Principles of Good Manufacturing Practice

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B. Arjmand et al. (eds.), *Biomedical Product Development: Bench to Bedside*, Learning Materials in Biosciences, https://doi.org/10.1007/978-3-030-35626-2_6

6.1 What Will You Learn in This Chapter?

In the middle ages, craftsmen were responsible for manufacturing and inspecting their products, and the quality was considered as their own honor. Industrial revolution altered the concept of quality drastically. Rise of inspections and separation of quality departments were the main outcomes of this alteration. On the other hand, statistical methods were the unprecedented approach to control the products variabilities and quality. In addition to statistical methods, "quality control" and "quality management" as novel concepts were the other achievements in the late nineteenth century. Actually, quality has been considered as an organizational idea, and in this organization all participants are responsible. Nowadays, with regard to ever developing and competitive atmosphere, the importance of quality policies and objectives is fully recognized, and also quality management system has been prominent everywhere from research to business and in every aspect of life. This chapter discusses the importance of quality and its performance in our lives and provides a brief description and background of GMP and some basic principles, guidelines, and modules of GMP.

6.2 Rationale and Importance

Recently, the importance of quality is globally accepted because the developments of each country depend on the applied standards and managements. Consequently, quality has become a burning issue for a growing number of countries. Therefore, products and services are no longer considered sufficient if they are not accompanied by quality and supported by adequate quality frameworks and systems [1, 2]. The quality concept is propounded with special sensitivity and greater attention to safety issues in biomedicine. The main purpose of good manufacturing practices (GMP) is to decrease the probable risks that may affect the end products/services. Some of the serious risks in healthcare systems include unintentional contamination, insufficient or too much active ingredients, mislabeling, etc., that can lead to ineffective treatment, adverse effects, and even death. In this regard, due to some reasons such as growing need for qualified human cell and tissue, increasing risk of contamination, and international harmonization, the quality management system (QMS) has found a special position in biomedical science. QMS is a set of all organizational quality principles applying as a guidance in establishments and quality assurance/quality control (QA/QC) procedures. QMS is a cumulative activity to produce and maintain a product or service with desired quality requirements against minimum costs. Altogether, QC, GMP, and QA as interrelationship concepts are subset of each other (Fig. 6.1). QC as the basic level of quality management is a set of procedures for checking or testing to verify and certify the end product/service accordance with the required quality criteria. QC is a subset of GMP with laboratory-based procedure. GMP as a guidance ensures that the required quality will be continued consistently. QA as the proactive organized arrangements is wider than QC and GMP. Further, QA is applied to the developing products/services to ensure that the output will meet the required quality specifications. In other words, QA as an organization-based process can plan and manage the required guidelines and standards to ensure quality.

Fig. 6.1 Quality relationship. QM, QA, GMP, and QC are interrelated concepts. The main target of these concepts is to attain total quality

6.3 Definition

GMP is described as "a part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization and products specifications." On the other hand, "GMP is that part of quality management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification" is another definition of GMP by the European Union (EU) [3]. GMP has various definitions all over the world, but all of them have similar principles, and their ultimate objectives are the same. In other words, GMP as a main objective of health systems includes a set of regulations, codes, and guidelines that describe the methods, equipment, and facilities required to manufacture and control biomedical products based on the appropriate standards. It covers variable areas such as pharmaceutical, biological, and cosmetic products, medical equipment, packaging and labeling, laboratory controls, etc. Safety, purity, identity, strength, and quality of a product can be ensured through the optimal commitment of GMP [4]. Implementation of GMP strictly depends on a rational inspection order. However, processes of GMP are strongly involved in leadership, collaboration, and consistency. Testing the quality of each batches of products during the manufacturing process instead of testing the entire products together at the same time in the batch release step is one of the basic tenets of GMP. In other words, the intended quality cannot be attained only through the final testing and detecting the errors. Hence, controlling and designing the quality into process and preventing the errors during the process will be more efficient and cost-effective [5, 6].

In spite of differences between GMP and cGMP, due to their similar final aims, sometimes they are used instead of each other. The word "current" in the cGMP emphasizes applying the most current and up-to-date techniques and methods, as well as expectations are dynamic. Therefore, this leads to making cGMP a more effective and efficient approach. On the other hand, applying novel technologies in cGMP makes it more reliable in QA than GMP. Given the fact that novel available technologies are more expensive than the

Table 6.1 Comparison between characteristics of GMP* and cGMP** as two main elements of quality management systems

Characteristics	GMP	cGMP
Applied to more than 100 countries	+	–
Application of novel and current technologies	+	++
Cost-effective	++	+
High-quality assurance value	+	++
Much broader	++	+

*Good manufacturing practices
**Current good manufacturing practices

old ones, implementation of cGMP is more expensive than GMP. Additionally, GMP is a broad concept and covers a wide range of situations and areas of science and business. However, cGMP is only limited to manufacturing processes. Finally, GMP is applied by more than 100 countries although only a few number of them adhere to cGMP principles. Altogether, in healthcare systems, the cGMP is more competent than the GMP in achieving the best outcomes (Table 6.1).

6.4 From Nineteenth Century to Now: History of GMP

In the early 1900s, home remedies, ointments, and "miracle elixirs" were applied to treat any discomforts. In the late nineteenth century, the production of vaccines without any regulatory controls was begun in a large amount. After in 1901, antitoxin derived from blood serum of horses was regularly used to treat diphtheria patients. Given the fact that these antitoxins were prepared locally and there was no uniform control, in St. Louis, Missouri, 13 children died from tetanus after treatment with the antitoxin from an infected horse named Jim [7]. In the same year, similar catastrophe happened with contaminated smallpox vaccine. In reaction to such incidents, the importance of health and high-quality raw materials was propounded officially for the first time [8]. Until 1902, there was no regulation to control these medications or vaccines, and the mentioned undesired events led to enact the "Biologics Control Act of 1902" [5]. It was the first act for controlling the biological products. Following to a published data about the contaminated meats in Chicago, the Pure Food and Drug Act in 1906 forbids selling unsanitary meat and fake labeling for the first time [9, 10]. Further, in 1941, a company's sulfathiazole tablets were adulterated with a kind of sedative called phenobarbital. Due to this negligence, 300 people died or got injured. According to this tragedy, FDA decided to reconsider and alter the QC and manufacturing requirements basically. Following these alterations, GMP was born in 1941. Then in the 1960s, thousands of children in the Europe were born with severe limb anomalies because their mothers had used thalidomide as a morning sickness pill. This phenomenon led to strengthen the FDA's regulations such as compulsory animal testing

before human trial and obtaining an inform consent from trial participants. Also, in accordance with the new amendment in addition to the safety, the effectiveness of the final product must be proved before marketing [5, 11]. The Laboratory of Hygiene of the Marine Health Service in Washington, D.C., was renamed to the Hygienic Laboratory of the Public Health and Marine Hospital Service in 1902. Subsequently, in 1948, its name was changed to "National Institutes of Health" (NIH) which covered a set of institutes related to biomedical researches. In 1972, the regulations of biological products were transferred to FDA. Eventually in 2010, the FDA Center for Biologics Evaluation and Research (CBER) started to control the safety of biological products as its main responsibility.

6.5 Good Manufacturing Practice Principles

GMP guidance is aimed to ensure that the outcome is safe for human consumption or use. All established GMP requirements follow a number of basic principles that are similar in nature. WHO-GMP guidelines have considered all requirements of different GMP texts and requirements especially in international trade arena in developing countries. The most compliant principles of GMP include (1) designing and constructing the facilities and equipment properly and identifying the responsibilities; (2) following written procedures and instructions; (3) documenting work; (4) validating the processes and evaluating the staff performances; (5) monitoring and regular inspections of facilities and equipment which prevent the accidents; (6) writing step-by-step operating procedures and instructions; (7) designing, developing, and demonstrating job competence; (8) protecting against contamination and promoting of the workplace quality and safety; (9) controlling the components and product-related processes and ensuring the quality of materials; and (10) conducting planned and periodic audit checklists that help to recognize the errors immediately and refine the noncompliant processes. In the road of globalization, more than 100 countries have accepted and followed the GMP guidelines as general standards, and they have mandated their manufacturers to make their own guidelines according to GMP principles. Given this universal acceptance, GMPs have become a principle in importing and exporting healthcare products/services which can facilitate the product/service presentation in a similar setting worldwide. Furthermore, an effective GMP can assist biopharmaceutical companies to get more qualified production, more profit, and less wastes.

6.6 Good Manufacturing Practice Regulations and Guidelines

GMP covers all aspects of production from raw material testing, premises and equipment, manufacturing control, personal hygiene of staff, laboratory controls, quality control department, packaging and labeling, end product testing, sale, records of medical cases, stability, and sterility of products. Each step in the production should have a precise written guidance to explain the procedures of the step in more details. Additionally, a general system is seriously required to control that the early determined principles are followed consistently at each step. There are several versions, amendments, and extensions of GMP guidelines. The WHO's version of GMP guidelines is less intransigent than European and

US ones, and it is easily applied by developing countries. In addition to WHO, considerations to other local and domestic issues are considered by regulators. On the other hand, harmonization is an important tenet which is necessary for applying the endorsed criteria and achieved through period conferences. Actually, GMP guidelines are a set of general principles covering the entire manufacturing and quality control processes. They are not comprehensive instructions of the process, as each system is responsible to arrange its detailed programs corresponded to established guidance to perform both business and regulatory requirements together.

6.7 Challenges and Future Perspective

Primarily, GMPs should be usable and feasible, possess the social acceptability, and describe the basis of risk adjustments. The best way for achieving these concepts is a proper measuring of customers' demands and effective workforce. Collaboration with agencies is a way to decrease the limitations of implementation of GMP. Subsequently, GMP regulations are enforced by different authorities all over the world, for example, FDA in the USA, MHRA in the UK, Therapeutic Goods Administration in Australia, Ministry of Health in India, and Iran Food and Drug Administration (IFDA) in Iran. Unfortunately, there are still impressive number of underdeveloped countries that are not in compliance with GMPs. Additionally, the mentioned and other authorities in other countries are faced with lack of trained staff. Sometimes staff do not have enough expertise and experiences. Also, generally there is no direct WHO supervision on these agencies and staff. Additionally, there is a prominent cultural misinterpretation of the GMP guidelines which needs to be overcome by providing national and regional guidelines and standards focusing on principles of international ones.

Generally, GMP has become an essential element in local and universal marketing. However, the compliance with GMP has not been commonly adopted in developing societies. Therefore, the governments are endured to invest heavily for upgrading the related standards, equipment, facilities, and man powers. From another point of view, these large investments raise the costs, and coping with this issue has become a troublesome domestic marketing of developing countries. Also, small size industries with less developed technologies make the competition with their counterparts difficult. "Market perspective" in developing countries is another difficulty that the governments are facing. Consequently, the manufacturers repine that they can profit without GMPs, and GMP execution has not expected profit for them. After all, strict GMP implementation for these countries makes an obstacle to develop [12]. One of the important tenets of GMP is to apply the novel technologies for enhancing its efficiency. Using current and updated data subsequently has been shown own benefits in the cGMP setting. However, application of novel technologies has its own limitations such as long-term finance, required facilities, adaptation of companies and related authorizations with them, etc. In summary, implementation of GMPs focusing on all their aspects and principles and trying to achieve a globalized setting is a major obstacle worldwide.

Take-Home Message

- GMP is a set of quality assurance practices which are aimed to guarantee the safety and good quality of products.
- GMP guidelines are used across 100 countries, for example, Australia, Europe, China, the Philippines, and Iran, while a few number of the countries are complied with the cGMP guidelines in comparison with GMP.
- GMP is enforced by different authorities all over the world. For example, FDA is responsible for the enforcement of GMP in the USA.
- There are different versions of GMP, but the WHO's version is the general reference, and most of the countries develop their own guidelines based on WHO-GMP following the similar basic principles.
- Every GMP guideline follows the 10 basic principles of WHO version.

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