Name two special challenges associated with the production of a biopharmaceutical product compared to a traditional orally-administered small molecule drug (e.g., insulin versus aspirin).
6. The term Good Manufacturing Practice is at times referred to as cGMP. What is the significance of the "c"?
7. Describe why regulatory agencies would visit a biomanufacturing facility and what their objectives might include.
8. The FDA regulates only the manufacturing of biopharmaceuticals and has no jurisdiction over the marketing of the drugs. a. True or b. False?
9. A change has recently been made with the acquisition of a new and larger fermentation tank. What type of inspection would one expect to receive from the Boards of Health?

    a. preapproval inspection
    b. routine inspection
    c. For Cause inspection
    d. no inspection required

10. A company receives a customer complaint for a product that was missing 5 tablets in a bottle of 10 tablets. What must the company's reaction be to the complaint?

    a. investigation
    b. recall
    c. send a notice to the FDA
    d. no action required
    e. hide the fact

## Activities

1. Consider the potential consequences if GMP compliance is not properly followed. Write a two-page paper discussing customer safety, company-related issues (financial loss, damage to reputation, etc.), legal issues, and other issues.
2. Search the recent news for a significant event within the last year in which a pharmaceutical company failed to meet some of the cGMP requirements and a product recall was initiated as a result. Describe what the deviation might have been and how it could be remedied.
3. Participate in a discussion with several classmates about the spirit and intent of regulations and how they relate to written requirements. Document your discussion and present it to the class.
4. Consider how training and education are fundamental requirements related to Quality Assurance efforts. Research different types of knowledge/skills related to QA and make a list of at least 10-15. What would be the most important to you? Why? Discuss your findings with the class.
5. Participate in a class discussion on the requirements for proper documentation. Select at least 5-7 points from the discussion that you think are the most important and write a two page paper on why you chose them.

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