Kalpana Kamnoore et al /J. Pharm. Sci. & Res. Vol. 11(8), 2019, 2910-2914

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Regulatory Requirements for Mobile Medical Applications for USA, EU and Other Countries.

Kalpana Kamnoore[1] , Dr M.P. Venkatesh*[2] ,Balamuralidhara V.[2] ,Dr. T. M. Pramod Kumar[3]

[1]M Pharm – Pharmaceutical Regulatory Affairs,
[2]Asst. Professor, Pharmaceutical Regulatory Affairs Group,Department of Pharmaceutics,
[3]Professor and Principal,
JSS College of Pharmacy,
JSS Academy of Higher Education and Research,
SS Nagara, Mysuru-570015, Karnataka, India

Abstract:

Mobile Medical Application (MMA) has shown rapid usage among public. It is necessary that they should be aware of the regulatory requirements for medical apps and health risks associated with it. These apps present unique challenges for regulation by the drug regulatory bodies worldwide. The regulatory requirements vary from country to country hence developers have to consider the regulations of particular country where they are marking the MMA. The aim of this article is to study regulatory requirements for approval of MMA for various countries like USA, EU and other countries.

Keywords: Mobile Medical application, Regulations, US FDA, EU.

INTRODUCTION:

Mobile Medical Application (MMA) consists of medical device which is connected to the mobile application which has been used to assist the human health. It is used as patient monitoring devices, wireless devices and personal digital assistants. Mobile Health is developing and rapidly growing field which has the probability to play a part in the revolution of healthcare industry. MMA includes various technical solutions which can measure human health conditions like heart rate, blood pressure, glucose level in blood, body temperature and brain activities.

The US and EU are two major markets for medical device in the world which provides stringent regulations for medical devices. So it is mandatory for the manufacturer to consider regulations and guidelines provided by these authorities to develop MMA. It is important to understand the regulatory process to market the mobile medical applications and challenges which comes while developing MMA. International Medical Device Regulators Forum (IMDRF) includes Global Harmonization Task Force members like EU, USA, Brazil, Japan, Australia and Canada. These countries have taken steps for progress in simplifying and harmonising medical device regulation. A major challenge for regulators is to frame regulations which will not compromise safety, privacy in the data, securing it and establishing accurate data. The objective is to study regulatory requirements for approval of MMA and to study policy for development of MMA.

Mobile medical application consists of:

- Medical Device Tools
- Technology for communication
- Access to internet including Network Infrastructure
- Software Technologies

DISCUSSION:

The Food and Drug Administration's has put forward their current mission to encourage and protect public health in the USA. Due to development of large number of medical device application, FDA is focusing on regulations for developing MMA as well as Marketing it in USA. USA regulatory authorities has divided medical devices in three classes which are depending on the risk associated with it. Classifications of such devices: Low risk is Class I, Moderate risk is Class II and High risk is Class III. The classifications are consigned by the hazard that the medical device presents to the patient and the level of regulatory requirements provide by FDA which determines the need to market the device legally in US market. The level of risk is increases from class I to class III and as per the increase in risk level regulatory control for it also increases. USFDA provided draft guidance on "Mobile Medical Applications." published in 2013. This guidance is used to provide in depth information on MMA regulations and use of software application on mobile platform. [1]

European directives has similar regulations to that of USFDA to permit free movement of medical devices from state to state inside the EU only after ensuring the performance of the device and safety associated with it. Previously, National regulations were sufficient to market the medical devices which are now replaced by European directive, applicable for all the member states. For any medical device to market in EU state it is mandatory to carry 'CE' marking on it which shows the compliance of the medical device to the given essential requirements. [2]

On 1st January 1993 three directives came into force which are regulating safety and marketing of the medical devices. As the time elapsed, these directives were modified and new directives got implemented.

FDA and EU regulators interested in regulating mobile medical apps which meets the definitions of medical device. FDA's guidance provides almost answers for the questions arising for development of MMA. Other countries like Japan, China and Canada also provided regulations for mobile medical applications which are not stringent as USFDA.

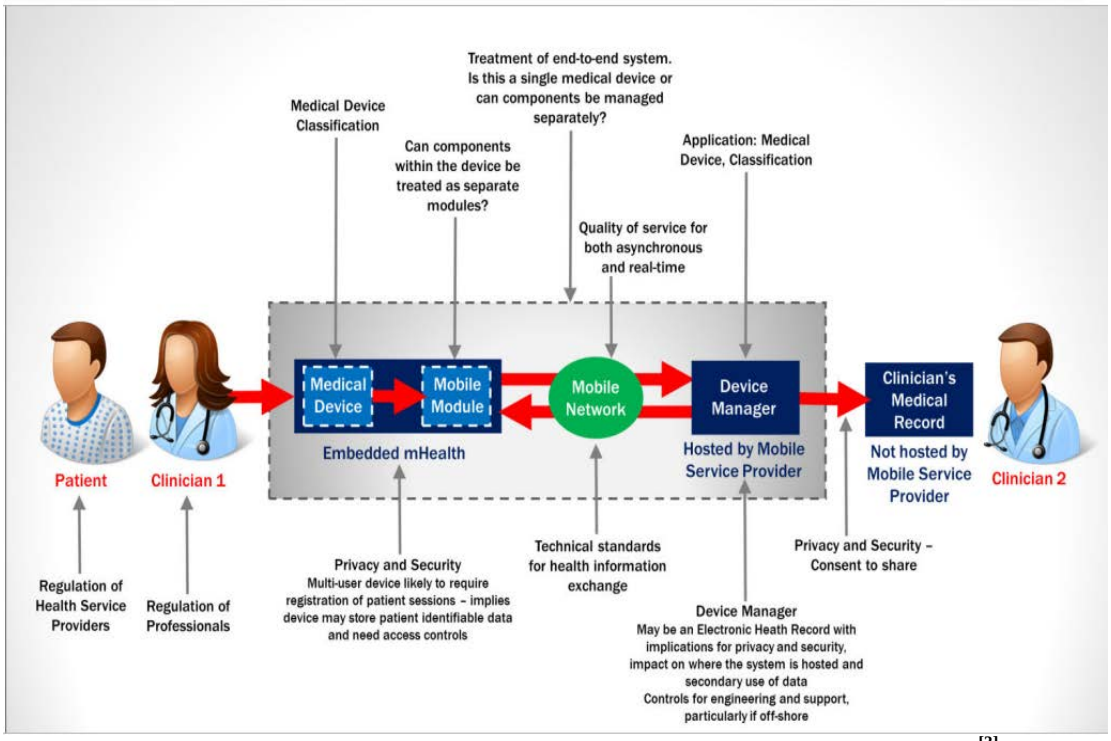

Fig.1: Policy and regulations for development of mobile medical application [3]

REGULATIONS FOR MOBILE MEDICAL APPLICATIONS:

1.0 UNITED STATES:

1.1 Definition:

"Mobile medical app" is a mobile app that meets the definition of device in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and either is intended:

- to be used as an accessory to the medical device
- to convert a mobile platform into medical device which is being regulated

1.2 FDA Regulations applicable to mobile medical applications:

Appendix E of FDA's guidance document provides an overview of the regulatory requirements needed for mobile medical apps.

Table 1: Categories of mobile medical applications by FDA [4]:

Application functionality	Example of MMA	Risk level
As an addition of approved medical device:which includes display of the condition, storing the data obtained, analysing the data, or transmitting the data obtained from patient health condition.	a. X-rays and MRI which displays the medical image b. EEG waveforms and bedside monitor which includes graphic data	High risk
Applications which is used to convert a mobile phone into a medical device	a. Use of smart watches connected to mobile applications to detect heart rate, blood pressure, etc. b. Urine-analysers or glucometers c. Attachment of transducers to make stethoscopes, spirometers	High risk
Applications for diagnosing & treatment options on the basis of patient specific condition	Prediction of the disease, treatment options for the disease, dosage calculators for it, etc.	Medium risk
Applications for normal health & education purposes	Heart rate monitors, thermometers, BMI calculator, medication reminders, health record systems, body fat calculators, steps calculator, etc.	Low risk

Specific requirements include:

- **Registration of the medical device and listing it under marketing devices**-
  Manufacturer of the mobile medical application must register under the FDA and the name of the developer mobile medical application should include under the list of medical devices marketed in the USA. This list must be updated annually and the registration should also get updated annually.
- **Approval or clearance of MMA by premarket notification i.e. 510(k) application**
  - Developers of Mobile medical applications must prepare and submit to the FDA a premarket notification i.e. 510(k) application with the risk classification appropriate to their application. Generally this application is applicable to low risk MMA.
- **Quality system regulation** - Quality system regulation has been provided by FDA for the developers which includes implement systems required and methods for the designing, producing and distributing of the devices which are safe and effective. There is also need for the verification and validation of the application developed. [5]
- **Labelling of the product** – 21 CFR part 801 gives information on labelling of medical devices including mobile medical application and developers should comply with it. [5]
- **Reporting of adverse events**- Mobile medical applications comes under FDA's medical device regulations, so any risk associated with the device after or before usage like any minor injury to death as well as malfunctioning of the it leading to incorrect data, risk to patient's health should be reported. Written report must be submitted by the developer to FDA if any instances are found. [5]

1.3 Categories of devices listed under FDA enforcement discretion: [1] [2]

- Self –management of the diseased condition without taking support of any treatment suggestions and any specific treatment for the disease.
- Providing patients simple tools which will help them to organise and to track their current health condition.
- For storing the data, detecting potential health condition which is given to health care provider to detect the medical condition of the patient.
- Providing easy access by mobile application data which gives information associated to patients health conditions and treatments
- Discovering automate simple things for health care providers.
- Assist patients to determine Personal Health Record or an Electronic Health Record systems;
- By connecting to medical device, mobile applications should enable to transfer, store, convert format, and display data associated to medical device in its original format.

1.4 Considerations and requirements after approval of MMA in USA:

The developers as well as the distributors involved in Mobile medical applications and mHealth apps must follow requirements and regulations post approval of the MMA as per the FDA. These include tracking of the application as well as system, reporting any adverse effect observed, reporting device malfunctioning, serious damages or death, and registering the establishment where the production of devices and applications are taking place and distributed.

Reporting of medical device of MMA is different from the conventional medical devices. Regulations have been set after approval of MMA for detection and correcting the problems in timely manner for assuring safety of the user. Any complaint about major injury or death or malfunctioning of the devices should be noted and FDA wants manufacturer and distributors to certify the developed product and place the system according to the problem reported.

2.0 EUROPEAN UNION

Regulation given by European Union as compared to that of US is more efficient and less centralised. Most of the mobile medical application comes under class I i.e. Low risk medical devices which is least harmful for the patient. Due to less health hazardous effect medical devices falling under this class does not require many legislation for approval and marketing in European Union states.

EU Directives given for medical devices are not thorough enough so it is difficult to place the app or its software in any category. Due to this, MEDDEV was issued which was last updated on January 2012 gives "Guidelines on the Qualification and Classification of Standalone Software Used in Healthcare within the Regulatory Framework of Medical Devices". [6] More detailed clarification on classification of any stand-alone device/ software used for medical purpose is provided in this guideline. This made manufacturer easy to decide whether the software they are developing comes under medical device or not. As per this guideline, MMA meets the definition of both the medical device and its accessories which depends on its intended use. Additionally, if the application is not the extension of medical device then it is considered as stand-alone device which comes under category of 'active medical devices'. If it is categorised under medical device then the software should be associated with medical purpose, some exceptions are laid down for them also.

2.1 Regulatory requirements for mobile medical application EU:

EU Directives published standards for mHealth technologies. These Directives provides essential requirements which are transferred into national laws of member states of European Union. Detailed specifications regarding technical standards are also provided in this directive.

Compliance of essential requirements given for the medical devices should be considered by both manufacturer and importer. MMA should contain CE

marking which gives conformity evidence which makes manufacturer easy to legally market and sell the product in member states of EU without any additional testing of the device. [7]

Following are the EU directives which give requirements applicable to mHealth technologies and devices [8]:

- **Radio & Telecommunications Terminal Equipment (R&TTE) Directive (1995/5/EC):** For all the products and devices which utilize the radio frequency spectrum for wireless communications and for those devices that connect to public telecommunications networks, this Directive is applicable. Verification and testing is needed by an EU notified body to assure the compliance with the R&TTE Directive's requirements.
- **Electromagnetic Compatibility (EMC) Directive (2004/108/EC)**:
  For all electronic equipment which results in generation of intentional or unintentional electromagnetic interferences, this Directive is applicable. US has given FCC's part 15 EMC requirements which are in parallel with EMC directives given by EU. This directive requirements is established by declaration of conformity which can be issued either by manufacturer or importers and it can be based on in-house testing or third party testing.
- **Low Voltage Directive (2006/95/ EC):**
  Any safety regarding issues related to electronic equipment that can be operated within specific voltage limit, this directive is applicable for them. Declaration of conformity also gives assurance to compliance of low voltage directives by manufacturer or importer which is based on third party testing or in-house testing.
- **Medical Device Directive (93/42/ EEC) and Directive on Active Implantable Medical Devices (90/385/EEC):**
  These both Directives collectively called as MEDDEV gives safety requirements for medical devices and implantable medical devices. Confirming the compliance of this Directive depends on the class of the medical device which is being evaluated. Manufacturer should provide Declaration of Conformity tested by notified body. In many cases of medical devices, there is necessary to maintain quality management system and it is mandatory for assessing risk associated to it as a part of evaluation process.

2.2 Considerations and requirements after approval of MMA in EU:

Proactive and reactive are the two categories given in European directives for post marketing activities at European level. There is increase in protection of Health and safety of patient using MMA by post marketing surveillance and vigilance conducted by manufacturer to identify the hazardous effects or incidents regarding MMA after its marketing.

Any hazardous effect, risk or risk regarding MMA should be notified immediately to manufacturer, importer or vendor which is then notified to the European Regulatory body as per regulations and guidelines.

3.0 OTHER COUNTRIES:

A. Canada

Regulatory requirements for mobile medical application:

Medical devices in Canada are regulated by Health Canada's Medical Devices Bureau of the Therapeutic Products Directorate and governed by Canada's Food and Drugs Act (Act) and Medical Device Regulations. In 2018, Health Canada established a revised regulatory approach digital health technology sector ensuring safety and effectiveness of medical devices. One of Health Canada's key areas of focus is the regulation of Software as a Medical Device (SaMD). Manufacturer developing mobile medical applications including software must comply with SaMD.[8]

Similar to US Federal Communication Commission (FCC), Canada provided technical requirements and regulations for wireless devices. Normally, developers of wireless devices submit their data from FCC testing that are connected to their application for approval from Canada regulatory body. In addition to the FCC testing, manufacturer has to perform other tests as per Canadian regulation. MMA developers outside the Canada required electing Canadian representative. For all the regulations of the medical devices, the responsible Canada's government agency is 'Therapeutic Product Directorate of Health Canada'. Canadian regulations classified medical electrical devices into four categories depending upon their risk level: manufacturer of medical device should categorise their device as class I, class II, class III or class IV. Once manufacturer has classified the device; manufacturer to obtain medical device licence before placing the device into market. The safety and effectiveness evidence is required for obtaining medical device license. For class II, class III and class IV medical devices medical device license is mandatory whereas for class I medical devices there are no specific requirements. It is mandatory to follow and maintain quality management system which is audited by third party and certification is provided [9].

B. Japan

Regulatory requirements for mobile medical application:

Wireless devices which are marketed and sold in Japan comes under authority of JATE i.e. Japan Approval Institute for Telecommunication Equipment. It is necessary to perform product testing and getting certification for approval through regulatory body prior to placing device into the market. Device testing depends on International electro-technical commission which depends on the data obtained from CE mark testing. Medical devices should comply with the requirements of Japan Pharmaceutical Affairs Law which is administered by PMDA. [9]

Like other countries Japan also classified medical devices based on the risk level to patient's health. Generally

premarket approval is required to consider before placing the device into the market. Manufacturer that does not belong in Japan have to hire Marketing Authorization Holder from Japan. MAH licensed by Japan's Ministry of Health, Labour and Welfare to manage the registration process regarding medical device.

C. China

Regulatory requirements for mobile medical application:

Wireless device which are manufactured and sold in China undergo Certification process by China's Certification and Accreditation Administration (CNCA) and approval is granted by placing CCC mark i.e. China Compulsory Certification mark before placing device into the market. CNCA generally conducts compliance testing in testing laboratories from China. In addition to the testing, factory inspection is also part of certification procedure. China's State Food and Drug Administration regulates Medical device. For all the devices importing from other countries it is necessary to undergo device certification process from SFDA. And for all the manufacturer seeking for registration process for marketing device into China should undergo testing from approved laboratory based in China and they should meet the standards specified by SFDA. [9]

D. Other territories including Africa, Asia Pacific and Latin America:

EU and USA have stringent regulations for Mobile medical application but other countries like Asia Pacific, Africa and Latin America are facing major breaks in regulations of MMA. These countries follow US and EU's regulations or sometimes they follow China's regulation.

CONCLUSION:

FDA has laid guidelines for manufacturers for Mobile medical applications that provides in depth information about regulations which must be followed by manufacturer whereas EU country provided various directives for regulations of MMA. USA and EU have developed stringent regulations for Mobile Medical Applications where as other countries like China, Japan, and Canada follow their own regulations which are not as stringent as USA and EU.

ACKNOWLEDGEMENT:

The authors thank JSS Academy of Higher Education and Research and JSS College of Pharmacy, Mysuru for providing the necessary facilities for carrying out this work.

REFERENCES:

1. Anon, Mobile Medical Applications. [online] Available at: https://www.fda.gov/medical-devices/digital-health/mobile-medical-applications [Accessed 5 Jun. 2019]
2. Larson R. A Path to Better-Quality mHealth Apps [Online]. 2018 [Accessed 25 June 2019]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6090170/
3. Anand A, Venkatesh M, Kumar P. Global Regulatory Approach Towards mHealth [Online]. 2016 [Accessed 25 June 2019]. Available from: https://www.researchgate.net/publication/307476545_Global_Regulatory_Approach_Towards_mHealth[Accessed 5 Jun. 2019]
4. Yetisen, A., Hurtado, J. and Vasconcellos, F. (2014). The regulation of mobile medical applications. [online] Available at: https://www.researchgate.net/publication/259725271_The_regulation_of_mobile_medical_applications [Accessed 25 Jun. 2019].
5. Anon, The U.S. FDA's Regulation and Oversight of Mobile Medical Applications. [online] Available at: https://legacy-uploads.ul.com/wp-content/uploads/sites/2/2014/05/UL_WP_Final_The-US-FDAs-Regulation-and-Oversight-of-Mobile-Medical-Applications_v6_HR.pdf [Accessed 4 Jun. 2019].
6. Holubová, A., Bradway, M., Arsand, E., Hallgren, D. and Hartvigsen, G. (2015). Do mobile medical apps need to follow European and US regulations or not: decisions exemplified by diabetes management app. [online] Available at: http://www.ep.liu.se/ecp/115/009/ecp15115009.pdf [Accessed 4 Jun. 2019].
7. Anon, (2014). The Regulation of Medical Device Apps. [online] Available at: https://www.weahsn.net/wp-content/uploads/The-Regulation-of-Medical-Device-Apps-v3-CN-2.12.2015.pdf [Accessed 5 Jun. 2019].
8. McMahon, E. and Dufrosne, Y. (2018). Software As Medical Devices And Digital Health In Canada: What's Next. [online] Available at: http://www.mondaq.com/canada/x/752662/Software+as+Medical+Devices+and+Digital+Health+in+Canada+Whats+Next [Accessed 7 Jun. 2019].
9. Anon, (2015). Achieving Global Approval for mHealth Devices and Products. [online] Available at: https://legacy-uploads.ul.com/wp-content/uploads/sites/40/2015/02/UL_WP_Final_Achieving-Global-Approval-for-mHealth-Devices-and-Products_v5_HR1.pdf? [Accessed 5 Jun. 2019].
10. Anon, (2019). Health Canada Regulatory Approval Process for Medical Devices. [online] Available at: https://www.emergobyul.com/resources/canada-process-chart [Accessed 27 Jun. 2019].