Good manufacturing practices for medicinal products for human use

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ABSTRACT

At international and national levels, there are public and private organizations, institutions and regulatory authorities, who work and cooperate between them and with Pharmaceutical Industry, in order to achieve a consensus of the guidelines and laws of the manufacturing of medicinal products for human use. This article includes an explanation of how operate and cooperate these participants, between them and expose the current regulations, following the line of European Community/European Economic Area, referencing, wherever appropriate, the practiced guidelines, outside of regulatory action of space mentioned. In this way, it is intended to achieve quality, security and effectiveness exceptional levels in the manufacturing of health products. Good Manufacturing Practice aim the promotion of the human health and consequently, to the improvement of quality of life. For achieve the proposed objectives, it is necessary to ensure the applicability of the presented concepts and show the benefits arising from this applicability.

KEY-WORDS: Good Manufacturing Practices, pharmaceutical industry, quality, regulatory authorities, security and effectiveness

Good Manufacturing Practices (GMPs) are a compilation of various guidelines/guidance documents/directives issued and elaborated by international organizations and institutions, in collaboration with Pharmaceutical Industry and several national regulatory authorities in different regions and countries, in order to be guaranteed the highest standards of efficacy, quality and safety in any process that involves the manufacture of health products. GMPs are guidelines which govern the production, distribution and supply of a drug. It is a necessary condition for marketing authorization (MA). The aim of this review is to map the regulation, production, distribution and consumption of pharmaceuticals.

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It is intended to show and provide the General/Current State of GMP for Medicinal Products for Human Use, emphasizing the importance of a continuous update, regulatory harmonization, its adoption and monitoring/inspection, in order to be able to achieve, through the greater consensus, the continuous evolution of quality assurance, safety and efficacy. This is possible through a close cooperation between the several national and international entities, achieving a regulatory harmonization of GMP for medicinal products for human use, as well as a more rigorous monitoring compliance of these, by the competent authorities. Since the middle of the beginning of the last half of the 20th century, all stakeholders in the health and pharmaceutical industry are making efforts in the conception, knowledge and applicability of guidelines for GMP. This article is in line with the latest GMP guidelines for Medicinal Products for Human Use, provided by the European Commission (EC), entitled Eudralex. The EC directives were followed, making reference to the guidelines to GMP for Medicinal Products for Human Use, where appropriate, which are available by regulatory authorities, national and international organizations and institutions such as US Food and Drug Administration (FDA), World Health Organization (WHO),

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the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and Pharmaceutical Inspection Co-Operation Scheme (PIC/S).

National and international organizations and institutions

International conference on harmonization of technical requirements for registration of pharmaceuticals for human use

International Conference on Harmonization is an international organization with the propose of making recommendations and implementing standards of the International Organization for Standardization (ISO) to achieve greater harmonization in the understanding and application of the guidelines and technical requirements for registration of pharmaceutical products. This organization is the only initiative that brings together the drug regulatory authorities and the pharmaceutical industry in Europe, Japan and the United States.[1,2]

Pharmaceutical inspection co-operation scheme

PIC/S was created in 1995, based on the convention, concerning the pharmaceutical inspection (Pharmaceutical Inspection Convention [PIC]), founded by the European Free Trade Association in 1970. It provides an activity and constructive cooperation in the field of GMP with several objectives such as the implementation, development and maintenance of harmonized GMP standard and quality inspectors systems in the field of drugs, as well as to facilitate cooperation and contacts between the competent authorities, regional and international organizations, increasing mutual confidence between them. All decisions are taken unanimously. Currently is composed of 43 Participants Authorities, most of them from Europe.[1,3-5]

World health organization

The quality of pharmaceutical products has been a concern for WHO. The definition of global standards is required in Article 2 of the Constitution of WHO, which states the duties to "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products.".[1,6,7]

The production and access of medicinal products with good quality was identified as one of the prerequisites for the delivery of health care at the International Conference on Primary Health Care in Alma-Ata in 1978. Similarly, the Conference of Experts on the Rational Use of Drugs, held in Nairobi in 1985, and WHO's Revised Drug Strategy, adopted by the World Health Assembly in May 1986, identified the effective functioning of national drug regulation and control systems as the only means to assure safety and quality of medicinal products. Ever since, the World Health Assembly has adopted many resolutions requesting the Organization to develop international standards, recommendations and instruments to assure the quality of medicinal products, whether produced and traded nationally or internationally.[1,6,7]

The provisions are fully consistent with other internationally recognized texts on GMP. GMP guidelines published by WHO should be considered as consultative documents and may need some adaption to the specific conditions of each country.[1,8]

European medicines agency

The European Medicines Agency (EMA) is a decentralized agency of the European Union (EU). The Agency is responsible for the scientific evaluation of medicinal products developed by pharmaceutical companies in the EU. Among the extensive functions assigned, EMA is responsible for emphasizing the development of guidelines, setting standards and contribution to international cooperation activities with authorities outside the EU. All decisions are valid in all EU Member States, as well as in the European Economic Area (EEA) countries Iceland, Liechtenstein and Norway. By law, a company can only start to market a medicine once it has received a MA.[1,9]

The Agency is the hub of a European medicinal products network, which includes over 34 national regulatory authorities, the European Commission, the European Parliament and other decentralized EU agencies like the European Monitoring Centre for Drugs and Drug Addiction, and the European Centre for Disease Prevention and Control.[1,9-11]

The EU, including the European Commission and the EMA, has confidentiality arrangements with the United States (US), more specifically with FDA, since September 2003. The arrangements allow the exchange of confidential information between the EU and the FDA as part of their regulatory and scientific processes. This includes information on advance drafts of legislation and regulatory guidance documents, as well as non-public information related to ensuring the quality, safety and efficacy of medicinal products for human and veterinary use. Since 2009, the FDA has assigned a permanent representative to the EMA's office in London and, moreover since early 2010, the EMA has assigned a representative to the FDA's offices.[12,13]

Directive 2001/83/EC provides the Community codes for medicinal products for human use. On 2004, the Council of the EU and the European Parliament decided some amendments (Regulation [EEC] No 2309/93 by Regulation [EC] No 726/2004).[1,14]

The Pharmaceutical Industry of the EU maintains high standards of Quality Management in the development, manufacture and control of medicinal products. A system of MA ensures that all medicinal products are assessed by a competent authority to ensure compliance with contemporary requirements of safety, quality and efficacy. A system of manufacturing authorizations ensures that all products authorized on the European market are manufactured/imported only by authorized manufacturers, whose activities are regularly inspected by the competent authorities, using quality risk management principles. Manufacturing authorizations are

required by all pharmaceutical manufacturers in the EU whether the products are sold within or outside of the same.[1,15]

US food and drug administration

Food and Drug Administration is an agency of the US Department of Health and Human Services, which is responsible for protecting the Public Health by assuring the appropriate regulation of medicinal products for human use, and through the encouragement of product innovations.[1,16] It provides the accurate and science-based information of the medicinal products to the public. In the field of the medicinal products, the responsibilities of the FDA are protecting the Public Health by assuring the safety, efficacy and quality of medicinal products, vaccines, biological products and medical devices. FDA's responsibilities extend to the 50 United States, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, American Samoa, and other US territories and possessions.[1,17]

The Center for Drug Evaluation and Research performs an essential public health task by making sure that safe and effective drugs are available to improve the health of people in the United States.[1,18,19]

In 2002, the FDA started a major initiative to improve the regulation of the Pharmaceutical Industry and the quality of the product. The initiative focuses on the FDA's program of current GMP (cGMP) program and covers human medicinal products, including human biological medicinal products such as vaccines. This initiative aims to improve the promotion and protection of public health, focusing on three major goals. The first goal is to focus cGMP requirements on potential risks to public health by providing additional attention and resources on aspects of manufacturing. The second goal is to ensure that the establishment and application of medicinal product quality standards do not prevent innovation and the introduction of new manufacturing technologies in the Pharmaceutical Industry. The third goal is to improve the consistency and predictability of the FDA approach and ultimately to ensure quality and safety.[1,19] The FDA regulations can be found in Title 21 of the Code of Federal Regulations (CFRs).[1,20,21]

Good manufacturing practice - the general/current state

Pharmaceutical quality system

This guideline describes a comprehensive model for an effectiveness quality system of medicinal products, based on the concepts of ISO quality and its implementation throughout all stages of the life cycle of the product. This guideline will growth the technological innovation and strengthening of the link between pharmaceutical development and manufacturing activities. The guideline applies to supporting the development and manufacture of substances of Pharmaceutical Industry, Active Pharmaceutical Ingredient and medicinal products, including biotechnology and biological products throughout the life cycle of the product.[1,22-27]

Quality assurance is a broad concept that includes all matters that individually or collectively influence the quality of a product, that is, management of the quality of raw materials, products and other components, services related to production, and management, production and inspection processes. It is applied in pre-production to verify what will be made meets specifications and requirements and also while manufacturing production. Two principles included in quality assurance are: fit for purpose" where the product should be suitable for the intended purpose; and "right first time" mistakes should be strongly eliminated. In order to achieve quality, there must be a system of comprehensive quality assurance and implemented it correctly. This last issue include the management of GMP, quality control and quality risk.[1,24,25]

Personnel

According to EC GMP, the management of an enterprise should determine and provide adequate and appropriate resources such as human resources, financial, materials, facilities and equipment to implement and maintain the Quality Management System and improve effectiveness. Effective coordination and management of human resources are key factors in the proper functioning of any enterprise. To this end, enterprise management has duties and responsibilities in staff recruitment as well as the delegation of tasks.[1,28-31]

Premises and equipment

Premises and equipment must meet and comply with all rules, according to the operations to be performed in order to minimize the risk of errors and should allow effective cleaning and maintenance.[1,32-34]

Documentation

Good documentation constitutes an essential part of the quality assurance system and it is the key to operate in compliance with GMP requirements.[1,35] All types of documents and media used should be fully defined in the manufacturer's Quality Management System. Documentation may exist in several forms (paper-based, electronic or photographic media). The objectives of the system of documentation must be to establish, monitor and record all activities with impact on all aspects of the quality of medicinal products.[1,35-37]

Production

Production operations must clearly follow the procedures. They must comply with the principles of GMP in order to obtain quality products and be in accordance with the relevant manufacturing and MA. Production should be performed and supervised by competent people. All handling of materials and products, such as reception and quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and where necessary, recorded.[1,38,39]

Quality control

Quality control is concerned with sampling, specifications and testing as well as the organization, documentation and release procedures which ensure that the required and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.[1,40,41] Quality control is not confined to laboratory operations, but must be involved in all decisions that may concern the quality of the product. The independence of quality control from production is considered fundamental to the satisfactory operation of quality control.[1,40-42]

Contract manufacture and analysis/outsourced activities

The guidelines that regulate the contract and analysis manufacturing describe the responsibilities of manufacturers towards the competent authorities of the member states with respect to the granting of MA and manufacturing authorizations. The introduction of guidance on the Activities Subcontracting is based on the Pharmaceutical Quality System of the ICH Q10 document in order to provide updated guidance on subcontracting activities regulated by GMP, beyond the current scope of operations of the contract manufacture and analysis.[1,43]

The preparation and analysis of contracts must be correctly set, agreed and controlled in order to avoid misunderstandings, which may result in an unsatisfactory quality of a product or work.[1,43-45]

Complaints and product recall

In accordance with Article 117 of Directive 2001/83/EC, Article 84 of Directive 2001/82/EC and the WHO, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market. The procedures should include procedures for evaluation by the Quality Control Unit.[1,46-49]

Self-inspection

The objectives of self-inspections are the evaluation and supervision of compliance of the manufacturer with GMP in all aspects of production and quality control. It must be designed to detect any deficiency in the implementation of GMP and to recommend corrective procedures.[1,50-52]

Basic requirements for active substances used as starting materials

The members of the ICH developed a guideline denominated Q7A. This guideline is intended to provide guidance regarding GMP for the manufacture of active substances under an appropriate system for managing quality. It is also intended to ensure that active substances meet the requirements for quality and purity that they purport or are represented to possess.[1,53-56]

It is noted that the guidelines of GMP does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by other parts of the legislation. At the same time, these guidelines are not intended to define registration requirements or modify pharmacopoeia requirements and do not affect the ability of the responsible competent authority to establish specific registration requirements regarding active substances within the context of MA/manufacturing authorizations. All commitments in registration documents must be met. These guidelines apply to the manufacture of active substances for medicinal products for human use and to the manufacture of sterile active substances only up to the point immediately prior to the active substance being rendered sterile. Although the sterilization and aseptic processing of sterile active substances are not covered, those issues should be performed in accordance with the principles and guidelines of GMP, as defined by local authorities, including active substances that are produced using blood or plasma as raw materials, in spite of excluding whole blood and plasma as there are other detailed technical requirements for the collection and testing of blood. It should be noted that these guidelines do not apply to bulk-packaged medicinal products.[1,55-58]

Manufacture of medicinal products

Manufacture of solid and semi-solid medicinal products

Since this type of medicinal products is particularly susceptible to microbial contaminants and other contaminants during manufacturing, it is necessary to follow preventive procedures and it should be a priority for the manufacturer MA holder.[1,59,60]

Manufacture of sterile medicinal products

The manufacture of sterile products requires special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination, being highly dependent on knowledge, training and attitudes of the personnel involved. This type of manufacture must strictly follow methods and preparation processes, carefully established and validated, since the quality assurance, is of particular importance. The manufacture of sterile products should occur in clean areas whose access must be achieved through airlocks for personnel and/or equipment and materials.[1,61-66]

Manufacture of biological active substances and medicinal products for human use

The methods employed in the manufacture of biological active substances and biological medicinal products for human use are critical factors in shaping the appropriate regulatory control, because the manufacture of these involves certain specific, considerations arising from the nature of products and manufacturing processes, being necessary take some special precautions. Unlike conventional medicinal products, which are normally produced and controlled using reproducible chemical

and physical techniques, biological products are manufactured through methods that involve biological processes and materials, such as cultivation cells or extraction of material from living organisms. These biological processes may exhibit inherent variability and hence, that the range and nature of the by-products may be variable.[1,67-69]

Manufacture of radiopharmaceuticals

Radiopharmaceuticals must be manufactured and handled with some special care. The regulatory procedures necessary for the control of radiopharmaceuticals are determined in large part by the sources of these products and the production methods. The level of risk depends essentially on the types of radiation emitted and the half-lives of radioactive isotopes. It is necessary to pay special attention to the cross contamination, the contaminant of radioactive isotopes and to waste disposal. Due to its short half-life, some radiopharmaceuticals are released and administered to the patients after their production, before completing all quality control tests. The EC guideline is applied to manufacturing procedures employed by industrial manufacturers, Nuclear Centers/Institutes and positron emission tomography (PET) Centers for the production and quality control of the following types of products: Radiopharmaceuticals, PET radiopharmaceuticals, Radioactive Precursors for radiopharmaceutical production and lastly Radionuclide Generators.[1,70-72]

The International Atomic Energy Agency is the agency that regulates the transport of radiopharmaceuticals and the requirements for protection against radiation.[1,70,72]

Manufacture of pressurized metered dose aerosol preparations for inhalation

The manufacture of pressurized aerosols for inhalation with metering valves, according to the GMP guidelines of the EC/EEA, requires a special consideration mainly due to the particular nature of these dosage forms. These medicinal products must be manufactured under conditions that minimize microbial and particulate contaminations. The quality assurance is fundamental for components with valve and to the uniformity of suspensions.[1,73,74]

Manufacture of medicinal gases

At the level of EC/EEA, the gases meet the definition of medicinal products of Directive 2001/83/EC (designated medicinal gases) are subject to the requirements of this Directive, including the manufacturing requirements addressing the manufacture of active substances gases and medical gases. In this respect, these guidelines deal with the manufacture of active substances from gases and the manufacture of medicinal gases. The delineation between the manufacture of active substances and the manufacture of medicinal products should be clearly defined in each MA dossier. The manufacture of active substances from gases must comply with the basic requirements for active substances used as starting materials and other guidance when needed.[1,75,76]

Investigational medicinal products

This class of medicinal products should be produced in accordance with the principles and GMP. Procedures need to be flexible as the process increases, and it should be appropriate to the stage of development of the product. It is noted that an increase in complexity in manufacturing operations requires a highly effective quality system.[1,77-79]

Medicinal products derived from human blood or plasma

The requirements for the collection, testing and quality control of medicinal products derived from human blood or plasma are defined by a system of quality assurance, based on the existence of a national structure which is independent of manufacturers, complying with the principles and guidelines of GMP. Those products are considered to be biological medicinal products due to their specific characteristics and the starting materials include biological substances, such as cells or fluids (including blood or plasma) of human origin. The provisions of CE apply to medicinal products derived from human blood or plasma, fractionated in or imported into the EU/EEA. Furthermore, apply to the starting material (e.g., human plasma) for these products and for stable derivatives of human blood or human plasma (e.g., albumin) incorporated into medical devices. However, it does not apply to blood components intended for transfusion.[1,80,81]

Manufacture of herbal medicinal products

The procedures and techniques used in the manufacture and quality control of herbal medicines are often substantially different from those used for conventional medicinal products. The herbal substance should be of suitable quality. The supporting data should be provided to the manufacturer of the herbal preparation/herbal medicinal product. A consistent quality assurance of herbal substances requires more detailed information on its agricultural production.[1,82-84]

These guidelines apply to all herbal starting materials: Medicinal plants, herbal substances or herbal preparations.[1,82,83]

Ionizing radiation in the manufacture of medicinal products

In accordance with the guidelines of GMP of the EC/EEA, a MA for a product which includes irradiation as part of its processing should also refer to the note produced by the Committee for Proprietary Medicinal Products.[1,85]

Ionizing radiation can be used during the manufacturing process for various purposes; it may be made by pharmaceutical manufacturer or an operator of a radiation facility under contract both of whom must hold an appropriate manufacturing authorization.[1,85,86]

Sampling of starting and packaging materials

Sampling is an operation where a small fraction of the batch is removed integrating operations to select a portion of a

pharmaceutical product for a specific purpose, in accordance with an appropriate procedure. This process should be carried out in accordance with written and approved procedures that are appropriate to the sample and the type of control intended to be applied to the sample and the sample material.[1,87-89]

Computerized systems

The EC through Annex 11 of GMP and FDA through the US 21 CFR Part 11 describes the requirements to be followed for computerized systems, electronic records and digital signatures.[1,90,91]

These guidelines apply to all forms of computerized systems used as part of the activities regulated by the GMPs. These systems are a set of software and hardware components, which collectively satisfy certain functionalities. There should be no decrease in product quality, process control or quality assurance, where the quality system is replaced by manual operations.[1,90,92]

Food and Drug Administration has established criteria by which electronic records, electronic signatures, and handwritten signatures executed to electronic records are trustworthy, reliable and generally equivalent to paper records and handwritten signatures executed on paper.[1,91,93]

Qualification and validation

The guidelines of GMPs qualification and validation of the EC/EEA describes the principles of qualification and validation which are applied in the manufacture of medicinal products. In these requirements, manufacturers identify what validation work needed to prove control of the critical aspects of their particular operations.[1,94,95]

Certification by a qualified person and batch release

The guidelines of the EC/EEA are a guide of GMP to holders of medicinal products with MA or for export. It also covers cases where the batch had different stages of production or test conducted at different locations or by different manufacturers, and where an intermediate or bulk production batch is divided into more than one finished product batch. The release of batches that were imported into the EC/EEA are also included in the domain of these guidelines, when there is and when there is no mutual recognition agreement between the EC/EEA and third countries. Investigational Medicinal Products are also under these guidelines.[1,96]

Parametric release

Parametric release is a system of release that provides assurance that the product is of the intended quality based on information collected during the manufacturing process and in accordance with specific GMP requirements, annexes and related guidelines. However, it does not mean that all tests specified should be executed in the finished product before release.[1,97-100]

EU guidelines, refers only to part of parametric release that deals with the routine release of finished products without carrying out a sterility test. According to these guidelines, the implementation of parametric release is in line with the European Pharmacopoeia.[1,97,98,100]

The PIC/S guidelines seek covers a wide scope that includes a reduction or elimination of finished products routine testing. These guidelines are not intended to be a barrier to technical innovation. Recommendations are not mandatory for the industry, but the latter should regard them as appropriate.[1,99]

Food and Drug Administration provides recommendations to applicants on the information to be included as support of parametric release for sterile products terminally subjected to sterilization by moist heat, at the time of submission of a new medicinal product. Currently, this agency requires that sterile products meet certain requirements for sterility before release to the market.[1,101]

Reference and retention samples

At the level of EC/EEA, the guidelines provided and prepared by the relevant organisms in this scope offer guidance on the taking and holding of reference samples of starting materials, packaging materials or finished products and retention samples of finished products. These guidelines also include guidelines on the collection and retention of samples of medicinal products for parallel import and distribution. Samples are retained in order to meet two objectives: First, to provide a sample for analytical testing; second, to provide a sample of the totally finished product. Samples are divided into two categories: Reference sample and retention sample.[1,102,103]

Quality risk management

About guidance on Quality Risk Management, ICH Q9 document containing guidelines on GMP to be followed in this context was elaborated. This guideline specifically provides principles and examples of tools of Risk Quality that can be applied to all aspects of pharmaceutical quality including the development, manufacture, distribution and inspection processes and submission/review of the entire life cycle of substances, medicinal products, biologics and biotechnology products including the development, manufacture, distribution and inspection and submission/review of the entire life cycle of substances, medicinal products, biologics and biotechnology products, including the use of starting materials, solvents, excipients, packaging and labeling materials, that allow for more effective and consistent risk-based decisions, either by regulators or the Industry. It is not intended to create new expectations beyond current requirements. The purpose of this guideline is to provide a systematic approach of quality risk management and serves as a base or resource, independent, supporting other documents relating to the quality of ICH and complements existing quality practices, requirements, standards and guidelines in the scope of Pharmaceutical Industry and regulatory environment, thus remaining optional character.[1,104-109]

Quality risk management can be applied not only in the manufacturing environment, but also in connection with the pharmaceutical development and preparation of quality part of the dossier for MA. The guidelines also apply to regulatory authorities in the field of pharmaceutical evaluation of the quality of the dossier for MA, GMP inspections and treatment of suspicions of quality defects.[1,22,107-109]

CONCLUSION

It is verified that there has been a major concern by all stakeholders in the whole process of manufacture of medicinal products in constantly updating and implementing guidelines of GMP for Medicinal Products for Human use, based on new techniques and methods, which have proved to be more useful for the entire manufacturing process and provide a better quality, safety and efficacy. It is noticeable a growing involvement by organizations and institutions whether public or private, regulatory authorities and the pharmaceutical industry in the reach of maximum harmonization guidelines of GMP for medicinal products to be applied in each country. To be achieved all these parameters, it is necessary that manufacturers are aware of the importance of good implementation and management of these guidelines, their responsibilities relating to the manufacture of medicinal products. It is important to have an effective system of Quality Control and Quality Risk Management; the control and inspection of GMP guidelines are key factors for the personnel within the manufacturer and external stakeholders as well as the importance of having an organization and effective management of all human resources and qualified personnel, motivated and responsible.

Thus, it is necessary to continue with the efforts already made, which provided the current state of GMP, overcoming barriers and reaching new goals, promoting public and individual health, leading to a better quality of life for society in general.

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