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Systematic Review

Approval and Legislation Involved in Development of Medical Devices in Dentistry – A Systematic Review

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ABSTRACT

A medical device is defined as "any an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent" and "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals". **Objective:** The objective of this systematic review was to outline the steps and necessary requirements needed for approval and legislation of new medical devices. **Methods:** Two databases; PubMed and Google Scholar were electronically searched for articles published from year 2011 to 2021. The following MeSH (Medical Subjects Headings) terms; "new medical devices", "Regulatory Bodies", "Approval Medical Devices", "Pre-market Post-market Approval" along with Boolean operators AND, OR and NOT were used to search for the articles. **Results:** It is evident from our study that risks associated with new medical and dental devices are being taken seriously by the governments of different countries and intensive work is done to minimize the risks and maximize the benefits of them. **Conclusions:** It is safe to say that we are entering a new era of safe medical practice along with new and better devices being available for the public. The reforms being made will help not only the hospitals and patients but will also assist the manufacturers in understanding the mechanisms involved in clearing their products for the approval. It will lead to advancement and reshaping healthcare system to combat many challenges faced by it and promote and protect the public health.

INTRODUCTION

A medical device is defined as "any an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent" and "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals" [1]. New medical and dental devices are launched by introducing a prototype. These prototypes have to go through a number of tests and later modified and improved till they are rendered safe and fit for the desired usage [2]. These tests include in-vitro mechanical tests, in-vivo animal tests and clinical trials. A number of factors have to be considered before designing the clinical trials which affect the final result and safety of these devices [3]. Clinical trials ensure that the new device is effective and safe when used in accordance with the advice of the manufacturers [4]. Many organizations exist to ensure the quality and efficacy of these new medical and dental devices like the Food and Drug Administration (FDA) in the United States [5] Figure 1, European Medicine Association (EMA) in Europe and The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan [6]. Specifically, the Centre for Devices and Radiological Health (CDRH) within the FDA is responsible for protecting and promoting the health of the public by making sure that the patients have

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prompt access to high quality, effective and safe medical and dental devices[7].

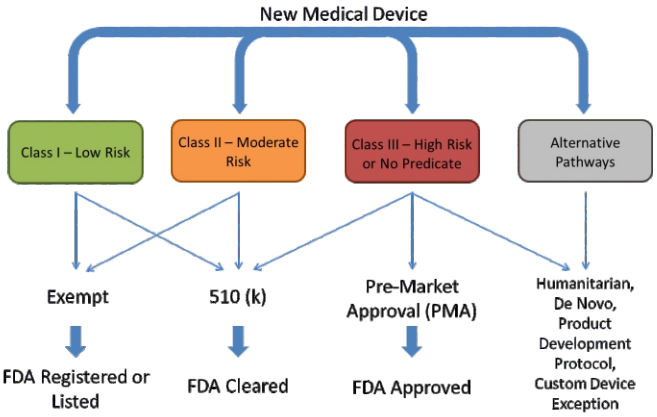

Figure 1: FDA Approval Pathway for Medical Devices

Premarket Approval: Approval of new devices is a technical process and most of the manufacturers are small scale business owners lacking the manpower and expertise to tackle these technical issues, thus delaying the approval and market entry of their product[8]. The FDA has divided medical devices into three regulatory classes according to their clinical usage; Class I, Class II and Class III [9]. The FDA depends on "valid scientific evidence" to classify and regulate medical and dental devices, "valid scientific evidence" being available to the general public. FDA was authorized to regulate the manufacturing as well the marketing processes of innovative medical and dental devices in 1976. The FDA has established two pathways for regulation of new devices, one being the 510(k) pathway and the other being the Premarket approval (PMA) [10]. 1976 onwards, devices that are rendered less complicated and risky are cleared through a rather simple process called 510(k) pathway without the need to perform clinical trials [11]. Whereas the approval of new high risk new medical and dental devices need to have Premarket approval (PMA) which requires clinical trials [12]. Pre-market approval (PMA) is more rigorous than 510(k) pathway as problems in the device may lead to severe adverse and undesirable effects requiring a very strict regulatory protocol before they can be certified safe [13]. 510(k) pathway is a submission made to FDA by the manufactures to acquire a certificate that their product is legally safe and effective for the desired purpose [14]. By law, 510(k) only requires 1 feasibility study and 1 pivotal study [15] but 510(k) is the strictest marketing protocol requiring class 1 and class 2 evidence [16] Table 1. Though Class I low risk devices are generally exempted from 510(k) pathway, clinical evaluation is a must for Class III high risk devices approval [17]. For example, new implanted devices are approved through 510(k) pathway mostly but a few of them need the more rigorous premarket approval(PMA) [18]. The FDA and sponsors collaborate to plan clinical trials according to the device's design and technology, its clinical use, collection of date and patients' benefits and risks [19]. Obtaining the 510(k) may need more than 5 years for high risk devices [20,21]. Also, the trend is changing now from only PMA to continual clinical study as long as the product is in the market [22] as studies have showed that very high risk devices could not generate enough quality clinical evidence before launched. According to studies, two thirds of high risk devices that had been cleared through 510(k) pathway were recalled by the FDA due to unsatisfactory results[23].

Class	Risk	Examples	Safety/Effective control	Regulatory Pathway
I	Low	Tongue depressor, hospital beds	General Control	Self-registration
II	Medium	Absorbable sutures,Blood pressure cuffs	● General Control ● Special Control	● Mostly 510K pathway ● Few devices under PMA ● 10-15% devices require Clinical trials
III	Highest	Implantable pacemaker, Coronary stent	● General Control ● Special Control ● Premarket Authorization	● PMA ● Almost all require Clinical Trials

Table 1: Classification of devices under FDA

Post-Market Surveillance: The post-market surveillance (PMS) is as important as the pre-market approval in ensuring the safety and effectiveness of devices[24]. After a device has been introduced, companies need a robust PMS plan including patient review to ensure the product is delivering what it was intended for[25]. Manufacturers are required by law to carry out clinical evaluation in "real life" to prove that the performance of their product is in line with the data they provided before the launch of the product [26]. Post market surveillance should provide (i) data regarding not up to the mark performance of the device, (ii) conveying benefits and risks to the manufacturers and (iii) data to the regulating authorizes for future reforms [27], Figure 2.

Much attention is given to pre-market approval(PMA) by the manufacturers to launch their product and establish themselves in the market [28] but the situation of post market surveillance remains defective with studies remaining incomplete for years[29].

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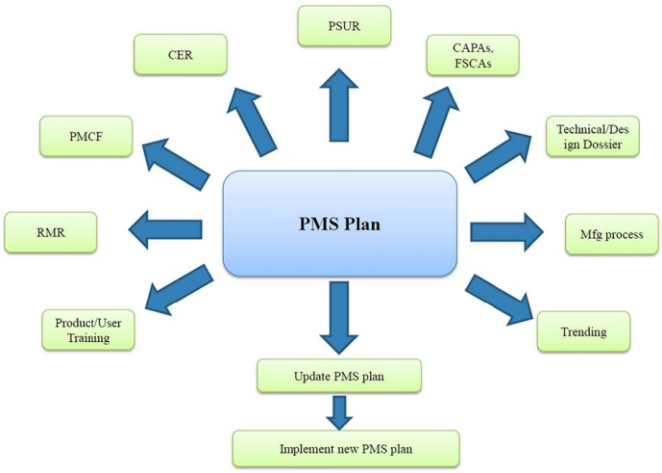

Figure 2: Output of the post-market surveillance (PMS) plan [25]

Controversy: The regulatory procedures for new medical and dental devices are considerably less than that of drugs which makes the data insufficient and prone to errors [30]. Studies have shown that wearable medical devices (WMD) even though hugely marketed have less than satisfactory safety data [31]. Currently, in Europe the pre as well as post market data of a new device is not sufficient enough to declare it completely safe [24]. Though post market surveillance may be useful but reporting an unfortunate event could take several months and it may have caused many disasters till that time [32]. Tort reforms have made the matters worse by making the clinicians bolder in use of high risk devices without considering the undesirable consequences [33]. Some organizations like EMA (European Medicines Agency) have come under criticism for allegedly placing the interests of manufacturing companies above those of the patients [34]. After UK left the European Union, commonly known as "Brexit", now a device approved by MDR will have to obtain another certificate; UK MDR through a "UK responsible person". The UK responsible person will have to take over the responsibilities of the manufacturer to get their devices registered and approved in UK, adding injury to the already complicated process of the regulatory system [35]. Japan is lagging behind other countries in providing access to innovative medical devices to its public [36]. In developing countries like Pakistan where medical malpractice and negligence is already prevalent, the guidelines and training regarding using innovative medical devices do not exist. The healthcare professionals are free to guide themselves through a new device generating very serious outcomes ranging from the death of patients to violence erupting in hospitals by the kin of the patients [37].

METHODS

Two databases: PubMed and Google Scholar were electronically searched for articles published from year 2011 to 2021. Our question was "Are the current regulatory system for new medical and dental devices around the world satisfactory?". The following MeSH (Medical Subjects Headings) terms; "new medical devices", "Regulatory Bodies", "Approval Medical Devices", "Premarket Post market Approval" along with Boolean operators AND, OR and NOT were used to search for the articles. Exclusion and inclusion criteria were established before the searches were made:

Exclusion Criteria:

1. Articles published in languages other than English
2. Studies done more than ten years ago.
3. Regulatory studies of drugs but not containing information about medical devices.
4. Commentaries
5. Editorial
6. Studies about the performance of innovative medical and dental devices but not their regulation and approval.

Inclusion Criteria:

1. Since articles regarding regulation of dental devices specifically were not available, medical and dental devices were included in the searches.
2. Articles from 2011 onwards containing information about the regulatory processes of new medical and dental devices.
3. Systematic reviews.
4. Review articles.
5. Original studies regarding the regulatory processes.

Studies on reforms on regulatory processes.

RESULTS

40 articles according to the inclusion and exclusion criteria were selected among the searches. Among the 40 articles, 29 (72.5%) were in the view that the current regulatory mechanism lacks authenticity and seriously need reforms owing to the following factors:

1. Insufficient clinical data provided to the regulatory bodies.
2. Poor and ambiguous clinical data.
3. Incomplete post market studies after being approved.
4. Clinical studies not done in different countries among different populations for safety evaluation while being provided to them after being approved in one country.
5. Regulatory authorities favoring manufacturers instead of the public health concerns.
6. Needing more filters for regulation of different

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medical devices.

7. Time consuming and tedious regulatory processes.
8. High risk wearable devices not having clinical trials before being launched.
9. Not holding manufacturing companies responsible for their products' disasters.
10. UK leaving the European Union and MDR not being application to the UK.

The regulatory bodies seem to be aware of the challenges and limitations of the innovative medical devices and remain committed to the cause of improving the system. Several steps are being taken and reforms are made to ease the pathways for cost-effective production of innovative medical devices. In this regard, dental devices are constantly undergoing reforms by the FDA and other agencies after they have been proven to be less risky after being successfully utilized by the clinicians and patients. A number of dental devices have been reclassified by the FDA like the endosseous dental implants were reclassified into Class II from Class III [38]. Similarly, FDA has also moved "saliva stimulator system" [39] and another dental device called "temporary mandibular condyle prosthesis" into Class II from previous Class III making the regulatory process more convenient and reasonable [39]. The FDA is also trying to exclude over the counter (OTC) denture kits (powder and liquid system) from the 510(k) pathway to be readily available without having to undergo tight scrutiny before they are made available to the consumers [40].

DISCUSSION

Instead of Medical Devices Directive (MDD), The Medical Device Regulation (MDR) was implemented in Europe in 2017 for new medical devices [41]. MDR will transform the medical device industry by moving many devices to higher risk category [42]. After MDR was implemented, manufactures were required to observe higher standards of protocol and regulatory pathways for their products [43]. Also, flexibility is allowed in the new reforms in MDR for special situation and devices where an innovative device may be used for rare disease not having any other treatment options and can benefit the patient or save their lives [44]. China too is seeking reforms in their medical devices industry owing to a demand in innovative technologies and huge growth of their market. Just like the FDA, China is reclassifying a number of medical devices, so the total time consumed by the regulatory authority China Food and Drug Administration (CFDA) for simple devices is considerably shortened making more time for the monitoring of medium and high risk medical and dental devices [45]. The Japanese government has done a commendable job of shortening the review and regulatory time period of new medical and dental devices from 21.1 months in 2015 to10 months in 2015 which will benefit not only the patients but also the manufacturing companies [46].

CONCLUSION

It is safe to say that we are entering a new era of safe medical practice along with new and better devices being available for the public. The reforms being made will help not only the hospitals and patients but will also assist the manufacturers in understanding the mechanisms involved in clearing their products for the approval. It will lead to advancement and reshaping healthcare system to combat many challenges faced by it and promote and protect the public health.

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