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Cost Effectiveness and Resource Allocation

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A review on the evolving environment of medical device real-world evidence regulation on market access in the USA

Lizheng Shi[1], Dennis Xuan[1] and Mihajlo Jakovljevic[2,3,4*]

Introduction

According to the United States Food and Drug Administration (FDA) a medical device is defined as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar [1]. As such, these medical devices are regulated by the Center for Devices and Radiological Health (CDRH) under the FDA and include pre and post market surveillance. The CDRH is responsible for ensuring the safety and efficacy of medical devices approved within the United States and has been the primary body of doing so since the passing of the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act of 1976 and formation of the organizational unit in 1982 [2].

In the decades since, the pace of advancing information and technology has required the FDA to continuously update their regulations towards medical devices and adapt to disruptions on a regular basis. This long-term underlying trend has largely been dictated by the accelerating pace of innovation in medicine [3], shortened product life cycle and higher patient expectations [4]. One such area of recent advancements include the use of real world evidence (RWE) and real world data (RWD) for regulatory decision making [5]. In fact, the FDA has considered the use of RWE to support regulatory decision making for medical devices when it concludes that the RWD used to generate the RWE are of sufficient quality to inform or support a particular regulatory decision since 2017 [6]. Since the publications of these guidelines, many medical devices have sought approval through some example pathways highlighted in the documentation such as post market surveillance as a condition of approval and the use of objective performance criteria and performance goals [7, 8]. A large amount of literature, panels, and discussion on the potential and real usage of RWE and RWD in regulatory decisions has also been generated composing potential templates for data gathering and distribution, important stakeholder analyses, and general improvements and augmentations to the current regulatory framework RWE/D can contribute [8–12].

As described, RWE and RWD are increasingly being accepted as part of the evidence package for regulatory approval within the United States. And there is an urgent need for stakeholders to clearly understand how to obtain regulatory approval swiftly and safely for medical devices. This literature review sets out to understand the state of medical device regulations in the USA towards the use of real-world evidence and data in market approval and help lead to better approaches for increasing access and approval to medical devices. Furthermore, after initiative originating from US academia and industry affiliated circles, RWE and RWD have rapidly taken hold rapidly taking roots in various health technology assessment (HTA) legislation and practice worldwide [13].

*Correspondence:
Mihajlo Jakovljevic
sidartagothama@gmail.com
[1]School of Public Health and Tropical Medicine, Health Systems Analytics Research Center, Tulane University, New Orleans, LA, USA
[2]UNESCO-The World Academy of Sciences TWAS, Trieste 34100, Italy
[3]Shaanxi University of Technology, Hanzhong 723099, China
[4]Department of Global Health Economics and Policy, University of Kragujevac, 34000 Kragujevac, Serbia

Methods

Search and selection criteria

A literature review was conducted to understand the nature of medical device regulation towards real world evidence and market access within the United States. The primary database searched was PubMed and the search window conducted spanned from March 1, 2019, to March 1, 2024. Search terms included "Medical Device Regulation", "Device Regulation", "Real world Evidence", "Real world Data", "United States", and "Device Market Access". Articles were initially screened by title and abstract by reviewers for relevance and comprehensiveness. These selected articles were later reviewed for further analysis and more comprehensive abstraction.

The literature search on device regulation yielded 3,789 results within the last 5 years from PubMed. From these, 15 papers were selected for abstraction and further review. Additionally, 2 articles were added manually from the FDA guidelines on medical devices as well as other government published materials were consulted.

Classification

Upon further review, these papers were then classified into 3 groups based on the primary focus of the article. The first group focused on assessing the current regulatory process. The second group reviewed standing legislation. And the third group showed examples of devices brought to market. Together, all three should offer a clearer picture of how device regulation is done in the USA as well as how it has been evolving in the most recent few years.

Results

Current regulatory process and legislation

History and role of the FDA and CDRH

The history of the FDA begins with its establishment under the auspices of the Federal Food, Drug, and Cosmetic Act of 1938. With respect to medical devices, the FDA was meant to serve as an agency which prohibited the marketing of medical devices bearing false or misleading labeling. However, one key modern element missing was the need for premarket review and approval of such products which the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act of 1976 was passed to address [14]. The Center for Devices and Radiological Health itself was established in 1982 and serves as the dedicated regulatory body within the FDA for medical devices.

This initial legislation also classified medical devices into 3 broad categories. Class 1 devices were defined as "Low-risk devices for which general controls such as good manufacturing processes are sufficient". Class 2 devices were defined as "Moderate-risk devices for which special controls such as performance standards are required. And Class 3 devices were defined as "High-risk devices that generally required per-market approval. Each class of device also came with its own associated path for market approval. Broadly speaking, Class 1 devices were exempt, Class 2 devices required a 510(k) submission, and class 3 devices required full pre-market approval. 510(k) submissions are generally used to show that a new device is sufficiently equivalent in safety and efficacy to a previously approved device [1].

Later legislation and published guidance sought to add and improve approval pathways for medical devices to adapt with the changing technological environment. Examples of these additional pathways and programs include [6, 14]:

- Expanded access for patients of rare diseases or life-threatening conditions.
- Separate approval processes for innovative class 1 or 2 devices (de novo).
- Modifications and conditional approval specifications to the 501(k) process.
- Expedited approval for devices which showed significantly more efficacy than the standard of care (Breakthrough Devices).
- Precertification and shortened review for certain software from qualified developers.
- Conditional approval based on RWE and RWD.

The most recent congressional research service report on the FDA regulation of medical devices describes the FDA's authority to regulate (1) medical devices; (2) medical device classification panels and regulatory classes; (3) device regulatory controls, including general and special controls, as well as premarket approval; (4) special programs to improve access to specific devices; and (5) post market surveillance systems [15]. Within this last section lies the concern of RWE and RWD usage in regulatory affairs with a section detailing the National Evaluation System for health Technology (NEST), a collaborative database to synthesize medical device data on clinical registries, electronic health records, and medical billing claims within the United States. According to the document, the RWE/RWD generated through NEST "may be used not only for purposes of post market surveillance, but it may also be used to support premarket regulatory decision-making and expanded indications for use after clearance or approval, among other things". In fact, it should be noted a guidance document on the use of RWE was published in 2017 and the CDRH had conducted an analysis of RWE used in regulatory decision making [6, 16]. We can therefore surmise that while the recommendations and guidelines set by the FDA towards the use of RWE/RWD in regulatory decision making are not binding, they are increasingly important in the contemporary

regulatory environment. Stakeholders from manufacturers, regulators, and other industry bodies should be aware of and make use of the impact RWE on medical device regulation.

Key standing legislation

- 1976: Medical Device Amendments to Federal Food, Drug, and Cosmetic Act [17].
  - Created the 3-class risk-based classification system for medical devices for use in safety and efficacy evaluation.
  - Established regulatory pathways for new medical devices to be brought to market.
  - Established key post market surveillance requirements:
    - Registration of establishments and listing of devices with the FDA.
    - Good Manufacturing Practices (GMPs).
    - Reporting of adverse events (AEs) involving medical devices.
  - Authorized the banning of devices by the FDA.
- 1990: Safe Medical Devices Act [18].
  - Improved post market surveillance of devices through:
    - Requiring user facilities to report medical device AEs.
    - Require manufacturers to perform post market surveillance on permanently implanted devices if permanent harm or death could result from device failure.
  - Authorized device recalls and the imposition of civil penalties for regulatory violations.
  - Defined and modified procedures for the establishment and evaluation of performance standards and devices, especially for rare diseases.
- 2002: Medical Device User Fee and Modernization Act [19].
  - Authorized the collection user fees to help the FDA improve efficiency, quality, and predictability of medical device submission reviews.
  - Authorized electronic registration of medical device firms and products.
  - Created FDA performance goals for decisions on certain premarket submissions.
  - Established the Office of Combination Products to serve as the focal point for drug/device combination products.
- 2016: 21st Century Cures Act [20].
  - Set the following mandates to speed patient access to new medical devices.
    - Codify expedited review for breakthrough devices.
    - Codify a process for submitting requests for recognition/non-recognition of a standard.
    - Expand and streamline the qualification process to exempt certain devices from premarket approval.
    - Permit the use of central Institutional Review Board (IRB) oversight.
    - Require the FDA to revise the regulation of combination products.
    - Expand qualification of rare disease for additional device approvals.
  - Clarified how certain digital health products can be regulated by defining the categories of medical software that can and cannot be regulated as devices.
- 2022: Food and Drug Omnibus Reform Act [21].
  - Enhanced oversight authority to conduct remote regulatory audits and inspect facilities that conduct research on devices.
  - Required that cybersecurity information be included in premarket submissions for certain devices and that sponsors of said devices must ensure cybersecurity.
  - Expanded certification of devices manufactured in foreign countries provide the same device is marketed in the United States and other regulatory criteria have been met.
  - Additional reforms and clarifications on FDA's authority and regulatory approval requirements.

Real world evidence usage

Challenges in regulatory activities

As bodies such as the FDA are increasingly making use of RWE in their regulatory decisions, the overall discussion of how such information should be used is still in flux. While the FDA and CDRH set the guidelines

and rules, they are not binding and there are still many challenges associated with using RWE in regulatory practices. Data challenges include availability, accessibility, reliability, harmonization, and interoperability [8]. Registry networks themselves are shown variable with respect towards data quality as well as patient engagement [22–24]. Additionally, there is a great amount of discussion surrounding the development of frameworks to assess the maturity of registry networks to provide RWE and highlight the need for the FDA to mandate evidence review combining RWE with traditional randomized clinical trials [9, 11, 25, 26]. Despite these challenges, the interest in how to utilize the massive amount of post market evaluation data to better provide safe and effective medical devices is still great. And as highlighted before, FDA have published guidance which has been followed to such an effect in various regulatory decisions and benchmarking studies [6, 8, 16].

Future of RWE

The future of RWE should focus on improving the transparency of presented data through the improvement of evidence collection, analysis, distribution. Improved standards and frameworks in the reporting of RWE should be considered to improve information readability, validity, and confidence for decision makers [23, 25, 27, 28]. Additionally, alternate performance measures outside of just safety and efficacy should also be considered such as cost and quality of life impact [9]. These would be important for health technology assessments as well as other important stakeholders such as industry groups, patient advocacy groups, and caregivers alike. And lastly, the advent of artificial intelligence (AI) and machine learning (ML) techniques combined with the increasing availability of RWD has galvanized great interest in the ability to bridge the evidence gap between clinical research and practical applications [29]. An approach which provides enhanced collaboration and input between all stakeholders and the FDA should be pursued to create a holistic picture of the impact medical devices have on society through real world evidence analysis. Given the increasingly competitive and mutually interdependent global landscape in this field, further AI developments originating in the US may impact those taking place in other leading economies worldwide and vice versa [30].

Market access and impact assessment

Market access in this article refers to the ability of patients to access medical devices or in other words, the regulatory approval and availability of medical devices. Currently the regulatory environment can still be considered highly fragmented for a variety of diseases despite the ongoing evolution of legislation, especially around digital health solutions [24, 28, 31]. Outside of the purely regulatory framework, impact assessment and accessibility is also important for the patient and caregiver. From there, there is a general consensus as well that the cost of devices and patient willingness to pay are important drivers of value [31, 32]. However, limited affordability of medical devices due to out-of-pocket spending, lengthy waiting lists, and administrative hurdles to reimbursement, create substantially different market access landscapes across wealthy Global North and developing Global South countries [33–35]. With this understanding, the importance of creating a holistic body of real-world evidence to assess safety, efficacy, and value for medical devices cannot be understated. Thus, there remains a need for a standardized and perhaps even mandatory RWE requirement for regulatory decisions regarding medical devices as well as other impact assessment analyses such as HTA.

Conclusion

The regulatory process for medical devices in the United States is complex and subject to a plethora of different laws and regulations. With respect to the use of RWE and RWD the fragmentation becomes even more pronounced [1, 31]. Currently, the relevant guidance on utilizing RWE/RWD is non-binding and subject to regulatory discretion [6]. Despite this non-mandatory requirement however for medical device approval, the incidence of regulatory decisions utilizing RWE/RWD has increased drastically in recent years [16]. The use of RWE/RWD in regulatory decision making has evolved as well to include not only safety and efficacy data, but also usage, cost, and patient information. This explosion of data as well as the implementation of AI and ML tools has heralded a new age in RWE application.

The application of RWE into regulatory decision making as well as impact analysis such as HTA done by relevant stakeholders has only increased since the FDA released their RWE guidance document. Ever increasing data and evidence generation on the horizon with the advent of AI tools will also continue to evolve in the United States and abroad. Overall, it should be noted that the growing set of interactions between regulatory approval, real-world evidence/data, and reimbursement for medical devices are increasingly being used to determine coverage and reimbursement decisions. Technological advancements in data collection and analysis will also drive regulatory change just as much as the medical devices themselves. Therefore, healthcare researchers should maintain a steady eye and interest in this space and continuously look for opportunities to conduct research to benefit policy and society.

Supplementary Information

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Supplementary Material 1

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D.X. did the initial literature search and data abstraction; All authors collaborated on the main manuscript text; All authors reviewed the manuscript.

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Declarations

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