

Medical device risk (re)classification: lessons from the FDA's 515 Program Initiative

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The 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act granted the US Food and Drug Administration (FDA) regulatory authority over medical devices. Congress intended for FDA's review requirements to correspond to the amount of information needed to provide 'reasonable assurance of safety and effectiveness' based on a device's risk profile, establishing a three-tiered system for classifying devices: low risk, moderate risk and high risk.¹ Low-risk devices are typically only subject to general controls (eg, good manufacturing practices) and exempt from premarket review. For moderate-risk devices, FDA additionally requires manufacturers to demonstrate 'substantial equivalence' to a previously authorised device, usually without clinical evidence of safety and effectiveness,² through the 510(k) pathway (table 1). High-risk devices undergo the most rigorous regulatory review through the premarket approval (PMA) pathway,³ which typically requires evidence from clinical study(ies) demonstrating reasonable assurance of safety and effectiveness.¹

FDA can reclassify the risk of a device type (eg, reclassifying a moderate-risk device as high risk or vice versa), and thus the corresponding premarket requirements, in response to a petition from a manufacturer or on its own accord to assure safety and effectiveness. FDA reclassified approximately 30 medical device types from 2013 to 2021, most of which were downclassified (ie, classified as lower-risk devices).⁴ While concerns have been raised about potential risks to patients after device downclassification,⁵ others have advocated for greater downclassification as a potential means to facilitate further device development and ease market entry.⁶

At the inception of FDA's medical device regulation programme in 1976, more than 170 high-risk device types were already on the

KEY MESSAGES BOX

- ⇒ The FDA classifies medical devices into low-, moderate-, and high-risk categories, which has implications for the amount of information manufacturers need to submit to provide 'reasonable assurance of safety and effectiveness' for market authorization.
- ⇒ Launched in 2009, the 515 Program Initiative aimed to finalise the reclassification of high-risk devices that had been available on the market before 1976, when Congress gave FDA the authority to regulate medical devices.
- ⇒ The 515 Program Initiative offers insights into how the agency synthesises postmarket data to recalibrate the risk classification for medical devices and lessons for modernising medical device classification more broadly to advance access to medical devices while maintaining patient safety.

market, ranging from artificial hip implants to cardiac defibrillators. To avoid disrupting patients' access to these devices, FDA elected to temporarily regulate these device categories under the 510(k) pathway, with the goal of eventually transitioning these devices to their final risk designation (either to high-risk devices that would require manufacturers to obtain PMA or to low-risk or moderate-risk 510(k) devices).⁷

Over time, FDA evaluated and reclassified these so-called 'preamendment' device types. Nonetheless, by 2009, FDA still had not issued final reclassification decisions for 26 high-risk medical device types, prompting the agency to launch the 515 Program Initiative to finalise the reclassification of preamendment Class III 510(k) devices.⁸ Three years later, the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) introduced a five-step administrative process for device reclassification: (1) collecting existing scientific information to evaluate risks and benefits, (2) convening advisory committee meetings, (3) issuing proposed

**Table 1** Major pathways for regulation of medical devices in the USA

| Pathway | Description | Examples |
|-------------------------------|--|--|
| Premarket approval | <ul style="list-style-type: none"> ▶ The most rigorous type of device marketing application required by the FDA. ▶ Involves the evaluation of the prospective clinical data establishing reasonable assurance of medical device safety and effectiveness. ▶ Used for the regulation of Class III (high-risk) devices. | <ul style="list-style-type: none"> ▶ Artificial heart valves ▶ Pacemakers ▶ Implanted prosthetics |
| Premarket notification 510(k) | <ul style="list-style-type: none"> ▶ Requires devices to be substantially equivalent to a device legally cleared for marketing ('predicate') in the USA by having similar intended use and technological characteristics. ▶ If there is a difference in technological characteristics, the new device must have the same effectiveness and safety profile as the predicate. ▶ Used for regulation of most Class II (moderate-risk) devices. | <ul style="list-style-type: none"> ▶ Catheters ▶ Blood transfusion kits ▶ Blood pressure monitors |

FDA, Food and Drug Administration.

risk classification, (4) reviewing public comments and (5) issuing final risk classification.⁸

In 2019, FDA finalised the reclassification of all preamendment devices. In this analysis, with the benefit of several years of experience after reclassification, we describe the medical device categories that were reclassified under the 515 Program Initiative and offer insight into regulatory decision-making and medical device safety, including implications for future reclassification decisions and clinical practice.

DEVICE TYPES RECLASSIFIED UNDER 515 PROGRAM INITIATIVE

Under the 515 Program Initiative, FDA finalised the reclassification of the remaining 26 preamendment device types. Twenty-five (96%) were therapeutic device types (table 2).

Twelve (46%) device types were indicated for cardiovascular disease, of which 6 (50%) maintained high-risk classification, 3 (25%) were downclassified and 3 (25%) were split-reclassified. Split-reclassification entailed both downclassifying the original device type as moderate-risk and creating a new high-risk device category to account for potential differences in the risk profile of other devices. Among the 26 device types, 3 (12%) were life-sustaining, of which 2 were downclassified, and 9 (35%) were implanted, of which 4 (44%) were reclassified as moderate risk. Two (8%) device types, both of which were maintained high-risk classification, were subject to post-market studies under the 522 Postmarket Surveillance Studies Program.⁹

Eighteen (69%) device types had at least one device subject to a Class I or II recall prior to their final reclassification. Class I recalls are issued when there is a reasonable likelihood of serious adverse events or death, whereas Class II recalls are issued when adverse events are temporary or reversible or there is a low probability of a serious adverse event.¹⁰ Of these 18 device types, all (100%) were subject to at least one Class II and 8 (44%) were subject to at least one Class I recall. Prior to their final reclassification, a total of 88 (median (IQR) 0 (0–1) recall per device type) and 699 (median (IQR) 1 (0–10) recall per device

type) Class I and II recalls had been issued for these 18 device types, respectively. Twelve (67%) of the recalled device types were downclassified or split-reclassified.

DEVICE TYPES MAINTAINING HIGH-RISK CLASSIFICATION UNDER 515 PROGRAM INITIATIVE

FDA maintained a high-risk classification for 10 (38%) of the 26 device types, often citing safety concerns based on evidence generated in real-world use of these devices following market authorisation. For instance, automated external defibrillator (AED) systems were categorised as Class III high-risk devices under the 515 Program Initiative.¹¹ During the 3 years prior to the reclassification decision, over 40 moderate-risk or high-risk recalls for AEDs had affected more than 2 million devices. Thus, given these significant safety concerns, FDA required stricter regulation through PMA.¹¹ Some public commenters were concerned that requiring PMA could limit the availability of AEDs, increase unnecessary costs, or hinder innovation.¹¹ Despite maintaining a high-risk classification for AEDs, FDA offered a 15-month extension for PMAs to ensure uninterrupted availability of these life-saving devices while manufacturers worked to validate their safety and effectiveness.¹¹

DEVICE TYPES DOWNCLASSIFIED UNDER 515 PROGRAM INITIATIVE

FDA downclassified 10 (38%) of the 26 device types to moderate risk; these devices were predominantly non-cardiovascular (7 (70%)) and non-implanted (6 (60%)). Though 2 (20%) of these device types were life-sustaining, FDA elected for downclassification after concluding that their clinical use was well-established without evidence of serious safety concerns. Consider membrane lung devices for long-term pulmonary support, which were redesignated as extracorporeal circuit and accessories for long-term respiratory/cardiopulmonary failure and are commonly known as extracorporeal membrane oxygenation. These devices were downclassified to Class II (moderate-risk) devices.¹² Although considered

Table 2 Characteristics of preamendment medical devices reviewed under the 515 Program Initiative

| | Total, N (%) (n=26) | Downclassified, N (%) (n=10) | Split-reclassified, N (%) (n=6) | Maintained, N (%) (n=10) |
|--|------------------------|---------------------------------|------------------------------------|-----------------------------|
| Purpose of use | | | | |
| Diagnostic | 1 (4) | 0 (0) | 0 (0) | 1 (100) |
| Therapeutic | 25 (96) | 10 (40) | 6 (24) | 9 (36) |
| Therapeutic area | | | | |
| Cardiovascular | 12 (46) | 3 (25) | 3 (25) | 6 (50) |
| Dental | 2 (8) | 2 (100) | 0 (0) | 0 (0) |
| Gastroenterology urology | 2 (8) | 1 (50) | 1 (50) | 0 (0) |
| General and plastic surgery | 1 (4) | 1 (100) | 0 (0) | 0 (0) |
| Neurology | 2 (8) | 0 (0) | 2 (100) | 0 (0) |
| Obstetrics/gynaecology | 1 (4) | 0 (0) | 0 (0) | 1 (100) |
| Orthopaedic | 3 (12) | 1 (33) | 0 (0) | 2 (67) |
| Physical medicine | 2 (8) | 2 (100) | 0 (0) | 0 (0) |
| Radiology | 1 (4) | 0 (0) | 0 (0) | 1 (100) |
| Implanted | | | | |
| Yes | 9 (35) | 4 (44) | 0 (0) | 5 (56) |
| No | 17 (65) | 6 (35) | 6 (35) | 5 (29) |
| Life-sustaining | | | | |
| Yes | 3 (12) | 2 (67) | 0 (0) | 1 (33) |
| No | 23 (88) | 8 (35) | 6 (26) | 9 (39) |
| Subject to 522 Postmarket Surveillance Studies Program as stated in final rule/order | | | | |
| Yes | 2 (8) | 0 (0) | 0 (0) | 2 (100) |
| No | 24 (92) | 10 (42) | 6 (25) | 8 (33) |
| Recalls issued before reclassification decision* | | | | |
| Class I | 8 (31) | 2 (25) | 2 (25) | 4 (50) |
| Class II | 18 (69) | 7 (39) | 5 (28) | 6 (33) |
| Advisory committee recommendation | | | | |
| Agreed with final classification | 25 (96) | 9 (36) | 6 (24) | 10 (40) |
| Disagreed with final classification | 1 (4) | 1 (100) | 0 (0) | 0 (0) |

*Class I and II recalls were not mutually exclusive.

life-sustaining, FDA found sufficient evidence that a comprehensive set of multiple special control measures, including the device's technological characteristics and parameters, biocompatibility testing, sterility, non-clinical performance evaluation, in vivo evaluation and special labelling requirements, together with general controls, could mitigate the identified risks and provide a reasonable assurance of safety and effectiveness.¹²

DEVICE TYPES SPLIT-RECLASSIFIED UNDER 515 PROGRAM INITIATIVE

FDA split-reclassified 6 (23%) of the 26 device types. For example, non-roller type cardiopulmonary bypass pumps (NRPs), which are non-implanted, non-life sustaining devices, were split-reclassified in June 2015.¹³ FDA classified NRPs with indications for use in cardiopulmonary and circulatory bypass into Class II (moderate risk).¹³ FDA found that while these devices could be associated

with serious safety risks, such as stroke, peripheral emboli and death, these risks could be mitigated through special controls, including non-clinical performance testing and labelling.¹³ For example, these devices must undergo non-clinical performance testing demonstrating that they do not create gaseous, particular, or thrombotic emboli that could lead to safety risks.¹³

Percutaneous ventricular assist devices (PVADs) were also originally cleared through the 510(k) pathway by demonstrating substantial equivalence to NRPs. However, after reviewing the existing evidence under the 515 Program Initiative, FDA found significant differences between PVADs and preamendment NRPs, along with insufficient evidence for the safety and effectiveness of PVADs.¹³ Thus, aligned with the majority of advisory committee's recommendations, FDA classified PVADs and other NRP devices for temporary ventricular support

as Class III and required manufacturers to submit a PMA application for authorisation.^{7 13}

IMPLICATIONS FOR FUTURE REGULATORY DECISIONS

Nearly 50 years after the passage of the 1976 Medical Device Amendments, FDA has gained significant post-market experience with a range of device types, some of which may warrant reclassification based on subsequent evidence that safety risks differ from those expected at the time of authorisation. While the 515 Program Initiative has concluded, medical device reclassification continues to occur, including at least two FDA downclassification decisions in early 2023,^{14 15} and thus, the initiative offers insight into several important factors that FDA may be considering when making device reclassifications.

First, it is important to note that the 515 Program Initiative was a time-consuming process with limitations, spanning 10 years from start to finish. The heterogeneity of the device types may have prolonged reclassification decisions. FDA could consider reviewing its experience and determining which aspects of the structured and transparent criteria established by FDASIA to guide reclassification decisions should be maintained for future reclassification decisions, whether resources were sufficient for the endeavour, and where there are opportunities to speed the process while ensuring stakeholder input and transparency.

Second, although FDA considered device safety history during reclassification, the agency's decisions were not entirely aligned with the available safety information. Three device types that were downclassified or split-reclassified were subject to at least one Class I recall after reclassification; all of these devices had also been subject to Class I recalls prior to the reclassification decision. Notably, one cardiovascular device (intra-aortic balloon pump) was subject to 18 Class I recalls before and has had another 69 Class I recalls after its reclassification date.

Recent research has found a higher risk of Class I recalls for 510(k)-authorised devices that were authorised for marketing based on recalled predicates.¹⁶ When downclassifying medical device types associated with Class I recalls, FDA could accordingly consider providing clear public justification for these decisions. FDA could also consider requiring 522 Postmarket Surveillance Studies for such devices to evaluate their safety and establish device-specific thresholds for upclassification to Class III based on study results, or if the postmarket surveillance studies are not conducted according to agreed on timelines. FDA could also establish a threshold for considering moderate-risk devices with multiple Class I recalls to be reclassified as high risk.

Third, FDA's willingness to de-emphasise recall history might have been influenced by the recommendations of its advisory committees and the lack of reliable clinical evidence. Among all device types reclassified under the 515 Program Initiative, advisory committee (panel) recommendations directly aligned with the final decision

to downclassify all device types, except for one instance where the panel recommendation was made prior to the release of the substantial evidence that changed the reclassification decision.¹⁷ This pattern is consistent with previous studies showing high rates of agreement between the advisory committee recommendations and FDA's final actions.¹⁸ To ensure better informed regulatory decisions and advisory committee guidance, FDA could consider requiring two independent clinical studies of medical device safety and effectiveness prior to convening an advisory committee.

Finally, and relatedly, based on the information available in the FDA's documentation of its final decisions, we did not find any reclassification decisions supported by newly conducted clinical studies. While FDA strongly supports the use of high-quality real-world evidence (RWE) to inform decision-making,¹⁹ there was often a lack of robust data documented in FDA's decisions for pre-amendment devices, even though these devices had often been widely used for many years and FDASIA explicitly required evidence reviews as part of the reclassification process. To improve RWE generation for medical devices, FDA has established the National Evaluation System for health Technology, which is intended to support medical device evaluations using multiple data sources, including clinical registries, electronic health records and administrative claims.²⁰ FDA could establish criteria for the evaluation of the rigour and reliability of these data needed to support downclassification or split-reclassification.

While downclassification might be feasible for certain well-established device types with acceptable safety profiles, for which the identified risks could be addressed through special controls, the agency must strike a balance between risk and benefit for regulated products. FDA's experience with the 515 Initiative Program offers important insights into how the agency synthesises postmarket data to recalibrate the risk classification for medical devices. Lessons from this initiative may have applications for modernising medical device classification more broadly to advance access to medical devices while maintaining patient safety.

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