An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

REGULATORY REQUIREMENT FOR REGISTRATION OF HIGHER-CLASS MEDICAL DEVICE IN INDIA, EU & TAIWAN: A COMPARATIVE STUDY

Ms. Grishmaben K. Desai*, Dr. Ronak R. Dedania, Dr. Vineet C. Jain, Dr. Zarna R. Dedania

Department of Pharmaceutical Regulatory Affairs, Bhagwan Mahavir College of Pharmacy, Surat, Gujarat, India

*Corresponding author E-mail:g77desai@gmail.com

ARTICLE INFO

Key Words

Regulations, manufacturer, registration, medical device

Access this article online

Website: https://www.jgtps.com/

Quick Response Code:

ABSTRACT

Medical Device is one of the fastest growing sectors and so are the associated regulations. The medical device industry is an industry managing different kinds of items covering a wide scope of utilizations. As the safety and effectiveness of medical devices are crucial to human wellbeing, the items must be overseen by strict guidelines as per the risk levels. Understanding and interpreting the medical device evolving regulations and requirements is important in the current global competitive market. The article focuses the current scenario of regulation and approval of the devices in India, European Union and Taiwan with respect to their regulatory bodies, which has different sets of procedure and guidelines for regulation of devices.

INTRODUCTION

A medical device is any device intended to be used for medical purposes. They are crucial components of patient care. They may be uncomplicated devices employed during medical examinations, such as tongue depressors and thermometers, or sophisticated life-saving implants like heart valves and coronary stents.As per GHTF harmonized definition, the term "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 purpose(s) of diagnosis, prevention, monitoring, treatment or alleviation of disease or diagnosis, monitoring, treatment, alleviation of or compensation for an injury or investigation, replacement, modification, or support of the anatomy or of a physiological process or supporting or sustaining life or control of conception or disinfection of medical devices or providing information for medical or diagnostic purposes by means of in vitro examination of specimens derived from the human body; and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means. Previously in many countries medical device regulations rarely existed and there were limited regulatory controls to prohibit the use of low-quality devices. Hence there was a compulsion to draft regulatory policies on medical devices to assess their quality, safety and efficacy. Fortunately, since the early 1980s, the regulatory paradigm for medical devices has changed exceptionally. Now with the availability of different regulations of the countries or region on medical

devices, there is a need to harmonize regulations in order to curtail regulatory hurdles and expedite access to high quality, safe and efficacious medical devices. With this background in mind, first various regulations and regulatory approval process for medical device in said region will be reviewed and then comparative grid of document requirements for registration will be discussed.

REGULATORY ASPECTS OF MEDICAL DEVICE IN INDIA

The Central Drug Standards Control Organization (CDSCO) which is a part of the Ministry of Health and Family Welfare currently regulates medical devices in India under Medical DeviceRule, 2017.Prior to implementation of the Medical Device Rules, 2017, notified medical devices were regulated as drugs (pharmaceutical products) in India under the Drug and Cosmetic Act,1940. Therefore, it was required to distinguish medical devices from pharmaceutical products. Secondly, there was an urgent need to provide a more conducive environment for local manufacturers to set up industries in India. The new rules have been formulated to promote domestic manufacturing and to regulate import and manufacturing in the region. The new regulations follow the GHTF (Global Harmonization Task Force) guidelines and are in consonance with these rules risk-based classification. In addition, inspections by notified bodies have been introduced in the new medical device rules. In consonance with global regulations, the new rules introduced a risk-based classification system. The device is classified as Class A, B, C and Din which class D device possess higher risk. The CDSCO classifies notified devices and publishes the list of devices from time to time on its website. Importers and manufacturers are required to follow the classification list to classify their devices.

QUALITY SYSTEM

The manufacture required to established quality management system as per Fifth Schedule of the rule which is harmonized with ISO 13485:2016. Notified Body accredited by the NAB audit[Carried out by National Accreditation Board for Certification Bodies (NABCB) under the Quality Council of India set up by the Ministry of Commerce and Industry, Government of India act] the manufacturing sites to verify conformance with the Quality Management System and other applicable standards as specified in the rules. For now, Intertek India Pvt. Ltd., UL India Pvt. Ltd, TÜV InterCert Saar India Pvt Ltd, TUV SUD South Asia Pvt. Ltd., TUV Rheinland (India) Pvt. Ltd., International Certification Services Pvt. Ltd. and BSI Group India Pvt. Ltd. are the Notified Bodies registered for the purpose.

CLINICAL INVESTIGATION

Clinical investigation shall be conducted in accordance with the approved clinical investigation plan (study protocol) and CDSCO-Good Clinical Practices guidelines. An application to conduct pilot or pivotal clinical investigation is made in Form MD-22 or MD-24 for IVD by the Sponsor/ CRO along with information specified in the Seventh Schedule of MDR and submitted online. Medical devices requiring clinical investigation but claiming substantial equivalence to a predicate device also requires CDSCO approval.

PRE-MARKET APPROVAL

The application shall be made through online portal of the Ministry of Health and Family Welfare in Form MD-7 for manufacture of medical device (obtain marketing authorization in MD-9). A manufacturing license is valid in perpetuity, subject to payment of license retention fee before completion of the period of five years from the date of its issue, unless, it is suspended or cancelled by State/ Central Licensing Authority. The fee (and renewal) for manufacturingper site is INR 50,000 and INR 1000 per product.

POST-MARKET MANAGEMENT

Manufacture shall submit Periodic Safety Update Report from the date of launch in the market and such report shall be submitted every six months for first two years followed by submission of the said report annually for the two more successive years. CDSCO in collaboration with Indian Pharmacopoeia Commission has the responsibility to conduct Materiovigilanceprogramme of India (MvPI). MvPI is meant to enable safety data collection in a systematic manner so that regulatory decisions and recommendations on safe use of medical devices being used in India could be based on data generated. The program is meant to monitor medical device-associated adverse events (MDAE), create awareness among healthcare professionals about the importance of MDAE

reporting in India and to monitor the benefit-risk profile of medical devices. It is also meant to generate independent, evidence-based recommendations on the safety of medical devices and to communicate the findings to all key stakeholders.

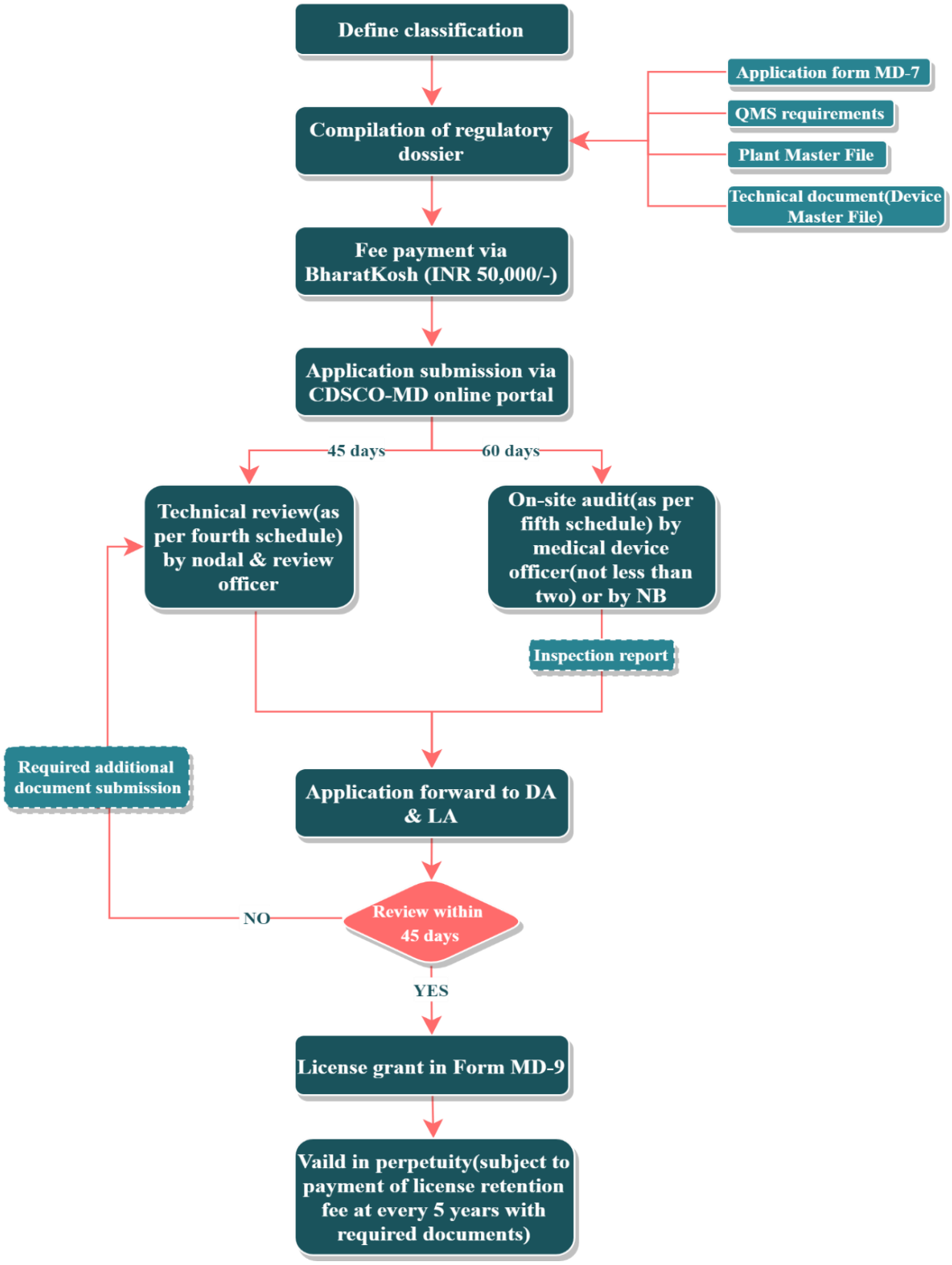

Figure 1: Registration procedure in India

REGULATORY ASPECTS OF MEDICAL DEVICE IN EUROPEAN UNION

Medical Device Directive (MDD) regulates the safety and marketing of medical devices in Europe since 1990s. In 2012, the European Commission proposed new regulation to integrate the current directives into Medical Devices Regulations (MDR). The adoption of Regulation MDR changed the European legal framework for medical devices, introducing new responsibilities for EMA and for national competent authorities. MDR gives the new approach which meant that products could be traded within Europe, as long as they complied with the 'essential requirements' of the legislation.

To comply with these essential requirements, standards were developed, by groups such as the International Organization for Standardization (ISO). These standards became 'harmonized' when they were accepted as allowing compliance to the essential requirements of the legislation. A listing of these standards, as they apply to medical devices, is available on the European Commission website. This regulation entered into force in May 2017 and has a staggered transitional period. The MDR has a transition period of three years and will fully apply from 26 May 2020. During the transition period, manufacturers can place devices on the market under the currently applicable EU Directives or under the new Regulations if they fully comply with these.

In light of COVID-19, on April 24, 2020, the European Commission extended the Date of Application for EU MDR by 12 months, which means medical device companies now have until May 26, 2021 to comply with the MDR. European Union (EU) follows a four-class scheme.

Devices are classified into class I (including Is and Im), IIa, IIb, and III. Class III are ranked as the highest and higher the classification the greater the level of scrutiny. Medical devices cannot be marketed in the European Union without adhering to the stringent regulations of the European Union; one of these regulations is the affixation of the Conformite "Europe" enne (CE) marking.

QUALITY SYSTEM

EN ISO 13485: 2016 is a harmonized standard applied by manufacturers to implement the quality system in the EU. In the EU, notified bodies accredited by a member state are designated to carry out conformity assessment based on the relevant Directives and issue certificates.

CLINICAL EVALUATION

According to the MDR, the manufacturer is obliged to carry out a clinical evaluation during the entire life cycle of a medical device. The clinical evaluation must be part of the quality management system.

The requirement for a pre-market Clinical Evaluation can be found in the Article 61 and in the Annex XIV, Parts A and B. The manufacturer must summarize the results of the clinical evaluation in a Clinical Evaluation Report (CER). This is a mandatory prerequisite for the initial CE mark.

PRE-MARKET APPROVAL

CE marking is a legal requirement for all medical devices to be sold in the EU. CE marking affixed on the product represents its compliance. To obtain CE certification, manufacturers must decide an appropriate conformity assessment route based on the classification of their devices.

POST-MARKET MANAGEMENT

The competent authorities of each member state in Europe are responsible for the post market surveillance, including adverse event reporting, vigilance reporting, and post market clinical follow-up.

In order to enhance the transparency of market surveillance, the European Databank on Medical Devices (EUDAMED) was established for exchanging legal information. In addition to vigilance information, EUDAMED contains data such as manufacturer registration, certificates issued, and clinical investigations. To register in EUDAMED manufacture required to prepare summary of safety and clinical performance (SSCP) which will be publicly available on the MDR EUDAMED database.

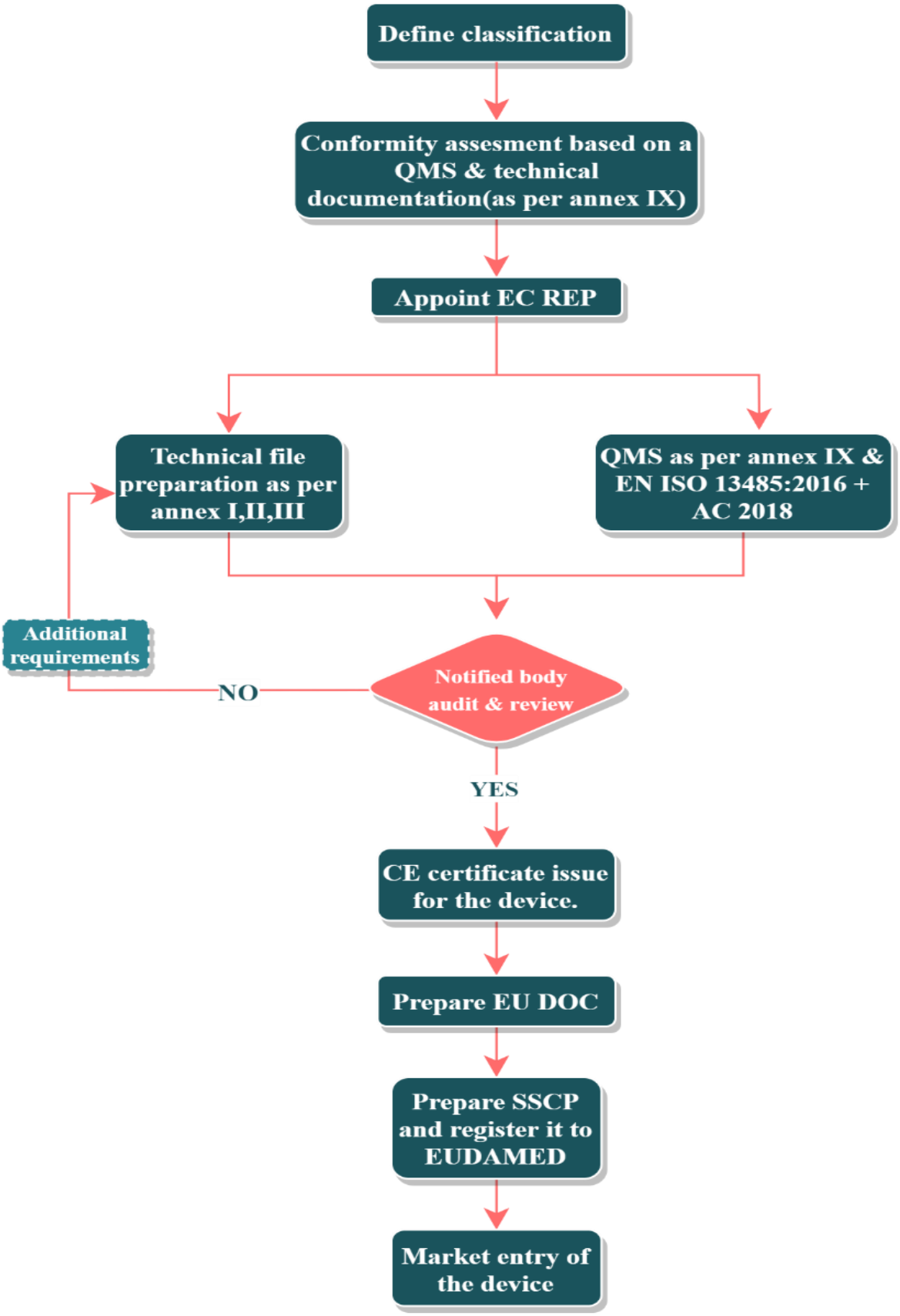

Figure 2: Registration procedure in European Union

REGULATORY ASPECTS OF MEDICAL DEVICE IN TAIWAN

In Taiwan, medical device regulations are mainly based on the Pharmaceutical Affairs Act. According to the Regulations for Governing the Management of Medical Devices, medical devices are divided into 3 classes (class 1, 2, or 3) and 17 categories based on their levels of risk and characteristics.

QUALITY SYSTEM

The TFDA requires manufacturers to establish a quality system based on article 57 of the Pharmaceutical Affairs Act and part 3 of the Good Manufacturing Practices for Medical Devices of the Pharmaceutical Good Manufacturing Practice Regulations, which is harmonized with ISO 13485:2003. It was set forth that all medical devices intended to launch in Taiwan must comply with the GMP requirements. For domestic manufacturers, the TFDA authorized organizations to conduct GMP on-site inspections of medical devices. To obtain the quality system certificate, foreign manufacturers can follow these modes: full quality system documentation (QSD)review, simplified mode for US and EU manufacturers, When the application is approved, the manufacturer will receive a GMP/QSD approval letter valid for 3 years.

CLINICAL EVALUATION

The Taiwan Food and Drug Administration (TFDA) with assistance from the Center for Drug Evaluation (CDE), handles applications of medical devices clinical trials to fulfil regulatory requirements in line with international norms. Centralized institutional review board system (CIRB) was set up by CDE under the authorization of MOHW to improve the efficiency of case review processes. The sponsors must have both IRB and TFDA approvals prior to beginning the study.

PRE-MARKET APPROVAL

In accordance with article 40 of the Pharmaceutical Affairs Act, medical device companies intending to market their products in Taiwan must apply for medical device licenses for devices in all classes. The registration requirements are based on "Regulations for Registration of Medical Devices," and the dedicated application documents differ among the 3 classes. For all class 3 devices, technical documents including product information, instructions for use, and preclinical testing reports must be provided, while clinical data may be exempted if documents of similar products are available. Manufacturers applying for class 3 registrations and market approval must submit documents of Essential Principles (EP) and Summary of Technical Documentation (STED).

POST-MARKET MANAGEMENT

The post a market management framework in Taiwan incorporates market sampling, follow-up review, reporting of adverse reactions, and recall. Besides, the TFDA requires makers of higher-class medical devices, for example, drug eluting stents, cardiac ablation systems, and intraocular lenses, to conduct a safety monitoring plan and submit obligatory periodic safety update reports in predefined timeframe at annually for 3 years.

REGULATORY REQUIREMENTS FOR REGISTRATION IN INDIA, EU, TAIWAN

Table 1: Regional Requirements

Documents/ Regulatory Requirements	Country		
	India	**European Union**	**Taiwan**
Regulation	Medical Device Rule, 2017 and its subsequent amendments	Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices	Pharmaceutical Affairs Act
Documentation Review Authority	CDSCO (Through online MD portal)	Notified Body	Taiwan FDA
Representative	-	European authorize representative	Local Taiwan Agent (Having valid Pharmaceutical license)
Time Frame	6-9 months	6-9 months	10-12 months
Fees	INR 50,000 per product and additional INR 1000 per product.	Depends on choosing of Notified Body Approx. 390 Euro	38,000 NT$
Regional Requirements			
Application Form/ Declaration/ Letter	1. Form MD-7 2. Cover Letter 3. Undertaking for QMS compliance	1. Application form Provided by EU Notified Body	Application Form Letter of Authorization Certificate of free sale
QMS requirements			
Certificate	ISO 13485 certificate	ISO 13485 certificate	QSD certificate

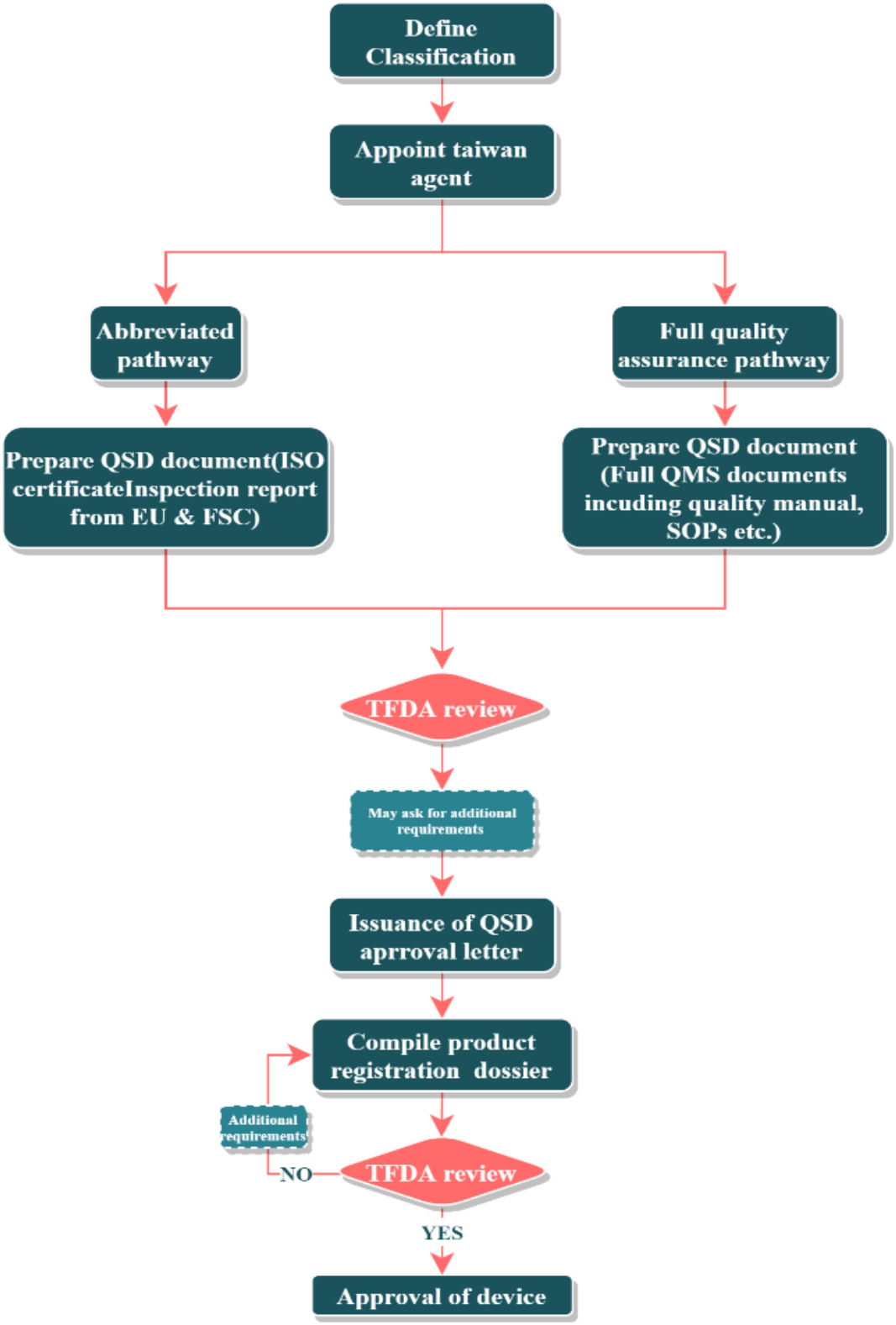

Figure 3: Registration procedure in Taiwan

Table 2: Dossier preparation requirements

PARAMETER	INDIA	EUROPEAN UNION	TAIWAN
General description of the device	General description of the device, its variants and its intended purpose	General description of the device, its variants and its intended purpose	General description of the device, its variants and its intended purpose
	Device specification	Device specification	Device specification
	-	UDI	-
	Classification	Classification	Classification
	-	Declaration of conformity	-
	-	Principles of operation of the device and its mode of action	-
	-	Summary of safety and clinical performance	-
	-	Raw materials, components, packaging Material	-
	-	Declaration on Medicinal Substances	-
	Previous and similar generations	Previous and similar generations	Previous and similar generations
Labelling / instructions for use/ Packaging Material	Label, Box	Box, Label including CE mark, Notified body number, EC REP.	Box, Label
	IFU	IFU translated into concerned member state language.	IFU translated to Mandarin Chinese
	-	Implant card	-
	-	-	Product Photo
Design and manufacturing information	Description of the design	Description of the design	Description of the design
	Description of the manufacturing	Description of the manufacturing	Description of the manufacturing
	-	Description of quality control	-
	Outsourced processes, subcontractors	Outsourced processes, subcontractors	Outsourced processes, subcontractors
Essential Principal Checklist	EP checklist as per CDSCO guidance document	General Safety and Performance Requirements	EP checklist as per GHTF guidance document
Benefit-risk analysis and risk management		Risk management plan	
		Risk analysis including risk control measures	
		Risk management report including the evaluation of residual risks and the evaluation of benefit-risk ratio	
Product verification and validation	Biocompatibility validation data	Biocompatibility	Biocompatibility
	General Testing		Engineering Testing
	-	Electrical safety and electromagnetic compatibility EMC (if applicable)	-
	Software verification and validation (if software used)	Software verification and validation (if applicable)	Software Verification and Validation
	Stability validation data	Stability, including shelf life	-
	Animal studies – Preclinical data	Other pre-clinical tests	Animal Studies
	Clinical evidence	Clinical evaluation	Clinical Evidence
	Medicinal substances data (if device contains Drug)	Information on Medicinal Product along with Drug Product dossier	Medicinal Substances
	-	Tissues or cells of animal origin (if applicable)	-
	-	Substances that are intended to be introduced into the human body (if applicable)	-
	-	CMR or endocrine-disrupting activity (if applicable)	-
	Sterilization Validation data	Sterile devices and devices to be sterilized (if applicable)	Sterilization
	-	Measuring function (if applicable)	-
	-	Combination with other devices (if applicable)	-
	-	Hygienic (re-) processing of devices (if applicable)	-
	Biological Safety	-	Biological Safety
Post-market surveillance	Post-market surveillance plan (PMS-Plan)	Post-market surveillance plan (PMS-Plan)	Post-market surveillance plan (PMS-Plan)
	-	Post-market clinical follow-up plan (PMCF-Plan)	-
	Periodic safety	Periodic safety	Periodic safety

	update report	update report	update report
	Post-market surveillance report	Post-market surveillance report	Post-market surveillance report

CONCLUSION

The medical devices are crucial components of patient care. Regulation of medical device around different region is very diverse. Every country has own set of regulatory standards which required to follow in order to get the marketing authorization. Here, India and European Union has different sector for medical device while in Taiwan it regulates under Pharmaceutical product. Developed market like EU also required more technical documentation for registration. Considering this fact there is need to harmonization of regulation to ease the registration process which eventuality lead to availability of quality product.

Acknowledgments: The author would like to acknowledge the support from principal of Bhagwan Mahavir College of Pharmacy, Surat, Gujarat and also thankful to Dr. Ronak Dedania and Zarna Dedania for reviewing the manuscript and providing the encouragement to carry out the work.

REFERENCES

1. The Global Harmonization Task Force Study Group 1. Definition of the Terms 'Medical Device' and 'In Vitro Diagnostic (IVD) Medical Device' May 16, 2012 Available from: http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n29r16-2005-definition-medical-device-050520.pdf

2. Arkala, "Medical Devices Regulatory Priorities in India", May 2018.

3. Bangera S., Latha MS, "New Regulations for Medical Devices in India", Applied Clinical Trails, 2019.

4. CDSCO: List of notified body register under MDR, 2017. Dec 30, 2019. Available from: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NTQwNw=

5. CDSCO, "Application processing by Officials in New Medical Devices" July,2018. Available from: https://cdscomdonline.gov.in/NewMedDev/resources/app_srv/NMD/global/pdf/CDSCO-guideline.pdf

6. MOHFW: CDSCO, "Medical device rule,2017", January 2017. Available from: https://mohfw.gov.in/sites/default/files/Medical%20Device%20Rules%2C%202017.pdf

7. Melvin, T., Torre, M. "New medical device regulations: the regulator's view" EFORT open reviews, 2019, 4(6), 351-356.

8. No authors listed. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EE Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02017R0745-20200424

9. European Medicines Agency (EMA), "Medical devices." Available from: https://www.ema.europa.eu/en/human-regulatory/overview/medicaldevices

10. EMERGO, The regulatory process for Medical Device. Available from: https://www.emergobyul.com/resources/all/process-charts/all?action=

11. MOH: TFDA, "Regulation for Registration of Medical Devices", March,2017. Available from: https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=L0030055

12. MOH: TFDA, "Pharmaceutical Affairs Act", January 2018. Available from: https://law.moj.gov.tw/Eng/LawClass/LawAll.aspx?PCode=L0030001

13. GHTF, "Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED)", March, 2007. Available from:www.imdrf.org/docs/ghtf/archived/sg1/technicaldocs/ghtf-sg1-n011r20-essential-principles-safety-performance-medicaldevices-sted.pdf