Review Article

Comparison of Registration Process of Foreign Medical Device Manufacturers in India, UK and Japan

Syed Mumeena*, AE. Prabhar, K. Vijay Kumar and Rama Rao Nadendla

Department of Pharmaceutical Management and Regulatory Affairs, Chalapathi Institute of Pharmaceutical Sciences, Lam Guntur, Andhra Pradesh, India.

ABSTRACT

The purpose of this study is to elucidate the importance of medical devices, regulatory requirements for the registration of foreign medical device manufacturers and to compare the regulatory process for the registration of medical device manufacturers in India, Japan and UK. One of the major issues for companies developing and producing medical devices is to be updated on the regulatory requirements and implement them in the process. One of the major reasons that companies want to register them in different countries is to expand their business. India is now an emerging country in which most of the research and development is going on and it is the important step to survive in the competition, Japan is a developed country in which using of medical devices is more due to increased ratio of aged people, UK is also having good market for medical devices as it was a developed country. But three of these countries had different regulations to maintain the quality of medical devices marketing in their countries.

INTRODUCTION

1.1 Medical devices

The term “medical devices” cover a vast range of equipment, from simple tongue depressors to haemodialysis machines. regulatory systems to place emphasis and initial resources on areas such as vendor and device registration, training, and surveillance and information exchange systems on the assessment of medical devices in use. WHO is reinforcing its role in providing technical support to Member States who wish to implement improved medical device regulatory systems. [1]

1.2 Global overview of medical device market

The global medical device industry has experienced significant growth over the last five years and is expected to continue, reaching approximately US $302 billion in 2017 with a CAGR of 6.1% during next six years (2011-2017).The medical device industry is comprised of surgical, cardiovascular, home healthcare, general medical and other devices.

As per the study, technological advancements may lead to nanotechnology applications and use of surgical robots as a new segment entering the medical device industry. These new segments are expected to improve the prospects for the market.[1]

1.3 The Global Harmonization Task Force has proposed the following harmonized definition for medical devices

“Medical device” means any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purposes of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease
- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury
- Investigation, replacement, modification, or support of the anatomy or of a physiological process
- supporting or sustaining life
- Control of conception
- Disinfection of medical devices

• providing information for medical purposes by means of *in vitro* examination of specimens derived from the human body
And activities that are most commonly subjected to regulation. [2]

1.4 Phases in the life span of a medical device

Fig. 1: Phases in the of lifecycle of medical device

We can control these critical phases by relating them to the government regulations as illustrated in the below figure.

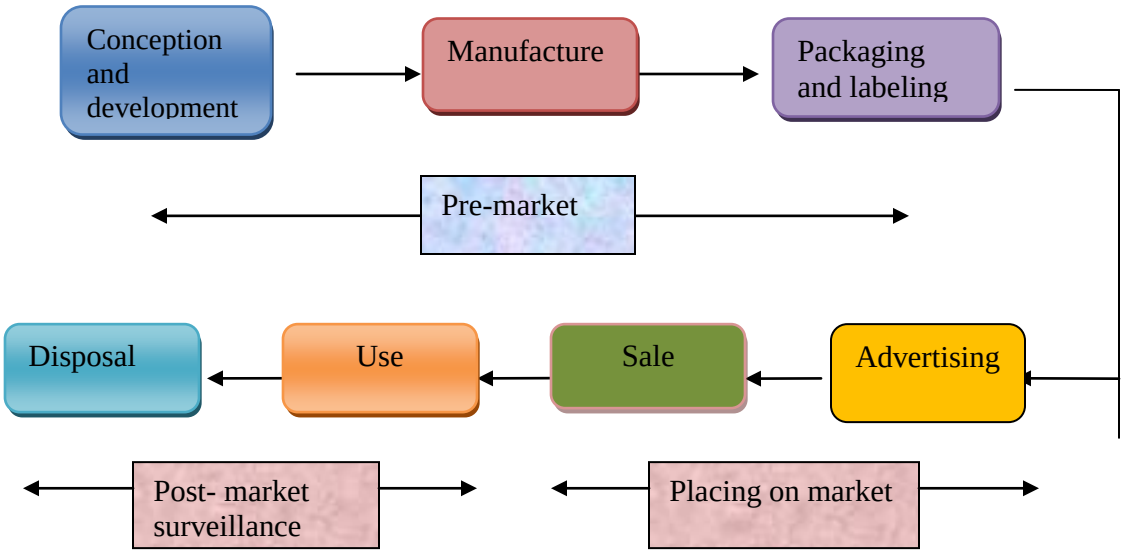

Fig. 2: Common stages of government regulations of medical devices.[4]

1.5 MEDICAL DEVICE MARKET IN INDIA

India is one of the largest medical device markets in Asia, and growing at an impressive 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. Medical device market is currently the fourth largest market in Asia with 700 medical device makers, and ranks among the top 20 in the world, according to data from the India Semiconductor Association.

Based on purchasing power parity, India represents the third-largest global economy. Before manufacturers can legally sell medical devices within India, they must be in compliance with India medical device regulations.[5]

1.5.1. India's medical device regulations overview

During the medical device registration process, the primary entity we work with is the Medical Devices Division of the CDSCO. The hierarchy of medical device regulatory entities in India is as follows:

→ Ministry of Health and Family Welfare
Drug Controller General of India - DCG (I)
Central Drugs Standard Control Organization (CDSCO - Medical Devices Division)[06]

1.6.1. MEDICAL DEVICE MARKET IN UK

The UK medical device market is valued at $9.9 billion in 2008 and thus placing this market as the third largest in Europe behind Germany and France. The NHS, the biggest consumer of medical devices, places barriers that might make it difficult for small companies to access the procurement rules, large scale requirements and pricing policy. In addition NHS hospitals are slow in adapting innovative medical technology.[7]

1.7.1. U.K's medical device regulations overview

The Medicines and Healthcare Products Regulatory Agency (MHRA) is a UK government agency which is responsible for ensuring that medicines and medical devices work and are acceptably safe medical devices. The MD Regulations set out the minimum standards for the manufacture and marketing of medical devices in the UK. The designated body for overseeing compliance with the MD Regulations is the Medicines and Healthcare Products Regulatory Agency (MHRA), an executive agency of the Ministry of Health.[8, 9]

1.6 MEDICAL DEVICE MARKET IN JAPAN

Japan is the third largest economy in the world behind the USA and China. The medical device market remains the second largest, behind only the USA. Japan's medical device market is projected to expand at a CAGR of 2.5% in the 2013-2018 periods, which should see it grow from an estimated US$29.8bn in 2013 to around US$33.6bn in 2018. Due to exchange rate differences, actual growth, when measured in local currency terms, is expected to be higher, at 3.1% during the forecast period.[10]

1.6.1. Japan's medical device regulations overview

The distribution of medical devices in Japan is regulated in accordance with the Japanese Pharmaceutical Affairs Law (JPAL) by the Ministry of Health, Labor and Welfare (MHLW) is in charge of safety, efficacy and quality of medical devices sold in Japan. a business license is required for all medical device manufacturers in the country and a company with this license is called a Marketing Authorization Holder (MAH). The MAH will then file regulatory approval applications for devices based on their type and classification.[10]

OBJECTIVES

The objectives of this work are to,

- Analyze the market scenario with respect to the approvals of medical devices.
- Explore the basic regulatory requirements of medical devices in selected countries –India, UK and Japan.
- Study and understand the approval process of medical devices by respective regulatory bodies in selected countries.

- Study the challenges faced by medical device sector selected countries in the medical device sector.
- Compare the organization, functions and registration procedures of the regulatory authorities of India, UK and Japan.

METHODOLOGY

The study was organized into 4 steps to achieve the objectives

1. Type of study
2. sources of data
3. comparison of regulatory concerns
4. Study process

1. TYPE OF STUDY

This is a comparative study, where effort has been made to study, compare and provide recommendations on harmonization of the regulatory framework for the approval of medical devices in India, Japan and UK.

2. SOURCES OF DATA

- Journal Articles published in peer-reviewed publications
- Websites of various regulatory agencies and organizations
- Guidelines and guidance documents issued by the regulatory authorities of the countries included in the study.
- Records and databases of various regulatory agencies

3. COMPARISON OF REGULATORY CONCERNS

Comparison mainly involved 4 phases

1. Comparison of general regulatory requirements.
2. Comparison of classification
3. Comparison of regulatory submission phase.
4. Comparison of approval regulatory requirements.

4. STUDY PROCESS

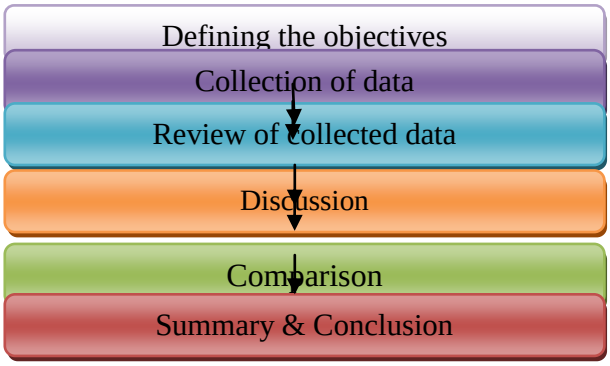

Fig. 3: Study process

DISCUSSION

5.1. MEDICAL DEVICE REGISTRATION IN INDIA

The lack of healthcare infrastructure, the government's plans mark an opportunity for private investors, and manufacturers of medical devices, as new facilities are constructed and existing ones are upgraded. Detailed regulation of medical devices is still under consideration[20].

In 2005, the Ministry of Health and Family Welfare (MOHFW) vide 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 manufacture under Section 3(b) (iv) (defined below) of the D&C Act. [21]

Definition

According to drugs and cosmetics act: Notified Medical Devices are currently covered under the definition of Drugs under the Act under Section 3 (b) (iv) which reads as follow:-

"b) "Drug" includes—

...(iv) such devices 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 "[23]

At present following notified Medical Devices are regulated under the said Act[22]

Table 1: List of notified medical devices

S.NO	NAME OF DEVICE
1	Disposable Hypodermic Syringes.
2	Disposable Hypodermic Needles.
3	Disposable Perfusion Sets.
4	Cardiac Stents.
5	Drug Eluting Stents.
6	Catheters.
7	Intra Ocular Lenses.
8	I.V. Cannulae.
9	Bone Cements
10	Heart Valves.
11	Scalp Vein Set.
12	Orthopedic Implants.
13	Internal Prosthetic Replacements.
14	In vitro Diagnostic Devices for HIV, HBsAg and HCV

Further the following products are regulated as “Drugs” under Drugs and Cosmetics Act and Rules there under which are considered as ‘Medical Device’ in the Country of Origin.

1. Blood Grouping Sera
2. Ligatures, Sutures, Staples
3. Intra Uterine Devices (Cu-T)
4. Condoms
5. Tubal Rings
6. Surgical Dressing
7. Umbilical Tapes
8. Blood / Blood Component Bags

The definition of "drugs" as specified under Section 3(b)(iv) of the Drugs and Cosmetics Act, 1940.[22,24]

According to the drugs and cosmetics (amendment) bill, 2013,

“Medical device means”-(i)Any instrument, apparatus, appliance, implant, material or other article, whether used alone or in combination, including the software, intended by its manufacturer to be used specially for human beings or animals for one or more of the specific purposes of,—

- **A. Diagnosis, prevention, monitoring, treatment or alleviation of any disease or disorder;**
- **B. Diagnosis, monitoring, treatment, alleviation of, or assistance for, any injury or handicap;**
- **C. Investigation, replacement or modification or support of the anatomy or of a physiological process;**
- **D. supporting or sustaining life;**
- E. **disinfection of medical devices**;
- **F. control of conception, And which does not achieve its primary intended action in or on the human body or animals by any pharmacological or immunological or metabolic means, but which may be assisted in its intended function by such means;**

(ii) An accessory to such an instrument, apparatus, appliance, material or other article;

(iii) a device which is reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system whether used alone or in combination thereof intended to be used for examination and providing information for medical or diagnostic purposes by means of invitro examination of specimens derived from the human body or animals;

(iv) Any new medical device. [23]

5.1.1.REGULATORY BODY(CDSCO) [25, 26]

5.1.1.REGULATORY BODY(CDSCO) [25, 26]

Medical device regulation, prior to sale, is relatively new in India, although pharmaceuticals have been regulated by the Central Drug Standard Control Organization (CDSCO) since 1940, under the Ministry of Health and Family Welfare.

Mission

To safeguard and enhance the public health by assuring the safety, efficacy and quality of drugs,cosmetics and medical devices.

Major functions

1. Regulatory control over the import of drugs,
2. Approval of new drugs and clinical trials,
3. Meetings of Drugs Consultative Committee (DCC) and Drugs Technical Advisory Board (DTAB),
4. Approval of certain licenses as Central License Approving Authority is exercised by the CDSCO hqrs.

5.1.2 REGULATORY FRAMEWORK[27]

At the moment, in India there is no single comprehensive specific law regulating medical devices. The import, manufacturing, sale and distribution of medical devices are regulated under the Drugs and Cosmetics Act, 1940 (India Act), the Drugs and Cosmetics Rules, 1945 (Rules); and the Central Drugs Standard Control Organization (CDSCO), under the Ministry of Health and Family Welfare (Ministry) is the principal regulator.

The Drugs Technical Advisory Board, which provides technicalguidance to CDSCO, proposed certain changes in the Rules, which among others provides a categorization of medical devices.

5.1.3CLASSIFICATION OF MEDICAL DEVICES[23,24]**:**

According to the new updated bill this classification is based on the risk level,

Class A: Low risk devices and equipment such as thermometers and tongue depressors;
Class B: Low to moderate risk devices including hypodermic needles and suction equipment;
Class C: Moderate to high risk equipment like lung ventilators and bone fixation plates; and
Class D: High risk devices such as heart valves and implantable defibrillators.

5.1.4. REGULATORY REQUIREMENTS[28]

The basic regulatory requirements must comply with foreign medical device manufacturers are:

1. India authorized agent
2. Understanding the Indian regulatory process
3. Requirements for the common submission format for the registration of medical devices in India
4. Import license

5.1.4.1. India authorized agent

Foreign Medical device companies that require registration in India must appoint an agent responsible for pre-certification and post-market surveillance inquiries.

→ ***Roles and responsibilities***[29]

- The India Authorized Agent is a person/company responsible for device registrations, acting as the liaison between the manufacturer and the Medical Devices Division of the CDSCO (Central Drugs Standard Control Organization).
- Foreign manufacturers of medical devices that are on the list of regulated devices must appoint an Indian Authorized Agent.
- In addition to being a resident of India, the India Authorized Agent representative must have prior experience in the industry, for example, as a medical doctor or pharmacist.
- The India Agent has significant responsibilities and is also legally liable for the product in India.

▪ The India Authorized Agent is granted, through Power of Attorney by the manufacturer, authorization to submit medical device registration documents and act as a point of contact for any inquiries related to the device by the CDSCO.

▪ The Agent is also involved in vigilance activities and acts on the manufacturer's behalf if an onsite inspection of the manufacturer's facility is required.

5.1.4.2 Understanding the Indian regulatory process[21, 23,27]

▪ India has no specific regulations for medical devices except Implantable Devices, Critical Diagnostic Kits and other Sterile Devices. The list of products falls under this category are notified and these products are also called as drug and a valid license is required to start commercial production.

5.1.4.3. Requirements for the common submission format for the registration of medical devices in India[30]

1. Covering letter:

2. Authorization Letter

3. Form 40: -A duly filled Form 40as per the Performa prescribed in the Drugs & Cosmetics Rules, signed & stamped by the Indian Agent along with name & designation[30].

4. Power of attorney: - The authorization by a manufacturer to his agent in India shall be documented by a Power of Attorney executed and authenticated either in India before a First Class Magistrate,

- It should be valid for the period of said Registration Certificate[30]

5. Requisite fee: -

(A) Schedule D (I):

- Particulars of the manufacturer and manufacturing premises
- Particulars of manufactured medical devices to be registered under the registration certificate
- Undertaking declaration.

(B) Plant Master File: -The manufacturer shall submit the duly signed and notarized information pertaining to manufacturing premisesconsists of following details.

- General information
- Personnel
- Premises and facilities
- Equipment
- Sanitation
- Production
- Quality controls
- Storage
- Documentation
- Medical device complaints and field safety corrective action
- Self inspection
- Contract activities

For the format of plant master file-

A duly filled Schedule D (II) as per the Performa prescribed in the Drugs & Cosmetics Act & Rules,

(A) **Executive summary (Not more than three A4 size pages):-** shall be provided by the manufacturer

- Introductory descriptive information on the medical device (the intended use and indication for use, Class of Device, novel features of the device (if any), Shelf Life of the Device and a synopsis on the content of the dossier).
- Information regarding Sterilization of the Device
- Regulatory status of the similar device in India
- Domestic Price of the device in the currency followed n the Country of origin Marketing History of the device from the date of introducing the device in the market.
- List of regulatory approvals or marketing clearance obtained
- Status of pending request for market clearance
- Safety and performance related information on the device

(B) Device description and product specification, includingvariants and accessories

- Device Description
- Product Specification
- Reference to predicate and/or previous generations of the device

(C) **Labelling**

(D) **Design and manufacturing information**

- Device design
- Manufacturing process

(E) **Essential principles (ep) checklist**

(F) **Risk analysis and control summary**

(G) Product verification and validation

8. Wholesale license: - issued by the State Licensing Authority[30].

1. **9. Free sale certificate:** - Free Sale Certificate should state that the proposed dev ice is freely sold in Country of Origin and can be legally exported[30].
2. **Manufacturing License/Plant Registration certificate:** - Duly notarized/ Apostilled/ Attested (by Indian Embassy the country of origin) and valid copy of the manufacturing license/ plant registration certificate[30].
3. **ISO 13485 Certificate:** - Duly notarized/Apostilled/Attested (by Indian Embassy in the country of origin) and valid copy of ISO 13485 Certificateinrespect of the foreign manufacturing site (s) [30].
4. **CE Full Quality Assurance Certificate:** - Duly notarized/Apostilled/Attested (by Indian Embassy the country of origin) and valid copy of CE full quality assurance certificate in respect of the foreign manufacturing site (s), if applicable[30].
5. **CE Design Certificate:** - Duly notarized/Apostilled/Attested (by Indian Embassy the country of origin) and valid copy of CE Design Certificatein respect of the proposed Device (s), if applicable[30].
6. **Declaration of Conformity: -** Duly notarized/Apostilled/Attested (by Indian Embassy the country of origin) and valid copy of **Declaration of Conformity** in respect of the proposed Device (s) [30].
7. **Inspection/Audit Report: -** Copy of latest **Inspection/Audit Report** carried out by Notified bodies/National Regulatory Authority/Competent Authority.

5.1.4.4. Import license[31]:-

After obtaining the Registration Certificate, a medical device importer can apply for an Import License from DCGI.

1. Covering letter
2. Authorisation letter
3. **Form 8**:- A duly filled **Form 8** (Application for license to import drugs (excluding those specified in Schedule X) to the Drugs and Cosmetics Rules, 1945) as per the Performa prescribed in the Drugs & Cosmetics Rules, signed & stamped by the Indian Agent along with name & designation of the authorized signatory.
4. **Form 9 :-** (Form of undertaking to accompany an application for an Import License) as per the Performa prescribed in the Drugs & Cosmetics Rules, signed & stamped by the Indian Agent along with name & designation of the authorized signatory or Duly Notarized, if Signed and stamped by the Manufacturer along with name & designation of the authorized signatory.
5. Requisite Fee
6. Wholesale License / manufacturing license
7. Registration Certificate.

5.1.5. REGISTRATION PROCESS[32]

→ Appoint an Indian authorized agent to interact with CDSCOon behalf of the foreign manufacturer the agent must possess a valid wholesale license(form20b and 20bA).

→ A foreign medical device manufacturer must submit the all the required documents to Indian authorized agent in order to get the approval for the registration of medical devices in India

→ Power of attorney must be granted to the agent to manage the registration process in India.

→ File application for registration certificate to CDSCO using form-40 by submitting the supported documents.

→ CDSCO review's submitted documents and approves the registration certificate.

→ CDSCO grants registration certificate in FORM-41. Certificate is valid upto 3years.

→ If in case CDSCO was not satisfied by the submitted documents, it informs the applicant for clarifications.

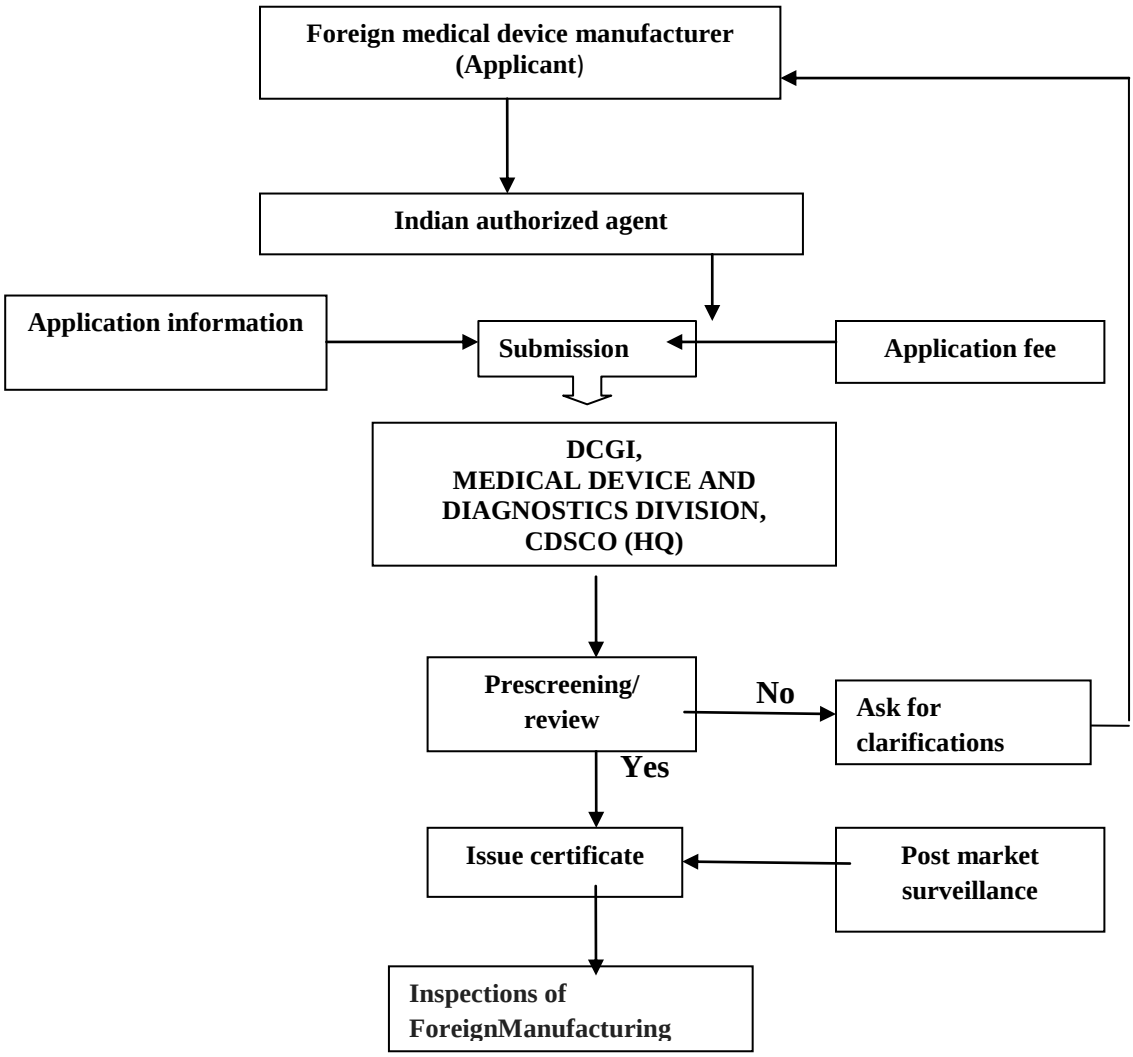

Fig. 7: Flow chart for medical device registration process in India

5.2. MEDICAL DEVICE REGISTRATION IN UNITED KINGDOM

Opportunity for importers: low elasticity of domestic suppliers to respond to changing demand. Threat for importers: The NHS, the biggest consumer of medical devices, places barriers that might make it difficult for small companies to access the procurement rules, large scale requirements and pricing policy. In addition NHS hospitals are slow in adapting innovative medical technology.[33]

Definition:

Article 1.2 of Directive 93/42/EEC (as amended)defines a medical device 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 purposes 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 disease,

- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,

- Investigation, replacement or modification of the anatomy or of a physiological process,

- Control of conception,

And which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means'.

5.2.1. REGULATORY BODY (MHRA)

The **Medicines and Healthcare Products Regulatory Agency** (**MHRA**) is a UK government agency which is responsible for ensuring that medicines and medical devices work and are acceptably safe.

The Medicines and Healthcare products Regulatory Agency was formed in 2003 with the merger of the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA).

In April 2013, it merged with the National Institute for Biological Standards and Control (NIBSC) and was rebranded, with the MHRA identity being used for the parent organization and one of the centers within the group

The MHRA is divided into three main centers:

- The National Institute for Biological Standards and Control (NIBSC),
- The Clinical Practice Research Data link (CPRD).
- MHRA Regulatory (the regulator for the pharmaceutical and medical devices industries)

MHRA aims and objectives

Aims

- Protecting public health through regulation, with acceptable benefit-risk profiles for medicines and devices.
- Promoting public health by helping people who use these products to understand their risks and benefits.
- Improving public health by encouraging and facilitating developments in products that will benefit people.

Objectives

- safeguard public health through our primary role in ensuring that the products we regulate meet required standards, that they work and are acceptably safe
- carry out our communication role through the provision of accurate, timely and authoritative information to healthcare professionals, patients and the public
- support research, ensuring through the application of Better Regulation principles that regulation does not stifle innovation
- influence the shape of the future regulatory framework through use of our effective European and International relationships
- Run an organization with a skilled and equipped workforce that is fit for the future.

Organization chart of MHRA:

A high-level organization chart of the MHRA is as follows,

Corporate executive team

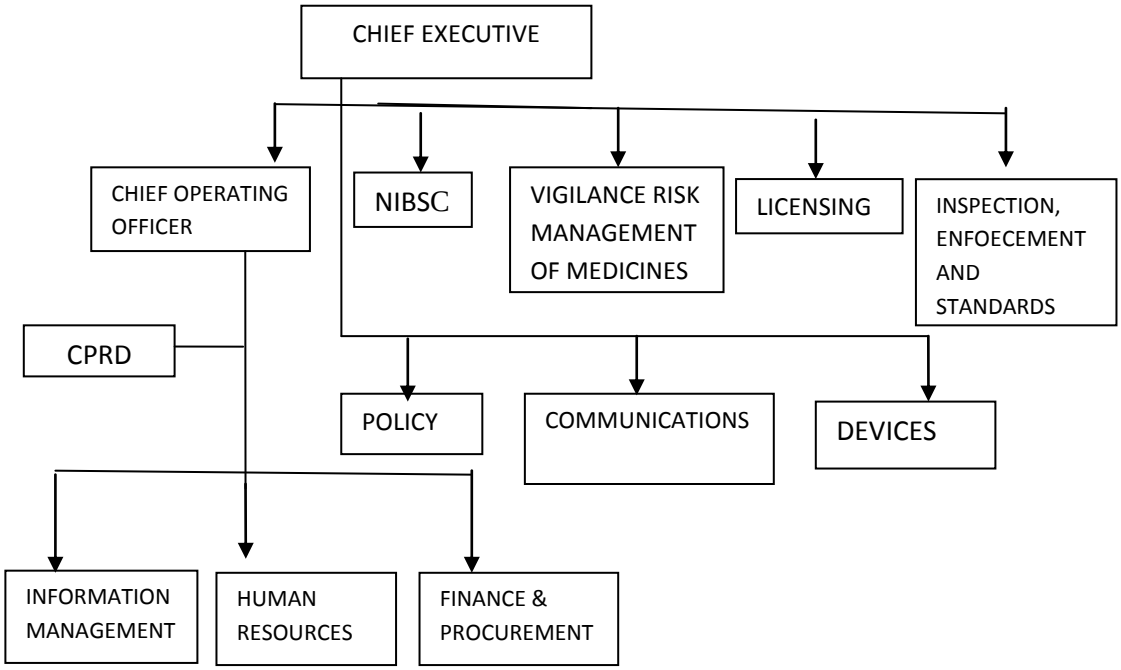

Fig. 8: Organization chart of MHRA

5.2.2. REGULATORY FRAMEWORK

- Each member state of the EU implements the Directives into their own national law; in the UK these are the Medical Devices Regulations 2002 (as amended) and they are issued under the Consumer Protection Act 1987.
- **"EU regulations apply directly to the UK and do not need to be transposed".**

The directives regulating medical devices in UK are as follows:

1. **Directive 93/42/EEC (The GeneralMedical Devices)**[34]:- Covers most other medical devices, ranging from, for example, first aid bandages, tongue depressors, hip prostheses, X -ray equipment, ECG and heart valves. It was the second medical device directive implemented in 1993.This directive contains 23 Articles and 12 Annexes which are as follows;
   a. Annex I lists 14 essential requirements and 54 subsets;
   b. Annexes II to VII describe six different routes to acquiring the CE marking;
   c. Annex VIII applies to custom-made devices;
   d. Annex IX outlines criteria for classifying medical devices;
   e. Annex X covers clinical evaluation;
   f. Annex XI describes the designation of Notified Bodies (NBs); and,
   g. Annex XII illustrates how the CE marking should be applied.

5.2.3. CLASSIFICATION OF MEDICAL DEVICES[33,35]

Medical devices are mainly classified into 4 types according to the medical device directive 93/42/EEC. Classification rules are listed in Annex IX of the directive

The classification determines which conformity assessment procedure the manufacturer must follow in accordance with the Annexes II, III, IV, V, VI and VII of the MDD.

Class I: This group covers low-risk devices. This type of classification includes devices that do not penetrate the body and the conformity assessment procedures are carried out by the manufacturer. There is no need for a Notified Body for class I devices.

E.g.: - Bandages, hospital beds, sterilization packaging, and dental mirrors.

Class IIa: These are low-medium risk devices. The intervention of a Notified Body is compulsory at the production stage for class II a devices.

E.g. Anesthetic gas masks, acupuncture needles, oxygen masks and spirometer peak flow meters.

Class IIb: These are medium-high risk devices these require inspection by a Notified Body with regard to the design and manufacture of the device.
E.g. Surgical lasers, infusion pumps (non-implantable), ventilators, intensive care monitoring equipment.
Class III: This group covers the most critical devices for which explicit authorization with regard to conformity is required before commercialization
E.g. Balloon catheters, prosthetic heart valves.
Classification of a medical device will depend up on a series of factors, including:

a. How long the device is intended to be in continuous use
b. Whether or not the device is invasive or surgically invasive, whether the device is implantable or active
c. Whether or not the device contains a substance, which in its own right is considered to be a medicinal substance and has action ancillary to that of the device.

CE MARKING

Before marketing a medical device within EU, the product should be marked with a CE (European conformity) mark. It is a legally binding statement by the manufacturer that their product has met all of the requirements of the Medical Devices Directive (MDD 93/42/EEC)where applicable. The Notified Body's four-digit number would appear below the CE Mark symbol. Once a medical device has been granted a CE mark in one Member State, it can be freely marketed within the entire European Economic Area (EEA)[36].

Fig. 9: CE mark symbol with notified body number

Notified body: A Notified Body is certification organization that the national authority (the Competent Authority) of an EU Member State designates to carry out one or more of the conformity assessment procedures described in the annex(es) of the EU Directives. It must be qualified to perform all the functions set out in any annex for which it is designated[45].

Procedure to obtain CE marking is follows

European Medical Devices Directives focus on the responsibility of the device manufacturers. Therefore CE marking for all medical devices requires among others a technical documentation, a risk analysis, a proof of compliance with the essential requirements of the directive and a product-related declaration of conformity issued by the manufacturer.

1. Selection of conformity assessment procedure
2. Essential requirements
3. Technical documentation
4. Clinical trials
5. Conformity assessment procedure
   a) EC type examination
   b) EC verification
   c) EC declaration of conformity (production quality assurance)
   d) EC declaration of conformity (product quality assurance)
   e) EC declaration of conformity (full quality assurance system)
6. Post-marketing surveillance and vigilance reporting

1. **Selection of conformity assessment procedure[34]**

Six conformity assessment routes for acquiring the CE marking are identified in Annexes II, III, IV, V, VI, and VII of the MDD. Each device class uses combination of these routes.
The conformity assessment routes do not apply to customer made devices or devices intended for clinical investigation, however they have to meet essential requirement.
Class I devices are the one with least risk. For products that are not sterile or do not measure anything manufacturer can self-certify these products by making your own declaration in

compliance with the Medical Device Directive (MDD) and can place the CE mark on product. If the product is either sterile or measures something, then a notified body gets involved for certification of sterility and measurements.

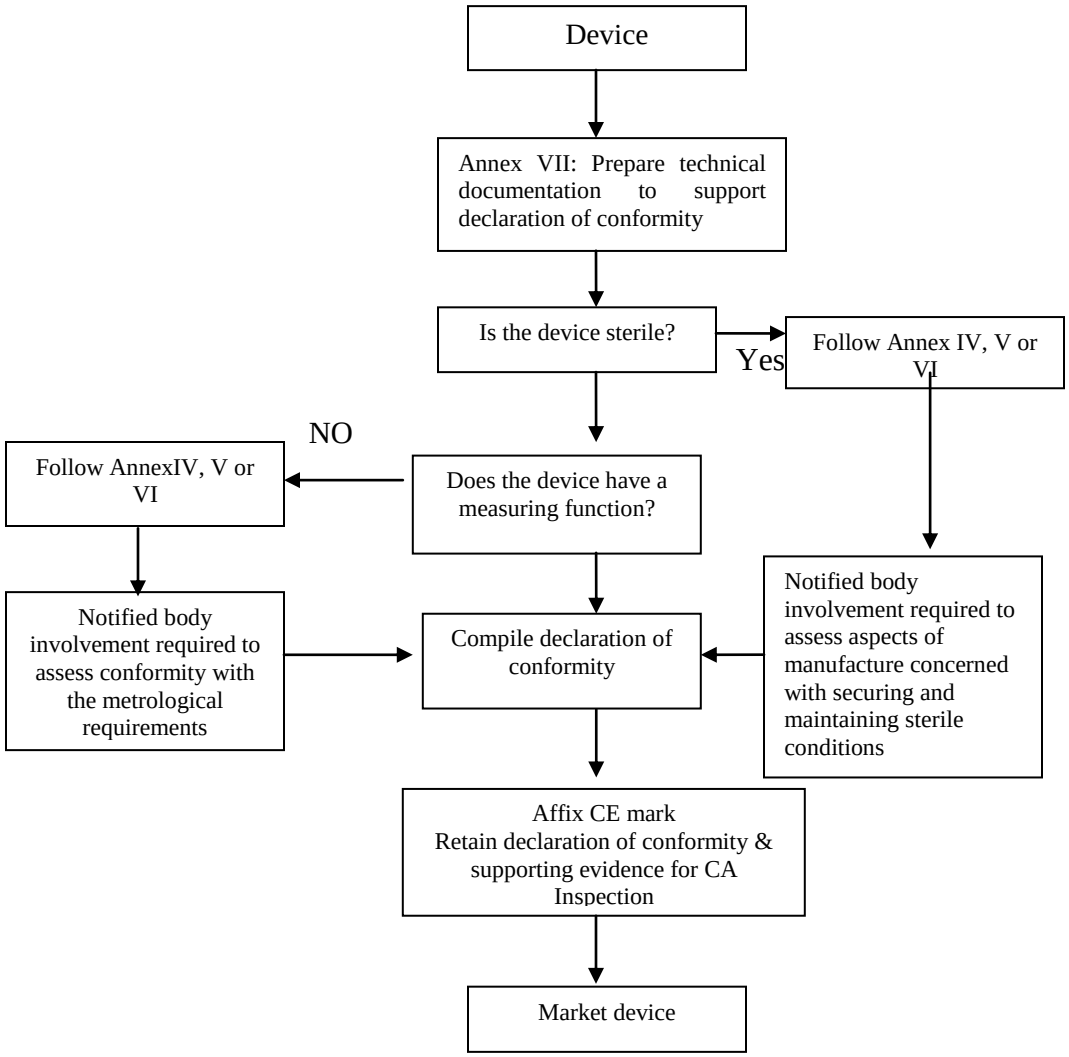

Fig. 10: CONFORMITY ASSESSMENT & ROUTE FOR CE MARKING OF CLASS I MEDICAL DEVICES[34,46]

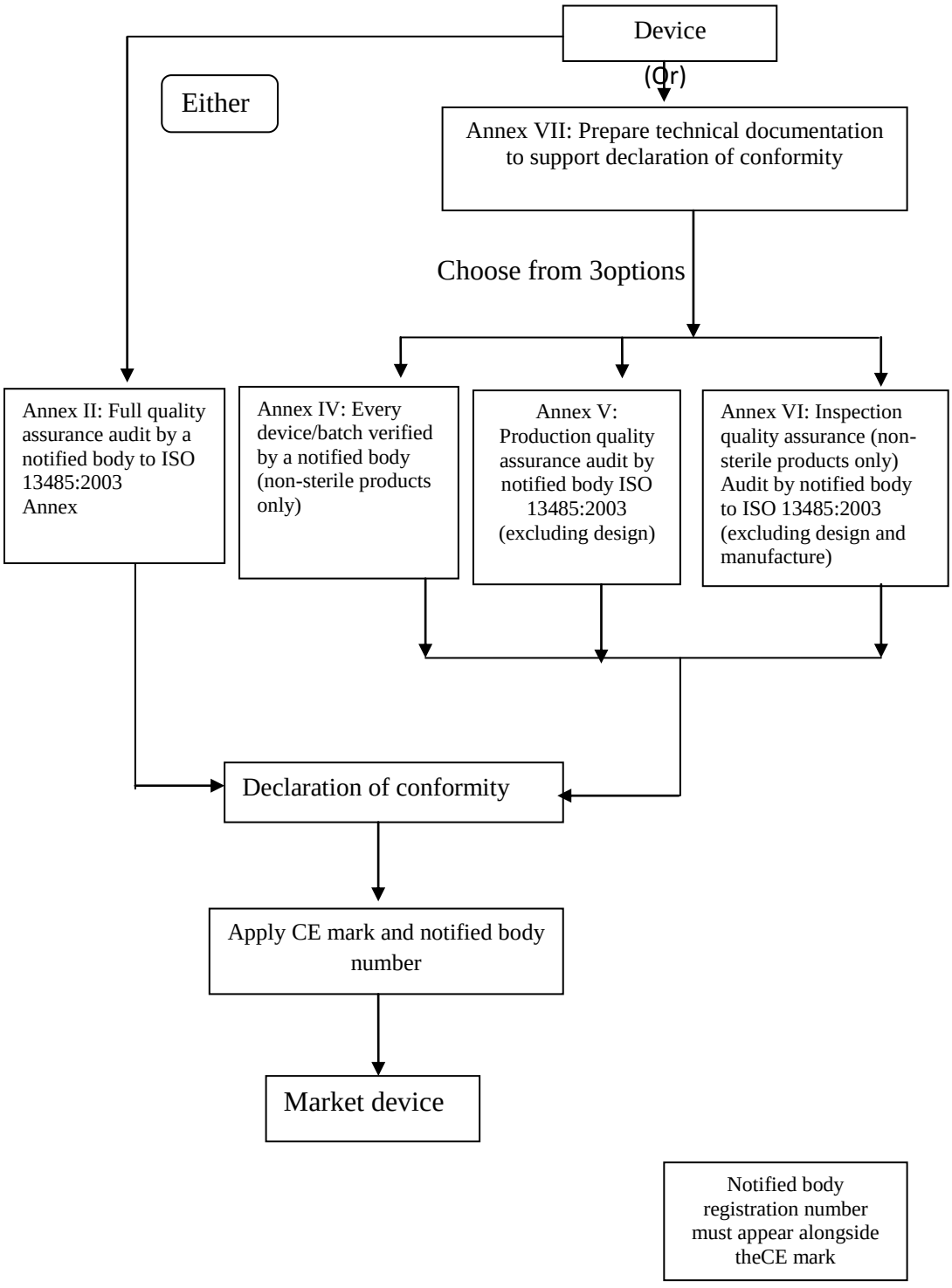

Fig. 11: CONFORMITY ASSESSMENT & ROUTE FOR CE MARKING OF CLASS IIa MEDICAL DEVICES[34, 46, 43]

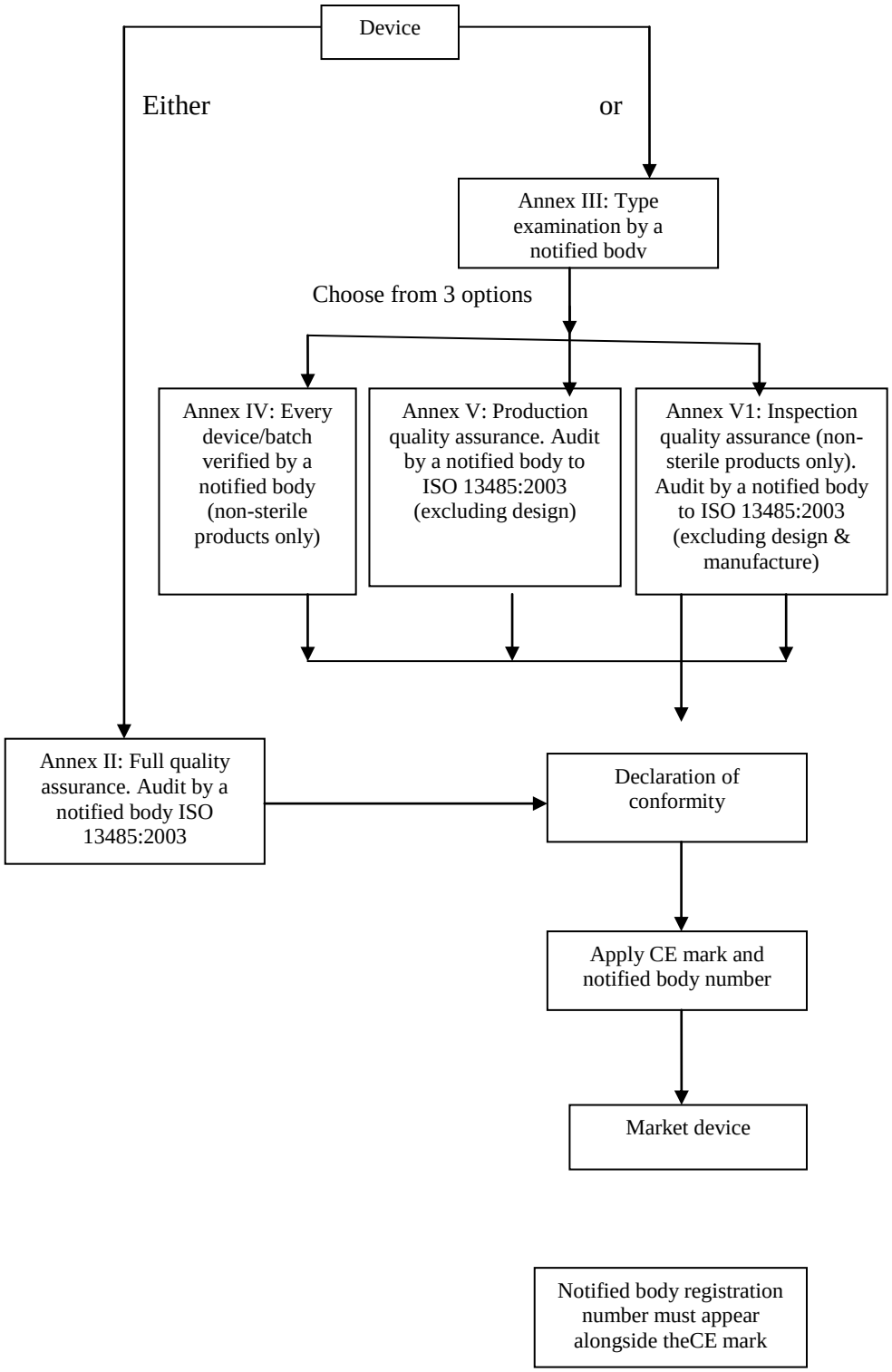

Fig. 12: CONFORMITY ASSESSMENT& ROUTE FOR CE MARKING OF CLASS IIb MEDICAL DEVICES[34, 46]

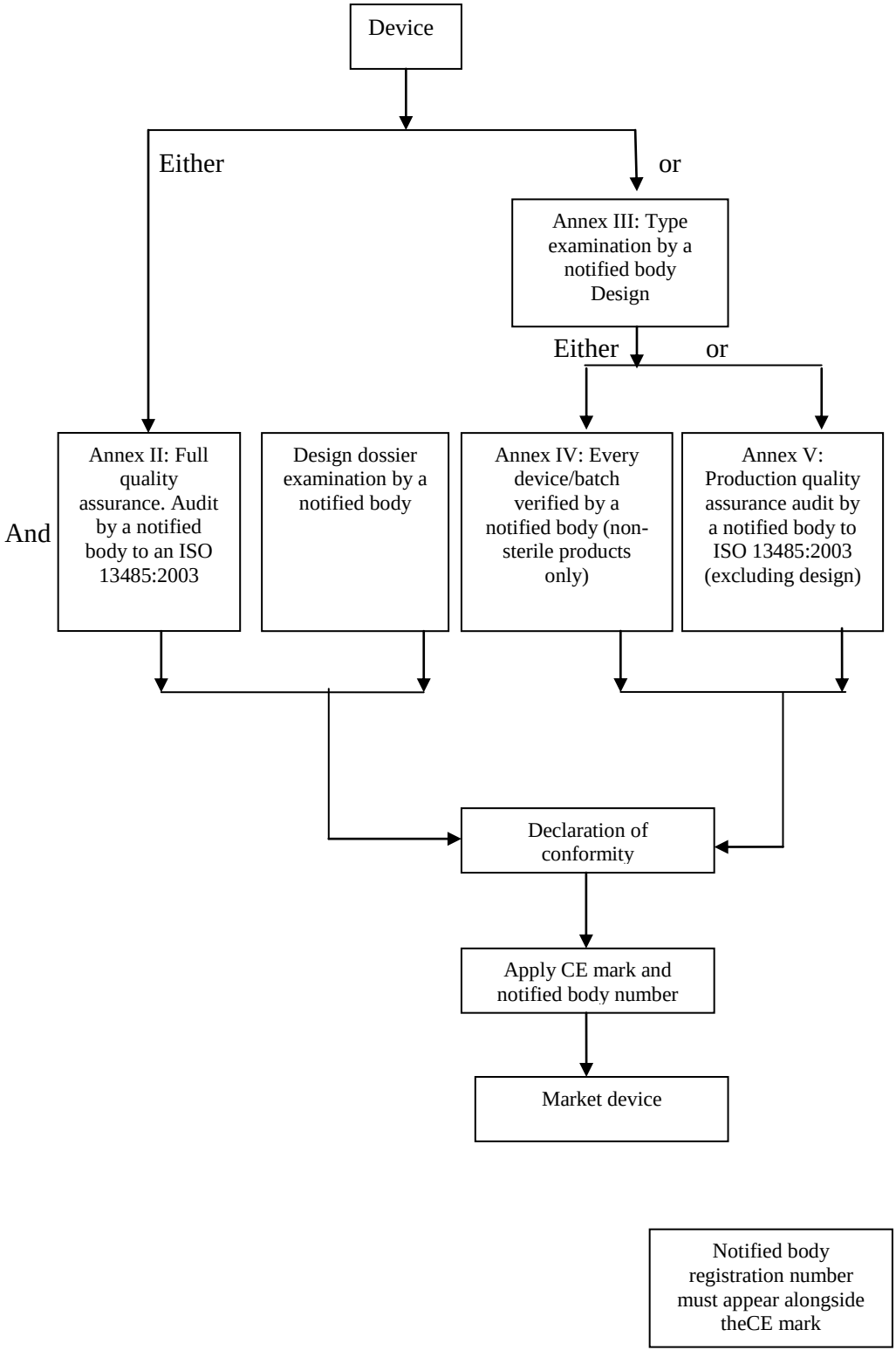

Fig. 13: CONFORMITY ASSESSMENT & ROUTE FOR CE MARKING OF CLASS III MEDICAL DEVICES[34, 46]

2. **Essential requirements**[34]

Essential requirements are mainly classified into two sections.

→ General requirements

→ Requirements regarding design and constructions

I. ***General requirements***[37]

- Devices must be designed and manufactured such that they will not compromise clinical condition or safety of the patients
- Design and construction of device must conform to safety principles
- Devices must be designed, manufactured and packaged such that they are suitable for the functions as specified by the manufacturer
- The characteristics and performance must not adversely affect the clinical conditions and safety of the patients
- Device must be designed, manufactured and packed such that characteristics and performance during the intended use will not be adversely affected
- Any undesirable side effect must constitute an acceptable risk when weighed against the performances intended

II. ***Requirements regarding***

A. Design and construction

- Chemical, physical and biological properties
- Infection and microbial contamination.
- Construction and environmental properties.
- Protection against radiation.
- Medical device equipped with energy source.

B. Labelling requirements

C. Quality requirements[38]

Manufacturer of a medical device must comply with the quality system requirements i.e. ISO 13485:2003, to apply for the CE marking. Following are the requirements of ISO 13485:2003

- Systemic Requirements
- Management Requirements
- Resource Requirements
- Realization Requirements
- Remedial Requirements

3. **Technical documentation**[39]

No matter whether the device is for clinical investigation, custom-made, class I, IIa, IIb or III, a technical documentation (device master file, technical file, design dossier) is always required. Particular requirements are given in the MDD, Annex II.3.2 (c) and 4.2, Annex III.3, Annex VII.3, and Annex VIII.3.1 and 3.2., Annex V.4.2 and Annex VI.4.2.

The recommended essential content of a technical file is as follows:

- A table of contents
- Manufacturer's declaration of conformity
- A general description of the device/device family, including any variants planned
- Design drawings, specifications, methods of manufacture, including method of sterilization and validation data
- Results of risk analysis
- Results of calculations and test reports
- Reference to applicable harmonized standards
- Evidence that the essential requirements have been met
- Clinical data
- Label and instructions for use
- Results of database researches and copies of relevant literature

STED FORMAT[40]

To harmonize the medical device regulations, Global Harmonization Technical Force (GHTF) published a guideline for technical documentation titled "Summary Technical Documentation for Demonstrating

Conformity to the Essential Principles of Safety andPerformance of Medical Devices (STED)". Contents of the STED as per the guideline are detailed.

1.Device description and product specification, including variants and accessories
- Device description
- Product specification
- Reference to similar and previous generations of the device

2.Labeling
- Labels on the device and its packaging;
- Instructions for use and
- Promotional material.

3. Design and manufacturing information
- Device Design
- Manufacturing Processes
- Design and Manufacturing Sites

4. Essential Principles (EP) checklist
5. Risk analysis
6. Product verification and validation

In addition, where applicable to the device, the STED should contain detailed information on

a. Biocompatibility
b. Medicinal substances incorporated into the device, including compatibility of the device with the medicinal substance
c. Biological safety of devices incorporating animal or human cells, tissues or their derivatives
d. Sterilization
e. Software verification and validation
f. Animal studies that provide direct evidence of safety and performance of the device, especially when no clinical investigation of the device was conducted
g. Clinical evidence

4. Clinical trials

All the manufacturers of medical devices must conduct clinical trials to assess the clinical safety or performance of the medical device evaluate whether the device is suitable for the purpose(s) and the population(s) for which it is intended. Depending on clinical claims, risk management outcome and results of clinical evaluation clinical investigation must be performed for devices of class I, IIa, IIb, III[41].

Contents of clinical trial application[42]

1**.** *Signed statements*
- Application must contain a statement that the device confirms to essential requirements
- Application must contain a statement indicating whether or not device incorporates human blood derivative
- For applications submitted under medical device directive 93/42/EEC must contain a statement whether device is manufactured utilizing tissues of animal origin

2. *General information*
- Date of submission
- Applicant's details
- Whether first submission or re-submission
- List of other member states participating in clinical investigation
- Confirmation of insurance of subjects

3. *Details of device*
- Identification details of the device
- Classification of the device
- Description of the device with drawings
- Summary of experience with any similar devices
- Risk benefit analysis
- Description of materials coming into contact with body
- Description of methods of manufacture

- Instructions for use
- Identification of any tissues of animal origin including details of sourcing and collection of animal tissues

4. *Clinical investigational plan*
   - Details of investigator
   - Name and address of institution where clinical investigation will be conducted
   - Copy of ethic committee opinion
   - Copy of informed consent
   - Copy of patient information sheet
5. *Investigation parameters and design*
   - Type of investigation
   - Aim and objective of investigation
   - Number of patients
   - Criteria for patient selection
   - Duration of study with start and finish date
   - Inclusion and exclusion criteria
   - Criteria for withdrawal
   - Details of post-market clinical follow up plan
6. *Data collection or statistics*
   - Description of end points and data recorded
   - Description and justification of statistical design, method and analytical procedures

A labelling requirement is all devices intended for clinical investigation must bear the wording exclusively for clinical investigation

5. **Conformity assessment procedure**[37]

i. EC type examination

A conformity assessment procedure for the product design which involves examination.

i. EC verification[43]

EC verification can be done by two ways

1. Method I: By testing every product
2. Method II: Statistical verification

i. EC declaration of conformity (production quality assurance)

Regardless of the classification of medical device, manufacturer must prepare an EU Declaration of Conformity (DoC) to sell medical devices in Europe.

ii. EC declaration of conformity (product quality assurance)

Manufacturer must ensure application of quality system approved for the manufacture of the products and carry out the final inspection as specified in regulations

Contents of application*:* It is same as that of the full quality assurance system application including the following

- Technical documentation on the types approved and a copy of the EC type examination certificates
- For active implantable medical devices, the techniques of control and of quality assurance at the manufacturing stage

iii. **EC declaration of conformity (full quality assurance system)**

Manufacturer must ensure application of quality system approved for the final inspection and testing of the product as specified in regulations.

Contents of application: It is same as that of the full quality assurance system application including the following

- Technical documentation on the types approved and a copy of the EC type examination certificates
- Quality records such as reports concerning inspections, tests, calibration and the qualifications of the staff concerned

In all the above three declaration of conformity, the notified body must audit the quality system to determine whether it meets the requirements.

6. Post-marketing surveillance and vigilance reporting[44]

Post-marketing surveillance helps the manufacturer to obtain an understanding of the performance of the device once placed on the market and provides continuous feedback that enables

manufacturers to maintain a high standard of product quality and consumer satisfaction. It is defined as the pro-active collection of information on quality, safety or performance of Medical Devices after they have been placed on the market.

5.2.4. REGULATORY REQUIREMENTS [47]

All Medical devices that are placed on the market in the UK have to comply with device-specific legislation:

- European Union laws – the Medical Devices Directives and Regulations
- UK laws – the Medical Devices Regulations

The basic regulatory requirements must comply with foreign medical device manufacturers are:

1) UK authorized agent
2) Understanding the UK regulatory process
3) Requirements for the registration of medical devices in UK
4) Other requirements

5.2.4.1. UK authorized agent[51]

Foreign Medical device companies that require registration in UK must appoint an agent responsible for pre-certification and post-market surveillance inquiries.

When submit the registration with MHRA, the appointed AR must provide written evidence that they are acting with the consent of a manufacturer located outside the EEA. This may take the form of a **Letter of Designation** or contract from the non-EEA manufacturer.

The letter should state the full name and address of the AR and that they are the designated EU authorized representative based within the UK, under the MDD 93/42EC. In the case of a notification/registration for an in vitro diagnostic device please quote the Directive IVDD 98/79EC.

5.2.4.2. Understanding UK regulatory process[48]

A typical approval process involves the following steps

1. The manufacturer confirming that the product is a medical device and determining the correct device classification.
2. Conducting relevant tests and clinical trials (if necessary) to demonstrate compliance with the requirements laid out in the relevant directives.
3. Compliance assessment of the manufacturer/device by an EU Notified Body for medium and high risk products.
4. Registration of low risk medical devices and all in vitro diagnostic products in the country where the manufacturer/representative is based.
5. Placing of the CE Mark on the product by the manufacturer based on Notified Body assessment or registration.
6. Post-marketing vigilance and monitoring of the device in use.

If a device has multiple uses, each application requires appropriate classification and assessment.

5.2.4.3.Requirements for the common submission format for the registration of medical devices in UK[48, 49]

i. CE MARKING: Notified Body is required for the registration of class IIa and class IIb medical devices in UK.

FORM RG2 FOR GENERAL MEDICAL DEVICES: for the registration of medical devices manufacturer should apply in FORM RG2 “general medical devices”.

Guidance to fill the application form is available in the application form itself

iii. HEADED DESIGNATION LETTER

The letter should state the full name and address of the AR and that they are the designated EU authorized representative based within the UK, under the **Medical Devices Directive 93/42EC**.

iv. HEADED CANCELLATION/TERMINATION LETTER

In the case of an overseas manufacturer employing a new AR, the MHRA will require a copy of the letter from the overseas manufacturer, to the old AR terminating their services, and the date the service or contact is due to end.

v.CHANGE OF COMPANY NAME

So that we can establish whether the allocation of a new registration number is appropriate any registrations where there has been a change of company name, including becoming a limited company, will need confirmation in writing stating whether there has been or has not been a change in the legal entity of the business e.g. enough changes to the operations or structure of the company, as to be wholly different to the previous registration.

i. ADDITIONAL DOCUMENTATION REGARDING THE DEVICES PLACED ON THE MARKET

Only require the RG2 and/or RG3 form, and the relevant letters in support of your notification if you are an authorized representative. If we have difficultly assigning the appropriate device code we may ask for further information.

5.2.4.4. OTHERS[48, 49]

5.2.4.4.1. IMPORTANT NOTE REGARDING THE REGISTRATION PROCESS

Once a valid notification form and payment have been submitted to us, there is no requirement for companies to wait for an acknowledgement letter from the MHRA before placing CE marked devices on the EU market.

5.2.5.REGISTRATION PROCESS[50, 52]

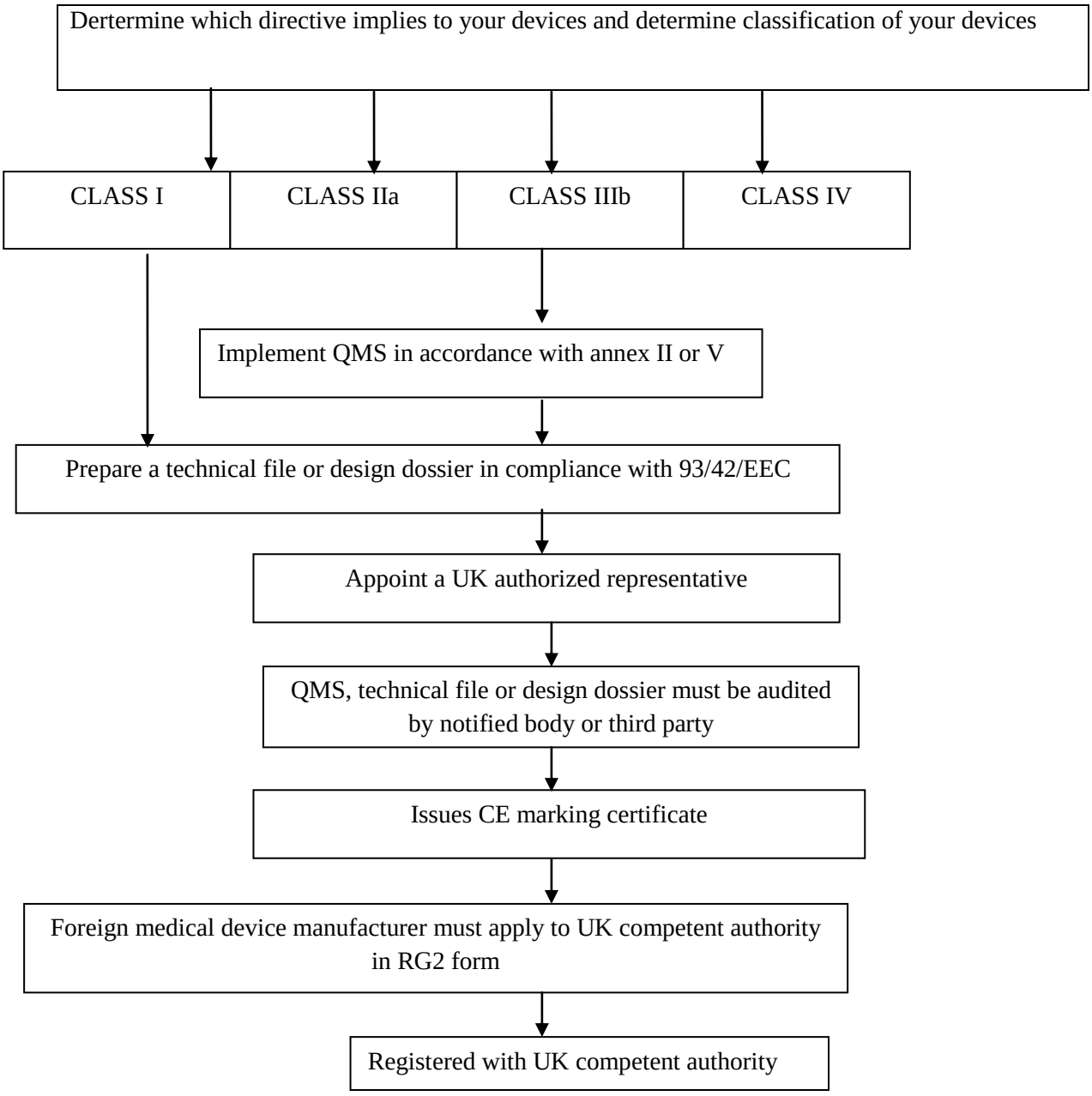

Fig. 14: Registration process of foreign medical device manufacturer in UK

5.2. MEDICAL DEVICE REGISTRATION IN JAPAN

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. [17]

DEFINITION

According to article 2 of PAL(PHARMACEUTICAL AFFAIRS LAW)

The term "medical device" in this Law refers to equipment or instruments intended for use in the diagnosis, cure or prevention of disease in humans or animals, or intended to affect the structure or functions of the body of humans or animals.

5.3.1. REGULATORY BODY

MHLW

The Ministry of Health &Labor and Welfare (MHLW) is regulatory authority of the pharmaceutical regulatory affairs in Japan.

Functions of MHLW

→ To give a marketing approval.
→ To issue a license for marketing authorization holder.
→ To issue a manufacturer license

PHARMACEUTICALS AND MEDICAL DEVICES AGENCY (PMDA):

The PMDA (KIKO) was established in April 2004, through the integration of the Pharmaceutical and Medical Devices Evaluation Center in the National Institute of Health Sciences, the OPSR, and part of the Medical Devices Center, and the PMDA started handling all consultation and review work from the preclinical stage to approvals and post-marketing surveillance[53]

The work of the PMDA can be divided into following categories:

- ADR relief work: Collection, examination and analysis, assessment & provision of ADR information
- Review and Implementation of works, such as examination, data analysis, etc. before administrative measures
  - Scientific review of Pharmaceuticals and Medical Devices application,
  - GLP/GCP/GMP/QMS inspection
  - Clinical trial consultation

5.3.2. REGULATORY FRAME WORK[54]

A foreign manufacturer (a person/ a company) intending to manufacture drugs, quasi-drugs, or medical devices in foreign countries and export them to Japan, is required to be accredited by the Minister of Health, Labour, and Welfare

The main regulatory agency in Japan for medical devices and pharmaceuticals is the Ministry of Health & Labour and Welfare (MHLW). A regulatory review agency under the MHLW called the Pharmaceuticals and Medical Devices Agency (PMDA) is in charge of safety, efficacy and quality of medical devices sold in Japan.

(a) Substantial reforms of safety measures for medical devices,
(b) Revision of the approval and licensing system and enhancement of post marketing safety measures,
(c) Enhancement of safety measures of biological products. This report highlights the above revised points and explains procedures for manufacturing and marketing medical devices in connection with PAL

Japanese medical issues, such as health insurance, medical product registration policy and hospitals are handled by the Ministry of Health, Labour and Welfare (MHLW).

Risk Information was suggested by a certain amount of accumulated information on Adverse Drug Reactions (ADR) reports or Early Post marketing Phase Vigilance (EPPV)[55]

5.3.3. CLASSIFICATION OF MEDICAL DVICES[56]:

Then generic names are classified to Class I, II, III or IV according to their risk level.

a. General medical devices - Class I:

General medical devices (Class I) are those other than specially controlled medical devices and controlled medical devices that are deemed by MHLW to pose an almost insignificant risk to human life and health in the event of malfunction or side effects.

Although they do not require approval, notification must be submitted to PMDA, and the requirements outlined below must be met.

EX: - X-ray film, steel surgical instruments, in-vitro diagnostic devices, etc.

b. Controlled medical devices/designated controlled medical devices - Class II

Medical devices categorized as Class II are further regulated as follows:

a. Medical devices, which have not applicable certificate standards, are categorized as controlled medical device, and need approval reviewed by PMDA.

b. Medical devices, which have and meet applicable certification standards, are categorized as designated controlled medical devices, and need certification reviewed by and Registered Certification Body (RCB).

c. Common requirements for class II medical devices.

→ The applicant must have a 2nd grade MAH license.

→ The manufacturer must have a license for a medical device manufacture.

→ Manufacturer must comply with the quality management system (QMS) requirements set by MHLW ordinance 169.

EX: - MRI units, electronic sphygmomanometers, electronic endoscopes, ultrasonograph equipment, dental alloys, etc.

c. Specially controlled medical devices-Class III and Class IV

EX**: -**

Class III: haemodialysis equipment, artificial bones and joints, mechanical ventilation apparatus, balloon catheters, etc.

Class IV: pacemakers, artificial cardiac valves, stents, etc.

5.3.4. REGULATORY REQUIREMENTS[57]

1. Appointing Japanese authorized agent
2. Understanding the Japan regulatory process
3. Requirements for the ACCREDITATION OF FOREIGN MEDICAL DEVICE MANUFACTURER
4. Other requirements

5.3.4.1. APPOINTING JAPANESE AUTHORIZED AGENT[58]

Manufacturers with no local presence in Japan must appoint a Marketing Authorization Holder (MAH) or Designated MAH(D-MAH) to manage their device registration process andliaise with the Pharmaceutical and Medical Devices Agency(PMDA), Japan's medical device market regulator

ROLE AND RESPONSIBILITIES OF MAH/ D-MAH[58]

MAH:

- The MAH controls the registration of the medicinal Products. The MAH is applicant and becomes the owner of approval/ certification
- The MAH need no signature from the foreign manufacturer if a supplement application or transfer application of the approval is submitted due the MAH is the owner of the approval. He can submit the application under their responsibility.

D-MAH:

- The foreign manufacturer is the applicant and becomes the owner of approval / certification. He controls the registration of medical device.
- Foreign manufacturer cannot obtain the license of MAH so the manufacturer must appoint a Japanese company who has the appropriate MAH license as D-MAH.
- The DMAH acts as the representative for the foreign manufacturer during and after the product registration process.
- Change of D-MAH is much easier compared to the case of MAH

5.3.4.2. UNDERSTANDING THE JAPAN REGULATORY PROCESS[59]:

There are two components of the Japanese PAL regulations that are key to doingbusiness in Japan: "Kyoka" and "Shonin."

"Kyoka" is a kind of business license required for Marketing Authorization Holders(MAH), manufacturers, repairers anddistributors. If the manufacturing facilities are located outside of Japan, these foreignmanufacturing facilities are required to obtain Foreign Manufacturer Accreditationinstead of a Manufacturer License.

To market medical devices in Japan, the MAH must register the device through thefollowing procedures. Emergo can assist you with any medical device approval inJapan, regardless of classification.

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

To register and market General Medical Devices (Class I devices), the MAH onlyneed 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 subjectto Pre-market Certification. Class II devices other than Specified Controlled Devicesare subject to Pre-market Approval.To register and market a Specified Controlled Medical Device, the MAH needs to file

Pre-Market Certification application with a Registered Certification Body (RCB) andobtain their certification. This procedure is quite similar to European CE markingusing a Notified Body. In fact, several European Notified Bodies are also authorizedJapanese RCBs. Each Specified Controlled Medical Device must apply internationallyharmonized standards as is the case with CE Marking

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

To register and market a “Highly Controlled Medical Device” the MAH needs to file aPre-market Approval Application with the PMDA and obtain their approval. Class IIdevices that are not Specified Controlled Devices are also subject to Pre-MarketApproval.

QMS Compliance Inspections[59]

The Japanese QMS is broadly equivalent to ISO 13485:2003, or, in other words, medical device GMPs.

Documentation requirements

A key difference between Japanese QMS and ISO 13485:2003 requirements is the production and maintenance of a document called the **Seihinhyojunsho**, roughly equivalent to a device master record (DMR).

The main contents of **Seihinhyojunsho(device master record)** is as follows

→ Generic name and trade name
→ Product approval date and number
→ Product functions and specifications
→ Operational procedure or usage
→ Product design, drawing, and specifications, or ingredients and quantity
→ Manufacturing method and procedure
→ In case of imported devices, name of country of production and/or export, names of countries where product is sold, and trade names in each country
→ Label and packaging
→ Test methods of product, materials, and components
→ Storage conditions and methods for product, materials, and components

In a preapproval inspection (i.e., to get product registration), PMDA needs to review the following documents before it determines whether to also perform an on-site inspection:

- A detailed floor plan,
- The quality management manual,
- Device information (including the Seihinhyojunsho),
- Manufacturing process flow, etc

In a post approval inspection (i.e., for renewal), additional documents must be submitted. Further required documents include, for the plant as a whole,

- A record of all product recalls in the previous five years and
- A declaration of compliance with Japanese QMS standards.
- Documents for selected products include the Japanese product registration application,
- ISO 13485:2003 certification,
- QMS surveillance reports for the past two years.

- The number of products manufactured per year for the past three years,
- Explanations for any changes to the quality control system.

5.3.4.3. REQUIREMENTS FOR THE ACCREDITATION OF FOREIGN MEDICAL DEVICE MANUFACTURER[60, 61]:

1. Accreditation category

Category of Accreditation of Foreign Manufacturers

Under the provision of Article 36 of the Pharmaceutical Affairs Law Enforcement Regulations, the category of the accreditation of a foreign medical device manufacturer shall be as specified below:

TABLE-02 Accreditation category of Medical Devices

Articles	
Article 36, Paragraph 4, Item 1	Accreditation for all or part of the manufacturing process of the medical devices designated by the Minister pursuant to the provisions of Article 43, Paragraph 2 of PAL as well as of the medical devices designated by the Minister as requiring due caution to be exercised in their manufacturing control and quality control pursuant to the provisions of Article 80, Paragraph 2, Item 3 of the Ordinance (e.g. cell/tissue therapy drugs, and specified biological products)
Article 36, Paragraph 4, Item 2	Accreditation for all or part of the manufacturing process of sterile medical devices (excluding manufacturing processes indicated in the Item 4)
Article36,Paragra4,Item 3	Accreditation for all or part of the manufacturingprocess of medical devices other than those indicated in the preceding two items (excluding manufacturing processes indicated in the next item)
Article 36, Paragraph 4,Item 4	Accreditation for only the processof packaging,Labeling or storage among the manufacturingprocesses of medical devices indicated in thepreceding two items

2. Application for Accreditation of Foreign Manufacturers

(1) An “Applicant” is required to submit “Application for Accreditation” (Form No. 18 inthe PAL Enforcement Regulations) that is addressed to the Minister in duplicate,and “Application for Accreditation Examination” (Form No.16-(2) in the Regulations)to Chief Executive of PMDA. Both applications need to be submitted toAdministration Division II, Office of Review Administration of PMDA.

A Japanese marketing approval holder who markets drugs and medical devices, etc.manufactured by a foreign manufacturer can make an accreditation application on the manufacturer’s behalf. However, the space of “Name of Applicant” on theapplication form should be filled out with the foreign manufacturer’s name (when an“Applicant” is a corporation, names of the corporation and their CEO). In addition,an “Applicant” is to be responsible to renew their accreditation every 5 years. Formore details on the renewal procedure, please refer to “Application forRenewal of Accreditation of Foreign Manufacturers”.

Examination Fees for the accreditation differ between on-site and documentexaminations. However, PMDA requires only document audit fee to be paid to ourbank account because, in principle, we do not conduct on-site inspection only for thepurpose of examining buildings and facilities of a foreign manufacturingestablishment to be accredited.

A target period to complete administrative processing (standard administrativeprocess time) of accrediting a foreign manufacturer is not specifically set. However,the period can be estimated to be about 5 months because the Minister’s licensingprocess for a domestic manufacturing establishment takes about 5 months.

When an “Applicant” intends to apply for a new accreditation, they cannot apply formultiple categories in one accreditation application. They need to submit anaccreditation application for one category and, at the same time, submit additionalapplications for the other categories, Application for Change/Addition inCategory of Accreditation of Foreign Manufacturers).

(2) Documents to Be Attached to Accreditation Application (Article 35, Paragraph 2 of the PAL Enforcement Regulations)

a. **A medical certificate** from a physician which indicates whether or not an "Applicant" has mental disorders or is addicted to narcotics, cannabis, opium or stimulant drugs". (When the "Applicant" is a corporation, medical certificates of their CEO and all the executives responsible for the services are required.)

b. **A curriculum vitae** of the person who is responsible to the manufacturing establishment"

c. **"List of products"**

d. "**A document on buildings and facilities of a manufacturing establishment**"

e. When radiopharmaceuticals are included (excluding cases that the amount ofradiopharmaceuticals is equal to or less than those designated by the Minister), adocument on the type of the radiopharmaceuticals and outlines of facilities forhandling such radiopharmaceuticals"

f. "When a system for marketing license, manufacturing license, marketing approval ormarketing certification of drugs and medical devices or an equivalent system isestablished in the country where the foreign manufacturer resides, a copy of thelicense certificate issued by governmental organizations etc. of the country undersuch system". The license certificate should be currently valid.

Note: Points to Consider (PTC) with Respect to Accreditation of ForeignManufacturers of Medical Devices and *In vitro* Diagnostics

(3) Application for Change/Addition in Category of Accreditation of Foreign Manufacturers

(4) Application for Renewal of Accreditation of Foreign Manufacturers

Unless an "Accredited Foreign Manufacturer" renews their accreditation, using aform of "Application for Renewal of Accreditation" (Form No. 20 in the PALEnforcement Regulations), within its 5-year effective period, their accreditationbecomes null and void.

5.3.4.4. OTHERS

(1) **Notification on Change (Article 100 of the PAL Enforcement Regulations)**

When an "(Deemed) Accredited Foreign Manufacturer" makes changes in the following matters, they must notify the fact to the Minister within 30 days by submitting a notification (Form No. 6) to PMDA.

→ Name or address of the person responsible for the manufacturing establishment
→ Name of the executives responsible for the services, when the manufacturer is a
→ Corporation
→ Name of the manufacturing establishment
→ Major part of buildings and facilities of the manufacturing establishment
→ Category and (deemed) accreditation number, when a foreign manufacturer obtains additional accreditations for another category, or discontinues operation of their accredited manufacturing establishment

5.3.5. REGISTRATION PROCESS[62, 63]:

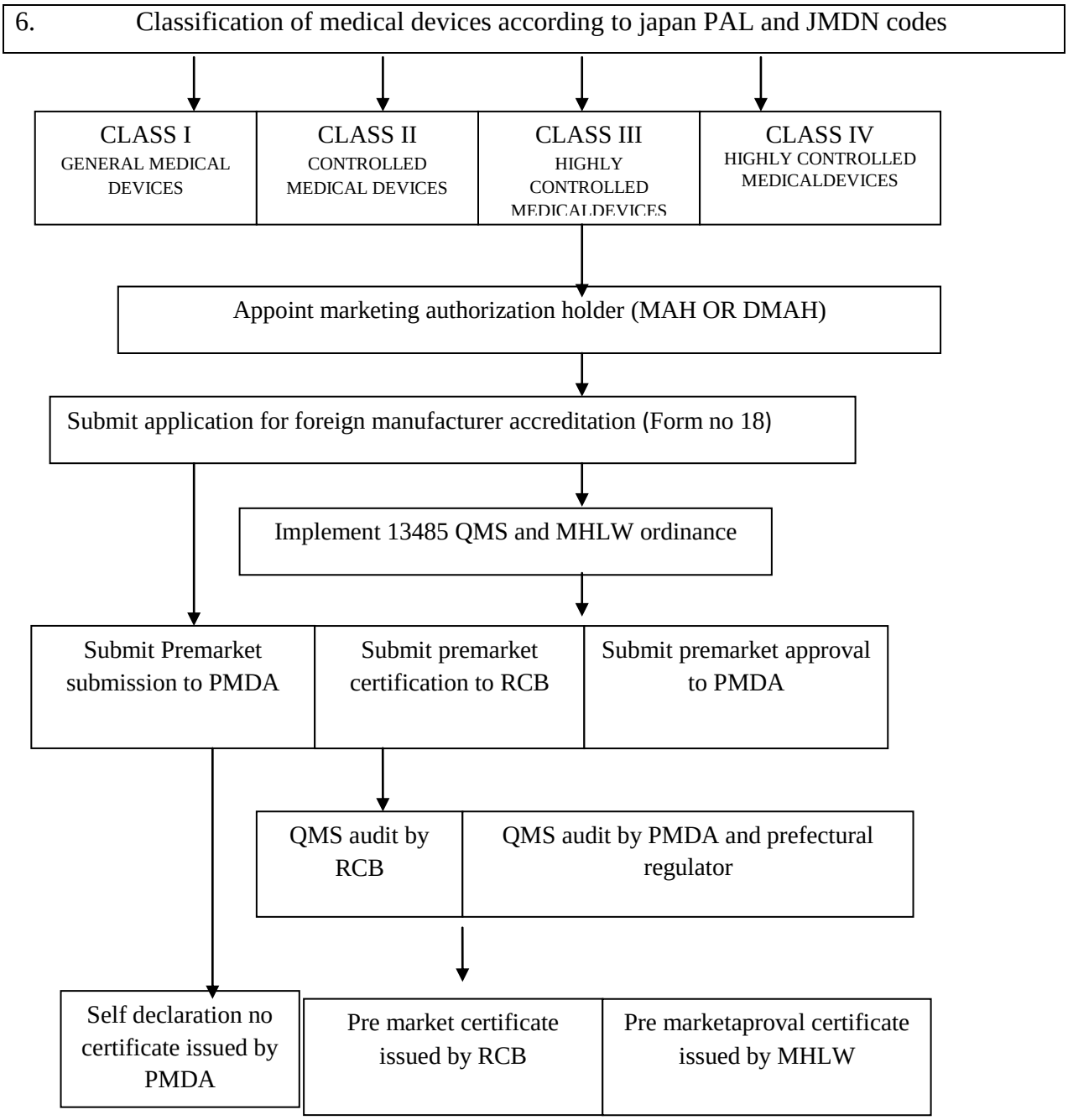

Fig. 15: Registration process of foreign medical device manufacturer in Japan

6.3. COMPARITIVE STUDY BETWEEN INDIA, UK AND JAPAN

Table 4: Comparison of medical device regulations in India, UK and Japan

REQUIREMENTS	***INDIA***	***UK***	***JAPAN***
Regulatory body	Central Drug Standard Control Organization (CDSCO)	The Medicines and Healthcare Products Regulatory Agency (MHRA)	Ministry of Health & Labour and Welfare (MHLW), review agency under the MHLW called the Pharmaceuticals and Medical Devices Agency (PMDA)
Regulations	Drugs and Cosmetics Act, 1940 (India Act), the Drugs and Cosmetics Rules, 1945 (Rules)	**Directive 93/42/EEC (The** General**Medical Devices), Medical device regulations (MDD)**	Pharmaceutical Affairs Law (PAL)
Definition of medical device	According to Section 3 (b) (iv) of Drugs and Cosmetics Act, 1940	Article 1.2 of Directive93/42/EEC**(The** General**Medical Devices)**	According to article 2 of PAL(PHARMACEUTICAL AFFAIRS LAW)
Classification	Notified and non notified medical devices according to Drugs and Cosmetics Act, 1940 According to new amendment bill based on the **risk level**classes A,B,C,D	According with the Annexes II, III, IV, V, VI and VII of the MDD based on risk level Class I Class IIb Class IIa Class III	according to their risk level General medical devices - Class I Controlled medical devices/designated controlled medical devices - Class II Specially controlled medical devices-Class III and Class IV
Regulatory requirements	• Appointing India authorized agent • Understanding the Indian regulatory process • Requirements for the common submission format for the registration of medical devices in India • Import license	• UK authorized agent • Understanding the UK regulatory process • Obtaining CE mark • Requirements for the registration of medical devices in UK	• Appointing Japanese authorized agent (MAH/DAH) • Understanding the Japan regulatory process • Requirements for the accreditation of foreign medical device manufacturer • Other requirements
Types of submissions	common submission format for medical devices according to drugs and cosmetics act, 1940	Submissions to obtain CE mark Registration certification submission	Premarket submission Premarket certification Premarket approval
Device applications	Form-40	RG2 form	Form-18 (accreditation) Form-16(2)(accreditation examination)
Documents required	• Covering letter • Authorisation letter • Form 40 • Plant master file • Device master file • Whole sale licence • Manufacturing licence • CE certificate / free sale certificate • Inspection/audit report • Quality management systems certificates	• Headed designation letter • RG2 form • CE marking certificate • Technical file • EC design examination certificate • EC full quality assurance certificate • EC verification certificate • EC product quality assurance certificate • Inspection report • Quality management systems certificates	• Covering letter • Form-18(accreditation) • Form-16(2)(accreditation examination) • Medical certificate • Curriculum vitae • Plant master file • Device master file • Manufacturing licence • Inspection report • Quality management systems certificates
QMS	ISO 13485:2003	ISO 13485:2003	MINISTERAL ORDINANCCE #169based on ISO 13485
Certifications	Registration certificate	CE marking certificate Registration certificate	Premarket certificate Premarket approval certificate

CONCLUSION

Our comparative study concludes that “regulations for the safety of patient is same but rules and procedures followed to implement that are different”, due to this reason a common framework and format like CTD cannot be implemented though the submission of the document is made electronically.

So, complete harmonization would be a very difficult task. As each country has their own requirements and regulations that allows them to maintain a level of control over their medical devices effectively and efficiently. The possibility of complete harmonization is remote and would be a huge undertaking for all of the countries involved.

REFERENCES

1. Global medical device market prospects discussed in new research report package published at market publishers.com [Internet] London: 2011 December 01 [cited 2014 August 02]; Available from: http://www.prweb.com/releases/2011/12/ prweb9006574.html
2. Dr Michael cheng. Medical device regulations: global overview and guiding principles. Switzerland. World Health Organization. 2003. P.54.
3. Sandra Brolin. Global regulatory requirements for medical devices [PhD thesis]. Sven Hamp, Malardalen University. [Cited 2014 May 04]; Available from: http://www.mdh.diva-portal.org/smash/get/diva2:121327/FULLTEXT01
4. Council Directive on the approximation of the laws of the Member States relating to active implantable medical devices. London. Official Journal of European Communities. 2007 October 11.P.35.
5. Indian medical device market outlook to 2017 published at RNCOS business consultancy services. [Internet]. [Cited sep, 2014]. Available from: http://www.deloitte.com/assets/DcomIndia/Local%20Assets/Documents/Lifesciences/Medical_technology_Industry_in_India.pdf
6. Emergo group services. Indian medical device registration and approval. Available from: http://www.emergogroup.com/services/india/india-medical-device-registration
7. David Topham. Medical devices; The UK industry and its technology development. Published by PRIME Faraday Partnership [Internet] [cited may, 2014]; Available from: http://www.lboro.ac.uk/microsites/mechman/research/ipm-ktn/pdf/Sector_profile/medical-devices-the-uk-industry-and-its-technology-development.pdf
8. Overview of medical device market in United Kingdom. Published By: Espicom Business Intelligence [internet] [cited july, 2014]; Available from: https://www.bharatbook.com/medical-devices-market-research-reports-167875/the-medical-device-market-uk.html
9. The Medicines and Healthcare products Regulatory Agency (MHRA); Registration of medical devices. [Internet]. Available from: http://www.mhra.gov.uk/Howweregulate/Devices/Registrationofmedicaldevices/index.htm
10. By Satoru Nagasaka, Benjamin Lang. An overview of pharmaceutical and medical device regulations in Japan. [internet] [cited April, 2014]; Available from: https://www.morganlewis.com/pubs/OverviewPharmadevicereg.pdf
11. Anuja R Shah, RK Goyal. Current status of the regulation for medical devices. [internet] [cited Nov, 2014]; Available from: http://www.ijpsonline.com/article.asp?issn=0250474X;year=2008;volume=70;issue=6;spage=695;epage=700;aulast=Shah
12. Ames Gross. Update on medical device regulations in India; published in regulatory focus. [internet] [cited Oct, 2014]; Available from: http://www.pacificbridgemedical.com/publications/update-on-the-medical-device-regulations-in-india/
13. DB Jeffery’s. The regulation of medical devices and role of medical device agency [internet] [cited December, 2014]; Available from: http://onlinelibrary.wiley.com/doi/10.1046/j.0306-5251.2001.01416.x/pdf
14. Dr. Bobby George. Regulation of medical devices [internet] [cited july 2014]; Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3146078/

15. Nassim Parvizi and Kent Woods. Regulation of medicines and medical devices: contrasts and similarities. Clinical Medicine 2014 Vol 14, No 1: 6–12. [internet]; Available from: http://www.clinmed.rcpjournal.org/content/14/1/6.full.pdf
16. Hasumati Rahalkar. Historical overview of pharmaceutical industry and drug regulatory affairs [internet] [cited September, 2014]; Available from: http://omicsgroup.org/journals/historical-overview-of-pharmaceutical-industry-and-drug-regulatory-affairs-2167-7689.S11-002.php?aid=8937
17. Sharma Devesh. medical device approval process in Japan. [internet] [cited December, 2014]. Available from: Available online at http://jddtonline.info
18. PMA Import/ Export [Internet] FDA; [updated 2010 September 03; cited 2014 May 25]. Available from: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/Pre-marketSubmissions/Pre-marketApprovalPMA/ucm050503.htm
19. Council Directive on the approximation of the laws of the Member States relating to active implantable medical devices. London. Official Journal of European Communities; 2007 October 11.P.35.
20. Medical device market in India 2013. DUBLIN (business wire) **research and markets [Internet] [cited sept,2014]**; Available from: http://pharmacychoice.com/News/article.cfm?ARTICLE_ID=1006565
21. Pacific Bridge Medical, Update on India's Medical Device Markets Webcast, published February 2007 [Internet] [cited feb,2014]; Available from: http://www.pacificbridgemedical.com/publications/2013-india-medical-device-market-update/
22. Central Drugs Standard Control Organization (CDSCO). Frequently asked question on registration and import of medical devices in India (under revision) [Internet]; Available from: http://www.cdsco.nic.in/writereaddata/FAQIMPORT%20&%20REGISTRATION%2002022013_DONEE.pdf
23. Rajdutt S.singh and Mrinali moudi. The Drugs And Cosmetics (Amendment) Bill, 2013: Regulations For Medical Devices And Conduct Of Clinical Trial [internet] [cited Sept, 2014]; Available from: http://www.mondaq.com/india/x/264918/food+drugs+law/TheDrugsAndCosmeticsAmendmentBill2013RegulationsForMedicalDevicesAndConductOfClinicalTrial/
24. Central Drugs Standard Control Organization (CDSCO), Drugs and Cosmetic Act 1940, amended [Internet] [cited may, 2014]; Available from: http://cdsco.nic.in/html/downloads.html.
25. Central drugs standard control organization(CDSCO); Guidance document on zonal and sub zonal offices [internet]; Available from: http://cdsco.nic.in/writereaddata/guidance_doc_fuct_cdsco_subzonal/Guiding%20documents%20for%20zonal%20&%20sub-zonal%20&%20port%20offices%2017.06.2011.pdf
26. Central drugs standard control organization (CDSCO). Medical device and diagnostic division. Organogram of medical devices [internet]; Available from: http://www.cdsco.nic.in/writereaddata/Medical%20Device%20organo.pdf
27. International Trade Administration, Medical Device Regulatory Requirements for India, updated [Internet] [Cited December, 2014]. Available from: www.ita.doc.gov/td/health/indiaregs.html.
28. Emergo group of services. India Medical Device Registration and Approval process [Internet]. Available from: http://www.emergogroup.com/services/india/india-medical-device-registration
29. Emergo group of services. India Authorized Agent Representative for Medical Device and IVD Companies with No Local Office in India [internet]; Available from: http://www.emergogroup.com/services/india/indian-authorized-agent-representative
30. Central drugs standard control organization (CDSCO); Guidance document on the common submission format for the registration of medical devices in India; [cited august, 2014]; page no 1-38.
31. Central drugs standard control organization (CDSCO); Guidance document on the common submission format for import license. [Cited January 2014]. Page no 3-11.
32. Emergo group of services. Indian approval process for medical devices. [internet]. Available from:

http://www.emergogroup.com/resources/download-regulatory-process-charts
33. Emerge group services. UNITED KINGDOM - UK Medical Device Industry and Demographic Data. Available from: http://www.emergogroup.com/resources/market-united-kingdom.
34. Wellkang Ltd. Guide on medical devices (MD/IVD) & European (EU/EC) Authorized Representative [Internet] 2010 March 21 [cited 2014 May 28]. Available from:: http://www.cemarking.com/medical-devices.html
35. Reference Guide for Manufacturers Selling Medical Devices in Europe, Canada and the United States. Canada. Industry Canada; 2010.P.189.
36. MaRS Discovery District. How Medical Devices are approved in Europe. 2010 [cited 2014 May 30]. Available from: http://www.marsdd.com/dmsassets/entrepreneurtoolkit/RegulatoryPDFs/How_Devices are_Approved_in_Europe.pdf?5fd50f
37. Emergo. CE Mark Consultants and CE Marking for Medical Devices [Internet]. [Cited 2012 May 14]. Available from: http://www.emergogroup.com/services/europe/ce-mark-medical-devices
38. EURLEX. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices [Internet]. Official Journal 169; 1993 July 12 [cited 2014 June 04]. Available from: http://eurlex.europa.eu/lexuriserv/lexuriserv.do?uri=celex:31993l0042:en:html
39. ISO 13485 2003. Plain English an Overview [Internet]. Praxiom Research Group Limited 2011 December 11 [updated 2014 July 17; cited 2014 July 26]. Available from: http://www.praxiom.com/iso-13485-standard.html
40. Recommendation NB-MED/2.5.1/Rec5: Technical Documentation. European Coordination Notified Bodies; 2000 February 29.P.24.
41. Study Group 1 of the Global Harmonization Task Force. Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED). GHTF; 2008 February 21. P.21.
42. Directorate General for Health and Consumers. Guidelines on Clinical Investigation: A Guide for Manufacturers and Notified Bodies. European Commission; 2010 December.P.10.
43. Guidance for Manufacturers on Clinical Investigation to be carried out in the UK. Medicines and Healthcare Products Regulatory Agency (MHRA); 2012 February. P.47.
44. Wellkang Ltd. Guide on medical devices (MD/IVD) & European (EU/EC) Authorized Representative [Internet] 2010 March 21 [cited 2014 June 01]. Available from: http://www.ce-marking.com/medical-devices-class-IIb.html
45. Wellkang Ltd. Guide on medical devices (MD/IVD) & European (EU/EC) Authorized Representative [Internet] 2010 March 21 [cited 2014 June 01]. Available from: http://www.ce-marking.com/medical-devices-class-III.html
46. Emergo. Medical device post-market surveillance and vigilance [Internet] [Cited June, 2014]. Available from: http://www.emergogroup.com/resources/articles/insights-on-surveillance-vigilance
47. The Medicines and Healthcare products Regulatory Agency. The Notified Body Bulletin No. 6. Retrieved September 25, 2012: Available from http://www.mhra.gov.uk/home/groups/esera/documents/publication/con007493.pdf.
48. Medicines and health care products regulatory agency. Routes to obtain CE marking [internet] Available from: http://www.mhra.gov.uk/home/groups/dtsbs/documents/websiteresources/con286776.pdf
49. Regulation of medical devices in UK. 2014-09-19 [internet] Available from: http://www.biolegis.com/uploads/txarticles/TheRegulationofMedicalDevicesintheUK.pdf
50. Medicines and health care regulatory agency. Registration of medical devices [internet]. Available from: http://www.mhra.gov.uk/Howweregulate/Devices/Registrationofmedicaldevices/index.htm
51. Medicines and health care products regulatory agency. Registration of medical devices: frequently asked questions [Internet]. Available from:: http://www.mhra.gov.uk/Howweregulate/Devices/Registrationofmedicaldevices/Registrtionofmedicaldevicesfrequentlyaskedquestions/index.htm

52. CE approval and registration process of medical devices in UK. Emergo group 2013 [Internet]. Available from: http://www.emergogroup.com/resources/europe-process-chart
53. Pacific Bridge Medical, Global Perspective. The Regulatory Environment for Medical Devices in Japan, published by the Regulatory Affairs Professionals Society May 2002, printed 06/12/2007.
54. JETRO, Investing in Japan, Regional Information, Pharmaceuticals and Healthcare; Available from: http://www.jetro.go.jp/en/Invest/region/medical/printed10/12/20
55. Pharmaceuticals and medical devices agency (PMDA). Approval business information [Internet]; Available from: http://www.pmda.go.jp/operations/shonin/info/iryokiki.html
56. Japan MDC. Medical device registration system in Japan [internet]; Available from: https://www.j-mdc.com/product.html
57. Emergo group of services; medical device consulting for japan; [internet];Available from: http://www.emergogroup.com/services/japan
58. Emergo group of services. Japanese marketing authorization holder (d-mah) for medical device companies [internet]; Available from: http://www.emergogroup.com/services/japan/dmah-representation
59. Emergo group of services. Japan PAL Quality Management System Compliance - MHLW Ordinance #169 [internet]; Available from: http://www.emergogroup.com/services/japan/quality-system-compliance-japan
60. Emergo group of services. Foreign Manufacturer Accreditation for Medical Device Companies Exporting to Japan [internet]; Available from: http://www.emergogroup.com/services/japan/foreign-manufacturer-accreditation
61. Application for Accreditation of Foreign Manufacturers; pharmaceuticals and medical devices agency [internet] Available from: http://www.pmda.go.jp/english/service/pdf/acc/application.pdf
62. Emergo group of services. Japan medical device approval process [internet]; Available from: http://www.emergogroup.com/services/japan/medical-device-approval-japan
63. Japan: Market Entry for Medical Devices A Seven Step Approach to Market Entry; Espicom Japan Medical Outlook 2011 [internet]; Available from: http://japan.nlembassy.org/binaries/content/assets/postenweb/j/japan/embassy-of-the-kingdom-of-the-netherlands-in-tokyo/import/ea/japan---a-seven-step-approach-to-market-entry.pdf.