International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

PRECISE AND COMPARATIVE REQUIREMENTS OF ACTIVE IMPLANTABLE MEDICAL DEVICE IN US, AUSTRALIA AND SINGAPORE

Vishal H. Parikh[1], Krupa C. Thula[1*], Dilip G. Maheshwari[2]

[1]Dept. of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad
[1*]Assistant Professor Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad
[2]Head of Department, Dept. of Quality Assurance and Pharm Regulatory Affairs, L. J. Institute of Pharmacy, Ahmedabad

***Corresponding author e-mail: krupathula@yahoo.com**

ABSTRACT

Medical device market has been improving its impact globally and it is the widely growing field now a days. The Cardiovascular Device industry is rapidly expanding its impact in the market and it will reach to $97 billion by end of 2015. Worldwide many people suffering from cardiovascular diseases and number of deaths has been reported every year. So, to improve the patient life and reduce the morbidity and mortality rate the strict rules and regulation has to be developed. Cardiovascular devices are life threatening devices and it is directly affecting the patient's life so strict and specific regulation is requiring for active implantable medical devices. In US, Food and Drug Administration high-risk medical device registered via the Pre-Market Approval process. In Australia, Therapeutic Goods Administration regulates the medical device under the Australian Register of Therapeutic Goods. In Singapore, Health Science Authority regulates the medical device under the Centre for Medical Device Registration. This article discuss about the general introduction about medical device, its classification, registration procedure, labeling requirements for active implantable medical device in US, Australia and Singapore.

KEY WORDS: FDA, PMA, TGA, DEAL, HSA, CMDR

INTRODUCTION OF MEDICAL DEVICE IN US [3]: FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, re-label, and import medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products such as lasers, x-ray systems, ultrasound, microwave ovens and color televisions.

- "An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related articles, including any component, part, or accessory, which is:
  - Recognized by the official National Formulary, or the United States Pharmacopoeia (USP).
  - Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation treatment, or prevention of disease, in a man or other animals.
  - Intended to affect the structure or any function of the body of a man or other animals, and which does not achieve any of its principal intended purposes through chemical action within or on the body of a man or other animals and which is not dependent upon being metabolized for the achievement of its principal intended uses."
- A medical device is designed to improve patient's health in diagnosis, therapy or surgery which are monitored and under strict regulations by the food and drug administration, FDA.

Medical devices are classified into three classes based on the US classification system, which defines the risk involved with the medical device and proper procedures that must be followed when using and manufacturing the device.

Classification:

Class 1: Simplest devices with fewest risks.

- Exempt from 510[k] notification and QSR.
- Toothbrush, oxygen masks, irrigating syringes.

Class 2: Devices with moderate risks

- Must submit 510[k] notification and QSR.
- Ultrasound imaging system, holter cardiac monitor, pregnancy test kit central line catheters.

Class 3: Technologically innovative devices

- Require **PMA** before marketing

PMA PROCEDURE FOR REGISTRATION OF MEDICAL DEVICE [1, 2]:

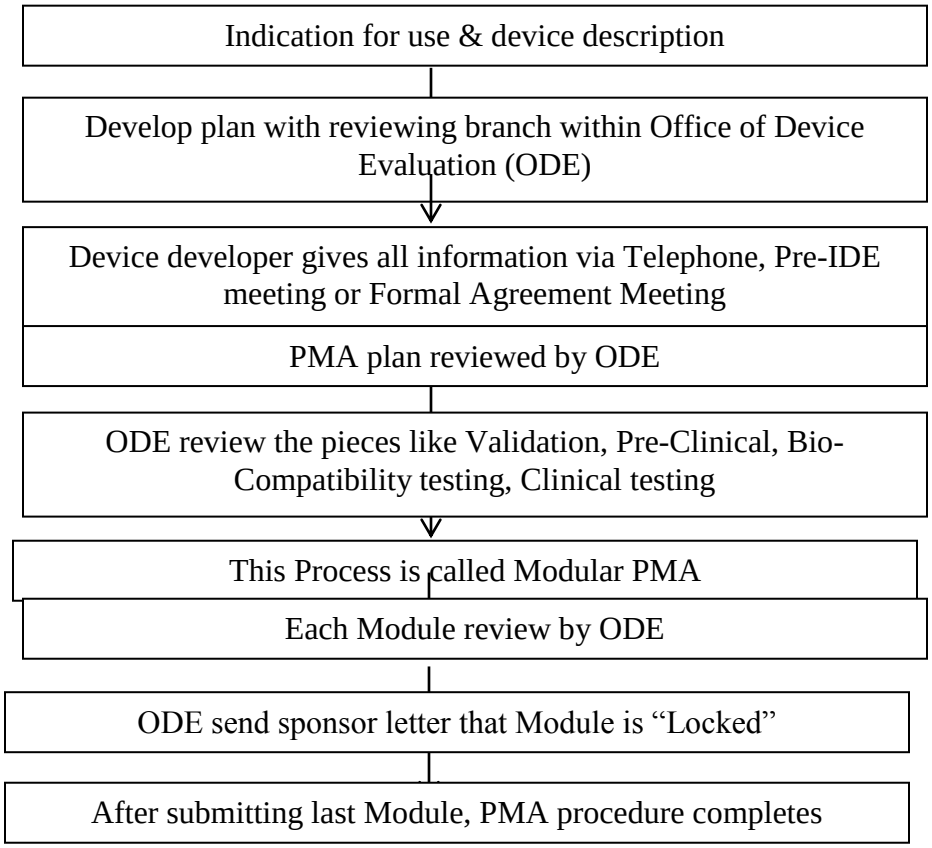

Figure 1: PMA process

PMA REVIEW PROCESS [1, 2]:

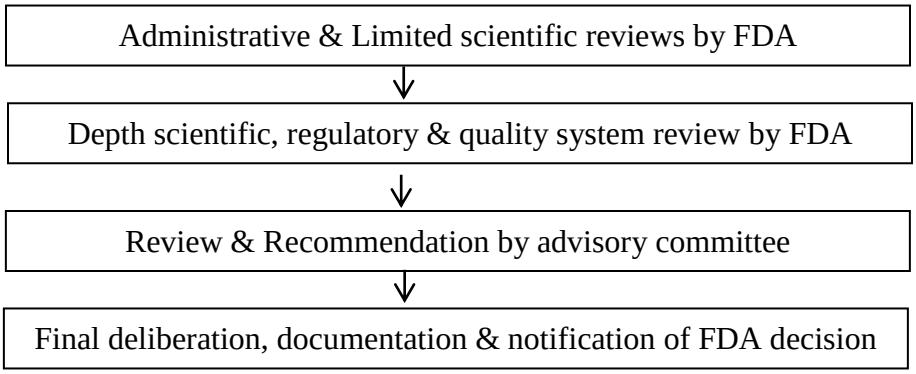

Figure 2: PMA Review process

MEDICAL DEVICE LABELING REQUIREMENTS [3]:

Labeling provision:

- Sec. **801.1** Medical devices; name and place of business of manufacturer, packer or distributor.

a) The label of a device in package specifies the name and place of business manufacturer, packer, or distributor.
b) The requirement for declaration of the name of the manufacturer, packer, or distributor shall be satisfied, in the case of a corporation, only by the actual corporate name which may be preceded or followed by the name of the particular division of the corporation. Abbreviations for "Company," "Incorporated," may be used and "The" may be omitted. In the case of an individual, partnership, or association, the name under which the business is conducted shall be used.
c) Device is not manufactured by the person but the name appears on the label is indicated as, "Manufactured for ___", "Distributed by _____".
d) Place of business shall include the Street Address, City, State, and Zip Code. Inclusion of the ZIP Code shall apply only to consumer commodity labels developed or revised after the effective date of this section. In the case of non-consumer packages, the ZIP Code shall appear on either the label or the labeling (including the invoice).
e) If a person manufactures, packs, or distributes a device at a place other than his principal place of business, the label may state the principal place of business.

Sec. 801.4 Meaning of intended uses:

- The words intended uses or words of similar import in 801.5, 801.119, and 801.122 refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such person's expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, For Example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. The intended uses of an article may change after it has been introduced into interstate commerce by its manufacturer.

Sec. 801.5 medical devices; adequate directions for use:

- An adequate direction for use means directions under which the layman can use a device safely and for the purposes for which it is intended. Section 801.4 defines intended use.

a) Statements of all conditions, purposes, or uses for which such device is intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising, and conditions, purposes, or uses for which the device is commonly used; except that such statements shall not refer to conditions, uses, or purposes for which the device can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner.

b) Quantity of dose, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and different physical conditions.
c) Frequency of administration or application.
d) Duration of administration or application.
e) Time of administration or application, in relation to time of meals, time of onset of symptoms, or other time factors.
f) Route or method of administration or application.
g) Preparation for use, i.e., adjustment of temperature, or other manipulation or process.

Sec. 801.6 medical devices; misleading statements:

- Among representations in the labeling of a device which devices misbranded is a false or misleading representation with respect to another device or a drug or food or cosmetic.

Sec. 801.15 medical devices; prominence of required label statements:

- A word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence required by section 502(c) of the act by reason, among other reasons:

1. The failure of such word, statement, or information to appear on the part or panel of the label which is presented or displayed under customary conditions of purchase.
2. The failure of such word, statement, or information to appear on two or more parts or panels of the label, each of which has sufficient space there for, and each of which is so designed as it likely to be, under customary conditions of purchase, the part or panel displayed.
3. The failure of the label to extend over the area of the container or package available for such extension, so as to provide sufficient label space for the prominent placing of such word, statement, or information.
4. Insufficiency of label space for the prominent placing of such word, statement, or information, resulting from the use of label space for any word, statement, design, or device which is not required by or under authority of the act to appear on the label.
5. Insufficiency of label space for the placing of such word, statement, or information, resulting from the use of label space to give materially greater conspicuousness to any other word, statement, or information, or to any design or device.
6. Smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter.

INTRODUCTION OF MEDICAL DEVICE IN AUSTRALIA [4]:

- The Therapeutic Goods Act 1989 defines a medical device as any instrument, apparatus, appliance, material or in combination, and including the software necessary for its proper application intended by the person under whose name it is to be supplied, to be used for human beings for the purpose of one or more of the following:
  - Diagnosis, prevention, monitoring, treatment or alleviation of disease,
  - Diagnosis, treatment, monitoring, alleviation, or compensation for an injury or handicap,
  - Investigation, replacement, or modification of the anatomy or of a physiological process,
  - Control of conception,

REGULATORY SYSTEM IN AUSTRALIA [4, 5]:

- The Therapeutic Goods Administration (TGA) is the government body that regulates therapeutic goods, including medical device in Australia.
- Australian regulatory framework is based upon the recommendation of the Global Harmonization Task Force (GHTF).
- The Australian regulatory system has the following features:
  - A classification scheme based on the level of risk.
  - Compliance with a set of essential principles to ensure that only safe, effective and quality medical devices are supplied.
  - Implementation of conformity assessment procedure, depending on the class of the medical device to demonstrate compliance with the essential principles including an implemented quality management system in accordance to ISO 13485:2003
  - A recognition of international medical device reference standard in order to demonstrate compliance to the essential principles e.g. IEC 60601-1
  - Implementation of regulatory controls for manufacturing processes.
  - Inclusion on the Australian Register of Therapeutic Goods (ARTG).
  - Implementation of post market surveillance system, adverse event reporting programs and vigilance activities.

Classification of medical device in Australia:

Table 1: Classification of medical device in Australia

Class	Risk Level	Examples
Class I	Low	Scalpel
Class IIa	Low-Medium	Hearing aids
Class IIb	Medium-High	Condoms
Class III	High	Vascular Stents
AIMD	High	Pacemakers

***GMDN code and term* [4, 5]:**

- The Global Medical Device Nomenclature (GMDN) code is a collection of terms, each with a unique, to describe and catalogue medical devices.
- The GMDN was developed according to the internationally recognized standards EN ISO 15225 and it has 3 levels.

1) Device Category: This is a broad categorization. There are 14 categories including: single use devices, dental devices, and in vitro diagnostic devices.
2) Generic Device Group: This level consists of the codes and the terms that define devices. This level is further broken down into preferred terms, template terms and synonym terms. Template terms can be recognized as having the word "specify" written after them. Template terms can be used to classify class-I medical devices only. Higher classes need to use preferred terms. Preferred terms consist of devices that have similar intended purposes or common technology. Synonym terms are terms that relates to a previous nomenclature.
3) Device Type: This is unique product identification provide by the manufacture for the purpose of the declaration of conformity, product type registration and traceability. It includes the make, model, and serial numbers of a device that would enable the manufacturer to identify the device.

Table 2: GMDN code required

Class	Type of GMDN Code required
I	Template Term
IIa, IIb	Preferred Term
III/ AIMD	Preferred Term + Unique Product Identifier

***Medical device registration using DEAL system* [4, 5]:**

- For the registration of medical device we need to create the e-business account for the DEAL (Device Electronic Application Lodgment) system.
- New user need to complete a client details form and e-business access.
- After getting the user name and password we can directly it on TGA online website on DEAL home page.
- Following information of Manufacturer's evidence added in system:
  - Client reference and details
  - Conformity assessment certification including the certificates details and if there are any restrictions on the scope
  - Class of the device
  - Conformity assessment procedure
  - Conformity assessment body
  - Manufacturer's details including name and address
  - GMDN code

Manufacturer's evidence currently takes between 5-10 days to accept by TGA.

MEDICAL DEVICE REGULATORY PROCESS IN AUSTRALIA [4, 5]:

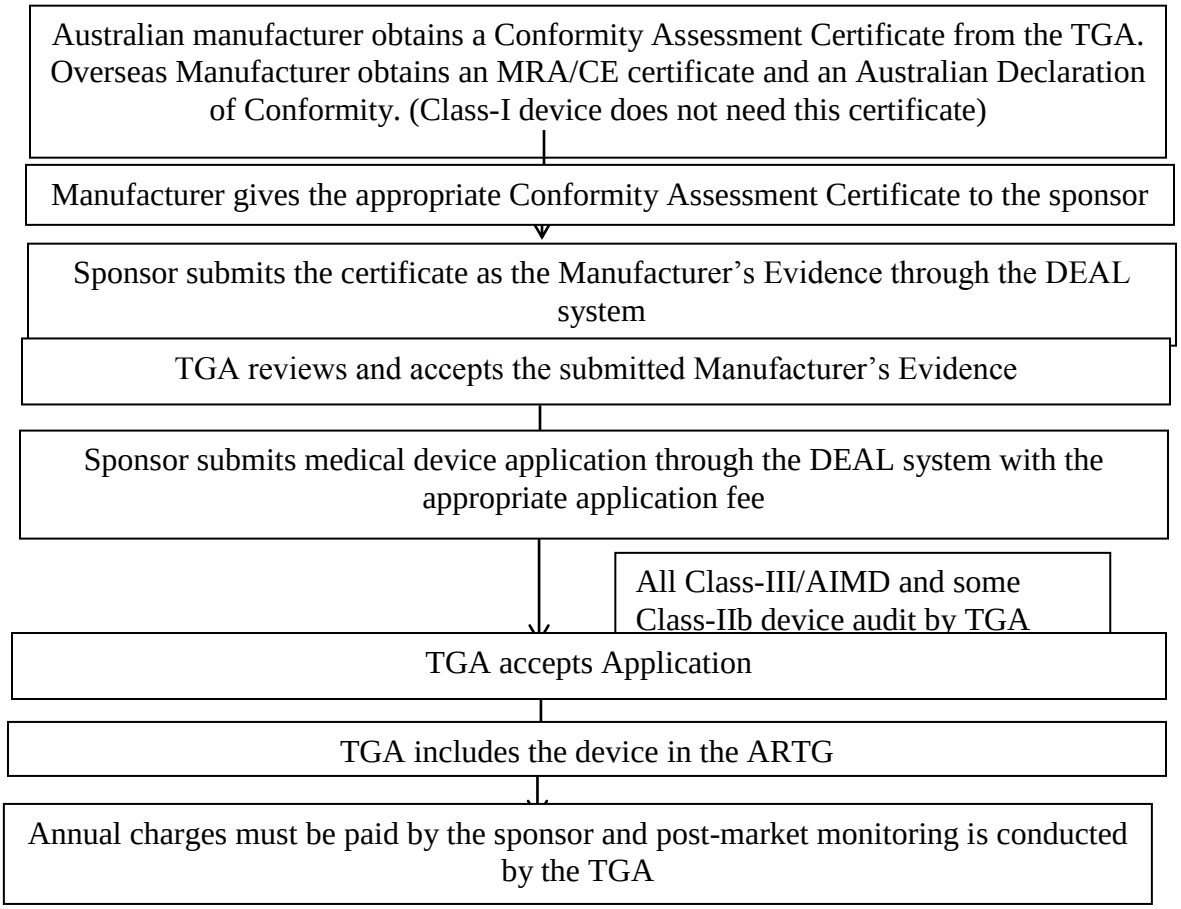

Figure 3: Medical device regulatory process in Australia

LABELING REQUIREMENTS IN AUSTRALIA [4, 5]: A medical device label is important as it communicates information including:

Identification of the

- device
- manufacturer of the device

- Information explaining how to use the device safely
- The Australian medical device labeling requirements follows the Global Harmonization Task Force (GHTF) labeling requirements.
- The requirements adopt a risk based approach to the content and level of detail that must be provided on a label. In general the level of information required increases with the classification of a medical device. More complex and higher risk devices require more information to be provided to facilitate the safe use of the device.

Contact details to be provided with a medical device:

- Name of the manufacturer and sponsor with the address must be provided with a medical device.
- The address is given and the physical location with sufficient detail to enable the physical location of the manufacturer and sponsor determined by the user of the device. A post office box address alone is not sufficient. Internet and email addresses are not considered to be physical locations.

Implanted devices:

The user of an implanted device may be considered to be both the:

Recipient of the device—the person who has the device implanted in his or her body.

The health professional that implants the device.

Table 3: Implanted device labeling requirements

Type of Device	Information	Examples
All Implantable Devices	Manufacturers should, wherever practical, provide information to the recipient about: The materials the device is made from The model and manufacturer If the device might trigger security screening machines (for example at airports) Whether there will be safety issues if a MRI machine is used on the recipient	Bone plates Bone Screws Staples Tissue Adhesive Sutures
Device with Electronic and Mechanic Action	For all implantable devices manufacturers should provide device registrations cards or similar documentation to the recipient, providing information about the implant, the manufacturer and the sponsor	Active Implantable Devices Heart valves
Devices that contain a medicine	For all implantable devices manufacturers should provide details of the medicine, in case of: hazard alerts adverse drug interactions between drugs in/on the device and other medicines the recipient may be taking or need to take Any contra-indications, warnings, restrictions, or precautions that may apply in relation to use of the device	Drug Eluting Stents and leads

INTRODUCTION OF MEDICAL DEVICE IN SINGAPORE [6]:

- Singapore, a small island nation in the South China Sea with a population of 5.5 million, has recently become a hot spot for sophisticated pharmaceutical research and manufacturing. In 2013, the country had average purchasing power parity (PPP) per-capita GDP of over $61,000, about $10,000 more than in the U.S.
- Singapore's chief medical regulatory body is the Health Sciences Authority (HSA). In 2007, the HSA passed the Health Products Act, allowing them to conduct mandatory product registration and regulate the supply, distribution, manufacturing, import, and advertisement of all health products. Registered medical devices are listed on the Singapore Medical Device Register (SMDR).
- The Singapore Medical Device Register (SMDR) is a database of all medical devices registered for use in human being under the Health Product Act (Medical Device Regulation). The register also includes medical devices registered with HSA before 31 March 2007 under the Voluntary Product Registration Scheme (VPRS) and evaluated in accordance to VPRS requirements. The SMDR is opened to all.

HSA REGULATION OF MEDICAL DEVICE [7, 8]:

- Currently, medical device product registration is voluntary in Singapore. (However, a few select types of devices, such as contact lenses and radiation-emitting devices, do require registration but are regulated by specific

guidelines, under the Contact Lens Practitioners Act and Radiation Protection Act, respectively).

- The Center for Medical Device Regulation (CMDR) regulates the voluntary registration system, which was introduced in April 2002. While the HSA has not yet implemented measures for a mandatory registration system, this voluntary scheme was established to keep up with the global trend of regulating and controlling medical devices through pre-market evaluation, manufacturing controls, and post-market surveillance. The CMDR encourages medical device companies to voluntarily register their devices. This process allows both the industry members and government officials to become more familiar with the system and also address any potential complications or "hang-ups" prior to the implementation of the system. An application to register a device should be submitted by a local representative in Singapore, who is a natural or legal person established in the country, and has been specifically designated to act on behalf of the medical device company.

Classification of medical device in Singapore:

Table 4: Classification of medical device in Singapore

Class	Risk Level	Device Examples
Class-A	Low Risk	Surgical retractors, Tongue depressors, Bandage, Walking aid
Class-B	Low-Moderate Risk	Hypodermic needles, Suction equipment
Class-C	Moderate-High Risk	Lung ventilator, Bone fixation plate
Class-D	High Risk	Heart valve, Pacemaker, Implantable defibrillator

Medical device registration process in Singapore [7, 8]**:**

- Before a device dossier or product registration application is submitted, the HSA must initially verify that the product qualifies as a medical device under the Health Products Act. Once it is confirmed to be a medical device, the application process can begin. There are four types of medical classes: A, B, C, and D. Class A devices are lower risk while Class D devices are higher risk medical products.
- Currently, class A devices do not require companies to submit a dossier for review. However, class B, C, and D products require a properly-formatted dossier detailing product information and evidence from clinical research. A medical device consultant can help you determine what is needed for compliance with HSA standards.
- Registration is electronic, via the Medical Devices Information and Communication System (MEDICS). Submissions are in English, according to the ASEAN Common Submission Dossier Template (CSDT) format. In general, devices that have already been registered with certain international regulatory agencies -- such as the EU, Japanese PMDA, or the U.S. FDA could qualify for an abridged, expedited or immediate registration in Singapore.

Class B, C, and D medical device registration process:

- For class B, C, and D medical devices, two evaluation routes are available: Abridged and Full. If the product has been evaluated and approved in at least one of the GHTF founding members (Australia, Canada, E.U., Japan and U.S.), it is likely eligible for the abridged evaluation. Abridged routes allow summaries for certain sections in the registration application. The product must, however, be the exact same (i.e. identical packaging, labeling, etc.). All other class B, C, and D medical devices must undergo the full evaluation route: online application submission through MEDICS, screening by HSA (ensuring all necessary parts are present), acceptance notice by HSA, review by HSA, and finally an evaluation decision and "regulatory decision."
- The CSDT includes sections on essential principles and evidence of conformity, device description, intended uses, indications, instructions of use, contraindications, warnings, precautions, potential adverse effects, alternative therapy, materials, other relevant specifications, other descriptive information, summary of design verification and validation documents, pre-clinical studies, software verification and validation studies, clinical evidence, results of

risk analysis, samples of labeling, and manufacturing information.

LABELING REQUIREMENTS [7, 8]:

Primary and secondary levels of packaging:

Contact Information: It is mandatory to include the name and contact details (address and/or phone number and/or fax number and/or website address to obtain technical assistance) of the Product Owner on the labeling.

The labeling for all medical devices should bear the following:

- Sufficient details for the user to identify the device and, where these are not obvious, its intended purpose, user and patient population of the device; also, where relevant, the contents of any packaging.
- An indication of either the batch code/lot number (e.g. on single-use disposable devices or reagents) or the serial number (e.g. on electrically powered medical devices), where relevant, to allow appropriate actions to trace and recall the devices.
- An unambiguous indication of the date until when the device may be used safely, expressed at least as the year and month (e.g. on devices supplied sterile, single-use disposable devices or reagents), where this is relevant. Where relevant, the storage conditions and shelf life following the first opening of the primary container, together with the storage conditions and stability of working solutions. For devices other than those covered by the above, and as appropriate to the type of device, an indication of the date of manufacture. This indication may be included in the batch code/lot number or serial number.
- The information needed to verify whether the device is properly installed and can operate correctly and safely, including details of the nature, and frequency of preventative and regular maintenance, where relevant any quality control, replacement of consumable components, and calibration needed to ensure that the device operates properly and safely during its intended life**.**
- Any warnings, precautions, limitations or contra-indications.
- The performance intended by the product owner and, where relevant, any undesirable side effects.
- An indication on the external packaging of any special storage and handling conditions that applies.
- Details of any further treatment or handling needed before the device can be used (e.g. sterilization, final assembly, calibration, preparation of reagents and/or control materials, etc.) where relevant.

CONCLUSION

Registration and Regulation of medical device is the important aspect for the Regulatory Agency of the different countries. Each and every country has developed his own guidelines for the regulation of Medical Device. Medical Devices are classified in to different classes as per their Risk based assessment. US is the developed nation it has 3 major classes of medical device and Australia also has his own classification based on hazardous nature of the device whereas Singapore is the developing nation in the Asian region it follows the GHTF requirements for the medical device registration. Now a days Singapore is the fast emerging market in the Asian region so it requires more and strict guidelines over the registration procedure for medical devices. In Singapore the registration procedure for the Class-D is not so much strict compare to US and Australia.

ACKNOWLEDGEMENT

The authors are thankful to Dr. K. Pundarikakshudu, Director of L. J. Institute of Pharmacy, Ahmedabad, India for providing all the facilities and encouragement to carry out the work.

REFERENCES:

1. U.S. Food and Drug Administration. PMA Submission Process (FDA); 1997. Medical Devices [cited 2015 Feb 13]; [about 37 p.]. Available from: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm
2. U.S. Food and Drug Administration. Pre-market Approval (FDA); 1997. Medical Devices [cited 2015 Feb 13]; [about 13 p.]. Available from: http://www.fda.gov/Medicaldevices/Deviceregulationandguidance/Howtomarketyourdevice/Premarketsubmissions/Premarketapprovalpma/Default.Htm
3. Douglas P, David M. FDA Regulatory Affairs. 2nd ed. Informa Healthcare: 2008. p. 125-166.
4. Australian Government Department of Health. Australian regulatory guideline for medical devices (ARGMD); 2011. Medical Devices and IVD's [cited 2015 Feb 13]; [about 4 p.]. Available from: https://www.tga.gov.au/publication/australian-regulatory-guidelines-medical-devices-argmd

5. Australian Government Department of Health. Australian Medical Device Guidance Document Number 25 (TGA); 2011. Medical Devices and IVD's [cited 2015 Feb 13]; [about 12 p.]. Available from: https://www.tga.gov.au/docs/pdf/devguid25.pdf
6. Pacific bridge.com. Singapore: Introduction of Singapore; [updated 2014 Feb 25; cited 2015 March 4]. Available from: http://www.pacificbridgemedical.com/publications/Singapore/.
7. Sidley.com. Singapore: Regulation of Medical Device; [updated 2011 Jun 9; cited 2015 March 4]. Available from: http://www.sidley.com/news/new-age-of-singapores-regulations-of-medical-devices-06-09-2011
8. Health Science Authority. Singapore Medical Device Register (smdr@medics); 2007. Medical Device Registration [cited 2015 March 4]; [about 3 p.]. Available from: http://www.hsa.gov.sg/content/hsa/en/Health_Products_Regulation/MEDICS_e-Services/Singapore_Medical_Device_Register_smdr_MEDICS.html