REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 02-A-23

Subject: Improving Research Standards, Approval Processes, and Post-Market Surveillance Standards for Medical Devices

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Referred to: Reference Committee E

INTRODUCTION

Resolution 523-A-22, "Improving Research Standards, Approval Processes, and Post-Market Surveillance Standards for Medical Devices" was referred by the House of Delegates (HOD). This report serves as the Council on Science and Public Health's (CSAPH) findings and recommendations regarding medical device regulation.

METHODS

English language articles were selected from searches of PubMed and Google Scholar using the search terms "medical device AND 510(k)" and "medical device AND post-market surveillance". Additional articles were identified by manual review of the reference lists of pertinent publications. Web sites managed by government agencies and applicable organizations were also reviewed for relevant information.

BACKGROUND

In the context of regulatory oversight by the Food and Drug Administration (FDA), a medical device has a broad definition. According to the Food, Drug and Cosmetic Act:

> a device is: an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:
> […]
> (B) 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, or
> (C) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

As such, the breadth of items captured within this regulatory framework is expansive: ranging from tongue depressors and eyeglasses to x-ray machines and hip replacements. In addition to physical objects used as medical devices, software and algorithms are also captured within this definition. As such, the FDA classifies software into two broad categories: software *in* a medical device and

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software *as* a medical device (SaMD). CSAPH recognizes that software, particularly SaMD, is rapidly becoming a large part of medical care and may warrant further examination beyond the findings and recommendations of this report, which are intended to be generalizable to all medical devices.

THE 510(K) REGULATORY PATHWAY

When applying for a new medical device, the device is first evaluated for risk category: I (lowest risk), II (medium risk) or III (highest risk). Risk category is determined by a variety of factors, such as by comparing the device to a similar, known, device. If a device is found to be like a device already approved by the FDA, it may be classified as low (class I) or medium (class II) risk. Examples of devices commonly found to be class I include electric toothbrushes, tongue depressors, bandages, hospital beds, and non-electric wheelchairs. Examples of devices commonly found to be class II include catheters, pregnancy test kits, syringes, contact lenses, and surgical gloves. Examples of devices commonly found to be class III include breast implants, pacemakers, defibrillators, and cochlear implants. Approximately 1% of all new medical device applications from 2003 to 2017 were evaluated as high risk (class III).[1,2]

If a medical device is found to be class I they are typically exempt from normal testing. If deemed a class II risk, manufacturers may submit a 510(k) application as pre-market notification (PMN) to the FDA. Class II risk devices are subjected to an equivalence evaluation comparing this product to one currently on the market through these 510(k) processes. 510(k) applications are processed within 90 days and once approved, the device is eligible for market. By contrast, class III devices must undergo pre-market approval (PMA) which requires two large clinical trials. According to a 2010 industry survey, pursuing pre-market approval in the United States takes on average 54 months to complete compared to 11 months in European countries.[3]

Medical device market approval differs from drug approval in a few critical ways, which may help illustrate why the 510(k) pathway is so desirable for medical device manufacturers. Table 1 in the appendix of this report highlights some of these differences. Clinical trial design for medical devices can be extremely difficult, and in some cases unethical. For example, a placebo control for a medical device could require a high-risk sham surgery. As such, subjecting all new medical devices to undergo clinical trials may substantially hinder innovation, particularly from physicians seeking small tweaks or customizations to products they use routinely.

But on the other hand, if a medical device does cause harm to a patient, one cannot simply discontinue having an implanted device without significant intervention unlike if they were experiencing adverse events to a new medication that could be quickly stopped. As such, the 510(k) pathway has been subject to intense public scrutiny, both in the media and by elected officials.[4] Many recalls of medical devices are voluntarily initiated by the manufacturer due to liability concerns or public perception decreasing sales rather than by official FDA action.

The FDA has recently begun piloting a new program within the 510(k) framework, called the Safety and Performance Based Pathway. This pathway provides an alternative to the current equivalence evaluation for a small subset of devices that are highly studied and well-known. In the Safety and Performance Based Pathway, the FDA sets forth explicit benchmarks that medical devices must satisfy to demonstrate safety and efficacy to gain 510(k) approval.[5] For example, if a resorbable surgical sutures manufacturer wished to market a new design, the FDA has guidance for the appropriate diameter, needle attachment, tensile strength, sterilization, shelf life and resorption profile for new suture designs to meet to receive 510(k) classification.[6] This pathway provides

added safety and efficacy requirements to this moderate risk class. However, participation in the Safety and Performance Based Pathway is currently optional.

DEVICE EQUIVALENCE

To be eligible for the 510(k) approval, a manufacturer must first establish that their device is "substantially equivalent" to a previously known, FDA-approved predicate device.[7] For the purposes of regulatory approval, the FDA considers both safety and functionality when determining equivalence. First, they investigate whether the device is to be used for the same primary purpose, and they then evaluate whether the device is expected to have a similar safety profile. For example, if a device were to change its power source (such as hardwired vs. rechargeable) with no other modifications, it would likely be deemed substantially equivalent. Similarly, if the material of the device were to change to another material known to be safe to the FDA, it is likely to be found substantially equivalent. A flowchart of the FDA decision making process has been included in the Appendix of this report.

However, there is a flaw with the approach of substantial equivalence. If a device is found to be unsafe after receiving market approval and then subjected to a recall, any *subsequent* devices which used the original, now-unsafe, device as their predicate are not subjected to any increased scrutiny or recalls. Recent analysis found that between the period of 2017 and 2021, the FDA initiated recalls of 156 devices using their highest risk categorization – devices with a reasonable probability to cause severe morbidity and mortality. Of those 156 devices recalled, 44.1 percent of them had received 510(k) approval using substantial equivalence to a device that had also been the subject of a recall.[8] Further, 48.1 percent of devices recalled within the studied period have themselves been used as the predicate for another device's 510(k) approval. This post marketing safety information and related devices draw significant attention to potential problems with the current 510(k) approval process with a lack of criterion for granting approval for devices outside the most well-studied and well-understood.

Post-Market Surveillance

It should be noted that the study described above only studied a cohort of devices which were the subject of FDA-initiated recalls. There are likely a non-trivial number of devices that are still being used as comparators for substantial equivalence that have been found to be unsafe and then production halted or voluntarily recalled by the manufacturer. However, there is limited publicly available information to monitor this risk. This scenario highlights the importance of rigorous post-market surveillance for devices that have been approved using the 510(k) pathway.

Among the post-market surveillance activities required by the FDA is the reporting of adverse events. Under Medical Device Reporting regulations (Title 21 Code of Federal Regulations part 803), manufacturers, importers, and device user facilities (such as a hospital, nursing home or outpatient treatment facilities) are mandatory reporters to the FDA regarding serious device malfunction, including death. Reports are made to the device manufacturer (if known) and the FDA. Health care professionals, patients, and caregivers are able to report suspected adverse events for medical devices using the FDA's MedWatch portal (https://www.accessdata.fda.gov/scripts/medwatch/).

Adverse events are viewable to health care professionals and the public using the FDA's Manufacturer and User Facility Device Experience (MAUDE) portal.[9] However, a 2019 exposé found that over 5 million incidents of reported adverse events were being kept from public view using an internal "alternative summary reporting" repository rather than the publicly available

MAUDE database.[10] Not only did this practice prevent physicians and patients from knowing the real risks of currently approved medical devices, it also prevented manufacturers of new devices from knowing the risk profile of substantially similar predicate devices they were using for 510(k) approval. The FDA has stated that it has since abandoned this practice of internal incident report storage.[11]

Health Equity Considerations

It should also be noted that implicit in the 510(k) substantial equivalence method of approval is that it tends to maintain the status quo. For example, most, if not all, pulse oximeters currently used in the United States are approved via the 510(k) pathway.[12] Pulse oximeters estimate blood oxygen saturation by shining light through the skin, typically on a fingertip or an ear lobe. Oxygenated blood absorbs red light more efficiently than de-oxygenated blood, thus allowing for estimates of oxygenation by simply measuring the amount of red light that passes through a tissue. However, oxygenated blood is not the only thing that absorbs red light – melanin, melanosomes, and melanocytes (ie, skin pigmentation), also absorb or scatter red light. A retrospective study found that practitioners missed hypoxemia diagnoses in 11.7 percent of Black patients compared to 3.6 percent of white patients due to pulse oximetry overestimating blood oxygenation.[13]

In the context of the COVID-19 pandemic, that suggests that excluding other factors, Black patients would be nearly 4-times less likely to receive oxygenation therapy such as a ventilator, which could prevent progression to acute respiratory distress syndrome.[14] As a result of these findings, the Food and Drug Administration (FDA) released a safety communication indicating oximeters may be less accurate in darker skin tones.[15] The failure of pulse oximeters to accurately measure oxygen saturation in all skin tones is a clear example of how inequity enters the health care system from many sources and can cascade. For example, even if a provider wished to start a patient on oxygenation therapy, Medicare reimbursement for supplemental oxygen therapy is only approved if a patient has a blood oxygenation reading less than or equal to 89 percent, which is less likely in Black patients if a pulse oximeter is used.[16] In November 2022, the FDA hosted an advisory committee meeting to discuss concerns of pulse oximeters and skin pigmentation. Dr. Jesse Ehrenfeld, president-elect of the AMA, was a participant of this meeting and delivered comments and recommendations on behalf of the AMA.

It is important to assess whether approving a new pulse oximeter design that reaches the same level of performance as a predicate device is appropriate as our appreciation of inequity grows and some categories of devices no longer match the values we wish to uphold.

Off-Label Use of Medical Devices

While the FDA has attempted to pilot programs, such as the Safety and Performance Based Pathway, that would improve the balance of fostering innovation and patient safety, they may not have the legislative authority or resources available to make these new programs mandatory. Without authority to pursue reforms to medical device regulation, there are concerns that the FDA may become more and more likely to begin regulating the practice of medicine to achieve similar goals.

The FDA has the authority to ban medical devices if they present a substantial deception to patients about the benefits or an unreasonable and substantial risk of injury. However, there are recent concerns of misuse of the banning process. In 2020, the FDA published a rule banning the use of electrical stimulation devices (ESD) for the treatment of self-injurious and/or aggressive behavior.[17] The FDA reported that the use of ESDs for this indication was unsafe and could lead to

significant physical and psychological harm. ESDs were still approved for other indications such as smoking cessation.[18] The approval of devices for specific indications while banning the same device for others is, per AMA policy, the FDA regulating the practice of medicine. The AMA has extensive policy and significant history defending the rights of physicians to practice medicine and protect off-label prescribing of pharmaceutics and devices.

Within the text of the FDA's rule on banning ESDs for aggressive behavior, they cite the 510(k) pathway as part of their justification for the banning of a specific indication, as they evaluate risk of a device based on its intended function, not on all potential functionalities. For example, daily wear vs. extended wear for gas permeable contact lenses are two separate risk categories. Evaluation of "substantially similar" for the purposes of 510(k) approval includes analysis of similar function. In 2021, the D.C. Circuit Court of Appeals overturned the ban, finding that the FDA was in fact regulating the practice of medicine, per the holdings of *Judge Rotenberg Educational Center v. United States Food and Drug Administration*.[19]

CONCLUSION

While the FDA has made strides in improving the 510(k) process for medical device approval, such as through the Safety and Performance Based Pathway, recent data have shown serious safety concerns. These safety concerns denote the need for the process to be re-examined to support the purpose and benefits of accelerated pathways along with providing the FDA with the statutory authority to address the larger, systemic issues without impeding on the practice of medicine.

RECOMMENDATIONS

The Council on Science and Public Health recommends the following be adopted, and the remainder of the report be filed:

1. Our AMA believes that to support innovation while protecting patient safety, approval pathways for medical devices should incorporate the following principles:
    a. Evidence-based, measurable performance benchmarks, such as those used in the Safety and Performance Based Pathway, should be used wherever possible for classes of known, well-studied medical devices; and
    b. For a subset of higher risk devices receiving approval but have not completed clinical trials, time-limited approvals may be appropriate, after which the manufacturer may be required to provide post-market data to support full device approval; and
    c. Medical devices with known safety concerns should not be usable as predicate devices for the purposes of proving substantial equivalence. In the event safety concerns of predicate devices arise after approval has been granted, additional due diligence should be initiated as appropriate; and
    d. Approval for medical devices should include criteria for adequate performance in racialized, minoritized, or otherwise historically excluded groups <u>when feasible.</u>~~;~~ ~~and~~
    e. ~~Reports of adverse events for medical devices should always be available in a publicly accessible, searchable database such as the Manufacturer and User Facility Device Experience.~~ (New HOD Policy)

2. That Policy H-120.988, "Patient Access to Treatments Prescribed by Their Physicians", supporting a physician's right to prescribe medical devices off-label, be reaffirmed. (Reaffirm Current HOD Policy)

APPENDIX

TABLE 1

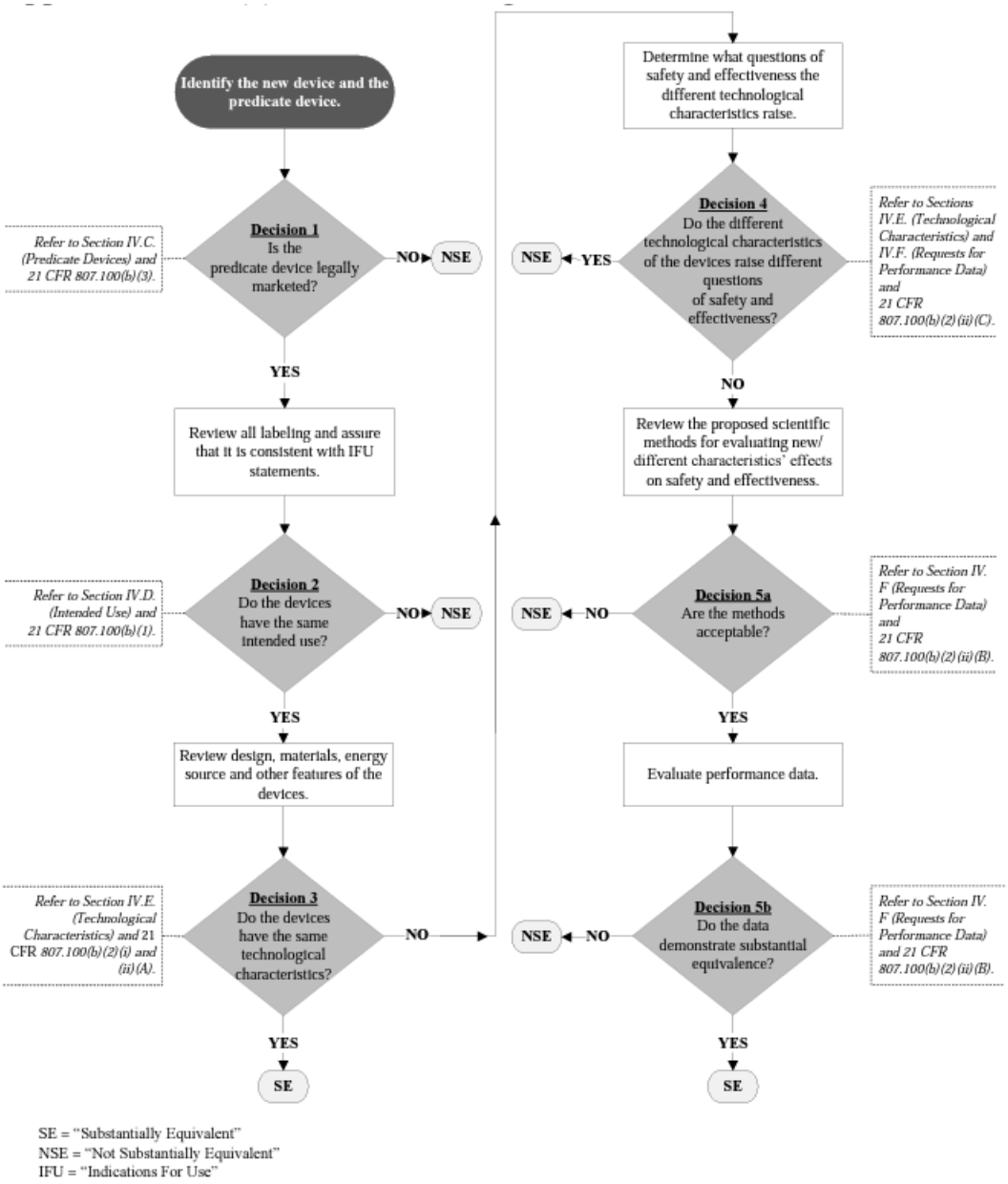
Comparison of regulatory requirements for drugs, biologics, and devices

Modified from Congressional Research Service, "Medical Product Regulation: Drugs, Biologics, and Devices", published September 29th, 2021. https://sgp.fas.org/crs/misc/IF11083.pdf.

	Drug	**Biologic**	**Class II (Medium Risk) Device**	**Class III (High Risk) Device**
Authorization Type	Approval	Licensure	Clearance	Approval
Submission to FDA	New Drug Application	Biologics License Application	510(k) notification	Pre-market approval
Clinical Trials?	Yes	Yes	No	Yes (few exceptions)
Evidence Required by FDA	Substantial evidence of effectiveness, adequate evidence of safety	Substantial evidence of effectiveness, adequate evidence of safety	Substantial equivalence to a known, approved device	Reasonable assurance that the device is safe and effective for its intended use(s)

FDA 510(k) Decision-Making Flowchart

Modified from Food and Drug Administration, *"The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]"*, July 28, 2014. Accessed January 23rd, 2023.



SE = "Substantially Equivalent"
NSE = "Not Substantially Equivalent"
IFU = "Indications For Use"

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