Indian Heart Journal 69 (2017) 1–5

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Editorial

FDA, CE mark or something else?—Thinking fast and slow

ARTICLE INFO

Keywords:
Device regulation
Substantial equivalence
MDA
PMDA
CE mark
EC type examination
Notified body
510 K
PMA
STED
Harmonization of regulatory approvals

ABSTRACT

There is a robust debate going on among the Medical Device stake-holders whether FDA is better or CE mark or something else. Currently process of obtaining an FDA approval is bogged down by ever-increasing unpredictability, inconsistency, prolonged time, and huge expense but CE mark has its own problems. Historically, the Japanese review process has tended to be the slowest among the big three but recently with the introduction of accelerated review process there has been a significant progress. While the goal of an innovator/manufacturer is to develop, manufacture and market a medical device that addresses an unmet clinical need, the requisite regulatory approval process can be very confusing. Not only there is a whole lot of jargon tossed around by regulatory affair professionals: "substantial equivalence," "PMDA," "CE mark," "Notified body," "510K" and "PMA" but the actual approval process can also be very tardy, inconsistent and expensive.

1. Introduction

"Developing a medical device that will be subject to scrutiny by FDA often strikes fear in the hearts of design engineers"

The regulation of medical devices is a relatively recent phenomenon unlike drug regulation which commenced in the late 60s, a knee jerk response to thalidomide tragedy. In US the Bureau of Medical Devices and Diagnostic Products was established in 1974 and Medical Device Amendments to the Food, Drug, and Cosmetic Act were enacted, to assure safety and effectiveness of medical devices in 1976. The formal regulation of medical devices in the Europe only began much later (in the mid 1990s).[1] However, device regulation has been distinguished from drug regulation only very recently. Despite global efforts to harmonize regulation of medical devices via groups such as the Global Harmonization Task Force (GHTF), there is a huge discrepancy among regulators all over the world. The differences lie in the concept, the classification of devices, the overall process, the quickness of approvals, their applicability across regions and the expense involved. Currently US contribute to 38% of medical device market, Europe ~ 25%, China ~ 21%.[2]

2. PIP breast implant scandal

The "PIP Breast Implant Scandal" brought the field of device regulation to the fore. Greater emphasis on physical appearance has led to a growing number of breast augmentation procedures among women in developed countries. As a matter of fact, breast implantation has become the second most common surgery performed in USA. Poly Implant Prothèse (PIP) was a French company that produced silicone gel breast implants. However, the company was preemptively liquidated following the revelation that they had been manufacturing and selling breast implants made from cheaper industrial-grade silicone (instead of the mandated medical-grade silicone they had previously used). The hundreds of thousands of implants sold globally by PIP from 2001 to 2010 were found to have a 500% higher risk of rupturing or leaking (than approved models), as well as being implicated in several deaths due to systemic toxicity and even cases of induced breast cancer.[3] The scandal, which produced fears of a massive health disaster, prompted a full recall of the company's implants by the French health ministry in 2010. All these "dangerous" implants had a CE mark on them but they had not been awarded a FDA approval yet because of "healthy ambivalence" among FDA regulators. Was this a failure of regulation or something else? This scandal brought to fore dialectic that while CE mark (vs. FDA approval) was quicker and easier to procure, was it safe enough?

3. Is CE mark directly comparable to US FDA or Japanese PMDA?

The simple answer is no. Conceptually, each of these regulatory processes differ in the aims of regulation and the process involved:

http://dx.doi.org/10.1016/j.ihj.2016.11.327

3.1. Aim of regulation

Essentially, the CE marking process focuses primarily on safety, but also on reinforced manufacturer obligation with respect to device claims i.e. to ensure that the device does what it claims to do. The FDA does this too, but has the additional requirement of evaluating efficacy. Once efficacy is evaluated, its value is also determined. In other words it also answers the question: 'does healthcare really need this device?' Finally, all this is indirectly but ultimately linked to healthcare reimbursements. Japanese PMDA also looks at the quality, efficacy and safety of the device. The CE relies more on self-regulation and conformity assessment whereas FDA relies more on approval by regulatory bodies.

3.2. Process of regulation

The regulatory process for CE mark is rather simple. It involves following the medical device directive (93/42/EEC) to identify conformity assessment procedures for that particular product. For Class III devices (implantable devices, which require highest assurance of safety and effectiveness before they can be used in clinical setting) essentially there can be two conformity assessment routes:

1. EC type examination (Module B) by a notified body followed by either device verification or production quality assurance audit by the notified body.
2. Full quality assurance (Module H) and design dossier examination by notified body.

Based on requirements of conformity assessment route chosen, a technical file is compiled and certification is obtained by a notified body. Subsequently the device manufacturer has to declare conformity and appoint an Authorized Representative.[4] Finally, CE Mark can be affixed to the product and/or its packaging and accompanying literature. After marketing the manufacturers are responsible for post-marketing surveillance. In devices Class I or Class II devices the regulatory process is even simpler.

3.2.1. Notified bodies

Notified bodies are standards organizations/companies supervised, audited and designated in each Member State of the European Union by the relevant Devices Agency (Competent Authority) of each country. They are the premarketing assessors responsible for the higher risk devices, overseen and audited by the National Agencies. The Notified Bodies check the development and the designs of the device by manufacturing plant visits and audits. They also review the clinical studies, which have been undertaken, monitor the quality control procedures and the production of the device.[1]

3.2.2. EC-type examination

EC-type examination is the part of a conformity assessment procedure in which a notified body examines the technical design of a product and verifies and attests that the technical design of the product meets the requirements of the legislative instrument that apply to it. It may be carried out in either of the following manner:

— examination of a specimen, representative of the production envisaged, of the complete product (production type),

— assessment of the adequacy of the technical design of the product through examination of the technical documentation and supporting evidence with/without examination of specimens.

3.2.3. Post-market surveillance

The EU relies more on post-marketing surveillance than on pre-marketing one. For example British Medical Device Agency (MDA), through its two complimentary schemes of Vigilance reporting and the Adverse Incident Scheme undertakes the process of surveillance. The first is mandatory for the manufacturer and concerns serious adverse incidents, whilst the second is voluntary and directed towards users.

The regulatory process with FDA, on the other hand is rather cumbersome. If the device manufacturer claims equivalence to a pre-existing approved device in market, it can go for pre-market notification [510(k)]. The philosophy of this process involves proving substantial equivalence between the new device and the predicate (legally marketed) device, rather than an independent demonstration of the new devices'safety and effectiveness. The substantial equivalence should be not only in terms of technological and design characteristics but also on performance data and should have same intended use as the predicate device. If substantial equivalence cannot be established the device is categorized as Class III and generally requires pre-market approval (PMA).

3.2.4. Process of pre-market notification [510(k)][5]

1. Pre-market notification submission made by the device manufacturer (at least 90 days before device introduction into market). The submission includes information on description of device, explanation of how the device functions, scientific concepts that form the basis of this device and significant physical and performance characteristics.
2. FDA classifies the device in appropriate device category.
3. If device is classified <Class III, it falls within the ambit of 510(k) and requires substantial equivalence to be proved in terms of technological characteristics, non-clinical bench performance/analytical studies, non-clinical animal and/or biocompatibility studies and clinical performance data. Table 1.
4. FDA can request for additional performance data on any of these aspects and keep the notification on hold (till it is satisfied with the data).

Table 1
Process of establishing substantial equivalence.

1. Technological characteristics (materials, design, and specifications).
2. Non-clinical bench performance or analytical studies- these may include a variety of tests –
   i) mechanical, electrical, and biological engineering performance, such as fatigue, wear, tensile strength, compression, flow-rate, burst pressure;
3. electromagnetic compatibility;
4. sterility;
5. stability/shelf life;
6. software validation;
7. other forms of non-clinical, including device-specific.

- Non-clinical animal and/or biocompatibility studies are typically requested when other forms of non-clinical bench performance testing are not sufficient to demonstrate substantial equivalence.
- Clinical performance data – When analytical or non-clinical bench performance testing data, or non-clinical animal and/or biocompatibility studies are insufficient, or available scientific methods are not acceptable, e.g., the scientific methods are deemed unacceptable because they are not clinically validated or are not supported by a valid scientific rationale, FDA may request clinical performance data to support a substantial equivalence determination.

5. If FDA is convinced that data is unable to prove substantial equivalence it can refuse notification and categorize it as Class III device.

3.2.5. FDA pre-market approval

A Premarket Approval (PMA) application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the class III device. There are administrative elements of a PMA application, but good science and scientific writing is a key to the approval of PMA application.[6] Conceptually, the review of a PMA is a four-step review process (details of this process are given in Table 2) consisting of:

- Administrative and limited scientific review by **FDA staff** to determine completeness (acceptance and filing reviews);
- In-depth scientific, regulatory, and Quality System review by appropriate **FDA personnel** (substantive review);
- Review and recommendation by the appropriate advisory committee (**panel review**); and
- Final deliberations, documentation, and notification of the FDA decision.

3.2.6. Data requirements

Stringent data requirements are to be met before approval can be considered. The data requirements pertain to technical sections, non-clinical laboratory studies and clinical investigations. Table 3. Generally clinical studies should be conducted in US. However, a study conducted under an investigational device exemption (IDE) outside the United States and submitted in support of a PMA must comply with the IDE regulation (21 CFR 812).

*3.2.7. Panel review **(21 CFR 814.44)***

FDA may refer the PMA to an outside panel of experts (advisory committee). In general, all PMAs for the first-of-a-kind device are taken before the appropriate advisory panel for review and recommendation.

3.2.8. Japan PMDA

Traditionally, Japanese had the slowest approval process. However with the institution of an **Action Program** there has been a significant progress.[7] An essential component of this plan is an accelerated review process which involves review of prior assessment, readiness for introduction of risk-management plan and utilization of medical information database. This Action Program also focuses on increasing the number of PMDA reviewers, increasing review fees, outsourcing designated Class II device reviews to registered certification bodies, a three-track review process, semiannual evaluation of review performances based on objective measures and an overall reorganization of the review department within Pharmaceuticals and Medical Devices Agency (PMDA).

The Japanese approval process is essentially approval of two aspects:

1. Device – This involves review against essential principals and summary technical documentation (STED) data subsets.
2. Manufacturing facilities – data reliability, GLP, GCP, GMP conformity, post-approval inspection.

3.2.9. Essential principles in Japan

It is a checklist of conformity to the essential principles (EP) specified in "the Standards for medical devices" as stipulated by the Japanese law. Broadly these EPs pertain to design and manufacture (toxicity, compatibility, hardness, wear and degree of fatigue, handling, etc), risk management, performance and function, durability, transport and storage and benefits of device.

3.2.10. STED

Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED) is a practical method to harmonize device regulation and bring Japan in line with other international regulatory bodies.[8] Similar in principle to FDA 510(k) it attempts show equivalence of a new device with a predicate device. It attempts to develop a common regulatory format for all the major regulatory bodies.

4. Regulatory bodies in developed world

In Canada, the Medical Devices Bureau of the Therapeutic Products Directorate is the regulatory body which requires Class III and IV device manufacturers to submit a Premarket Review Document (a summary of safety, effectiveness and clinical studies).

Table 2
Steps in the PMA Application Process.

1. ODE (Office of Device Evaluation) filing review
2. OSB (Office of Surveillance and Biometrics) statistical review for filing
3. OC (Office of Compliance) review of manufacturing information for compliance with the Quality System regulation (21 CFR 820).
4. PMA filing decision
5. Day-100 Meeting
6. Quality System Inspection(s) by the FDA field personnel. An FDA manufacturing inspection is conducted for all original PMAs and may be conducted for PMA supplements requesting approval of alternate or additional manufacturing and sterilization facilities.
7. Bioresearch Monitoring (BIMO) Audit (audit of clinical study data)
8. Substantive review coordination and completion in areas such as:

- Preparation of FDA Summary of Safety and Effectiveness Data (SSED)
- Nonclinical Studies
- [Microbiological, Toxicological, Immunological, Biocompatibility, Shelf Life, Analytical (for IVDs), Animal, Engineering (Stress, Wear, Fatigue, etc.)]
- Clinical Studies
- Panel Meeting Decision and Mailing (if panel meeting is appropriate)
- Panel Date (if appropriate)
- Transcripts Received, Reviewed and Placed in Administrative Record
- QS/GMP Clearance
- Final Response from OC for GMP/BIMO
- Final ODE Decision Memo
- Approval Package
- Approval Order, SSED, Final Draft Labeling

Table 3
Data Requirements.

1. Technical Sections: The technical sections containing data and information which should allow FDA to determine whether to approve or disapprove the application.
2. Non-clinical Laboratory Studies Section: Non-clinical laboratory studies section includes information on microbiology, toxicology, immunology, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests.
3. Clinical Investigations Section: Clinical investigations section includes study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information from the clinical investigations

The Therapeutic Goods Administration (TGA) is medical device regulator in Australia, where device approval is similar to Europe. Korea's regulatory authority is the Korea Food and Drug Administration (KFDA) which requires higher risk device manufacturers to submit a Technical File followed by type testing by a third party and clinical study data as part of the submission. Korean Good Manufacturing Practices certification is also to be obtained (via a third party organization which works together with KFDA) by conducting a compliance evaluation. Currently, Singapore also requires product registration but devices which are already approved in another market such as the U.S., Canada, or Europe may follow an abbreviated registration process.

5. Regulatory bodies in less industrialized world

In many parts of developing world, regulation of devices is still evolving. Western regulatory bodies rely on data from clinical studies performed in West. They generally include Caucasian populations, but have very few participants from other races, with typically <1% Asian population. Furthermore, even if population differences are not considered, the practice environment in West is much different from many parts of the World.[8] Thus there is a healthy on-going debate whether West developed regulations are sufficient for this part of world as well or country specific clinical studies are required (enrolling population from index area). A pragmatic approach to this issue may be to apply the principle of "substantial equivalence" here as well. If the index population can be shown to be equivalent (with respect to given outcomes) to the "predicate" population, there may be no need to undertake a fresh study –"to re-invent the wheel." However, despite this, the differences in practice environment will have to be considered and applying the principle of substantial equivalence may be warranted, here as well. A good solution to circumvent this problem could be to enroll a diverse population all over the world in the "initial" study itself. Thus there is a need to relook whether Western guidelines and regulatory framework developed in context of these guidelines is applicable to vast majority of population swath all over the world.

In China the medical device regulatory authority is the State Food and Drug Administration (SFDA), The approval requires submission of a dossier to the SFDA as well as type testing. Class III products (manufactured outside of China) are subject to an onsite product audit and are also likely to require clinical studies conducted in China prior to approval, in particular for devices which contact the central nervous system.

In context of Latin American (LATAM) countries there are efforts to harmonize regulations, so that now regulatory process in most countries is broadly similar. The basic features are:

- Require a Technical File or Report similar to a CE Technical File (technical description, device safety test results, biocompatibility data, labeling, etc).
- A Certificate of Free Sale (CFS) issued by the public health authority in the country of origin, which demonstrates that the device is cleared for sale in origin country.
- Product registration for 5 years (in most countries)
- Devices are classified into four risk classes (I, II, III, and IV), ranging from low risk to high risk.
- Most countries require certain regulatory documents to be translated into local language, and notarized.

However, there are some differences. In Brazil (the largest medical device market in LATAM) the approval process is most meticulous but also notoriously lengthy and submission costs are the most expensive in entire LATAM. In Mexico on the other hand, the devices that are cleared for sale in the U.S. or in Canada can undergo a fast track process where the only requirement is to get the technical documents translated into Spanish and notarized.

Hong Kong does not currently require medical devices to be registered in order to be commercialized and registration is voluntary. New Zealand's medical device regulator is called MedSafe under Ministry of Health. Devices must be registered on MedSafe's database. There is no pre-market approval process in New Zealand. A local sponsor that has the legal responsibility for the medical device must be identified by the manufacturer.

6. Tips to regulatory process

Among all the regulatory processes the quickest and the cheapest is 510(k). Thus if the new device is similar to some existing, approved device and it is possible to prove substantial equivalence to it, it may quickly get an approval. Once US pre-approval notification is achieved it would be easier to go for Japanese PMDA approval (STED route) and simultaneously apply for CE Mark. On the other hand if substantial equivalence is not possible/cannot be proved, then it may be easier to go for CE Mark as also plan a US clinical study in guidance with US FDA. In the initial international study, it could be a good idea to enroll some patients from India, China and other countries as well so that this study can be used in regulatory processes of these countries as well.

7. Advantages and limitations of current regulatory bodies

CE Mark certifies that the medical device conforms to the European Standard of electronic engineering and that its use is considered reasonably safe. The process is simpler, less expensive and it relies more on self regulation (the onus is on the manufacturer) and post-marketing surveillance. However, CE is only half-way mark because re-imbursement approval will still be needed for each individual country. Regarding FDA approval, 510 (k) is simpler and quicker and relies on proving substantial equivalence. With 510(k), the quality management system assessment may be delayed and the device placed on market (whereas quality management system assessment happens before approval in CE mark) for some time. FDA inspects to 21 CFR 820 only sometime after 510(k) clearance is given, even a year or so later. However, if substantial equivalence cannot be proved the approval process i.e. PMA could be lengthy, expensive, inconsistent (instances of early recall) and generally requires a

Table 4
Comparison among regulators.

	FDA	CE	PMDA
Concept	Safety, Efficacy and Device consistency	Only Safety and Device consistency	Safety, Efficacy and Device consistency
Process	Tedious and inconsistent	Simple and consistent	Simple and consistent
Speed of Approval	Slow if PMA required	Fast	Fast
Pre-Approval	More important	Less important	More important
Post-approval Surveillance	Important	Very important	Important
Responsibility	Both Manufacturer and Regulator	Self regulation	Both Manufacturer and Regulator
Applicability	Whole of US, Mexico	EU but approval by individual country still required	Japan

clinical study conducted in USA. On the brighter side, once achieved, it is directly applicable to not only in all US (38% of world market), but also in Mexico and indirectly to many other countries of the world. Japanese PMDA now relies on accelerated review process and is also working on the concept of substantial equivalence particularly with FDA approved devices. Comparison of three regulatory bodies is discussed in Table 4. An issue with all these regulatory processes is that even if some of them look at efficacy (FDA, PMDA), they certify to only a threshold of efficacy. In other words it confirms a certain level of quality but is unable to differentiate/discriminate between value of approved products i.e. unable to determine the relative usefulness of product and thus its fair re-imbursement price. Another major limitation of these regulatory bodies is that there is no mechanism of recall (once approved) even after a product has outlived its usefulness and has even become obsolete.[9]

8. Harmonization of regulatory approvals

Harmonizing regulatory approval processes is the need of the hour and may benefit not only device industry but individual country as well (by allowing a beneficial innovation to reach quickly to the needy and at a cheaper cost). The idea is to have a standardized format and submit essentially the same documentation to more than one Regulatory Authority or Conformity Assessment Body (in all regulatory classes). In 1992 GHTF, a voluntary partnership between government and industry representatives from the US, Australia, Canada, the EU and Japan joined together to promote international harmonization in the regulation of medical devices. Subsequently, countries such as Japan, Australia and Canada have adopted this harmonized approach as an acceptable format and content, within their regulatory framework. There is also a Japan–US "Harmonization-By-Doing" (HBD) Pilot Program which was launched in December 2003 to develop harmonized clinical trials and clinical trial requirements between Japan and the US along with a focus on regulatory convergence.[10]

9. Back to PIP breast implant scandal

At the peak of the PIP scandal it was considered a failure of EU regulation. However, it has to be appreciated that this is not a failure of regulation, rather an illegal activity, substituting an approved clinical grade material with industrial grade material, a case for law enforcing agencies rather than regulators.

10. Conclusions

There are multiple regulatory bodies all over the world with a different aim, process and application. This creates a lot of confusion in the minds of manufacturers. There is a need for harmonization, rationalization and standardization of submission process.

"*When a man cannot choose, he ceases to be a man*"

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Available online 27 December 2016