ejpmr, 2017,4(7), 378-382

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

REGULATORY ASPECTS INVOLVED IN MARKETING AUTHORIZATION OF MEDICAL DEVICES -OVERVIEW

***Mohammed Sayeed and Dr. B. Vasudha**

Anurag Group of Institutions (Formerly Lalitha College of Pharmacy), Hyderabad.

***Corresponding Author: Mohammed Sayeed**

Anurag Group of Institutions (Formerly Lalitha College of Pharmacy), Hyderabad.

Article Received on 09/05/2017 **Article Revised on 30/05/2017** **Article Accepted on 20/06/2017**

ABSTRACT

This article states requirement of Marketing Authorization Application to get registration of Drug Product to EEA. The procedures for application of marketing authorization are: Centralised procedure, National procedure, Mutual recognition procedure, Decentralised procedure.

KEYWORDS: MAA, EU, Rapporteur, Co-Rapporteur, EMA.

ABSTRACT

Formerly with more augmented disabilities, Medical devices have become decisive device in many circumstances. As these are more perilous, the manufacturer should endow with an ideal medical device in aspects of safety & quality. To produce a homogeneous device globally, there should be some standards to be followed within an explicit country and standard throughout the globe, complying with the quality. In milieu of this resemblance of device globally, International Organization for Standard (ISO) has issued a standard, ISO 13485. This article is made to furnish the details about ISO 13485 and the Quality management system followed by United States manufacturer's to market their devices within the country, i.e., 21 CFR Part 820.

KEYWORDS: Medical devices, ISO 13485, 21 CFR-Part 820.

INTRODUCTION

Definition: A medical device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes".[1]

Classification of medical devices

The medical devices in US are classified into three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The classification of medical devices also depends on the intended use, indications for use and the risk that a device imposes on the patient and/or on the user.[2]

The three classes and the requirements which apply to them are (device class and regulatory controls)

1. Class I (low to moderate risk): General controls. E.g.: Tongue depressors, arm slings, and stethoscopes
2. Class II (moderate to high risk): General controls and Special Controls E.g.: Physiologic monitors, x-ray systems, gas analyzers, pumps, and surgical drapes.
3. Class III (high risk): General controls and Premarket Approval (PMA) E.g.: Pacemakers, replacement heart valves and total joint replacements.[3]

The General Controls are the baseline requirements of the Food, Drug and Cosmetic (FD&C) Act that apply to all medical devices, Class I, II, and III.

The Special Controls are regulatory requirements for class II devices. The general controls alone are insufficient for providing reasonable assurance of safety and effectiveness of the device and these special controls provide such assurance.

Class III devices, supporting or sustaining human life, highly risked, for which general controls and special controls are insufficient to provide reasonable assurance of the safety and effectiveness of a device. For marketing of these devices a premarket approval application (PMA) is required.[4]

The marketing of Class I or II devices is done through the path of 510K, if it is not an exempt. The devices classified as exempt, are subject to the limitations on exemptions.[2]

Quality Standards for Medical Devices A standard is a document that provides requirements, specifications, guidelines or characteristics that can be used consistently to ensure that materials, products, processes and services are fit for their purpose. As the medical devices are more allied with risk factor, there should be no negotiation on their quality. To ensure the quality of medical devices, some standards are customized globally and within each specific country. Every manufacturer should meet these precised standards before marketing the medical devices.[5]

ISO 13485 ISO International Standards ensure that products and services are safe, reliable and of good quality, it is published by ISO, the International Organization for Standardization, and is available through National Standard Bodies. Some medical devices such as pacemakers and diabetic pumps can hoard countless lives, but they also pose a huge threat to human life if proper safety and quality procedures are not followed. To ensure the quality of devices, a standard ISO 13485 is established relating to quality management systems in the field of Medical Devices, including IVD (In Vitro Diagnostics). ISO 13485 have become global standard for those who manufacture medical devices, as they endow with a proven guideline for maintaining assurance and managing risk.[6]

ISO 13485 "specifies requirements for a quality management system where an organization needs to demonstrate its ability to provide medical devices and related services that consistently meet customer requirements and regulatory requirements applicable to medical devices and related services". ISO 13485 solves two concerns for medical device manufacturers: Supplying customers and end-users with safe medical products and superior patient outcomes.

The standard is used by an organization for the design, development, production, and installation and servicing of medical devices. ISO 13485 is also used by internal and external parties, including certification bodies, to assess the organization's ability for meeting the customer and regulatory requirements. Its primary objective is to facilitate harmonized medical device regulatory requirements. The standard is based on eight quality management principles: customer focus, leadership, involvement of people, process approach, and system approach to management, continual improvement, fact-based decision-making and mutually beneficial supplier relationships.[7]

21 CFR Part 820[8] The manufacturers of devices should establish and follow quality systems to ensure that their products consistently meet the applicable requirements and specifications. The current Good manufacturing practices (cGMP's) are strictly followed in US for the manufacture of FDA regulated products, these requirements were stated in part 820 (21 CFR part 820) which was first authorized by section 520(f) of the Federal Food, Drug, and Cosmetic Act (the act), which became effective on December 18, 1978, and was codified under part 820.[5]

In 1990, FDA revised the cGMP regulation to add the design controls authorized by the Safe Medical Devices Act. It was revised, to benefit the public and the medical device industry. Further, the revision made for cGMP regulation to be consistent, for the extent possible, with the requirements for quality systems contained in applicable international standards. After an extensive effort, the part 820 revision was published on October 7, 1996 and was effective from June 1, 1997.

The regulation does not prescribe in detail how a manufacturer must produce a specific device. Rather, it provides the framework that all manufacturers should follow by requiring that manufacturers develop and follow procedures, fill in the details that are appropriate to a given device according to the current state-of-the-art manufacturing for that specific device.[5]

Salient Features of quality standards
ISO 13485[6]

- Implementation of a Quality Management System helps to motivate staff and provide a better definition of roles and key responsibilities.
- Implementing a Quality Management System specifically tailored for the medical devices industry helps the organization to demonstrate its ability to systematically provide medical devices and services that consistently meet customer requirements, meet applicable regulatory requirements (compliance) and safety standards.
- Cost savings can be made through improved efficiency and productivity, as product or service deficiencies will be highlighted and corrected.
- Improvements can be made on a systematic and monitored base, resulting in less waste, less inappropriate or rejected work, and fewer complaints.
- Provides a systematic approach to risk management.
- Systematic, smoother, transparent and documented handling of activities required by regulation such as post-marketing followup and surveillance, complaints handling, CAPA implementation, field actions or product recall handling, vigilance and competent authorities reporting, and clinical experience enrichment.
- Systematic incorporation, at an early stage and within the design and development process, of the regulatory requirements impacting on the product itself and its technical features
- Help creating a systematic vision embracing the medical device lifecycle, medical device packaging,

its labelling, its installation, its servicing, and its usability. This includes the information provided together with the medical devices, the commercial claims, the unspoken user expectations, the feedback from users or patients, the risks associated with use, the benefits brought to the single patient and to the Community, the costs and the disposal of the medical device.

21 CFR Part 820[9-11]

21 CFR Part 820 provides standards for a company to set policies, operating procedures, guidelines and objectives that will promote product quality.

- Developing the Quality System Structures
- Keeping management informed
- Improving Customer Service
- Responsibility and ownership sharing
- Improving timeliness trends
- Strategies for enlisting support
- The Design Review
- Sustaining Systems

Comparison of ISO 13485 with 21 CFR Part 820[12, 13]

21 CFR 820 is applicable to the manufacturers of finished medical devices sold in the United States, including foreign manufacturers who import devices. Some manufacturers might be subject only to certain requirements, depending on the operations they are engaged in. (6) Medical device manufacturers that sell their products in the global market find it advantageous to get ISO 13485 certification because ISO standards are recognized worldwide. Certain countries require such certification and many customers also prefer medical devices that are ISO certified.

Table 1: gives a detail comparison between the both.

S. No	21 CFR 820	ISO 13485
1	Quality system refers to a medical device manufacturer's responsibilities, procedures, processes, and resources for implementing quality management. (Subpart B)	Quality management system requirements were developed to satisfy international medical device regulations. (Clause 4)
2	Require controls in design, document, purchase, and production process. This entails establishment of processes to ensure that a medical device conforms to specifications. (Subpart C,D,E,G)	Requires establishment of a quality management system for medical devices. A manufacturer must have quality procedures that are documented, controlled, and effectively implemented and maintained. (Clause 4)
3	Each manufacturer must have sufficient personnel with the necessary background, training, and experience. It must have established procedures for identifying training needs and ensuring that employees are adequately trained to perform their jobs. Training should be documented.(Subpart B, Sec. 820.25)	A manufacturer must ensure that its personnel have the right experience, education, training, and skills. Acceptable levels of competence must be defined. Training needs must be established and assessed. A record of competence must be maintained.(Clause 6)
4	Require establishment and maintenance of non-conformance and corrective and preventive action (CAPA) procedures. Non-conformances relating to product, processes, and quality system should be investigated and actions needed to correct and prevent recurrence must be identified. Corrective action has to be validated to ensure effectiveness and all activities pertaining to Non-conformance and CAPA must be documented.(Subparts I,J)	Remedial processes are required. Quality should be monitored and measured by gathering customer feedback, setting up internal audits, establishing a nonconformance procedure, and analyzing quality information. Non-conformances must be corrected, recorded, and prevented.(Clause 8)
5	Requires procedures for identifying products.(Subpart F)	Requires development of procedures to identify and track products.(Clause 7)
6	When computers or automated data processing systems are used as part of production or the quality system, the manufacturer should validate computer software for its intended use according to an established protocol. Validation activities and results should be documented.(Subpart G, Sec. 820.70)	Requires validation of monitoring and measuring software before use. Revalidation should be conducted when necessary.(Clause 7)
7	Complaint means any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it	Customer complaint: written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety or

	is released for distribution. (Sec 820.3)	performance of a medical device that has been placed on the market (Clause 3)
8	The term "labelling" means all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers or accompanying such article. The "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this Act that any word, statement, or other information appear on the label. (Sec. 210)	Labelling: Written, printed or graphic matter affixed to a medical device or any of its containers or wrappers, or accompanying a medical device, related to identification, technical description, and use of the medical device, but excluding shipping documents (Clause 3)
9	Inputs relating to product requirements shall be determined and records maintained. These inputs shall include: a) functional, performance and safety requirements, according to the intended use b) applicable statutory and regulatory requirements c) where applicable, information derived from previous similar designs, d) other requirements essential for design and development (Sec 210)	Design input means the physical and performance requirements of a device that are used as a basis for device design.(Clause 7)
10	Quality policy: Management with executive responsibility shall establish its policy and objectives for, and commitment to, quality. Management with executive responsibility shall ensure that the quality policy is understood, implemented, and maintained at all levels of the organization. (Sec 820.20)	Quality objectives: Top management shall ensure that quality objectives, including those needed to meet requirements for product, are established at relevant functions and levels within the organization. The quality objectives shall be measurable and consistent with the quality policy. (Clause 5)

CONCLUSION

ISO 13485 is a tool which reassures that the medical devices are being manufactured through a systematic approach to make them safer for use. Device manufacturers need to follow ISO 13485 for marketing their device globally, and also need to comply with regulations in individual countries. US follow 21 CFR 820 for medical devices and ISO 13485 certification is not acknowledged in FD & C act. Unlike US and European Union, other countries do not have the resources to conduct inspections outside their own borders. Thus, they must rely upon a regulatory standard to assure the organization for quality system compliance. If a manufacturer meets the requirements of ISO 13485, the device can easily meet the quality requirements in many regulated countries including the US.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my colleagues & my M. Pharm friends, who gave me the appropriate guidance and has shown interest and encouraged me to carry out work on this review article.

CONFLICT OF INTEREST Author declares that there are no conflicts of interest.

REFERENCES

1. U.S. Food and Drug Administration [Internet]. Silver spring, MD; 2012 April [cited 2016 Feb 24] Available from: http://www.fda.gov/aboutfda/transparency/basics/ucm211822.htm.
2. U.S. Food and Drug Administration [Internet]. Silver spring, MD; 2012 Dec [cited 2014 Feb 24] Available from: http://www.fda.gov/%20MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ default.htm (Cited on 2016 Feb 24).
3. PocCENT, point of care Center for Emerging Neurotechnologies [Internet]. USFDA; 2014[cited 2016 Feb 24]. Available from: http://www.ece.uc.edu/POC-CENT/funding/Additional%20Information/fda-classification.
4. U.S. Food and Drug Administration [Internet]. Silver spring, MD; 2015 April [cited 2016 Feb 24]. Available from: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ ucm2005378.htm (Cited on 2016, Feb 24).
5. ISO, What is a standard? [Internet]. Geneva; 2016 [cited 2016 Feb 24]. Available at: http://www.iso.org/iso/home/standards.htm.
6. ISO, International Organization for Standardization [Internet]. Geneva; 2016 [cited 2016 Feb 24]. Available at: http://www.standards.org/standards/listing/iso_13485.
7. Willett N. Quality Magazine. Quality Management: The Need for ISO 13485 [Internet]. 2011 Jan [cited 2016 Feb 25]. Available at:

http://www.qualitymag.com/articles/87898- quality-management-the-need-for-iso-13485.
8. U.S. Food and Drug Administration [Internet]. Silver spring, MD; 2014 Jun [cited 2016 Feb 25]. Available from: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/QualitySystemsRegulations/.
9. Incra Med, Medical Device Solutions [Internet]. Ireland; 2010 [cited 2016 Feb 25]. Available from: http://incramed.com/main/page_training_solutions_device_design.html.
10. Incra Med, Medical Device Solutions [Internet]. Ireland; 2010 [cited 2016 Feb 26]. Available from: http://incramed.com/main/page_training_solutions_fda_qsrs.html.
11. Incra Med, Medical Device Solutions [Internet]. Ireland; 2016 [cited 2016 Feb 26]. Available from: http://incramed.com/main/page_training_solutions_capa.html 12. Master Control, Compliance Accelerated [Internet]. Utah; 2016 [cited 2016 Feb 26].Available from: http://www.mastercontrol.com/iso13485/ISO_13485_Certification.html.
12. 13485 Store [Internet]. US; 2003 Aug 5 [cited 2016 Feb 26]. Available from: http://13485store.com/downloads/compare-iso-9001-and-iso-13485-to-fda-qsr.pdf.