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Review Article

A COMPARATIVE STUDY OF MEDICAL DEVICES AND THEIR REGULATIONS IN US, EU, INDIA, AND CHINA

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ABSTRACT

The usage of medical device is on the rise due to the rise in incidence rate of chronic diseases, irregular health check-ups, and sedentary lifestyles and also rising cases of obesity, diabetes, neuro-based disorders, heart diseases, and chronic diseases relating to lifestyle disorders. Availability of hassle free home monitoring medical devices that can be used even by patients with no knowledge about the technical aspects made their way into patient homes. Even in the presence of restraining factors such as high cost and reimbursement issues, the opportunities for medical device professionals lie in the technological advancements and usage of internet of medical things in modern healthcare and the latest trend toward developing smart medical devices with fast development in (AI) and (ML). The usage of medical devices is on the rise due to medical device development is undergoing a huge technological advancement due to emergence 3D printing which allows development of devices designed specifically as per patient requirements. Medical devices like freestyle liber system by Abbott laboratories eliminate need for routine finger pricking as it has sensor that measures and records glucose levels through clothing of the consumer. Quickie Q300 M mini Wheelchair fits even in tight doorways, navigates restaurants, that are crowded and also in difficult living spaces. Harmonization of medical devices registration across the markets is essential to paue way for their easy approval and also in dealing with the withdrawn issues related to quality, safety, and performance. This review involves a comparative study of medical device regulations in four regions (US, EU, India and China).

Keywords: MDR, MDD, Pre-market notification, NB, CE marking.

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INTRODUCTION

In 1976, Congress responds the medical device amendments to the FD and C act, giving to FDA to control the power of device. FDA may have filed accusations of adulteration or misbranding before the medical device amendments, but it lacked the power to ask for premarket testing, review, or approval. FDA's medical device authority has changed as a result of subsequent legislation, most recently the FDASIA of 2012 [1].

In EU From 2009 through 2016, the market for medical devices in Europe is anticipated to expand at a CAGR of about 7%, surpassing $150 billion.

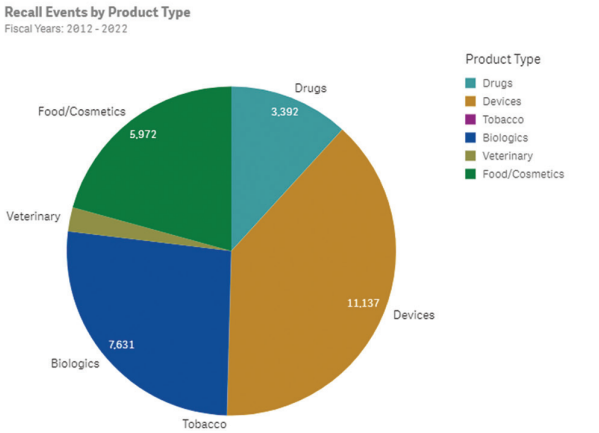
The updated Medical Device Directive, 2007/47/EC, was approved in September 2007 and went into effect in March 2010. According to the medical device in the EU market, it must have CE labeling, and to obtain a CE certificate, the maker must adhere to EU directives [2].

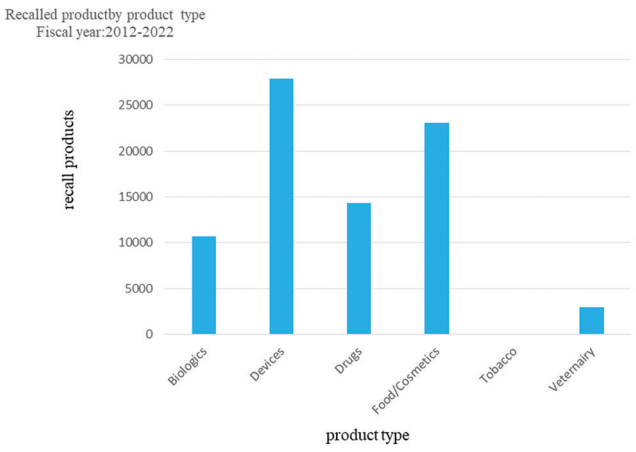
The NB that can be chosen by the manufacturer in any EU nation directly manages high-risk equipment. Design reviews and CE certificates from notified bodies should be submitted to the competing authority for products in higher risk classes. The notified bodies are in charge of CE marking (NBs) [3,4].

In 2007, the Indian medical device market was ranked fourth in Asia and placed in top twenty in the world. According to Global Data, the medical device marketed in India will grow rapidly, rising from $10.4 billion in 2014–$17.6 billion by 2020, and representing a 9.4% CAGR. However, more than 70% of equipment sold in the country is imported, the majority of which comes from the United States [5,6].

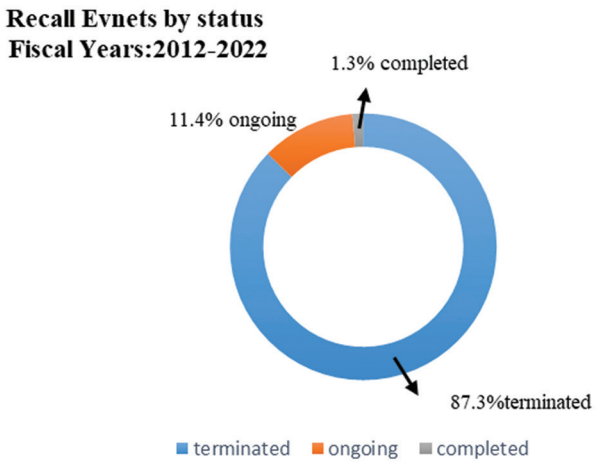
State food and drug administration (SFDA's) pre-market approval is required for manufacturers before they may sell their products in China.

The regulations for the supervision and administration of medical device in China consist of two primary rules that must be fulfilled (2000) [1].





From the data available from USFDA, when compared to the other products categories including biologics, drugs, veterinary, food/cosmetics, and tobacco in the US from 2012–2022, medical devices have the higher range.



According to the above pie chart, it shows that 87.3% of the recall event have terminated, 11.4% are ongoing, and 1.3% have completed.

CLASSIFICATION OF MEDICAL DEVICES ACROSS MARKETS

Table 1.

REGULATIONS OF MEDICAL DEVICES IN US

Pre-market approval (PMA)

Device producers are required by means of federal regulation to notify the FDA of their reason to market a scientific machine a minimum of 90 days before advertising.

Clinical evidence is needed. In preferred maximum, new Class III devices require Level I or Level II proof for FDA clearance. To use the device for premarket scientific trials, researchers should first achieve an investigational device exemption (IDE) [7,8].

Details of the design study can have a significant impact on the time and value of obtaining clinical device approval, and discussions with the FDA will help negotiate clinical endpoints.

PMA review

On receipt of the PMA, FDA will decide whether or not the utility is no longer sufficient to start considerable evaluation. The corporation has 45 days to decide to submit the utility and notify the applicant of the submission, and then a 180 days from the date of acceptance for a pre-market approval assessment.

If FDA rejects a PMA as insufficient, the problem is going to be a PMA reference variety and the candidate of the reason for the refusal. After 45 days of the refusal applicants can supply greater information, the 180-day clock will reset on resubmission [9,10].

Pre-marketing notification (PMN)

The PMN is also granted as a 510 (k) petition, allowing the sponsor to verify that the device is truly identical to the approved and marketed device. It is a quick process to confirm.

PMN Evaluation Process: For PMN, sponsor presents two applications (one of which must be electronic or electronic copy) and CDRH Document Control Center usage fee.

Senders are given 180 days to clarify pricing and digital reproduction issues. Once applicants have purchased a fee and an electronic copy, they will receive a confirmation letter confirming their identity. Application received date and assignment application is usually the only control known as 510K [11].

Humanitarian device exemption

Humanitarian device is expected to the treatment or illnesses that effect fewer than 4000 human beings in the US. Applying for an humanitarian device exemption is comparable to applying for a PMA, besides that no scientific proof of concept is required, as it may additionally even take years to locate sufficient topics to be ready ample to behavior a scientific trial to gain statistical importance [12].

Approved HDEs allow the use of HUDs, however only in facilities to set up a local Institutional Review Board to be in charge of medical checking out of the device, and solely after approval through the nearby IRB [13].

FDA has 30 days to behavior a regulatory evaluation to determine if the application is whole sufficient approval for notification, and then substantive review, or not approval inside 45 days of receipt (i.e., will supply extra information) supplied as needed [14].

De novo requests

Most of the new devices that do no longer have class III mechanical characterization and must go through a full PMA process and submit a class I or II authentication of scientific efficacy. However, sponsors can appeal to reclassify low-risk or moderate-risk units that had not been established as this devices.

This is categorized as *de novo*, the PMN method is an alternative to the more rigorous pre-market approval device approved as *de novo* devices, so it acts a predicates for other devices [15].

IDE

Under the food and drug cosmetic act and these guidelines, and individual institutions or organizations may sponsor studies of systems to determine their protection and effectiveness before conducting clinical trials, the sponsor should get an approval from an Institutional Review Board. Informed consent from searching subjects on enrolment in the study [16].

The investigational tool release will enable him to use the investigational tool in studies investigating the need to gather protection and efficacy statistics needed to support her 510 k submission to the PMA utility or FDA.

MEDICAL DEVICE APPROVAL PATHWAYS IN US

Figure 1.

APPROVED MEDICAL DEVICES IN US FY 2022

Table 2.

REGULATIONS OF MEDICAL DEVICES IN EUROPE

The previous AIMD directive 90/385/EEC and the MDD 93/42/EEC were supposed to be improved through the new MDR 2017/745.

In Fig 2, the following components are connected to some of the significant adjustments, expanded definition of the word medical device, which will now cover goods designed to anticipate and diagnose diseases as well as those without a clear medical purpose.

Increased Medical device evaluation as well as the reclassification of a few device types to class III, including surgical meshes and implants to replace damaged discs in the spine [19].

New (stricter) designation standards and roles for NB to ensure their possess the necessary skills and abilities.

Only under specific conditions and if the manufacturer satisfies certain requirements, new (stricter) suggestions for the notified bodies to adhere to when evaluating high-threat Magnitude III scientific devices have been released [4,20].

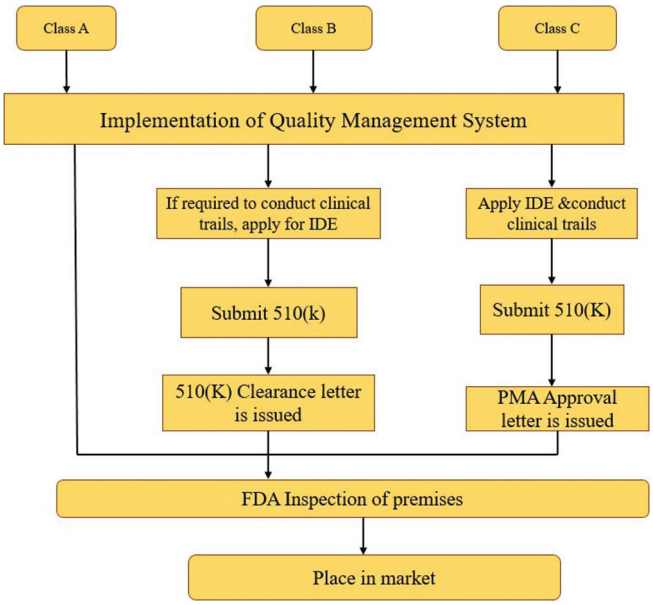


Figure 1: Medical devices approval pathway in US [17].

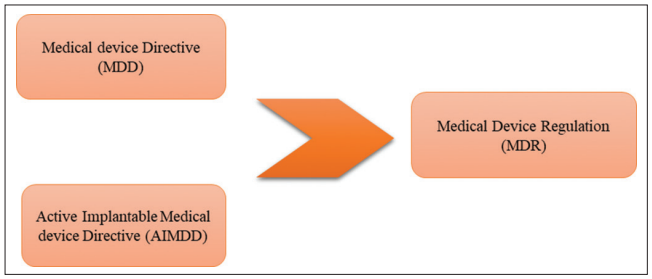


Figure 2: The changes in EU regulations

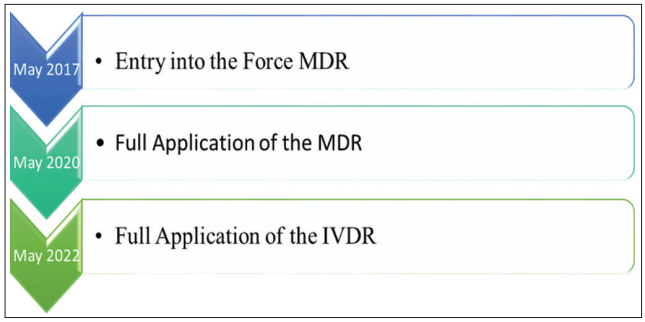


Figure 3: Timeline for implementation of the new regulations [21].

DIFFERENCE BETWEEN MDR AND MDD REGULATION IN EUROPE

New requirements in EU MDR

1. Medical devices that do not have any intended purpose medicinally
2. Medical devices with single use that is reprocessed
3. Medical devices that are intended for the purpose of sterilization, cleaning, and disinfection
4. Medical devices that are intended for incorporation of human tissues that are non-viable
5. Medicinal products that are used as Ancillaries
6. In Fig 3, Medical devices that are active and used for implantation.

Requirements from MDD that is gone

MDR had added new provisions and regulations, but there is no removal of any old provisions.

Table 1: Classification of medical devices in US, Europe, India, and China

S. No.	Countries	Classification	Examples
1	US	Class I (Low risk)	Hospital beds, adhesive bandages
		Class II (Moderate risk)	Blood pressure cuffs, sutures
		Class III (High risk)	Pace makers, vascular graft
2	Europe	Class I (Low risk)	Surgical guaze, wheel chairs
		Class II a (Medium risk)	Ultra sound equpiment
		Class II b (Medium – high)	Infusion pumps, surgical lasers
		Class III (High risk)	Stent-grafts, prosthetic joints
3	India	Class A (Low risk)	Thermometers/ tounge depressors
		Class B (Low – moderate)	Hypodermic needles
		Class C (Moderate – high)	Lung ventilator
		Class D(High risk)	Heart valves
4	China	Class I (Low risk)	Examination gloves
		Class II (Moderate risk)	Monitors, electro cardiogram machine
		Class III (High risk)	COVID-19 test kits, ventilators

Important areas of change

- Major changes – Medical device classification and UDI (Unique identifier for medical devices)
- Moderate changes – PMS, clinical evaluation requirements, and rules for classification of clinical investigation
- Small changes – The person responsible for regulatory compliance, stakeholders of medical device eco-system, and their lifecycle [22].

MEDICAL DEVICE APPROVAL PATHWAY IN EUROPE

Figure 4.

INDIAN MEDICAL DEVICES REGULATIONS

Scientific instruments are currently regulated as medicinal products by the DCGI of the Central Drugs Standard Control Organization. The lack of a distinction between medicine and tools has caused difficulty for overseas authorities in the medical device market. Entry may not made only once. Countless lists of regulated devices have to be merged with specific laws for certain devices, and some devices are no longer regulated at all [24]. With numerous new clinical entity regulation recommendations and countless other larger reforms still pending inside the Indian government, India is attempting to solve these concerns.

While these policies and reforms promise to clearly unify and expedite the method of producing and importing medical units into India, they additionally pose their own personal challenges and issues. The CLAA, a division of CDSCO, will attend meetings with the medical device advisory committee as the leading regulatory framework for scientific devices [24]. The CLAA also establishes and enforces protective standards, appoints notified bodies, oversees assessment actions, PMS, issuing of warning letters, and recalls the activities.

In 2006, the concept of a new regulation was once posted for review. The proposed act is known as the medical devices regulation bill of 2006. The new law will come into force on the December 31, 2009 [25,26].

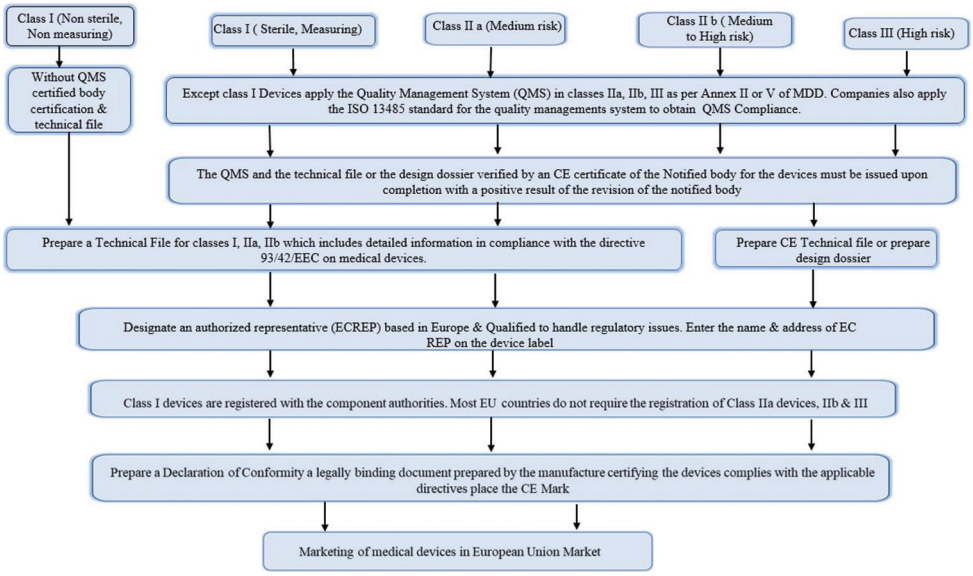


Figure 4: Medical device approval pathway in Europe [23].

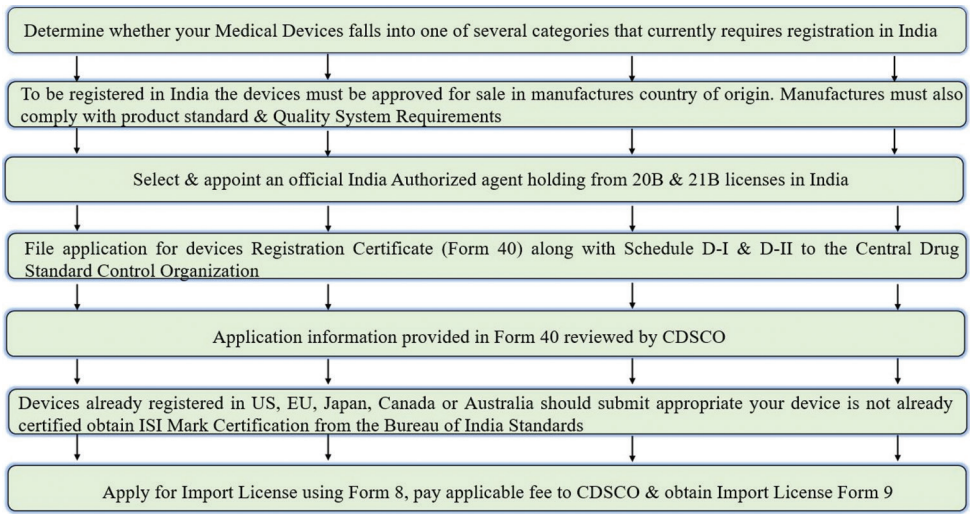


Figure 5: Medical device approval pathway in India [27].

Table 2: List of medical devices approved by USFDA in the year of 2022 [18]

S. No.	Device name	Category	Date
1	FoundationOne CDx – P170019/S014	Laboratory test	05/31/2022
2	GORE TAG Thoracic Branch Endoprosthesis – P210032	Stent	05/13/2022
3	Alinity m CMV Assay – P210022	Laboratory test	05/05/2022
4	AccelStim Bone Growth Stimulator – P210035	Stimulator	05/03/2022
5	ENROUTE Transcarotid Stent System – P140026/S016	Stent	04/28/2022
6	Organ Care System (OCS) Heart System – P180051/S001	Portable enclosure	04/27/2022
7	Thoraflex Hybrid – P210006	Aneurysm	04/19/2022
8	Aveir Leadless Pacing System – Aveir Leadless Pacemaker, Model LSP112V (Right Ventricular); Aveir Delivery Catheter, Model LSCD111; and Aveir Link Module, Module LSL02 – P150035	Leadless pacemaker system	03/31/2022
9	EVO/EVO+VISIAN Implantable Collamer Lens – P030016/S035	Implantable collamer lens	03/25/2022
10	Et Control – P210018	Software feature	03/17/2022
11	eCoin Peripheral Neurostimulator – P200036	Bladder control	03/01/2022
12	Evoke Spinal Cord Stimulation (SCS) System – P190002	Spinal cord stimulation system	02/28/2022
13	CardioMEMS HF System – P100045/S056	Heart monitor	02/18/2022
14	FoundationOne CDx – P170019/S029	Laboratory test	02/18/2022
15	Eversense E3 Continuous Glucose Monitoring System – P160048/S016	Glucose monitor	02/10/2022
16	Senza Spinal Cord Stimulation (SCS) System – P130022/S042	Spinal stimulation system	01/17/2022
17	Prometra Programmable Infusion Pump System – P080012/S068	Infusion pump	01/12/2022
18	Nucleus 24 Cochlear Implant System – P970051/S205	Cochlear implant	01/10/2022

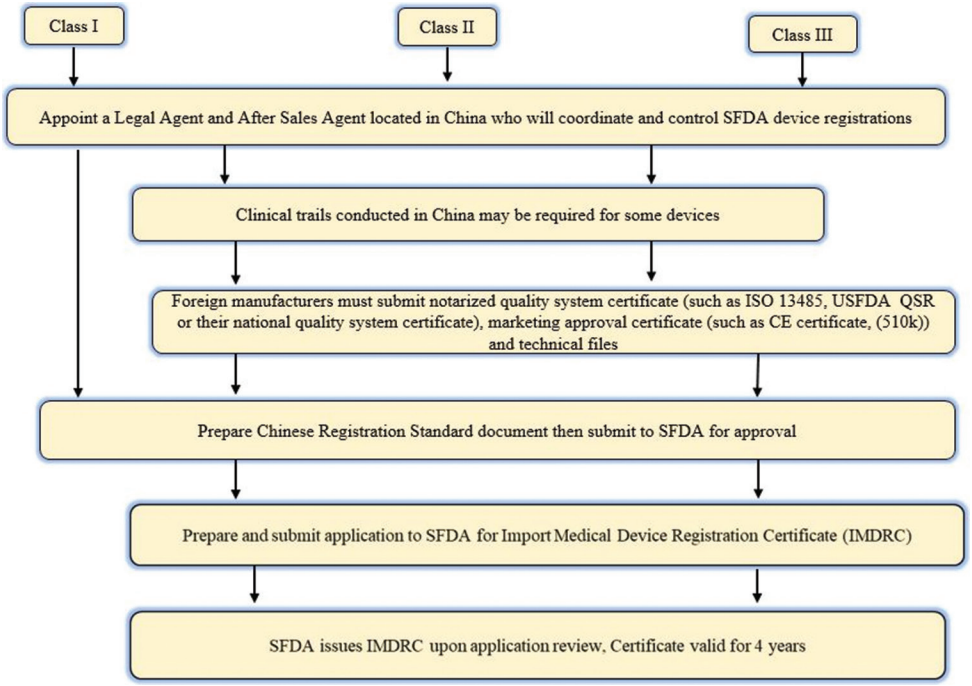


Figure 6: Medical device approval pathway in China [32].

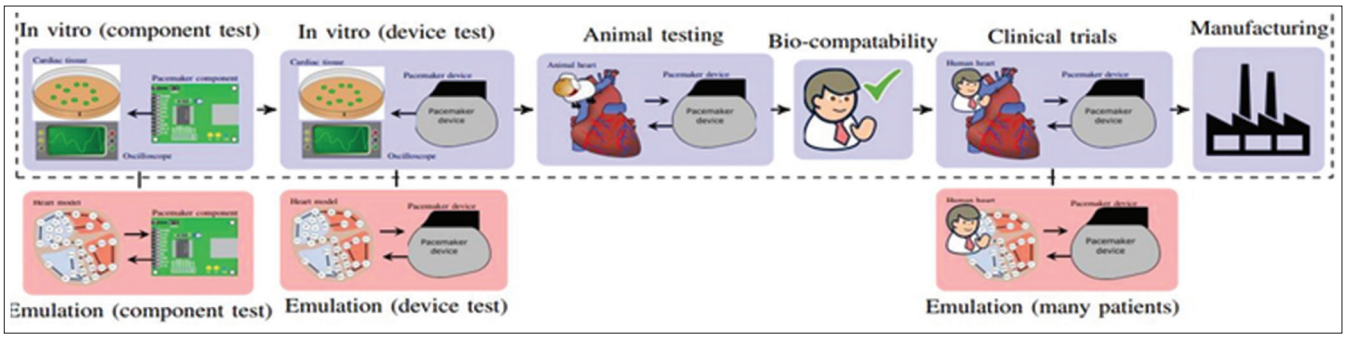


Figure 7: Emulation models are used as an addition to the current FDA-approved approach to enhance pacemaker certification

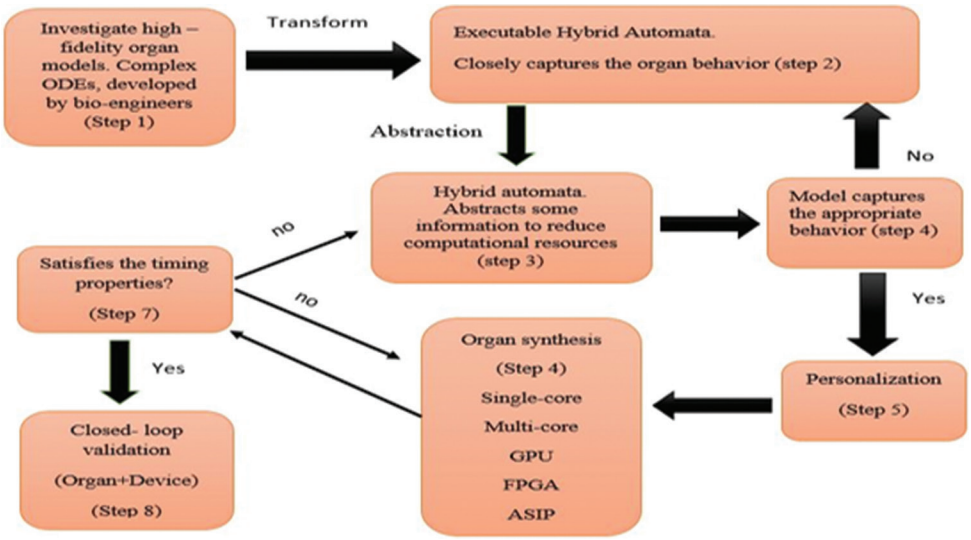


Figure 8: Proposed methodology overview

Table 3: Comparisons of MDD and MDR

S. No.	Attributes	Medical device directive	Medical device regulation
1	Articles	23	123
2	Annexes	12	17
3	Rules	18	22
4	Pages	60	175

Table 4: Clinical dimension

S. No.	Regular	Phase I	Phase II	Phase III	Phase IV
1	Number of devices	50	250	500	1000
2	Number of investigators	10	50	100	200

INDIAN APPROVAL PATHWAY FOR MEDICAL DEVICE

Figure 5.

REGULATIONS OF MEDICAL DEVICES IN CHINA

Up to the 1990s, the EU changed every member state rule in the domain of medical device with one among three directives the guidelines. The EU medical device market ensuring medical device safety and a high standard of human health protection [28]. These regulations were created rather late and these guidelines forth monitoring and administration of medical device were formed in the year of 2000. This marked a turning point in china's history of medical device regulation. These regulations granted the china FDA the power of supervise medical devices guarantee the efficacy, safety, and safeguard people's lives and health [29].

Changes in medical device regulation in China

The revised rules for the oversight the management of medical devices were published by the Chinese legislation in 2014. The new regulations, which include 80 articles compared to the previous ones, 48 articles, include numerous revisions regarding the device registration clinical trials, adverse events recalls, and other topics. In Table 3, the new rules are in line with the national 12th 5-year plan's objective of promoting domestic enterprises R and D while accelerating innovation and enhancing public health protection, the government updates the laws to keep up with the economy and the medical device industry's rapid expansion. The final category is preparation materials published by the CFDA or its connected organizations, such as CMDE, and standards published by the CFDA and Chinese standardization organizations in accordance with the new rules system [30,31].

MEDICAL DEVICE APPROVAL PATHWAY IN CHINA

Figure 6.

CASE STUDY

A cardiac pacemaker: Rethinking the validation process for medical devices

A person's death or serious injury could occur as a result of a medical gadget that is safety-critical. One hundred and ninety-seven (16.3%) of the recalls between 2006 and 2011 involved computers and were deemed safety-critical. 2,447,894 gadgets were subject to these 197 recalls. In fig 8, the Food and Drug Administration has given its approval to these devices. This demonstrates that there is room for improvement in the existing validation process for medical devices that must meet safety standards [33,34].

Investigators are focusing on creating real-time heart models that are adequate for closed-loop evaluation of cardiac pacing devices, often known as emulation, in an effort to improve the pacemaker validation method.

Reproducing elevated pharmaceutical models of human heart available to develop patients at the biological, cellular, and organ stages specific therapy and minimizes the invasiveness of many procedures.

In Fig 7, the closed-loop evaluation of commercial implantable cardioverter-defibrillator devices is not appropriate for these simulation models since they need a lot of computer resources. On the other hand, computer models are more abstract and are utilized to represent biological processes. Such a model also applies to formal verification. However, it may not provide real-time response [35].

For closed-loop evaluation of pacemakers, human cardiac models based on non-linear hybrid automata, linear hybrid automata, and temporal automata have been employed [36,37].

The capacity of these models to accurately represent the dynamic response of the heart cells varies. Emulation models for pacemaker evaluation are becoming more popular, but they still need to be included in the current FDA validation process six stages of tests that are included in the procedure [38-40].

FDA guidelines on current pacemaker validation

1. *In vitro* (component test): Getting accurate biophysical models of cardiac behavior to use as reference models is the first step. They can be explained by the use of intricate ordinary differential equations (ODEs)
2. *In vitro* (device test): To closely mimic the performance of elevated models, the models are converted into method for analysis like hybrid automata
3. Animal testing: Emulation models or abstract computing models suitable for real-time reaction are to be developed
4. Biocompatibility: For a material which has been tested and used previously in direct blood contacting devices, a sponsor may submit information available in publications or other legitimate sources
5. Clinical investigation: The objective of the study must be defined such that the study will constitute a demonstration of reasonable assurance of the safety and efficacy for the device.
6. Manufacturing: Each unit must work in accordance with the specification, which must be guaranteed during the production process.

Three of the six FDA steps may be enhanced by emulation models; in the first two stages, the emulation model can increase the number of pacemaker test cases required for validation. Importantly, the cardiac models could be customized throughout clinical trials using an individual patient's electrocardiogram and tested under various cardiac circumstances. In fig 9, to test pacemakers, for instance, the heart model may be made to demonstrate tachycardia.

Emulation design is used to enhance the peer review since they allow for the early detection of software flaws; however, creating organ models that can be validated in closed-loop still presents a hurdle [41].

We outline the initial step-by-step procedure for creating emulation models as guidance.

- Step – 1: Getting accurate biophysical models of cardiac behavior to use as reference models is the first step. They can be explained by the use of intricate ODEs
- Step – 2: To closely mimic the performance of elevated models, the models are converted into method for analysis like hybrid automata
- Step – 3: Emulation models or abstract computing models suitable for real-time reaction are to be developed
- Step – 4: Validation models that capture the appropriate behavior required for medical device validation
- Step – 5: This concept is customized to represent a patient's unique behavior

Table 5: Medical device comparison in US, Europe, India, and China

S. No.	Comparison	US	Europe	India	China
1	Regulatory Authority	USFDA	EMA	CDSCO	NMPA
2	Classification	Class I Class II Class III	Class I Class II (a) Class II (b) Class III	Class A Class B Class C Class D	Class I Class II Class III
3	Regulatory pathway	510 (K) Application, PMA	Multiple pathways	Market Authorization application to competent authority	By NMPA Approval pathway
4	Fees for available pathways	MIDUFA FY2017 510(K)$ 4,690 PMA $ 234,495	Fee varies for member state	Manufacturing license: Rs. 6,000/-license fee Rs. 1,500 Registration fee Import license: $ 1,000/-Registration fee $ 5,000/-Inspection of premises	Initial registration for class III Devices-39,000 Initial registration for class II Devices-26,500 Registration renewal for class II and III Devices-5,000
5	Quality management systems requirement	21 CFR Part 820	ISO 13485 or as per applicable annex of 93/42/EEC	BIS 15575 or ISO 13485	ISO 9001
6	Assessment of technical data performed	By USFDA	By National Regulatory Authority	By CDSCO	By CFDA
7	Medical device regulation	21 CFR Part 800 21 CFR Part 801	MDD-93/42/EEC AIMDD- 90/42/EE IVDMDD- 98/79/EC	Drugs and Cosmetics Act, 1940	SC[2014] NO 650 CFDA[2014] NO 4
8	Validity of license	Annual Establishment registration is required	3 years for Class II a, II b and III	3 years from the date of approval, for Notified Devices	5 year
9	Labelling requirements	As per 21 CFR Part 801	As per annex I 93/42/EEC	As per Drugs and Cosmetics Act 1940, GSR703	Medical device manual and label management regulations issued by CFDA
10	Timelines for approval	Class I : 1 month Class II: 3–6 months Class III: 18–30 months	Class I: 1 month Class II: 3–6 months Class III: 9–15 months	6–12 months for notified devices	Class II and Class III: 12–15 months

- Step – 6: The theory must be synthesized on a platform that can be executed
- Step – 7 and 8: When the model's timing properties are satisfied, it is finally prepared for closed-loop validation using a specific medical device [42,43].

Comparison of the execution platforms in terms of quality

Platform	Scalability	Cost	Flexibility	Example
Single-core	Low	Low	Med.	Cardiac conduction system
Multi-core	High	Med.	Med.	Neuron behaviour in brain
GPU	High	Med.	Low	Neuron behaviour in brain
FPGA	Med.	Med.	Med.	Cardiac conduction system

Timing properties

The pacemaker frequently samples its probes are implanted, and in the heart during closed-loop validation, we must make sure that the controller's sample period is consistently larger than or equal to the executable heart model reaction time.

The execution platform must also be time-predictable and not show any timing irregularities.

Various execution platforms are presented in the section before this one. The majority of platforms employ processors that are designed to enhance average performance while ignoring extreme case performance. In table 4, we advise choosing an embedded device that is compatible with current static timing analysis software [35,44].

DISCUSSION AND RESULTS

Comparison between medical devices in US, Europe, India, and China

Table 5.

FINDINGS

1. Medical device market value stands around US $ 434.2 billion in 2021 growing at CAGR of 6.3%
2. By2027, it is estimated to reach USD 625.3 billion
3. Medical devices volume is around 6.64 billion with growth at CAGR of 4.2%
4. The biggest market for medical devices is North America, followed by Asia Pacific
5. Factors that do not favor entry of new players is medical device market is huge requirement of capital to develop new medical devices, legal issues, cost of R and D setup, high distribution expenses, and marketing costs
6. Huge distribution networks and efficient supply chain are required and this gives a tough competition to new entrants entering the medical device industry
7. Medical device market with the highest growth rate is the Asia Pacific with a CAGR of 71% category of medical devices that have the highest growth rate is the patient monitoring devices with a CAGR of 7.3%

8. They are easy to use enabling real time monitoring at hospitals and home especially for COVID patients and examples include pulse oximeters, capnography monitors, anesthetic system, and wireless patient monitoring devices
9. Half of the medical devices market share is accounted by syringes, needles, and catheters. The reason being easy availability and usage in the administration of parenteral nourishment, fluids, and medications
10. The category of medical devices that dominate new applications for new medical devices is the respiratory medical device category
11. Diagnostic devices are the category of medical devices that has the highest market show
12. Cardiology-related medical devices hold 19.2% of the global market share when categorized by application
13. 51.2% of the global market share is held by hospitals and surgical centers when categorized by endues and by region.

CONCLUSION

The medical device regulations are different in these countries, but PMA and post-market process is done for the marketing of quality products.

In addition to US FDA, medical device regulations are growing harmonization of International Standards between US and EU Medical Device Requirements.

Understanding the regulatory requirements for medical devices can play a critical role in the success and timely impose on safe and effectiveness technologies.

Therefore, we believe that efforts to improve medical device regulatory system in both academic and professional contexts and strong support to all stakeholders.

These diverse categories of medical devices require a strict and graduated framework of control for their endorsement and execution within the showcase which has been accomplished to a certain level.

The validation of medical devices can be enhanced with the usage of emulation models real-time reaction is ensured through emulation organ models allowing for closed-loop device validation and improved test coverage.

We provided a strategy that researchers new to modeling organs for the validation of medical devices can follow. We also talked about ways to synthesize the organ models so that timing aspects, which are crucial for closed-loop validation, may be examined.

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AUTHORS' CONTRIBUTION

1. Have made a substantial contribution to the concept or design of the article; or the acquisition, analysis, or interpretation of data for the article;
2. Drafted the article or revised it critically for important intellectual content;
3. Approved the version to be published;
4. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this article.

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