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Review Article



Overview of current Regulations governing Medical Devices

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Abstract

Medical Device (MD) is one of the fastest growing sector and so are the associated regulations. From lack of even policies and guidelines to stringent MD legislations in others, the requirements vary across countries. Understanding and interpreting the global MD evolving regulations and requirements is important (for not just the manufacturers, importers, wholesalers and distributors but even the clinicians) in the current global competitive market. This review is an attempt to do that by giving an overview of the prevailing MD regulations in United States (U.S), Europe and India.

Keywords: Medical Device, Center for Devices and Radiological Health, 510(k), CE mark, FDA, CDSCO.

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1. Introduction

A MD can be briefly defined as *any appliance, software, material, or other article intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, treatment, or alleviation of disease*. MDs vary according to their intended use and indications. Examples range from simple devices such as tongue depressors, to advanced devices such as implants, prostheses and heart valves. There is substantial difference between the regulatory frameworks for MDs as compared to pharmaceuticals. The regulatory agencies typically differentiate MDs into different classes, based on their design complexity, their use characteristics, and potential for harm, if misused. Collectively, the U.S., Japan and European Union (EU) manufacture over 2/3rd of the MDs in the world. As per the market report published by Lucintel, the global MD market is expected to reach an estimated \$409.5 bn by 2023 (1). India is the 4th largest MD market in Asia, importing about 70% of MDs for its domestic needs (2). It was valued at \$4 bn as of 2016 and is likely to cross \$10 bn mark by 2020, thereby registering a CAGR of 15%, albeit from a small base. Prices of some MDs have been noted to be quite high despite their manufacturing and associated import costs being much lower. With sizeable percentage of MDs in emerging markets being

imported, countries need to frame guidelines & regulations to address all aspects related to MDs, ranging from its development, manufacturing process, registration to post-market surveillance requirements such that safe, affordable, high quality products are available for appropriate use.

2. United States

In the U.S., MDs are regulated by the U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH). The establishment (manufacturers, initial importer, specifications developer, contract sterilizer, re-packager and/or re-labeler) must register their facilities, list their products/devices with the FDA as per FDA 2891- 21 CFR Part 807 (3). Any foreign establishment engaged in manufacture, preparation, propagation, compounding or processing of a device offered for import into U.S. must identify a U.S. Agent for that establishment, who must reside in U.S or maintain a U.S. place of business. In addition, they are required to report adverse events (within predefined timelines), adhere to other general/specific regulatory controls such as good manufacturing practice (GMP) and adequate directions for use or a clear definition of an unsafe dosage or methods or duration of application. There are basically three pathways for MDs in the U.S.

i) Pre-market notification (PMN) also termed as the 510(k) pathway, which requires device manufacturers to register and notify the FDA (at least 90 days in advance) of their intent to market a MD. The 510(k) submission must demonstrate how the proposed MD is substantially equivalent (SE) to a MD that is already approved and on the U.S. market (a predicate). This advance notification period is meant for FDA to determine whether the proposed device is SE to a predicate device or not. The order from FDA, clearing the device is a must for commercial distribution under the 510(k) pathway.

ii) Premarket approval (PMA) pathway, is a stringent type of device marketing application. The FDA determines whether the application has "sufficient and valid scientific evidence that provides reasonable assurance that the device is safe and effective for its intended use". FDA has 45 days to determine whether the application is sufficiently complete to begin a substantive review, and needs to notify the applicant accordingly. The PMA review is a 180 day process.

iii) Humanitarian device exemption (HDE) pathway- A humanitarian use device (HUD) is one that is expected to treat or diagnose conditions that affect fewer than 4,000 individuals in the U.S. annually. Within the FDA, the Office of Orphan Products Development handles HDE. The application for an HDE is comparable to that for a PMA, except for that one need not provide scientific evidence of efficacy by justifying that it could take years to do a clinical study with a statistically significant sample size (4).

Passage of the Medical Device User Fee and Modernization Act (MDUFMA) of 2002, instituted user fees for pre-market reviews of MDs. The FDAs Reauthorization Act (FDARA) of 2017 reauthorized the MD user fee program (MDUFA IV). For fiscal year 2019, the 510(k) notification, attracts a user fee of \$10,953, while the annual fee for Class III MDs is \$11,275. There is also an annual establishment registration fee of \$4,884. It also authorized among other things, risk-based inspection scheduling for device establishments. The classification system at FDA is based on intended use and level of risk associated with the device, rather than on technologies and procedures (5).

Class I includes devices that are subject to only the 'general controls' such as registration and listing, record keeping, GMPs, and other general provisions of the Act. Most of the devices under this class are exempt from premarket review.

Class II includes those that are subject to not just 'general' but 'special controls' as well such as performance standards, post-market surveillance, patient regulations, or guidance documents. Most of these require only pre-market entry notification, while some are exempt from 510(k).

Class III devices, represent the highest level of risk and require PMA through the submission of clinical and nonclinical data (e.g. design and manufacturing data) to demonstrate safety and effectiveness, but not necessarily

efficacy. Devices that are not found by the FDA to be SE to a predicate, require PMA letter from FDA.

Most devices (barring a few exemptions) are required to carry a Unique Device Identifier (UDI) so as to maintain traceability throughout the entire distribution chain. The FDA-accredited issuing agencies for UDI are GS1 (www.gs1.org); Health Industry Business Communications Council (HIBCC - www.hibcc.org); and International Council for Commonality in Blood banking automation (ICCBBA – www.iccbba.org).

FDA is also making efforts to revamp the 510(k) process, wherein MD firms would have to base new products on devices that are not older than 10 years. The guidance offers manufacturers additional flexibility in how to demonstrate substantial equivalence between a new device and a predicate device. However, some sections in the industry feels that the proposed 10-year cut off criteria could be subjective (6). In FY2019, FDA has released guidance documents focusing on supporting continued innovation and safety in digital health realizing that digital health devices have the potential to improve our ability to accurately diagnose and treat diseases (7). As part of its aim to help accelerate MD product development, CDER intends to publish additional guidance documents in FY2019 and update, or delete guidance documents that no longer represent the agency's current thinking on regulatory issues.

3. Europe

In the EU, since the 1990s there have been 3 harmonized Directives that apply to MDs viz:

- Medical Devices Directive 93/42/EEC
- Active Implantable Medical Devices Directive 90/385/EEC
- *In Vitro* Diagnostic (IVD) Directive 98/79/EC

These Directives outline the safety and performance requirements for MDs and classifies them as Class I, IIa, IIb and III. The manufacturers have to meet the requirements of the EU Directive to get the *Conformite Europeenne* (CE) marking on a MD. For marketing and distribution of the MDs in the EU without additional controls, CE marking is mandatory. For certification, the manufacturer may apply to the Notified body (NB, defined as a public or private organization that has been accredited to validate the compliance of the device to the European Directive) of their choice in any EU country (8).

In September 2012, the European Commission adopted a proposal for a separate regulation on MDs and on *in vitro* diagnostic (IVD) MDs. The main reasons behind coming up with new regulations were the problems with diverging interpretation of the current Directives as well as the incident concerning fraudulent production of the PIP silicone breast implants, which highlighted weaknesses in the legal system in place, thereby bringing down the confidence of patients, consumers and healthcare professionals in the safety of MDs (9). The new MD Regulation (EU) 2017/745 and IVD Regulation (EU) 2017/746 entered into force on

25th May 2017. It will replace the existing three Directives and will be applicable from May 2020 (for MDs); and by mid-2022 (for IVDs). The manufacturers have been given this transition period to adapt to the new MD/IVD regulations. Till such time the NBs are designated to certify against the new regulations, all MDs must satisfy the essential requirements specified in these Directives.

The key changes brought about in MDR (EU) 2017/745, include (10):

- Inclusion of aesthetic products & devices manufactured using devices of non-viable human tissues or cells
- Manufacturers to provide summary of safety and clinical performance to the public (for Class III devices & implants)
- Post-market clinical follow up requirements
- ‘Common Specifications’ for high risk MDs

On the other hand, the key changes brought about in IVD Regulation (EU) 2017/746, include (11):

- Genetic testing
- Performance evaluation
- Reference laboratory testing
- New risk classification system for diagnostic MDs
- Involvement of NB, in majority of diagnostics

The new MD and IVD regulations are expected to bring in more scrutiny of technical documentation; have stricter measures for NBs (resulting in a drop in their numbers); provision for unannounced visits of sites by NBs; liability coverage, especially for ‘authorized representative’; strengthened Clinical trial (CT) rules and post-market clinical follow-up addressing concerns over the assessment of product safety and performance (12). The Eudamed Database and associated electronic systems of the Commission, too are designed to result in better traceability of devices through the supply chain, bringing in overall transparency and better access to information to the public. However, there are also apprehensions from certain experts that the stringent regulations will lead to delays in getting CE mark approvals and bring in a significant reduction of innovative MDs receiving CE mark. The EU MDR is expected to dramatically alter the operations of MD manufacturers and even impact the composition of their existing as well as future portfolios (13). Companies would need to revisit their product portfolio in light of the MDR/IVDR, and develop a comprehensive regulatory strategy to implement the changes to stay compliant.

4. India

In India prior to 2005, very few MDs such as disposable hypodermic syringes, condoms, tubal rings and metered dose inhalers were required to be registered. In October 2005, the Ministry of Health (MoH) further

notified 10 sterile devices (“Notified Medical Devices”) and consequently regulated those through the Central licensing authority (Central Drugs Standard Control Organization, CDSCO) their import, sale and manufacture under Drugs & Cosmetics (D&C) Act. In June 2006, CDSCO introduced MD guidelines. In January 2017, Indian MoH notified via GSR. 78 (E) separate regulation ‘Medical Devices Rules, 2017’ (effective from 1st January 2018) covering all major aspects right from definition, classification, roles of NBs, procedure for grant of CT approval, manufacturing or import license, labelling, post approval changes, and applicable fees for filing applications (14). It is a risk based classification with Class A (low risk), Class B (low-moderate), Class C (moderate-high) and Class D (high risk). The components and accessories to a MD or companion IVD devices have been separately classified. The notification includes a listing of a total 351 MDs in 16 categories with their risk class as well as another list with a total of 247 IVD devices in 22 categories with their risk class as per the applicable provisions of MDR, 2017 (15).

The Indian Pharmacopoeial Commission (IPC) has also brought out draft guidance in 2018, which serves as an essential reference manual for MD industry, policy makers and healthcare professionals. Under the new rules, registration of manufacturing facility is no longer required to be done. ‘Third Party Conformity Assessment and Certification’ through NB’s has also been included. The NBs (which could be from within or outside India) are accredited by the National Accreditation Board for Certification Bodies (NABCB) and are permitted by the government to audit all MDs and their manufacturing sites, to verify that they conform to the quality management system and all other applicable standards prescribed by the Bureau of Indian Standards (BIS). Where no relevant standard of any MD has been laid down, such device shall conform to the standard laid down by the International Organization for Standardization (e.g. ISO 13485) or the International Electro Technical Commission (IEC), or by any other pharmacopoeial standards. Manufacturing of Class A and B MDs are regulated by State licensing authority (SLA). However, manufacture of Class C and Class D MDs are regulated by the CDSCO and could attract pre-inspection of the manufacturing facility. SLA oversees sale and distribution of all the 4 classes of devices (5). One can obtain license for manufacturing & distribution or import and subsequent distribution/sale, by applying in specific forms, which is dependent on class of MD & whether manufacturing is to be carried out at one’s own premise or at 3rd party premise (under loan license). Some of the forms used to apply or obtain license are enlisted below:

- Form MD- 1: Application for grant of certificate of registration of a notified body.
- Form MD- 3 and 4: Application form to obtain a license to manufacture for sale/distribution of MDs in Class A & B at own premise, and under loan license, respectively.

- Form MD- 5 and 6: License issued for manufacturing of Class A & B MDs at own premise, and under loan license, respectively
- Form MD- 9 and 10: License issued for manufacturing of Class C & D MDs at own premise, and under loan license, respectively
- Form MD-14: Application form to import MDs from overseas manufacturer
- Form MD-15: License issued to import and for sale/distribution of MDs in India

Provisions for regulation of CTs of investigational MD (i.e. new devices) have also been included under the

new rules. There is a two-tier CT process, in which safety needs to be assessed in a smaller number of patients (pilot/exploratory) before a larger pivotal (confirmatory) efficacy study is initiated. For *in-vitro* diagnostics (IVD) devices, ‘Clinical performance evaluation’ needs to be furnished. Application fees for some key submissions are tabulated below (Table 1). Imported MDs where the manufacturer possesses a ‘Certificate of Free Sale’ in Australia, Canada, Japan, the EU, or the US are not subject to CTs. Commercially available MDs are required to include either its package insert or user manual. In addition, manufacturers are required to notify major adverse events reported globally within 15 days to CDSCO.

Table 1 Regulatory filing fees for registration, licensing, import and conduct of clinical investigation

Notified Body		
Registration	INR 25,000	
Manufacturing license or loan license		
Class A or B	Per site: INR 5,000 and for each distinct MD: INR 500	
Class C or D	Per site: INR 50,000 and for each distinct MD: INR 1,000	
Clinical		
Permission to conduct pilot or pivotal clinical investigation.	INR 1,00,000	
Permission to conduct clinical performance evaluation	INR 25,000	
Import license		
	For MD	For IVD devices
Class A	Per site: \$1,000 and for each distinct MD: \$50	Per site: \$1,000 and for each distinct IVD device: \$10
Class B	Per site: \$2,000 and for each distinct MD: \$100	
Class C or D	Per site: \$3,000 and for each distinct MD: \$1,500	Per site: \$3,000 and for each distinct IVD device: \$500

In order to restrict the cartelization and unethical profiteering at every level in MD sector, India’s price regulator – National Pharmaceutical Pricing Authority (NPPA), has been trying to bring in more number of MDs under the ambit of National List of Essential Medicines (NLEM). Once under NLEM, such devices will automatically fall under the purview of price control and companies will be forced to import/manufacture/sell them at an MRP fixed by the regulator (5). As of February 2019, 23 MD categories have been notified to be regulated by CDSCO. All implantable MDs and other high end equipment’s like CT scan & MRI scan equipment’s, Defibrillators, X-ray machines etc. too have been notified. MoH has decided now to regulate manufacturing, import and sale of all MDs across the country, and implement it in a phased manner. MoH is also contemplating setting up a national registry for all implantable high-risk MDs (in lines of UK and Australian agency registries) to effectively monitor their adverse events in patients. It would also facilitate issuance of safety alerts to manufacturers and consumers. The country’s highest advisory body - the Drug technical advisory board (DTAB), has recommended to government to constitute a separate vertical body under CDSCO and hire officers to regulate the manufacture and sale of MDs in the country (16). In its effort to consolidate its database of MDs, MoH is also insisting upon MD companies to register their devices on

CDSCO portal. It is also proposed that from 1st January 2022, each MD approved (for manufacture for sale, distribution or import), must have for better traceability a ‘Unique device identification number’ which would have details of Global trade number, Production identifier number (Lot number, software version, etc.). India’s new MD rules are by and large aligned with the global device regulations as in Global Harmonization Task Force countries (GHTF, a voluntary international group of representatives from MD regulatory authorities and trade associations from Europe, US, Canada, Japan and Australia). For a sector, where there were no separate regulations, this is a welcome move.

5. Conclusion

Diverse international regulatory requirements necessitate developing an integrated regulatory strategy and plan which could be adopted for registering MDs in different countries and for streamlining their business planning. Regulatory agencies need to work towards achieving harmonization of systems and processes to raise the standards of MDs in their respective country (17). Despite pathways being laid down for approval of MDs, there are devices which are being sold outside of the established distribution chain without following the regulatory norms. Globally, the regulators have been trying to identify and plug in the loopholes and combat their unlawful sales. With India’s joining the list of

select countries with MD legislations, it is expected to ease regulation of MD import, manufacturing and development by freeing the industry from rules which were designed primarily for the pharmaceutical sector.

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Conflict of Interest

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