Overview

Quality

What is Quality?

> "Quality is the result of a carefully constructed cultural environment. It has to be the fabric of the organization, not part of the fabric." — Philip Crosby

In the pharmaceutical industry, and particularly in pharmaceutical manufacturing, one will hear the term *quality* on a regular basis. Thus it is important to develop a clear understanding of the term and how it relates to the industry.

The term *quality* is used in many contexts today, usually to provide a ringing endorsement of an item being promoted, such as a quality service, a quality car, etc. Consumers today expect high standards of quality in everything they purchase; they expect the products to perform both as promoted and as advertised. They also expect government agencies to ensure the quality of their product and service by monitoring and regulating such at the point of production or provision. For example, a person purchasing a new automobile might give it a careful inspection, checking that everything is as expected (e.g., check that the body parts are properly aligned, test the operation of some of its parts, test-drive it, etc.). Despite the person's best efforts, however, the evaluation will be only cursory: no testing can be done to verify that the automobile's steel parts meet particular composition and thickness specifications; that engine part clearances are exact; that braking performance is optimum under all conditions; etc. Consumers generally assume that these finer and less readily accessible details are correct. Thus many people will feel reasonably confident that such details are confirmed and that someone has tested them to ensure that they are indeed correct.

Similarly consumers take quality for granted when purchasing food, pharmaceuticals, biopharmaceuticals, and biotechnology products. One rarely asks *how*, *why*, and *who* concerning the quality of these types of products. Even less frequently do they question the meaning of the term *quality* when used to refer to products like medicines. Thus it is of paramount importance to examine this term as it relates to pharmaceutical and biopharmaceutical products.

This overview will examine both the rigorous efforts undertaken at the various industry levels to ensure product quality as well as the role of governmental regulators in ensuring that quality standards are met and maintained. This section will also explain how "quality" (as it pertains to the area of medicines) primarily concerns the safety and effectiveness of the product.

Many definitions for the term *quality* have been used over the years. A renowned expert in the field, Joseph Juran, provides two definitions for the term. The first concerns "meeting customers' needs and expectations," while the second speaks to "freedom from deficiencies." Juran published the first edition of his *Quality Control Handbook* in 1951 and is considered to be one of the founders of modern quality thinking. In reference to the earlier example concerning the automobile purchase, Juran's definitions can easily be applied; a "quality" automobile must meet the customer's needs and expectations and be free from deficiencies.

It is important to understand the distinction between two different (and at times confusing) usages of the term *quality*. In some contexts the term is used to refer to the attribute or property of a product. Other times it refers to the specific department or group within the organization that has a particular knowledge or responsibility concerning the achievement of

the quality attribute. In distinguishing between the two, it is important to remember that the quality "attribute" will *always* be required, but the quality "department" may not always be required. In some organizations everyone has a responsibility for quality and no dedicated organizational department exists. And though some would argue that this is the best way to achieve quality standards, laws exists in the pharmaceutical industry today that *require* organizations to maintain an independent quality group to focus solely on the quality attribute.

Within this textbook the quality "department" will be referred to as the Quality Unit (QU). The text also refers to the two major sub-divisions of the QU—Quality Assurance (QA) and Quality Control (QC). The activities of both of these organizational departments are outlined in greater detail in the ***Quality Assurance, Microbiological Control,*** and ***Quality Control Biochemistry*** chapters.

The primary customers for biopharmaceuticals include medical practitioners, regulators, and the patients who receive the biopharmaceutical products. All are concerned primarily with the safety and effectiveness (efficacy) of the product, and the collective needs and expectations of all must be met. With this in mind, the Quality Assurance group is responsible for assuring/guaranteeing/certifying that the quality of the item under consideration meets expectations.

The Quality Control group is responsible for controlling the quality of the item under consideration. Thus there is an element of measuring and/or testing to compare against a standard, and items that do not meet this standard are discarded. In the manufacture of biopharmaceuticals, the basis for these quality requirements is derived from:

1. customer expectations
2. good business practices
3. good science practices
4. conformance to regulatory expectations

The Quality of Medicines

Medicines have been used for thousands of years, and even in ancient times people desired them to be both effective and safe. Ideas as to how these quality characteristics could be achieved routinely, however, have evolved over time, particularly over the last 100 years.

The era of industrial-scale medicine began approximately 150 years ago, and with this new era came new challenges. No longer did a familiar and trusted individual prepare a specific medicine; it instead came prepared from a factory familiar to neither the patient nor the doctor. Thus it became more difficult to determine not only the quality of the medicine but also the production techniques.

Distinctive challenges arise with assuring and controlling the quality of medicines versus the quality of other types of consumer products. The user of a medicine, for example, generally cannot determine from simple examination whether or not that medicine is of an appropriate quality. The quality of each dose of that medicine, however, can be a life or death matter for the user. Thus for an organization's staff members who contribute to the manufacture of

medicines, the patient's need for quality assurance (i.e., effectiveness and safety) must be their highest priority.

Requirements for the highest quality medicines are not only ethical responsibilities but in all modern countries are enforced by a detailed and complex set of laws. These laws regulate all aspects of the development, production, advertising, and sale of medicines. These laws have evolved in many instances in response to problems that arose in various countries (e.g., thalidomide, sulfanilamide elixir, the spread of AIDS through blood products, etc.). These types of laws are administered and enforced by governmental agencies with specific expertise in, and responsibility for, products such as medicines and/or food. Examples of these agencies are the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in the European Union. These regulatory agencies are empowered to issue licenses or authorizations for products prior to their entry into the market as well as for the facilities that manufacture these products. The agencies also regulate many other aspects of activities relating to the development, testing, and authenticity of medicines. As a result of these stringent government regulations, all major pharmaceutical companies have a Regulatory Affairs Unit that works closely with the Development, Manufacturing, and Quality departments. This unit provides the relevant information supporting the safety, efficacy, quality, integrity, and purity of the biopharmaceutical to the FDA, EMA, and similar agencies around the world.

The key quality requirements for any pharmaceutical product are the ones that ensure the product is safe, effective, and pure. A safe product means that the therapeutic pharmaceutical product will not produce unexpected adverse effects in persons using it. So, when working in the pharmaceutical industry, think about quality in terms of how we can ensure that quality is met, continuously improved upon, and measured. An effective product is one that will alleviate symptoms and/or prevent illness. A significant amount of the work that goes into medicine development involves clinical trials, which are designed to demonstrate that the medicine is effective for treatment of a specific condition. Finally, pure means that the composition of the product, as it is to be administered (including impurities), must be precisely known and not contain impurities in greater than permissible concentrations. Medicines are rarely 100 percent pure; they often contain some level of impurity. Thus a great deal of thought and effort goes into determining the impurities that are to be expected in the medicine and their potential impact on the patient.

No medicine will be 100 percent safe and 100 percent effective. There is always a possibility that certain people might have unusual reactions to a medicine because of their genetic make-up, or unanticipated reactions can occur due to interactions between the multiple medications one is using. The FDA does not guarantee that medicines are risk-free, but the agency strives to reduce potential risks to acceptable levels. Thus when medicines are licensed it is always on the basis of their risk-to-benefit profile. This means that if the potential benefit of the medication significantly outweighs the risk, the product can be authorized for marketing.

Quality Assurance (QA) and Quality Control (QC)

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.

The concept of QC is much older than QA and originated thousands of years ago. 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.

QC roles and responsibilities are often exceedingly diverse but all are directed toward the same end goal of creating a quality product. Some groups focus on raw materials used in the manufacturing processes, others focus on the facilities where the product is made, and still others concentrate on the product itself, including both in-process intermediates and actual drug product.

From an organizational viewpoint, QC is often divided into **QC Microbiology** and **QC Biochemistry**. QC Microbiology deals with all of the microbiological testing associated with the biopharmaceutical product and the environment in which it is manufactured. Understanding and controlling the environmental microbiology is particularly important in biopharmaceutical manufacturing since: 1) the products being manufactured can often be degraded by environmental microbes, and 2) the patient can be exposed to microbial contaminants in the product, often bypassing the normal bodily defense mechanisms. QC Biochemistry, on the other hand, generally encompasses all of the biochemical testing procedures plus chemical, immunological and cell biological testing required to assess biopharmaceutical purity. For example, an organization's group that focuses on the QC of raw materials is responsible for assuring that the starting materials used in the manufacturing process meet pre-determined expectations/specifications established by industry guidelines, government regulations, and the organization’s needs. This group assures that the strength, efficacy, and potency of the raw material meet those expectations/specifications. Another group that focuses on biochemistry or bioassays evaluates the biochemistry or biological activity of a drug product as well as its process intermediates. The group monitors the biochemical structural characteristics of the drug product/intermediates or the bioactivity throughout the process. Although the

responsibilities vary between these groups, each functions as part of the QC department, which greatly contributes to the successful production of quality product.

When QC tests are executed in manufacturing they are generally performed in order to determine if the result obtained for the product being testing “meets specification” or is “inside/outside of spec.” A specification is a limit or set of upper and lower limits expected for a particular result (e.g., “the pH will be between 5 and 6” or "there will be less than 100 colony forming units (cfu)/mL”).

Quality Systems Thinking

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 System 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 can occur.

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.