MEDICAL DEVICE REGULATION IN US, EUROPE, CHINA AND INDIA

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REVIEW ARTICLE

Ganesh GNK*, Nishanthini.B, Lakshmi T.Vidhya

Department of pharmaceutics, JSS College of Pharmacy (A Constituent College of JSS University, Mysore), Ooty, India.

**Corresponding Author's E-mail: Ganesh_gnk@rediffmail.com*

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ABSTRACT

Medical Device is an emerging market in last two decades since the use of medical device is escalating throughout the world. Millions of patients worldwide depend on Medical Device for the diagnosis & Management of diseases. Regulation of the Medical Device varies within the country are based on their own Regulatory bodies. In US Medical Devices are regulated by FDA- Centre for Devices & Radiological Health, in EU they are regulated by European Medical Agency, in China they are regulated by State Food & Drug Administration and in India they are regulated by Central Drug Standard Control Organization. Regulations of these countries and IMDRF, MDPWG were reviewed. Advantage of harmonizing regulations also reviewed.

Keywords: FDA, CDHR, 510(K) process, PMA, CE marking, notified bodies, CDSCO, SFDA, IMDRF.

INTRODUCTION

Medical Device is defined as any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purpose and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of: Diagnosis, prevention, monitoring, treatment or alleviation of diseases and Investigation, replacement or modification of the anatomy or of a physiological process. The Medical Devices sector helps save lives by providing innovative health care solutions regarding diagnosis, prevention, monitoring, treatment and alleviation. Examples of medical devices range from simple devices such as tongue depressors, medical thermometers, and disposable gloves to advanced devices such as computers which assist in the conduct of medical testing, implants, and prostheses. (1, 2)

MEDICAL DEVICE REGULATION IN US

The United States remains the largest Medical Device market in the world with a market size around $110 billion, and has reached $133 billion by 2016. There are more than 6,500 medical device companies in the US.

On May 28, 1976 the Medical Device Amendments Act was published and the FDA was given the Authority to regulate all the Medical Devices. The final rule is posted in the Federal Register, Title 21 CFR, parts 800-1299. In 2002 Medical Device User Fee and Modernization Act was included to the federal register to established sponsor user fees for application reviews and set performance target for review times.

Within the FDA, The Center for Devices and Radiology Health (CDHR) is responsible for ensuring the safety and effectiveness of Medical Device. It is also responsible for eliminating unnecessary exposure to radiation-emitting products. Under the CDHR, the Office of Device Evaluation is responsible for all pre-market reviews of applications, the pre-market notifications 510(k), the pre-market approval PMAs and also Investigational Device Exemption (IDE). Office of Surveillance and Biometrics is the office that IS responsible for the post-marketing activities or adverse event reports with regards to Medical Devices. (3)

Generally Medical Device classified into 3 types. In US Medical Devices classified based on the Risk associated with the use. They are as follows:

- Class I Medical Devices are defined as non-life sustaining. These products are the least complicated and their failure posses minimal or no risk. This class of medical device is subjected only to general control that is lowest level of regulatory control.
- Class II Medical devices are more complicated and present more risk than Class I. It requires general control and also special control to prove the safety and efficacy. Class II devices mostly pass through 510(K) commonly known as pre-market notification.
- Class III Medical Devices sustain or support life and their failure is life threatening. It is subjected to most stringent regulatory control. These devices require pre-market approval (PMA) which needs clinical trial data to ensure the safety and efficacy of the Medical Devices.

Medical Devices are brought to market using one of the seven pathways:

- Pre-market notification known as the 510(K),
- Pre-market approval (PMA),
- The Humanitarian device exemption (HDE),
- De novo process
- The product development protocol (PDP),
- The customer device exemption (CDE), and
- The expanded access option.

About 90% of Medical Devices that are brought to the US market are through the 510 (K) process, 5% of Medical Devices brought to market by PMA and the remaining 5% of devices are brought to market using remaining five pathways. It costs about $31 million to bring a Medical Device onto the market under the 510 (K) pathways in 2014, compared to about $94 million for PMA. (4) The brief pathaway for the registration of medical devices in US is explained in Figure 1.

Pre-market notification 510(K) process

A 510(K) is a premarket notification made to the FDA to assure that the device to be marketed is safe and effective. 510(K) submission demonstrates that a device is substantially equivalent to a predicate device (one that has been cleared by the FDA (or) market before 1976). Substantially equivalent means that the new device has the same intended use same technological characteristics as the predicated device.

510(K) process is required when;

- Introducing a device into commercial distribution for the first time after May 28, 1976.
- Different intended use for a device which already have in commercial distribution.
- Changes or modifications of a legally marketed device and that change could significantly affect its safety and effectiveness.

FDA is responsible for giving marketing clearance for the device through 510(k) process. It takes almost 30 or 90 days for the FDA to give clearance. (5)

PMA process

Pre-market approval (PMA) is the process of scientific and regulatory review department of the FDA to evaluate the safety and effectiveness of Class III Medical device. A device substantially different from existing devices must undergoes a PMA process.

Class III Medical Device is more risk associated. General and special control examinations was not sufficient to prove and assure the safety and efficacy, therefore it requires a PMA application under section 515 of the FD&C Act. It requires clinical study to prove the safety and efficacy. FDA regulation requires around180 days to approve the PMA. (6)

De Novo process

It is the fastest growing pathway for bringing devices into the market. Devices of a new type that FDA has not previously classified based on risk are automatically classified into Class III by the section 513(f)(1) of the FD&C Act.

FDA reviews De Novo request for new categories of devices that are not high risk.

It is confirmed based on 2 criteria:

1) It should have low to moderate risk, and also meet the standards for Class I & II devices under section 513(a)(1) of the FD&C Act.

2) Risk benefit ratio of the new device should be understandable; it should come under the General and Special control.

If these criteria met, De Novo request is accepted by the FDA and the device is classified in Class I & II. Future devices within the device type can be cleared through the regular 510 (K) process using the De Novo device as the "predicate" (7, 8)

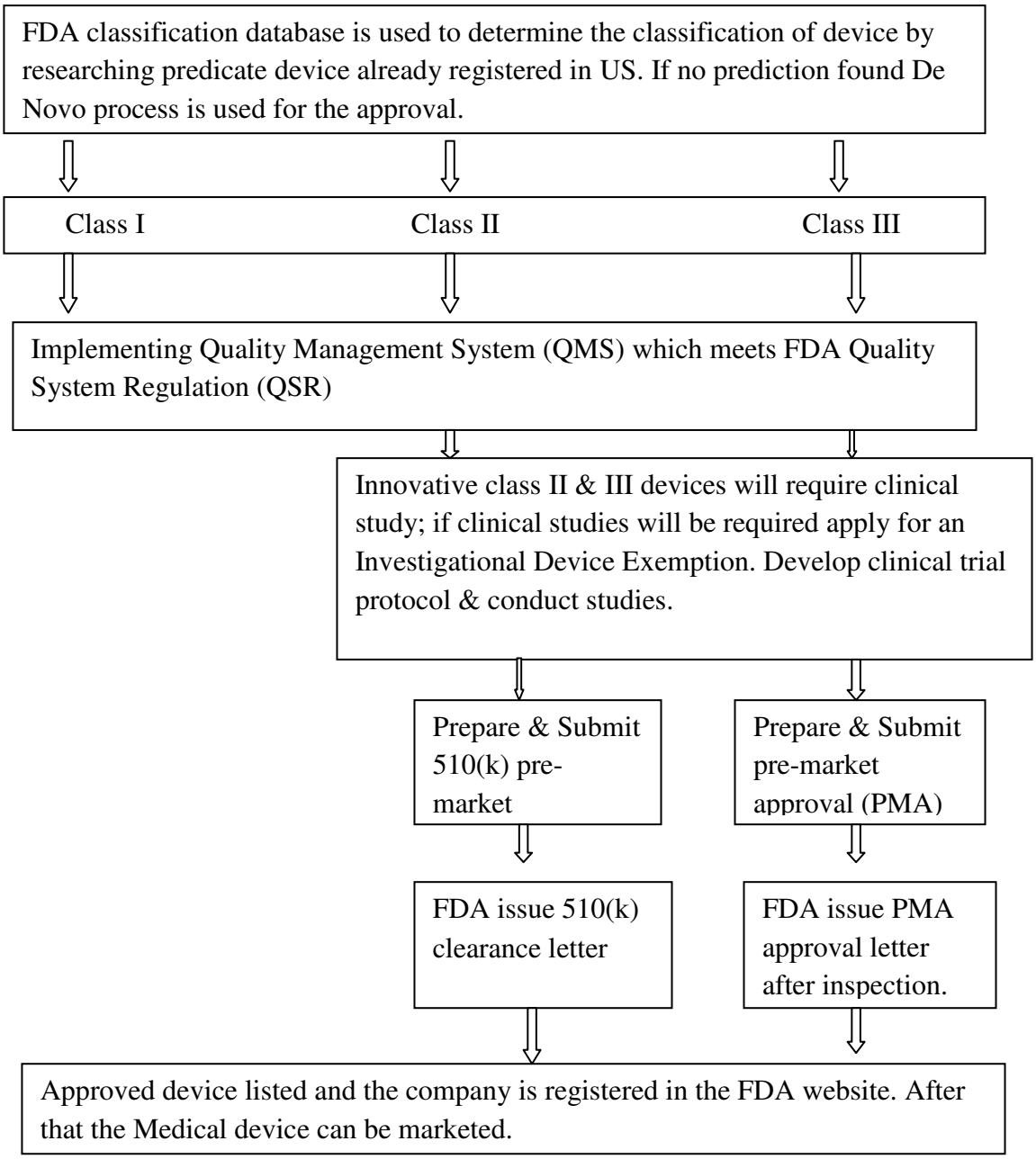

Figure 1: Registration Process for Medical Devices in US

MEDICAL DEVICE REGULATION IN EUROPEN UNION

The Medical Devices is essential to the health care of EU citizens. The diversity and innovativeness of this sector contribute significantly for enhancing the safety, quality and efficacy of health care in the EU. The Medical Device market in the EU accounts for one third of the global market with around $122.5 billion in yearly revenue. It reinvest 8.5% of sales (around $10 billion per year) into research project and development, making it possible for EU citizens to benefit from the latest medical technologies years earlier than in the US or Japan. The Europe medical devices market is expected to grow at a compound annual growth rate (CAGR) of about 7% from 2009-2016 and is expected to exceed $150 billion by 2016. The new 2007/47/EC Medical Device Directive was approved in September 2007 and was effective from March 2010. While all high-risk devices newly that are introduced into the market will have to undergo rigorous clinical trials.

Until 1990 each country had its own approach for the approval of Medical Devices, to regulate the uneven and complex market.

Medical Devices are regulated in the European Union by three EC Directives:

- Directive 90/385/EEC on active implantable Medical Devices.
- Directive 93/42/EEC on Medical Devices and
- Directive 98/79/EC on In-vitro Medical Devices.

These directives outlined requirements under which a medical device could be marketed across all E.U Member states.

Based on Annex IX of Directive 93/42/EEC Medical Devices are classified based on the “risk-based” system. It grouped into four product classes: Class I, Class IIa, IIb and Class III. Class I and IIa is considered as low-risk devices, the manufacturer may make a declaration of conformity with the essential requirements and based on the self assessment without the involvement of the Notified Body (NB). For the Class II b and Class III requires Notified Body involvements.

The way in which devices are regulated in the EU is very different from the way they are regulated in the United States, especially in terms of the clinical data required for premarket approval. CE marking is necessary to market the Medical Device in the European Union, for getting CE Certificate the manufacturer must compile with the EU directives. Device approval in each country is regulated by the competent authority, and the inspection will be carried out by the authority to confirm manufacturing standards and technical files. High-risk devices are directly handled by the Notified Bodies, which can be selected by the manufacturer in any EU country. For higher risk class devices design examination and CE certificates issued by a notified body should be submitted to the competed authority. (2) The process for the registration of medical devices in EU is briefly described in Figure 2.

CE marking

Medical device manufacturer need to exhibit CE marking on their products in order to ensure that devices are safe and fit for their intended use. The letter “CE” is the abbreviation of the French phrase "Conformité Européene". The CE Marking on a product is a manufacturer’s declaration that the product complies with the essential requirements of the relevant European health, safety and environmental protection legislation and it ensures the free movement of the product within the EFTA & European Union single market. CE marking is done by the Notified Bodies (NBs). (9)

Notified Bodies (NBs)

It is a private or public organization that has been accredited to validate the compliance of the device to the European Directive, Manufacturer have the rights to choose the NBs from the Member states in the EU. Competent authorities in each state will nominate the Notified Bodies and the NBs have the power to grant the CE mark. (10, 11)

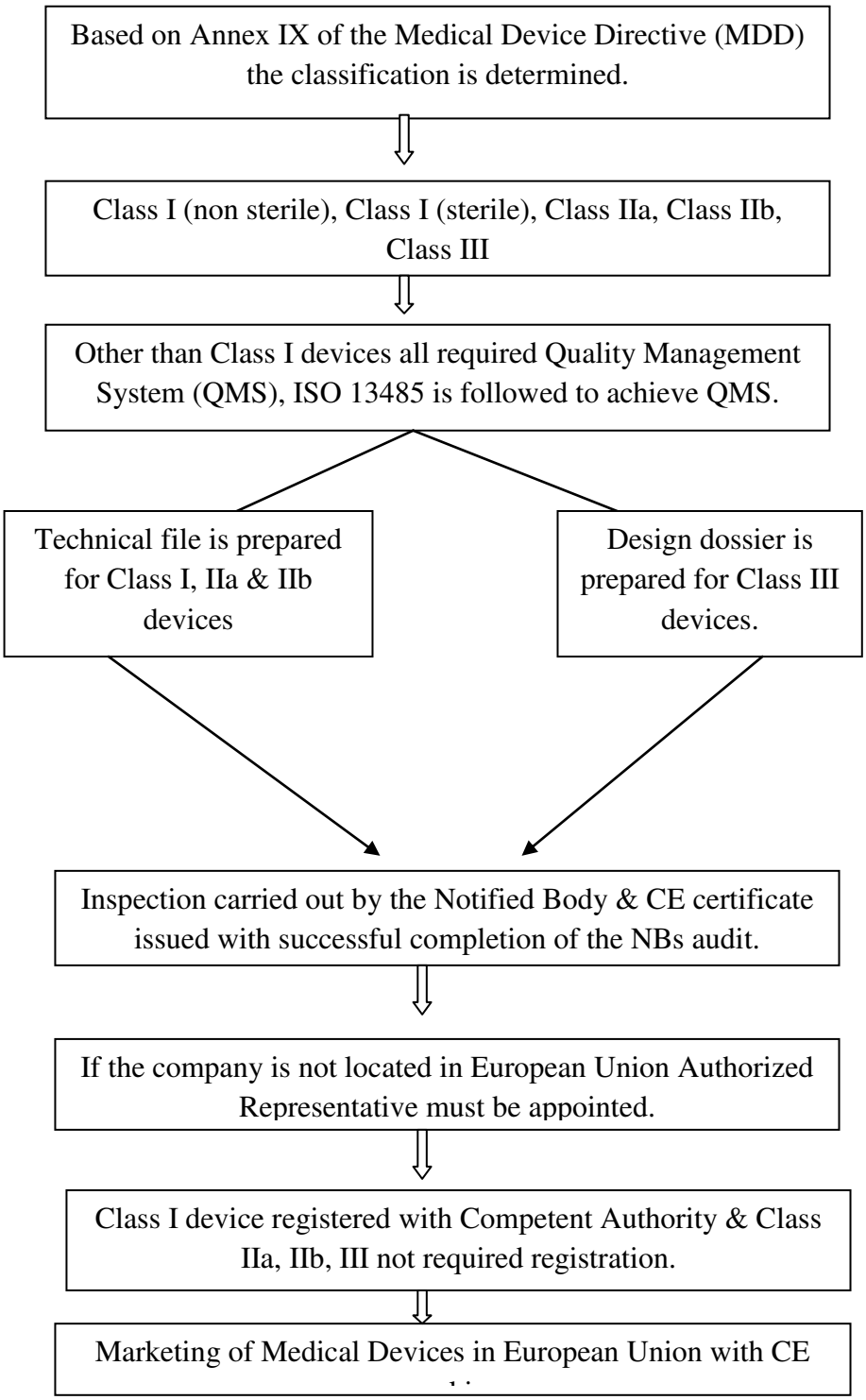

Figure 2: Registration Process of Medical Devices in EU

MEDICAL DEVICE MARKET IN INDIA

Many in the international investment community have identified healthcare in India as a major business opportunity as the sector expands to meet the needs of India's growing middle-class, a population of around 300 million with rising income increasing expectations and greater access to healthcare services.

India's Medical device market is top twenty in the world in 2007 and fourth largest market in the Asia. The medical devices space in India will see impressive expansion rising from $10.4 billion in 2014 to reach $17.6 billion by 2020,

representing a robust Compound Annual Growth Rate (CAGR) of 9.4% according to research and consulting firm Global Data. But more than 70% of Medical equipment sold in the country is imported, mostly from the United States.

In India Medical Device is regulated by the CDSCO (Central Drug Standards Control Organization) which comes under Ministry of Health & Family Welfare. In 2004, steps were initiated towards creation of a specific MDs Division within the CDSCO. Medical Device guidelines published in 29th June 2006. Schedule M III of Drug & Cosmetic Rules guidelines published to control the Medical Device Manufacturing and to produce quality Medical Devices. (12)

In India Medical Device classified as Class A (device involved lowest risk levels), Class B (low to moderate risk), Class C (moderate to high risk), and Class D (highest risk). This classification is based on GHTF classification. As like EU India also considers third-party conformity assessment by Notified Bodies & also India is moving towards implementing the ISO 13485:2003 QMS for Medical Devices.

For marketing the Medical Devices in India valid wholesale license is required in Forms 20B & 21B and also need import license in Forms 8&9 from CDSCO. Medical Devices listed under the Notified Medical Devices & IVDs, must have to register with the CDSCO before marketing. (13)The registration process for registering the medical devices in India is briefly explained in Figure 3.

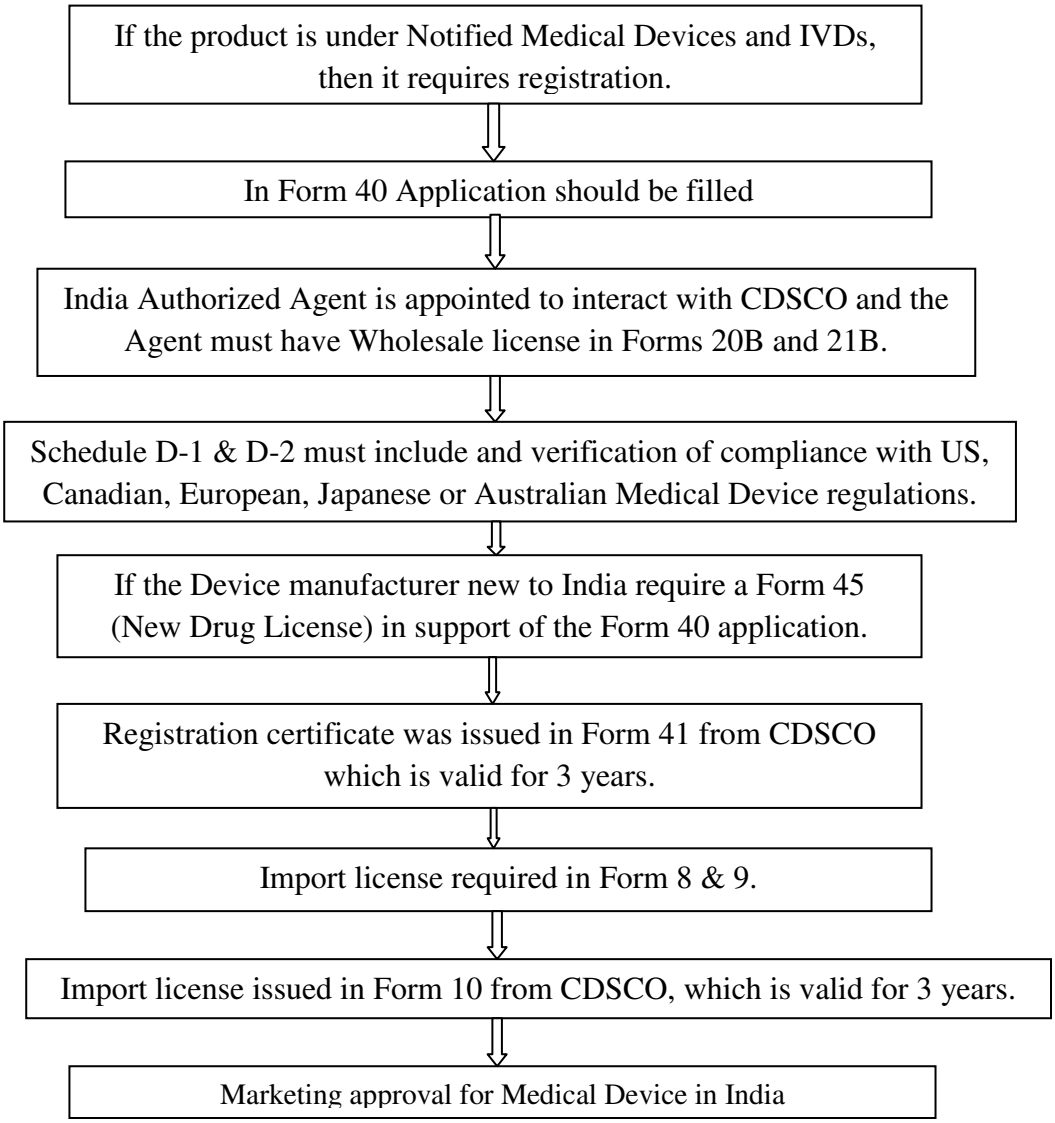

Figure 3: Registration Process of Medical Devices in India

MEDICAL DEVICE REGULATION IN CHINA

Before entering into the Chinese market, manufacturer needs to obtain Pre-market approval from SFDA (State Food & Drug Administration). Two main regulations should be followed in China 1) "Regulations for the supervision & Administration of Medical Device" (2000).

2) "Measures for the administration of the Medical Device registration" (2004).

In China, Medical Devices are Classified into 3 classes, namely class I, II&III based on risk of using the device.

Class I – Medical Devices for which safety can be ensured through routine administration.

Class II – Medical Devices for which further control is required to ensure their safety of use.

Class III – Medical Devices that are implanted into the human body (or) use for life support, (or) pose potential risk to the human body & thus require strict safety surveillance. (14)

All Class III & Imported devices are managed directly by the control of SFDA. Some of the Medical Device required (CCC) China Compulsory Certification in addition to the Medical Device registration. The CCC mark is managed by the Chinese quality & quarantine authorities (AQSIQ).

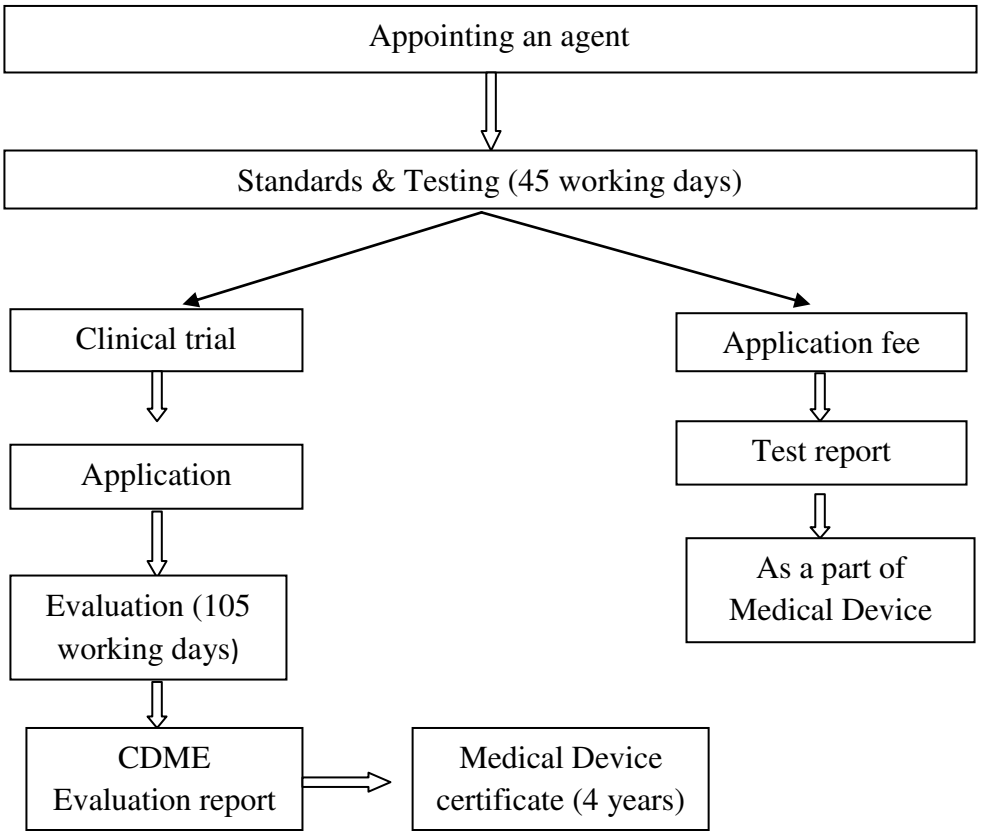

Figure 4: Registration Process of Medical Device in China

According to the provisions of Medical Device registration, application for Medical Device registration can only be carried out by a Chinese legal entity, Medical Device will be covered by Chinese national standards (GB Standards), Professional/ sectorial standards (YY Standards) stipulated by the SFDA. Manufacturer is required to submit a statement confirming that the applicable Chinese Standards are adopted, without modification & if there any modification the manufacturer can make addition & add corresponding requirements to

SFDA on standards relevant to device. Test is carried out to check the Standards, after that applicable fee have to paid by the manufacturer. The registration process in China is briefly explained in figure 4.

Clinical trial should be conducted in China for Class II & III Medical Devices. There is no need of getting approval procedure for conducting clinical trial studies in China but the manufacturer is required to notify the local regulatory authority about the on-going clinical study. After getting valid test report & clinical trial report, application can be submitted to the SFDA. The application should be submitted in Chinese Language. If the application is accepted by SFDA then the application is forwarded to CDME after which the Evaluation starts. After completion, CDME will issue an evaluation report to SFDA. Medical Device registration certificate will be issued by the SFDA which is valid for 4 years. (15)

Harmonization of Medical Device Regulations

The International Medical Device Regulators Forum (IMDRF) is a voluntary group of Medical device regulators from around the world who have come together to build on the strong foundation work. Previously it was known as Global Harmonization Task Force (GHTF). (16)

In Southeast Asia-The Medical Device Product Working Group (MDPWG) were formed for Medical Devices regulatory harmonization. (17)

Benefits of Harmonization

- Ensure the Safety, effectiveness, performance & quality of Medical Device
- To promote technological innovation
- Facilitating international trade
- Improve the efficacy of national economies & their ability to adopt change and remain competitive.
- Reduce the cost to market the product

CONCLUSION

The regulation of Medical Devices in US, Europe, India & China are different, But in these countries pre-market process & post-market process is carried out for the marketing of quality products. In US, the 510(k) process is carried out by the 90% of the manufacturer; the pre-market approval process is more complicated than 510(k). Clinical studies are strictly required for High-risk devices. In EU clinical studies are carried out strictly in past 5 years but more focus should be placed on clinical studies in EU to control the risk, But in EU more research activities takes place in Medical Device Sector than in US and Japan, the growth is expected more than US in future. In India the government is expected to develop a regulatory structure leading to quality products being developed by manufacturers. However, the current regulatory structure lacks active participation from the government, Global Harmonization Task Force (GHTF) guidelines can be adopted to improve the sector and focus has to make on clinical studies.

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CONFILCT OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. World Health Organization [Internet]. 'Medical Device Regulations Global overview and guiding principles', Official website of Geneva World Health Organization; 2003 [Cited 2017 Jul 11]. Available from: www.who.int/medical_devices/publications/en/MD_Regulations.pdf
2. Wikipedia [Internet]. Medical Device introduction and Approval process; 2017 [Cited 2017 Feb 11]. Available from: https://en.wikipedia.org/wiki/Medical_device
3. ASGE Technology Assessment. The role of the U.S. Food and Drug Administration in device evaluation and monitoring. J Gie.2010; 72(1):5-10
4. Daniel B. Kramer, M.D., Shuai Xu. Regulation of Medical Devices in the United States and European Union [Internet]. J Med 2012 Mar [Cited 2017 Feb 17]; 366:848-55. Available from: http://www.nejm.org/doi/full/10.1056/NEJMhle1113918#t=article
5. Gupta Sandeep kumar. Medical Device Regulations: A current perspective. J Young Pharm. 2016; 8(1):6-11.

6. FDA [Internet]. 'overview of device regulation', Official website of US food and drug administration; 2015 Aug [Cited 2016 Feb 12] Available from: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/
7. FDA [Internet]. 'overview of device regulation', Official website of US food and drug administration; 2017 Mar [Cited 2017 Feb 12] Available from: https://www.fda.gov/Medicaldevices/Deviceregulationandguidance/Howtomarketyourdevice/Premarketsubmissions/Premarketapprovalpma/Default.Htm
8. FDA [Internet]. 'overview of device regulation', Official website of US food and drug administration; 2016 Sep [Cited 2017 Feb 15] Available from: https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/premarketnotification510k/
9. The European Parliament and the Council of the European Union. Directive 2007/47/EC of the European Parliament and of 5 September 2007. Official Journal of the European Union [Internet]. 2007 Sept 30 [cited 2017 Jan 14]; 75(3):[about 35pp.]. Available from: http://ec.europa.eu/consumers/sectors/medical-devices/files/revision_docs/2007-47-en_en.pdf
10. Emergo [Internet]. European CE marking Regulatory process for Medical Device; 2017 [Cited 2017 Feb 02] Available from: https://www.emergogroup.com/resources/europe-process-chart
11. Value in Health 18 (2015) A335-A766 – CE Marking [Internet] 2015 [Cited 2017 Feb 13] Available from: http://www.valueinhealthjournal.com/article/S1098-3015 (15)02806-5/pdf
12. Emergo [Internet]. India CDSCO Medical Device Registration and Approval; 2017 [Cited 2017 Feb 07] Available from: http://www.emergogroup.com/services/india/india-medical-device-registration
13. Paddock R. Medical Device Regulatory profile for India, office of Health and Consumer Goods, [Internet]. [India]: International Trade Administration; 2010 Jan [cited 2017 Jan 15]. Available from: http://www.ita.doc.gov/td/health/indiaregs.pdf
14. EU SME Centre [Internet]. [Beijing]: Guidelines on Medical Device Registration; 2016 [cited 2017 Jan 26]. Available from: www.eusme centre.org.cn
15. Sall B. Regulation of Medical Device article [Internet]. [Beijing]: 2008 [cited 2017 Jan 26]. [about 41pp.]. Available from: http://www.crcnetbase.com/doi/pdfplus/10.3109/9781420073553-6
16. A Kaushik, KS Saini, B Anil, and S Rambabu. Harmonized Medical Device Regulation: Need, Challenges, and Risks of not harmonizing the Regulation in Asia. J Young Pharm [Internet]. 2010 Mar [cited 2017 Jun 14]; 2(1):[about 6pp.]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3035876/
17. George B. Regulation of Medical Devices. Perspect Clin Res [Internet]. 2010 Sep [cited 2017 Jun 24]; 1(3):[about 3pp.]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3146078/

