MEDICAL DEVICES AND THEIR APPROVAL PROCEDURE IN INDIA

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REVIEW ARTICLE

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ABSTRACT

Therapeutic treatment based on medical devices is providing technologically advanced solutions for the management of several diseases. Thereby continues to grow in market at tremendous rate. However, these treatments also carry significant risk with them, which if neglected can lead to life threatening consequences. Therefore rules and regulations are required for monitoring the entry of such devices into the market. Presently Regulatory bodies governing such regulations are at their initial stage and are improving at each step to safeguard public health as well as to ensure that effective and technologically advanced inventions reach out patient.

Keywords: Drug and Cosmetic Act 1940 and Rules 1945, CDSCO, FDA Regulations.

INTRODUCTION

With the advent of technology and increased scientific development, the amount of research in the field of medical devices has shot-up. Increase in the production of these devices seeks for new and improvised regulations on their manufacture in order to maintain quality and prevent the injection of improper products into the market. Every country has its own regulatory body for the fulfillment of this purpose. Regulatory bodies have come up with certain guidelines for the import, manufacture, sale and distribution of these devices. In most of the Asian countries including South Korea, Malaysia, Thailand, Indonesia, Vietnam, Philippines and Singapore, medical devices are regulated separately from drugs. However, in India medical devices are regulated along with drugs under the same Drugs & Cosmetics Act 1940. (1) Presently, the Indian government is keen on separating medical devices from drugs in order to encourage R&D, manufacture and imports into the country. This article deals with the approved procedure for medical devices in India. (1)

At the federal government level, the regulatory authority that governs the regulations of medical devices in India is the Central Drug Standards Control Organization (CDSCO) under the Ministry of Health and Family Welfare. Manufacturers can leverage their approvals in US, Canada, Europe, Australia or Japan for "Registration of Medical Devices" in India. According to the CDSCO, a medical device in India is any such device intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, as may be specified from time to time by the Central Government by notification in the Official Gazette, after consultation with the Board. (1) The CDSCO is responsible for medical device registration and regulation of New Drugs (ND) and Clinical Trials (CT) in the country. It lays down the standards for drugs, controls the quality of imported drugs, coordinates the activities of State Drug Control Organizations and provides expert advice with a view of bringing about uniformity in the enforcement of the Drugs and Cosmetics Act. (2)

BACKGROUND

In the past, there were no regulations for the manufacture of these devices in India. Manufacturers could manufacture any kind of medical devices without any jurisdiction. But in the year 2006, it became compulsory for the medical devices entering India to be in

compliance with the Indian Medical Device Regulations set forth by the CDSCO. In the last few years, the Indian medical regulatory system has become very complicated. There are about 30 device "families" that outline the medical devices that need to be registered.

Registration of Medical Devices in India

Registration of medical devices in India involves six main steps (Figure 1) which are described as follows. (3)

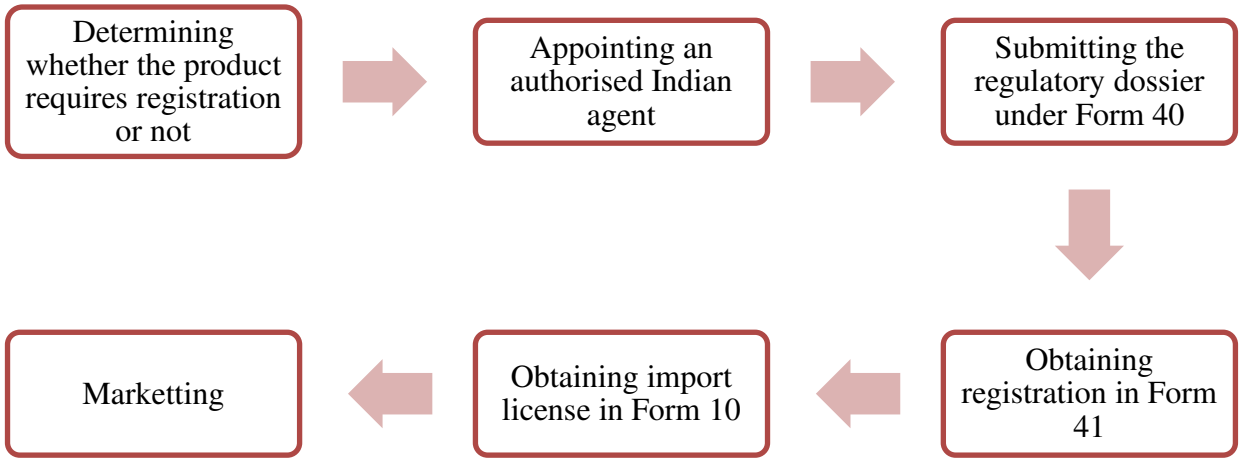

Figure 1: Steps involved in registration of medical devices in India

Determining whether the product requires registration or not

First and the foremost step is to determine whether a specific device requires registration or not. Only the notified medical devices come under the regulations that are specified in the Drugs & Cosmetics Act 1940 and presently 22 medical devices are notified under this act. Some of the devices are regarded as "Drugs" under Drugs & Cosmetics Act 1940 & Rules 1945 and are also termed as non-notified medical devices (Table 1).

Table 1: List of notified and non-notified medical devices as per Indian Drugs & Cosmetics Act (3)

Notified Medical Devices	Non-notified Medical Devices or Drugs
Disposable Hypodermic Syringes	Blood Grouping Sera
Disposable Perfusion Sets	Ligatures, Sutures and Staplers
In-vitro Diagnostic Devices for HIV, HbsAg,	Intra Uterine Devices (Cu-T)
Cardiac Stents	Condoms
Drug Eluting Stents	Tubal Rings
Catheters	Surgical Dressings
Intra Ocular Lenses	Umbilical Tapes
I.V. Cannulae	Blood/Blood Component Bags
Bone Cements	
Heart Valves	
Scalp Vein Set	
Orthopaedic Implants	
Internal Prosthetic Replacements	
spinal needles	
Orthopaedic Implants	

Some devices that are not mentioned in the above list of the notified medical devices are required to undergo registration process with CDSCO. It is often recommended in the cases where manufacturer is unclear about the regulatory status of their product in India, to review their device application by Drugs Controller General of India (DCGI) and obtain a No Objection Certificate (NOC). The CDSCO after examining the product information and other related documents will issue a written statement on the regulatory status of the products. The process will take about 4 to 12 weeks for the CDSCO to review the application and issue the NOC.

If the product is not registered in any of the countries like USA, Europe, Japan, Health Canada or Australia, an applicant needs to prove the efficacy and safety of it by conducting clinical trials in India to get registration certificate. If the product is registered and marketed in any one of the above mentioned countries but not in the country of origin, he can apply for registration certificate directly.

Appointing an authorised Indian agent

In case of a foreign manufacturer, the regulations in India require them to have a representative who will act on their behalf as the point of contact for inspection authorities. These representatives act as a liaison between the manufacturer and the CDSCO's Medical Device and Diagnostics Division who will assist in the process of device registration, approval process and vigilance/adverse event reporting.

The authorized Indian agent should have a wholesale drug license in Form 20B and 21B. The manufacturer will be the holder of the registration certificate and can freely appoint multiple distributors in the country.

Submitting the regulatory dossier under Form 40

A dossier has to be prepared with the required list of documents to start the registration process (Table 2). Compilation of Registration dossier should be done as per the proforma provided by CDSCO. Form 40 should be duly filled, signed and stamped by Indian agent (in case of foreign manufacturer) along with the name and designation. Name and address of the Indian agent should be as per their drug sale license and renewal license.

Applications for Registration/Import License of Medical Devices should be submitted to the DCGI, CDSCO. If device manufacturers are new to India, they have to submit Form 45 (New Drug License) in support of the Form 40 application.

The number of employees as on the date of preparation of Plant Master File will be considered for the purpose of registration. Therefore, it should be included in the Plant Master File. Requisite fee of 1500 US Dollar for the registration of manufacturing premises as per as Drug and Cosmetic Act and 1000 US Dollar for single medical device and 1000 US Dollar for each additional devices proposed to be imported is to be paid at notified branches of Bank of Baroda under the Head of Account "0210 - Medical and Public Health, 04 - Public Health, 104 - Fees and Fines" adjustable to Pay and Account Officer, DGHS, New Delhi in the form of a Treasury Challan (TR6). Original receipt of TR 6 should be submitted along with the application for registration.

Table 2: List of documents to be appended with regulatory dossier

S. No.	Document	S. No.	Document
1	Form 40	8	Declaration of Conformity
2	TR6 Challan	9	Free Sale Certificate
3	Power of Attorney	10	Certificate of Marketability from GHTF countries
4	Schedule D(I)	11	Other Regulatory Approvals
5	ISO 13485 Certificate	12	PMS report
6	Full Quality Assurance Certificate	13	Plant Master File
7	CE Design Certificate	14	Device Master File

Direct payment by the manufacturer through Electronic Clearance System (ECS) to the bank (Bank of Baroda, Kasturba Gandhi Marg, New Delhi) is also acceptable. Original receipt of the transfer will be treated equivalent to Bank Challan; if bank approves that they have received the payment.

The time for registration process can take anywhere between 6 to 9 months. If the products do not have a predicate in India the processing time will increase and special committee will be appointed to determine the products' safety and efficacy for the Indian market.

Obtaining import license in Form 10

Obtaining registration certificate in Form 41

After the submission of documents, the application will be pre-screened according to a checklist made by the CDSCO and may send one or more query letters to the agent. If the application is complete in all respects and the information specified in Schedules D-I and D-II are in order, the licensing authority will, within nine months from the date of receipt of the application, issue such Registration Certificate in Form 41.Validity period of a Registration Certificate is three years from the date of issue, unless, it is suspended or cancelled.

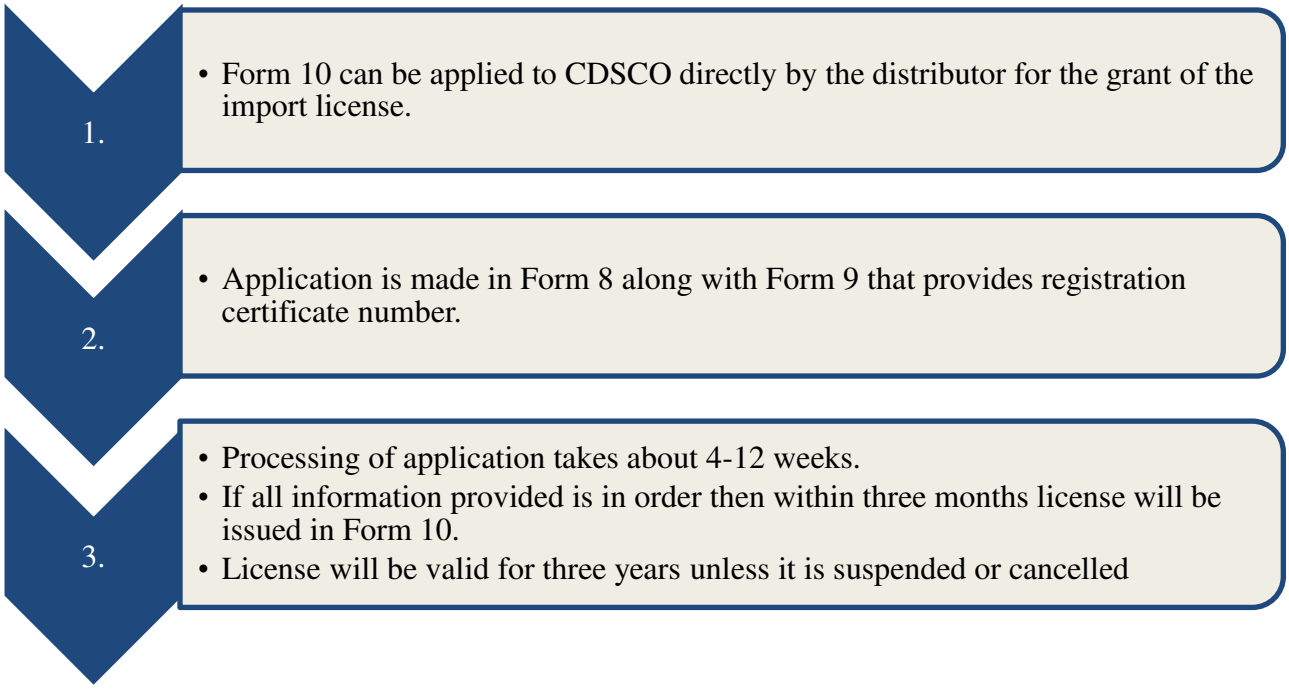

Figure 2: Steps for obtaining import license (3).

The devices, having valid Import Licence, can be imported from any notified ports of India. Multiple Import Licences are not required for importing from different notified ports. Similarly they can be stocked in any other wholesale licence premises other than stated in the Import Licence. There is no need to register notified products that are imported and locally processed for 100% export only and which will not be marketed in India.

Test License in Form 11 has to be obtained to import small quantities of drugs / medical devices/ diagnostic kits, for the purpose of examination, test or analysis. Materials procured under Form 11 can't be used for commercial purpose. Test license is valid for duration of one year from the date of issue unless it is suspended or cancelled.

Registration Certificate and Import Licence are required even for the import of components of Medical Devices. An importer cannot import a registered notified medical device having residual shelf life less than 60 % even for commercial or testing purpose. A one-time permission for import of regulated medical device cannot be granted without having valid Import Licence in Form-10.

Marketing in India

Once the registration certificate and the import license are issued, the product can enter the Indian market. The authorized Indian agent should report any change, adverse events, recalls in other countries etc., to the CDSCO as and when they happen.

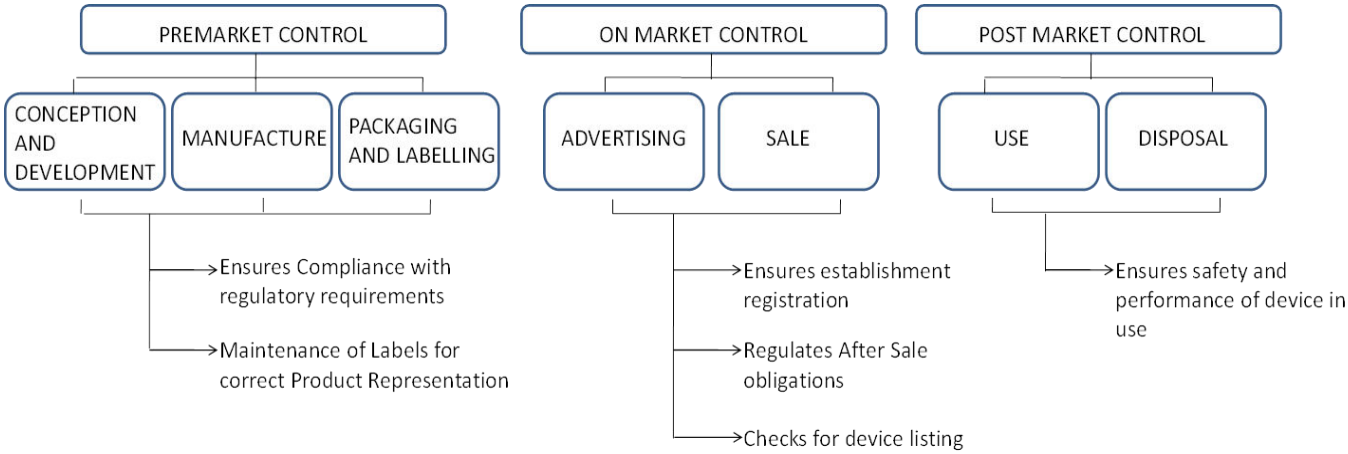

Figure 3: Different stages of Regulatory control and their roles

More about Registration and Import of Medical Devices in India

- **Damage of Registration Certificate**: If the original Registration Certificate is defaced, damaged or lost, a fee of three hundred US dollars [or its equivalent in Indian rupees] should be paid for a duplicate copy.
- **Reporting of changes**:

Table 3: List of changes that requires fresh registration and changes that do not require

Changes that requires **FRESH** registration	Changes that **DON'T** require **FRESH** registration
1. Changes related to manufacturer • Change in constitution • Change in name	1. Changes in shelf life
2. Changes with respect to Importer/ Indian agent • Change in name • Change in constitution	2. Changes in method of testing
3. Changes in Indications/ Directions for Use: fresh application should include power of attorney incorporating changes in indication.	3. Minor changes in manufacturing process that do not affect final product specification
4. Any changes in the constitution of the firm or the address of registered office	4. Updation in IFU like warnings, precautions, safety instructions, labels and packaging
5. Adverse events related to product should be immediately reported to CDSCO	
6. Acquisition/Merger with other company	

- **Labels and labeling requirements in India**: Medical device manufacturers must follow the labeling requirements and must be done on every medical device packaging. On 25th September, 2014 the CDSCO issued amendments to the Drugs and Cosmetics Rules, 1945. An important amendment for medical device manufacturers to observe is Rule 109A – labeling requirements.

Table 4: Requirements in labeling as per Rule 109A

RULE 109A – LABELLING REQUIREMENTS	
1. Proper name of the medical device	8. The words "FOR CLINICAL INVESTIGATION ONLY", if the device is intended for clinical investigation
2. Details necessary to identify and use device properly	9. The words "Physician's Sample—Not to be sold", if a medical device is intended for distribution to the medical professional
3. Name of the manufacturer and address of manufacturing premises	10. Manufacturing license number should be mentioned (except for imported devices)
4. Correct statement of the net quantity (in terms of weight, measure, volume, number) and the number of the devices contained in the package and the date of manufacture and date of expiry	11. Devices which are not sold to customer or patient directly and are sold for use by hospitals or diagnostic labs, additional label or sticker should be there on outer pack
5. Indication that the device contains medicinal or biological substance	12. The import licence number, name and address of the importer and address of the actual manufacturing premises, date of manufacture should be provided
6. Distinctive batch number or lot number (a) Indicate, wherever required, any special storage or handling conditions applicable (b) Indicate, if the device is supplied as a sterile product, its sterile state and the sterilization method	13. Shelf life of the device can be stated on the label instead of date of manufacture
7. Warnings or precautions Also if device is intended for single use	14. Labels may bear symbols recognized by the Bureau of Indian Standards. ISO Symbols are acceptable on labels of registered notified medical devices being imported into India and therefore, can be incorporated on the labels.

- Labeling must be done on every outer covering in which the medical device is packed. Original labels or colored copies of original labels should be submitted along with the application of registration/ re-registration of medical devices incorporating all details as per Rule 96. Labels submitted should include all models for which registration is sought.

- The label of registered notified medical devices imported must include the names and addresses of the legal manufacturer, actual manufacturer and the name and address of importer on which the Import License in Form 10 has been issued. Importers of registered notified medical devices are currently allowed to incorporate India-specific requirements like name and address of importer, import licence number on imported medical devices post landing in India at customs warehouse or place approved by the CDSCO prior to release into market.

➢ **Registration of "New" Medical Devices**

The procedure for registration of new medical devices is presented in Figure 4.

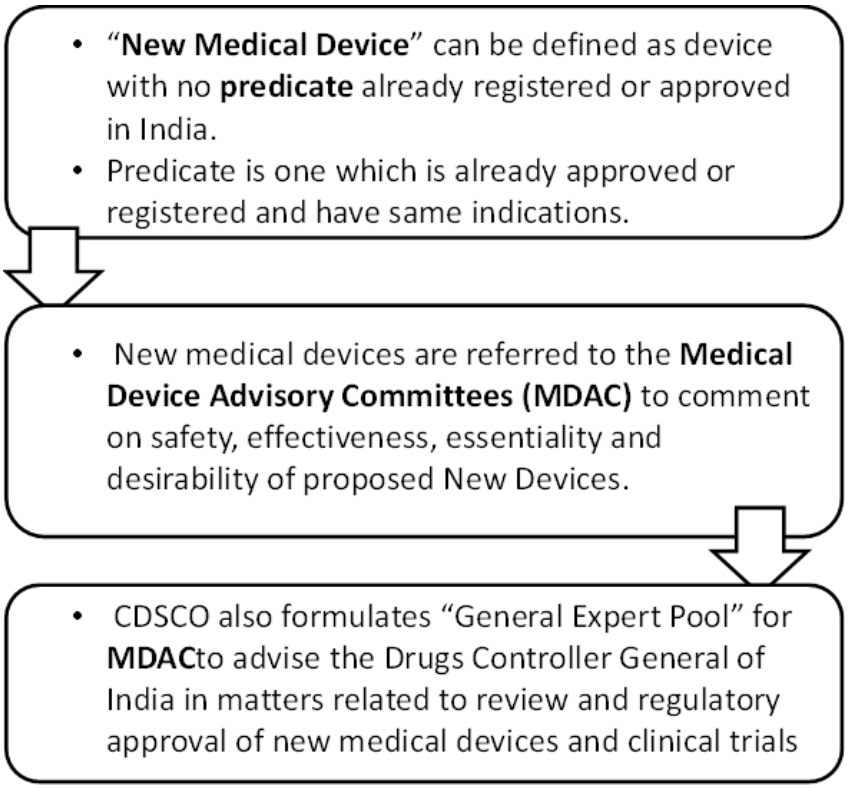

Figure 4: Process for new device registration

- **Status of application**: A third party/Authorized Consultant cannot ask the status of the application. Either the applicant or his authorized Regular employee may ask the status of their application if it is beyond the time limit prescribed under Drugs and Cosmetics Act and Rules.

  Also only subject expert or technical person of the company can make the presentation, on behalf of the applicant, when asked by the CDSCO.

- **Veterinary Medical Devices**: The regulatory requirements for import, manufacture and labeling of veterinary medical devices are same as devices meant for human beings.

- **National Medical Device Policy CDSCO Regulation 2015**: The recently issued draft National Medical Device Policy-2015 by the Department of Pharmaceuticals (DoP), mandates institutional frameworks such as Common Testing Centres, Centres of Excellence, Made in India marking (BIS) for medical devices and a Skill Development Committee under National Medical Devices Authority. The government should set up common medical device testing facilities as per the policy to facilitate medical devices testing in manufacturing hubs.

- **Regulatory Challenges for Medical Devices in India:** Manufacturers are attracted to the Indian market due to its reliance on imports. However, the challenge is that the Regulatory Body in India is currently at its infancy and regulations may be revised within short periods resulting in uncertainty over the approval process. It might be a good idea to keep a track of everyday news (1, 3).

Medical Devices Market in India

Market of Indian medical devices is worth 3 billion USD making it Asia's fourth largest market, which provides excellent business opportunity to both national as well as international investors (Figure 5). During early 90s, this market was dominated by domestic players but now scenario has changed due to opening of Indian market. Fact that 75% of the sales are generated by imported medical devices or devices that requires imported material shows that Indian medical device sector is now dominated by MNC's. Many multinational operations have come in India and because of such dominancy in Indian market; domestic

manufacturers export more than 60% of their output. (3)

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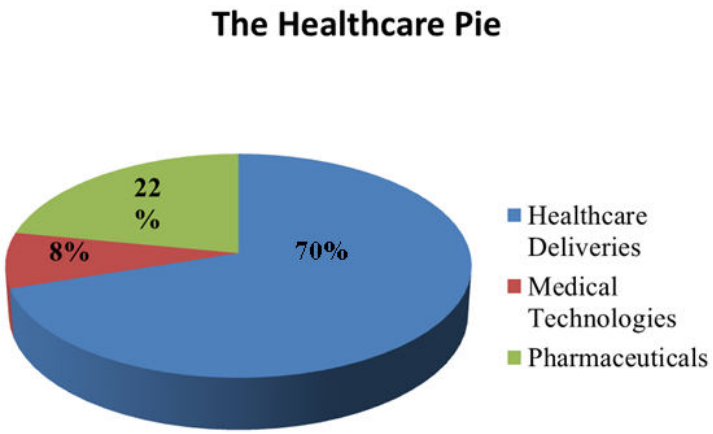

Figure 5: Healthcare pie chart indicating medical devices market in India

US FDA's Regulations on Medical Devices

The legal authority of US, the FDA (Food and Drug Administration) assures safety and effectiveness of the medical product. (4) FDA's Centre for Devices and Radiological Health deals with pre and post marketing regulations of medical devices. The FD&C (FDA Drug and Cosmetic) Act contains provisions or regulatory requirements that define FDA's level of control over these products. FDA formulates, publishes and enforces regulations in order to fulfill the provisions of the FD&C Act that apply to medical devices.

Most of FDA's medical device and radiation-emitting product regulations are in Title 21 CFR Parts 800-1299. This final regulation cover various aspects of design, clinical evaluation, manufacturing, packaging, labeling, post market surveillance of medical devices and also provides standards and product reports that apply to radiation-emitting products. (5)

Currently, the CFR is updated to e-CFR (Electronic Code of Federal Regulations). It is an unofficial editorial compilation of CFR material and Federal Register amendments produced by the National Archives and Records Administration's Office of the Federal Register (OFR) and the Government Printing Office. The OFR updates the material in the e-CFR on a daily basis. (4)

US FDA Registration Process for Medical Devices

All companies planning to manufacture, sell or import medical devices in the United States need to register their products with the US FDA. The Medical Device Amendments of 1976 to the Federal Food, Drug and Cosmetic Act categorised medical devices into three regulatory classes (6) (Figure 6). These classes are based on the degree of control that is required to assure their safety and efficacy. Figure 7 highlights the regulatory procedure for registration of different classes of medical device in US.

Comparing Indian and US Regulations

The Indian regulations as opposed to the US regulations are very new and in their infant stage. However, both of them have their own rules and regulations that need to be followed.

- US FDA has classified medical devices into three classes based on the risk associated with the device and their registration depends on the class in which they fall. Whereas, in India according to CDSCO guidelines medical devices are either notified or notified devices depending on utility and not according to their safety. Notified devices require registration whereas non-notified may or may not require any registration.

- In India if product is registered in US or Europe, there is no need to conduct clinical trials in India but if no predicate is available in US or European market, clinical trials are required. In US, if no predicate is available

in US FDA list then clinical trials are necessary.

- Both the countries allow the appointment of agents as representatives of the manufacturers.

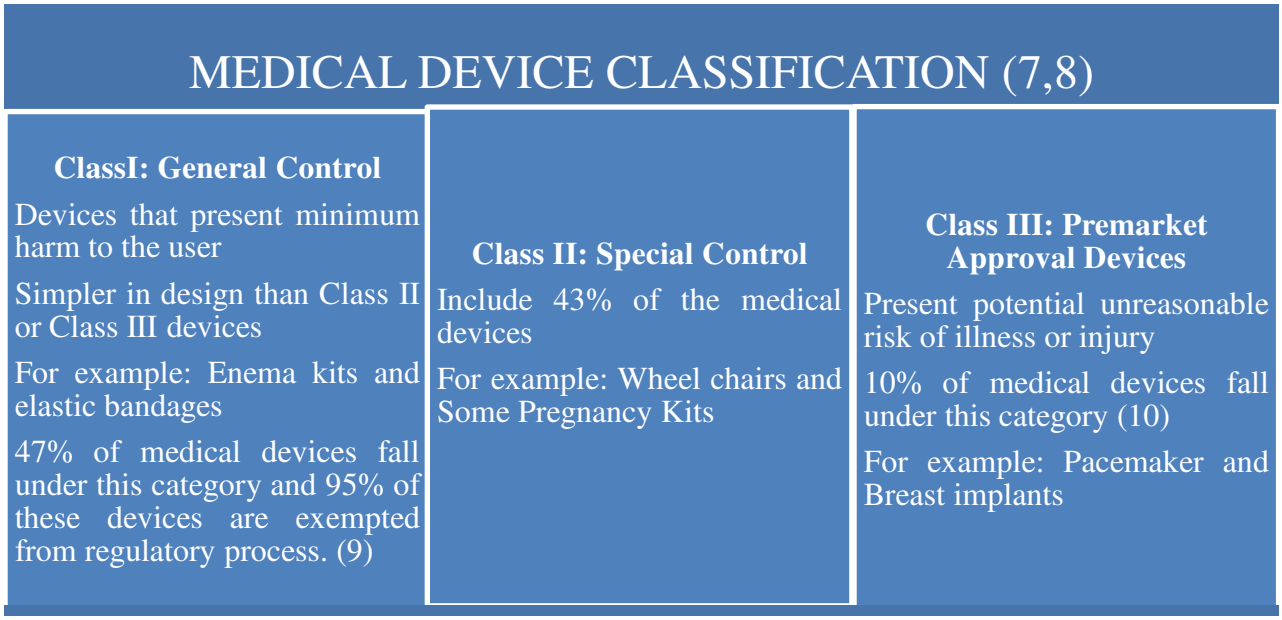

Figure 6: Classification of medical devices according to US FDA (10-11)

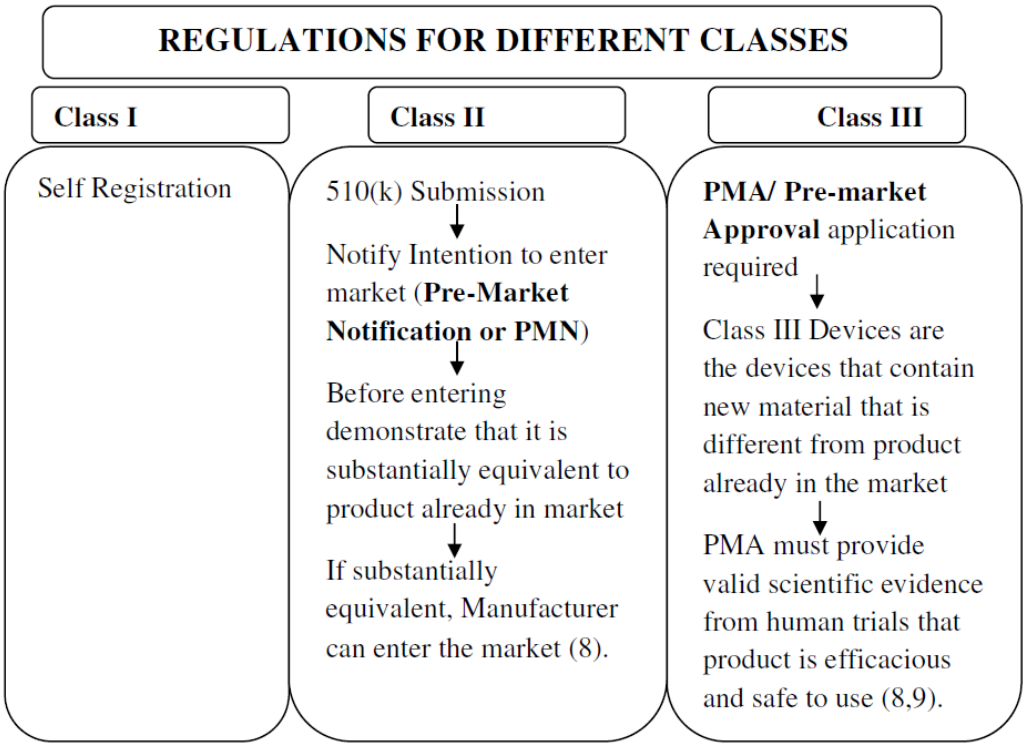

Figure 7: Regulatory procedure for registration of different classes of medical device (1)

Table 5: Registration process of medical devices according to USFDA (11-13)

BRIEF OVERVIEW OF THE REGISTRATION PROCESS	
Step 1: Identification of the class of the medical device	• FDA databases are used to determine the class to which medical device belongs based on the Predicate available in the market. (6) • Three-letter Product Code and seven-digit Regulation Number associated

	with the predicate devices needs to be identified. • If no predicate found, 513(g) or De Novo process can be used. (8)
Step 2: Quality Management System	• Found in 21 CFR Part 820 should be implemented. • Commonly known as FDA Good Manufacturing Practice (GMP) and meets FDA Quality system Regulations. • Assures proper design, supervising and control of manufacturing processes.
Step 3: Pre-Sub feedback	• Pre Submission feedback needs to be obtained for class II and class III from FDA before entering the market to determine whether product require clinical trials or not.
Step 4: IDE (Investigational Drug Exemption).	• If clinical trials need to be done then, manufacturer needs to apply for IDE. • IDE allows manufacturer to use investigational device for collecting data related to safety and efficacy which are required for PMA and in some rear situation in PMN submission. • Distribution of the investigational device is limited to the areas mentioned in IDE application and investigation is supervised by IRB (Institution Review Board) comprising health expert and lay person to assure that ethical principles are followed while conducting the study. • IRB determines the initial risk factors as well as the level of significance of associated risk with the device. • FDA can overrule any risk identified by the IRB. • If IRB determines that a device/clinical study significant risk is associated with the device, the applicant must submit an IDE application to the FDA. (9)
Step 5: PMN and PMN submission	• For class II 510 (k) or PMN (Premarket Notification) application should be submitted and for class III PMA (Premarket Approval) application should be submitted along with the submission fee. (9, 14)
Step 6: Inspection	• For class III FDA conducts facility inspection for all the suppliers that are involved in design and production of the medical device. • All should be complaint with FDA QSR.
Step 7: Approval	• For class II FDA issues 510 (k) clearance letter and for class III FDA issues PMN clearance letter. • Clearance letters are posted online.
Step 8: Form 483	• FDA conducts random inspections after issuing registration certificate. If found non-complaint with the regulations FDA can issue form 483
Step 9:Local Representative	• If the manufacturer has no local presence in the US, FDA Agent representative can be applied as a local point of contact with the FDA.
Step 10: Registration	• Devices can be listed and companies can be registered using FURLS system on the FDA website in accordance with 21 CFR Part 807. • The appointed US Agent must be specified. • The FDA Establishment Registration and Listing must be renewed on a yearly basis.
Step 11: Authorization	• The FDA listing on their website will serve as authorization to commercialize the device in the US. • Device can now be sold in US • This authorization will continue until and unless some major changes are done for example design, intended to use etc. (15)

CONCLUSION

India has advanced into a "World Pharmaceutical Hub" whereas its regulatory authority is still struggling to keep pace with the international industrial growth. According to the report commissioned by Indian parliamentary committee in 2012, CDSCO struggled with staffing shortage and infrastructural issues affecting its responsibilities to ensure public safety. (16) Following this criticism, CDSCO not only updated its mission statement as "To safeguard and enhance the public health by assuring the safety, efficacy and quality of drugs, cosmetics and medical devices," but has also moved beyond the past issues to correct its flaw and become a world class regulator comparable to the US FDA and EMA (European Medicines Agency).

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Medical device reporting for Manufacturers [Internet]. Maryland: Food and Drug Administration; 2013 [cited 2016 Aug 12]. Available from: http://www.fda.gov/Medical Devices/DevicesRegulationandGuidance/GuidanceDocuments/ucm094529.htm
2. The Drug and Cosmetics Act and Rules [Internet]. India: Ministry of Health and Family Welfare; 2005 [cited 2016 Aug 13]. Available from: http:// cdsco.nic.in/Medical_div/Final%20 Guidance_ Doc_RC_31-10-2012.pdf
3. Code of Federal Regulations [Internet]. United States: Food and Drug Administration; 2014 [cited 2016 Aug 11]. Available from: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ucm134499.htm
4. Fox DM, & Zuckerman DM. Regulatory reticence and medical devices. Milbank Q. 2014; 92: 151-9.
5. Buch B. FDA medical device approval: things you didn't learn in medical school or residency. American Journal of Orthopedics (Belle Mead, NJ). 2007; 36: 407-12.
6. Pena C, Bowsher K, Costello A, De Luca R, Doll S, Li K, et al. An overview of FDA medical device regulation as it relates to deep brain stimulation devices. IEEE Trans Neural. Syst.Rehabil. Eng. 2007; 15: 421-4.
7. Samuel AM, Rathi VK, Grauer JN, & Ross JS. How do orthopaedic devices change after their initial FDA premarket approval? Clinical Orthopaedics and Related Research®. 2016; 474: 1053-68.
8. Learn if a Medical Device has been cleared by FDA for marketing [Internet]. United States: Food and Drug Administration; 2014 [cited 2016 Aug 15]. Available from: http://www.fda.gov/MedicalDevices/ResourcesforYou/Consumers/ucm142523.htm
9. Rathi VK, Krumholz HM, Masoudi FA, & Ross JS. Characteristics of clinical studies conducted over the total product life cycle of high-risk therapeutic medical devices receiving FDA premarket approval in 2010 and 2011. JAMA. 2015; 314: 604-12.
10. Scott B. Oversight Overhaul: Eliminating the Premarket Review of Medical Devices and Implementing a Provider-Centered Postmarket Surveillance Strategy. Food & Drug LJ. 2011; 66: 377.
11. Sorenson C & Drummond M. Improving medical device regulation: the United States and Europe in perspective. Milbank Q. 2014; 92: 114-50.
12. Rome BN, Kramer DB, & Kesselheim AS. Approval of high-risk medical devices in the US: implications for clinical cardiology. Curr Cardiol Rep. 2014; 16: 1-9.
13. Dhruva SS, Bero LA, & Redberg RF. Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices. JAMA. 2009; 302: 2679-85.
14. Food, Administration D, Health UDo, & Services H. Medical device reporting: Manufacturer reporting, importer reporting, user facility reporting, distributor reporting. Fed. Regist. 2000; 65: 4112-121.
15. Donawa M. Medical device reporting: the US final rule. Med. Device Technol. 1996; 7: 14-16, 18, 20-11.
16. Mezher M. India takes Inspiration from FDA, EMA in bid to improve CDSCO [Internet]. India: Michael Mezher; 2015 [cited 2016 Aug 17]. Available from: http://www.raps.org/Regulatory-Focus/News/2015/06/29/22795/India-Takes-Inspiration- From-FDA-EMA-to-Improve-CDSCO/aspx

