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“A Comprehensive Study on Medical Device Regulation in India, Japan and Europe.”

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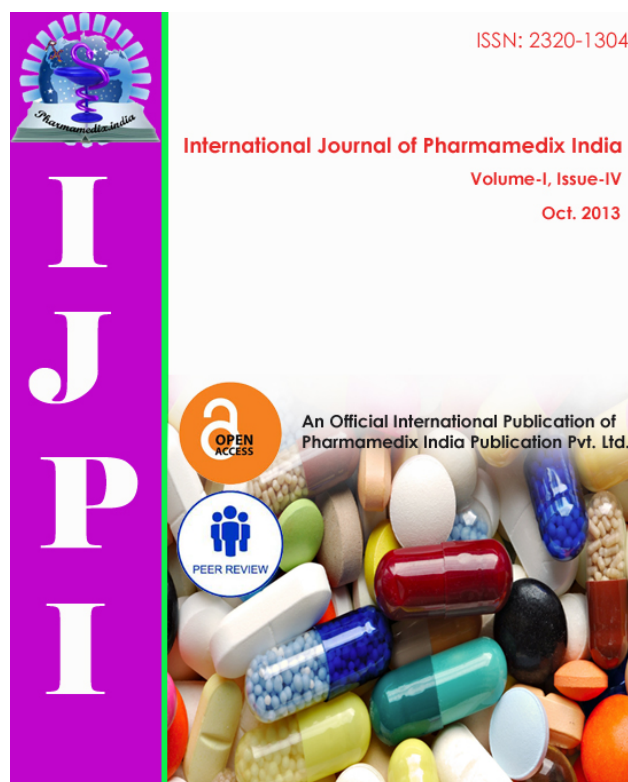
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Abstract:

All devices carry a certain degree of risk and could cause problems in specific circumstances. Several medical device issues cannot be detected until extensive market experience is gained. As an example, an implantable device could fail in a manner that was not predictable at the time of implantation; the failure may reflect conditions unique to certain patients. For alternative devices, part failure can also be unpredictable or random. This current approach to device safety is to estimate the potential of a device changing into a hazard that could result in safety problems and harm. This estimate is commonly referred to as the risk assessment. The regulatory authority of various countries has their own standards for approval or disapproval of medical devices.

Keyword: Bureau of Indian Standards, CDSCO, Medical Device Directive, Ministry of Health and Family Welfare.

Introduction

Medical devices are essential for safe and effective hindrance, diagnosis, treatment and rehabilitation of unhealthiest and disease. The achievement of health-related development goals, as well as Millennium Development Goals depends upon proper manufacturing, planning, regulation, assessment, acquisition, management and use of medical devices that are of good quality, safe and compatible with the settings within which they are used ^[1]. Hazard is a potential for an adverse event, a danger. Risk is a measure of the combination of

a. Hazard;

- b. Likelihood of occurrence of the adverse event;
- c. Severity or adverse event, a source of danger.

Risk could be measure of the all possible hazards, followed by risk analysis to estimate the risk of every hazard. In general, risk assessment is based on experience, evidence, computation, even may be guesswork. Risk assessment is complex, as it can be influenced by personal perception and other factors such as cultural background, economic conditions, and political atmosphere. In practice, risk assessment of medical devices relies on the experience of health care professionals and on safety design engineering.

Medical Device regulation in India

Prior to 2005, no regulations whatsoever existed for medical devices in India. Nowadays there are registration procedures for certain classes medical devices regulated under the provisions of the Drugs and Cosmetics Rules. Comprehensive legislation regulating medical devices is pending. India will move toward the use of international standard ISO 13485: 2003 quality management systems for medical devices, published by the Bureau of Indian Standards (BIS) as Indian national standard IS 15579: 2005^[2].

Currently, manufacturers of medical devices which require registration can leverage their approvals in the US, Europe, Canada, Japan or Australia to register their medical devices in India. The complete technical documentation used to support those submissions (i.e. 510(k) application, CE Technical File/Design Dossier, Health Canada Medical Device License) must be provided with the device application. This form should be submitted per medical device family. During the medical device registration process, the first entity we work with is the Medical Devices Division of the CDSCO. The hierarchy of medical device regulation in India is as follows ^[3].

Ministry of Health and Family Welfare

- Drug Controller General of India - DCG(I)
- Central Drugs Standard Control Organisation (CDSCO - Medical Devices Division)

Registration and Approval of Medical device in India

India is one of the largest medical device markets in Asia, and growing at a powerful rate. Increased health awareness, a growing middle class and government health initiatives mean the market is expected to grow about 15% per year for the next several years.

If manufacturers want to legally sell medical devices in India, they must be in compliance with India medical device regulations. The purchase of medical devices is completed through international tenders issued by government owned and personal hospitals ^[2].

Undoubtedly, the medical devices and surgical instruments are currently not covered under the restrictive framework in India. But, any device which is intended for internal or external use in the diagnosis, treatment, prevention of disease or disorder in human beings and animals, as may be specified by the Central Government by notification in the Official Gazette would be considered as a drug under the D&C Act and provisions of D&C Act and Rules made therein would be applicable on such device. Regularly Ministry of Health and Family Welfare, Government of

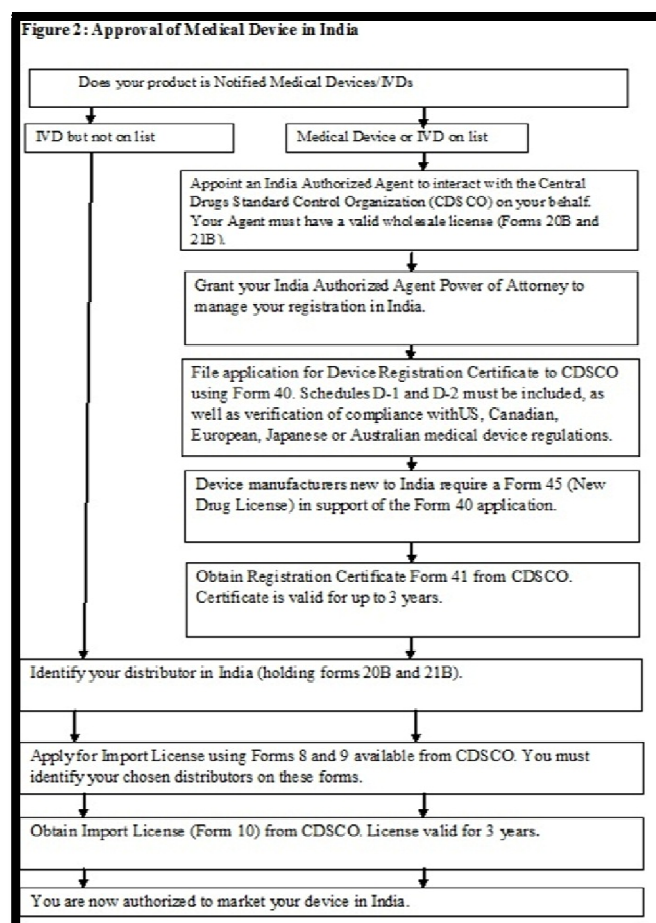
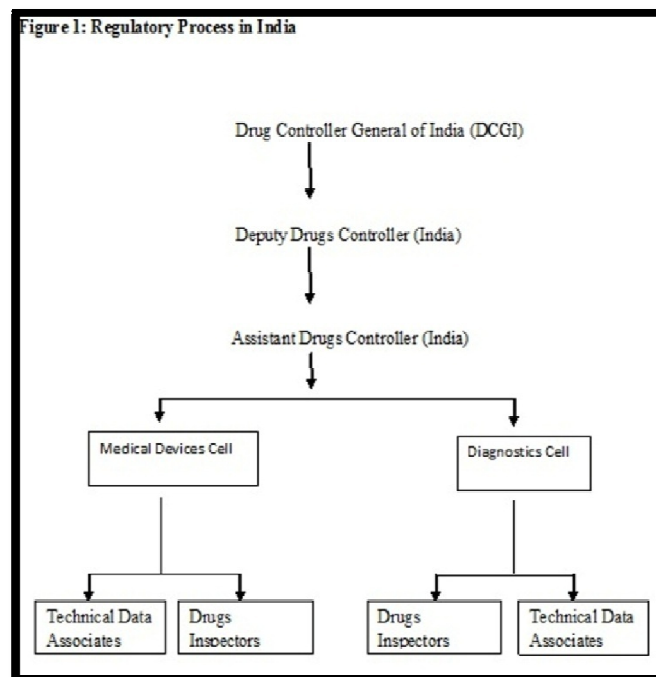
India gazette notifications has notified certain medical devices as drugs under the D&C Act.

Prior to 2005, only medical devices such as tubal rings, disposable hypodermic syringes, metered dose inhalers, condoms etc were required to be registered in India. In 2005, the MOHFW (Ministry of Health and Family Welfare) gazette notification dated 6 October 2005 further notified 10 sterile devices (“Notified Medical Devices”) to be considered as drugs and consequently regulated their import, sale and production under Section 3(b) (iv) of the D&C Act [2,3].

Regulation for Notified Medical devices

In India, the Central Drugs Standard Control Organization (‘CDSCO’) is the main regulatory body currently regulating import, sale and production of medical devices which have been notified as drugs by virtue of Section 3(b) (iv) of the D&C Act. The CDSCO had laid down standards for drugs, cosmetics, diagnostics, devices and issues licenses to drug manufacturers and importers. It additionally lays down amendments to Acts and Rules, regulatory measures and regulates market authorization of new drugs, clinical trials in India and standards of imported drugs etc. The CDSCO also have separate division which is called Medical Device Division in order to facilitate matters related to Notified Medical Devices. The power structure of medical device division of the CDSCO in

India is shown in above figure no1 and in figure 2 there is general approval of notified medical device and IVD [4, 5].



Medical Device regulation in Japan

For foreign manufacturers, complying with Japan's Pharmaceutical Affairs Law (PAL) of 2005 can be challenging. Moreover in Japan few English language documents have been issued by the Ministry of Health, Labour and Welfare (MHLW) and its division, the PMDA (Pharmaceuticals and Medical Devices Agency). Language barriers and a complex registration process make Japan one of the most time consuming markets for medical device manufacturers to enter

There are two components of the Japanese PAL regulations that are key to doing business in Japan: "Kyoka" and "Shonin". In Japan "Kyoka" is a kind of business license required for Marketing Authorization Holders (MAH), manufacturers, repairers and distributors. If the manufacturing facilities are settled outside of Japan, these foreign producing facilities are required to obtain Foreign Manufacturer Accreditation instead of a Manufacturer License ^[6].

Japan Medical Device Regulations and Approval Process

The regulator of medical devices and pharmaceuticals in Japan is the Pharmaceuticals and Medical Devices Agency (PMDA), which handles medical device and pharmaceutical registration. Japanese medical issues, such as health insurance, medical product registration policy

and hospitals are handled by the Ministry of Health, Labour and Welfare (MHLW).

High-risk medical devices must be approved by the PMDA (approval of Shonin required), while lower-risk medical devices may apply to Notified Bodies rather than the PMDA (approval of Ninsho require). In addition, foreign manufacturers will need accreditation from the PMDA ^[7]. Risk Information was suggested by a certain amount of accumulated information on Adverse Drug Reactions (ADR) reports or Early Post marketing Phase Vigilance (EPPV) ^[8].

For high-risk medical devices approval, medical device companies will also need to have a quality management system (QMS) audit. Japanese regulators are very cautious in approving high-risk foreign medical device products, so the process can be lengthy and troublesome. Third-party compliance consultants can help companies expedite approval from the PMDA ^[9,10].

Classification

To market medical devices in Japan, the Marketing Authorization Holder (MAH) must register the device through the following procedures generally Todokede, Ninsho and Shonin for medical devices in Japan. Classification of device according to the Japanese Pharmaceutical Affairs Law (PAL) is shown in figure 3.

- Pre-market Submission (Todokede) - CLASS I MEDICAL DEVICES

To register and marketing of General Medical Devices (Class I devices), the MAH only need to file Pre-Market Submission to PMDA with no assessment by the PMDA.

- Pre-market Certification (Ninsho) - CLASS II MEDICAL DEVICES

Only Class II devices which are specified as Specified Controlled Devices are subject to Pre-market Certification. The devices other than Specified Controlled Devices (Class II) are subject to Pre-market Approval.

To register and market a Specified Controlled Medical Device, the Marketing Authorization Holder (MAH) needs to file Pre-Market Certification application with a Registered Certification Body (RCB) and obtain their certification. This procedure is somewhat similar to European CE marking using a Notified Body. However, several European Notified Bodies are also authorized Japanese Registered Certification Body (RCB). Each Specified Controlled Medical Device must apply internationally harmonized standards as is the case with CE Marking and approval time for medical device is shown in figure 4.

- Pre-market Approval- CLASS II, III & IV MEDICAL DEVICES (Shonin)

To register and market a “Highly Controlled Medical Device” the MAH

needs to file a Pre-market Approval Application with the PMDA and obtain their approval. Class II devices that don't seem to be Specified Controlled Devices are also subject to Pre-Market Approval ^[7,9].

Compilation of a Japanese Device Master File (Seihinhyojunsho)

The creation of a Device Master File, called a "Seihinhyojunsho," is an essential step in obtaining approval to sell a medical device in Japan. The Seihinhyojunsho is very nearly similar to a European Technical File, but contains extra information that addresses the specific labelling, Marketing Authorization Holder (MAH) and packaging requirements imposed by Japan's Pharmaceutical Affairs Law (JPAL).

This file is separate from the device registration application file (Ninsho, Todokede, Shonin) created during the regulatory approval process. The PMDA that is Japan's Pharmaceuticals and Medical Devices Agency is very particular about the content of the Seihinhyojunsho and the supporting documents and details submitted for the Seihinhyojunsho cannot differ from the same information submitted for the Todokede or Shonin and Ninsho. Even the smallest differences can cause delays ^[9,11].

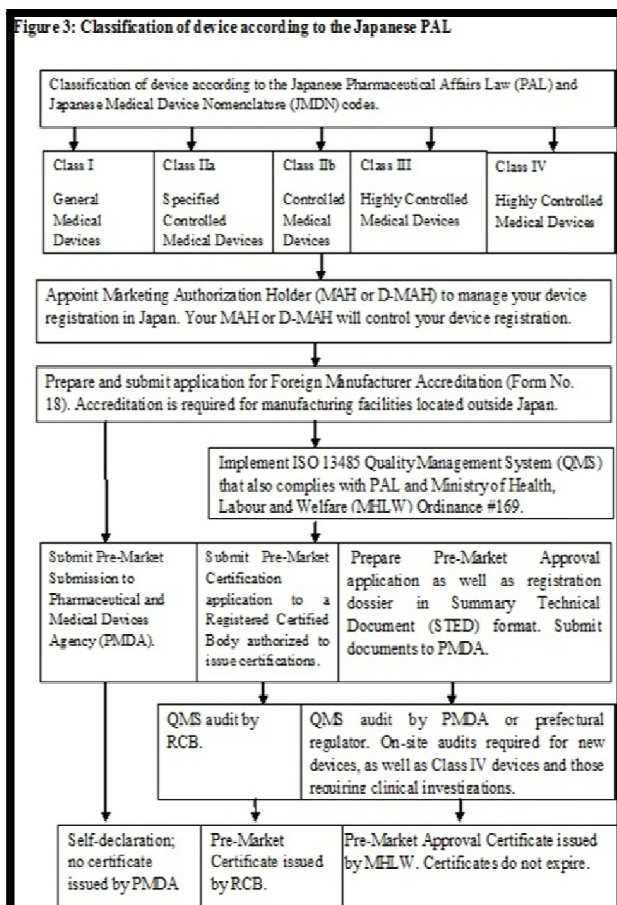


Figure 4: Approval time for medical device

Class	Approval time (granted by PMDA or Registration Certification Body)
Class I General Medical Devices	1
Class IIa Specified Controlled Medical Devices	4 to 5
Class IIb Controlled Medical Devices	7 to 9
Class III Highly Controlled Medical Devices	9 to 11
Class IV Highly Controlled Medical Devices	13 to 16

Medical Device regulation in Europe

All Medical device and IVD companies prepare the necessary documentation in order to achieve CE Marking certification for their products. The mandatory component is the CE Technical File (called a Design Dossier for Class III devices).

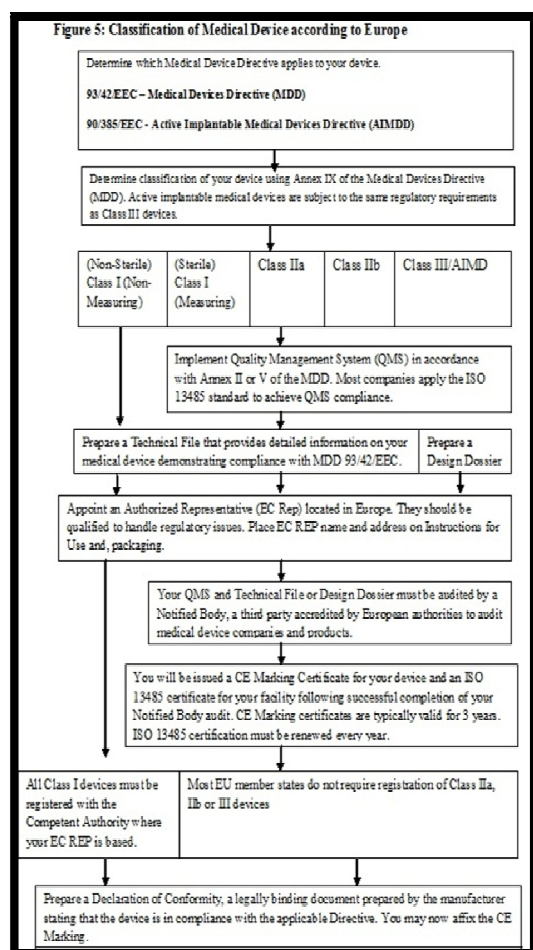
A CE Technical File is a comprehensive collection of information and documents detailing everything about your medical device. It is necessary to understand how to assemble this information and present it properly is important. If you manufacture a Class I device or self-certified IVD, CE Marking Technical File required may be a less complex. In the case of Class IIa, IIb and Class III devices (or self-testing IVD), CE Marking Technical File required may be a more complex. Classification of medical device is shown in figure 5 and approval time for medical device is shown in figure 6^[12, 13].

For obtaining CE certification and marketing your medical device in the EU requires the following steps

- First step to prepare a CE Marking Technical File or a Design Dossier (for a Class III device) that includes data proving compliance with the MDD, IVDD or AIMD.
- Second step is to obtain CE Marking certificate from a Notified Body or self-certify your compliance with the

MDD (Class I non-sterile, non-measuring devices).

- Third step is to select and appoint a European Authorized Representative to act on your behalf within the EU [12, 14].



The EU Technical File is subject to review by a Notified Body if the medical device is Class I with measuring or sterile function, Class IIa, IIb, and III (Design Dossier), or self-testing IVD(IVD classification is shown in figure 7). Once placed on the market, a national competent authority has the right to review EU Technical Files regardless of classification at any time. An incomplete or irregular Technical File may result in

unexpected delays or even prevent market entry [12, 14].

The components of a CE Mark Technical File include:

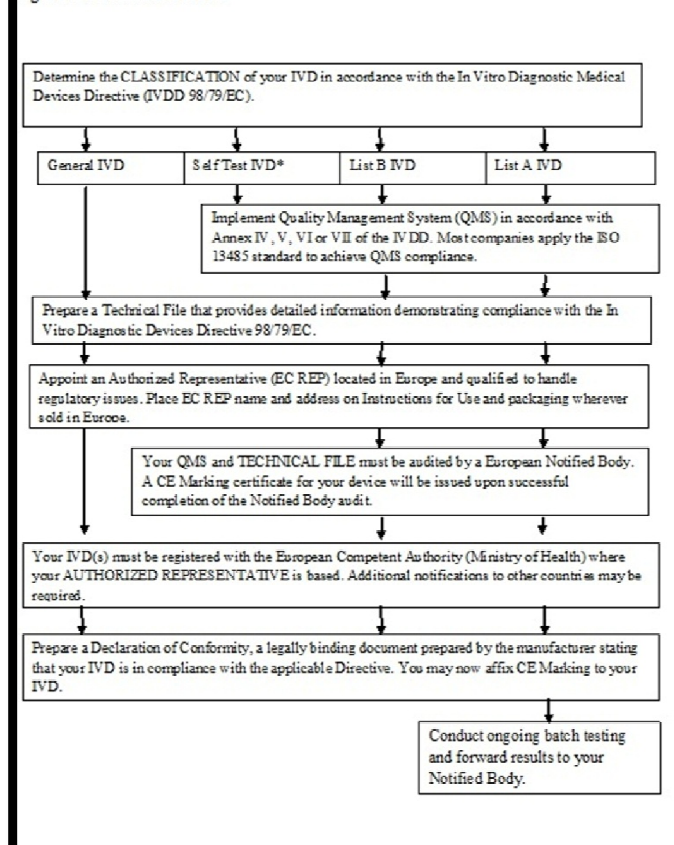
- Description of the product family and justification for why each product falls within the product family.
- Detailed account of the intended use of the device(s) including how the medical device(s) functions, what it does, where the device is used, what it is used with, and who uses it.
- Description of components, specifications, packaging and literature.
- The manufacturing process.
- Listing of accessories.
- Location of design responsibility and manufacturing facilities.
- Classification of the device and rationale for classification.
- The chosen route to compliance according to the applicable Directives.
- Declaration of Conformity that states the manufacturer's compliance with applicable Directive(s).
- Lifetime/shelf life of products and environmental limitations.

- Retention of QA, Competent Authority and Notified Body records.
- Vigilance reporting and Medical Device Reporting procedure.
- How and when to contact Competent Authorities.
- Name of, and contract with, your Authorized Representative in Europe.
- Subcontractor names and addresses, if applicable.
- Essential Requirements.
- Design input specifications.
- Application and references to Standards and Guidelines.
- Testing results and clinical evaluations.
- Risk analysis.
- Instructions for Use and Labelling.

Figure 6: Approval time for medical device in Europe

Class	Approval time
Class I*: NONSTERILE, NON MEASURING	1
Class I- STERILE OR MEASURING	3-5
Class IIa	1-3
Class IIb	2-6
Class III	6-9

Figure 7: Classification of IVD



Conclusion

Although there is a continuous process of harmonization taking place all around the world, still we have a tendency to see an enormous challenge, which is yet to be overcome by the Regulatory agency in case of medical device regulation. This is due to the heterogeneity in the regulatory landscape of the various countries. Therefore, to satisfy these challenges, plenty of strategic planning is required before the development of any medical device. Risk management systems and Quality management systems are in most countries required, except for medical devices class I. Certificates of ISO 13485 and ISO14971 are required or recommended.

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