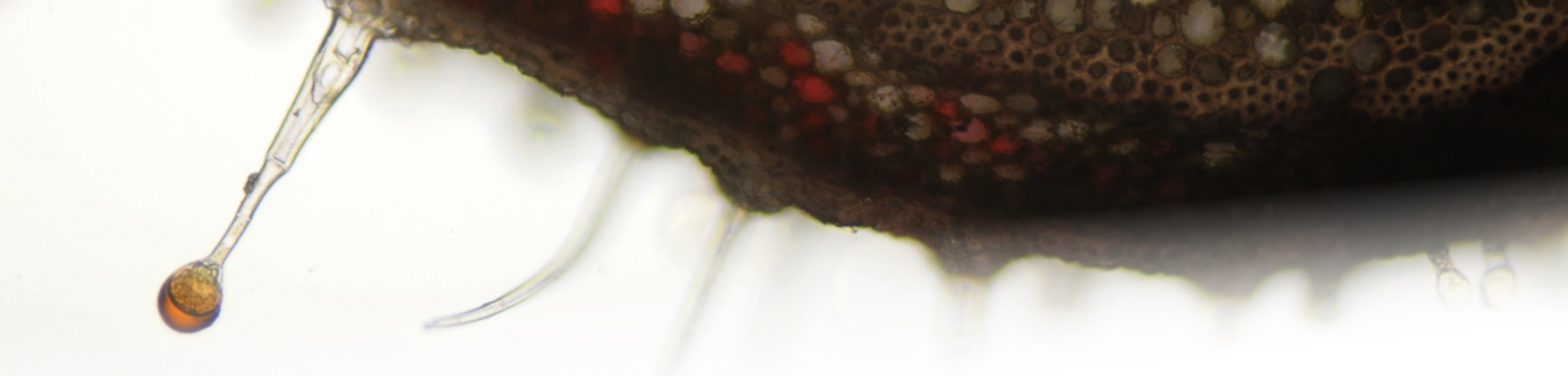

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FDA Device Oversight From 1906 to the Present

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Abstract

This article examines the history of device oversight by the US Food and Drug Administration (FDA). Significant regulatory changes occurred in response to injuries caused by Dalkon Shield intrauterine devices. This article summarizes those changes as well as continued efforts by the FDA to strengthen device oversight and address areas of concern.

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Genesis of Device Oversight

The dramatic expansion of device use in health care demands that clinicians understand device regulation and its strengths and weaknesses as a key ethical and clinical responsibility. In 2018, the US Food and Drug Administration (FDA) approved more than 100 novel devices, a number that surpassed the prior year's record and represented a fourfold increase over 2009.[1] Medical product oversight began with a focus on food and medications during the early 20th century, spurred by public concern about the danger posed by common food additives, such as formaldehyde.[2] As a result, the Pure Food and Drug Act was signed into law in 1906,[3] creating a federal entity that would become the FDA. The Federal Food, Drug, and Cosmetic Act of 1938 authorized product oversight by the FDA,[4] but even with amendments[5] in 1962 inspired by the tragic health consequences of sulfanilamide[6] and thalidomide,[7] the FDA did not regulate devices until 1976, when complications associated with the Dalkon Shield spurred new legislation.

Lessons From the Dalkon Shield

A contraceptive device inserted into a woman's uterus for pregnancy prevention, the Dalkon Shield was marketed to American women beginning in 1971 as a better alternative to contraceptive pills.[8] Its use skyrocketed, with approximately 2.2 million devices implanted in American women by 1974.[9] Due to limitations in regulatory requirements at that time, no federal oversight of the device's premarket assessment occurred.[10,11] Postmarket research revealed a 4.7% pregnancy rate and a 6.3% rate of device expulsion (ie, displacement from its proper uterine position) in Dalkon Shield users—far higher than the rates touted by the manufacturer.[12] Furthermore, women who

became pregnant were at higher risk for complications, including septic pregnancy and maternal death.[13] Despite reports of significant morbidity and mortality associated with use of the device, removal of the Dalkon Shield from the market was slow; voluntary recall was not issued until late May of 1974, months after the manufacturer became aware of hazards.[14]

The importance of pre- and postmarket device regulation and the dangers of decentralized regulatory authority were illuminated by the Dalkon Shield, leading to the passage of the Medical Device Amendments of 1976.[15] These amendments assigned ultimate regulatory authority for devices to the FDA; established a 3-category, risk-based classification system for devices (I, II, III); and required postmarket adverse events reporting. Two regulatory pathways for devices were also established: premarket approval (PMA) and premarket notification, known as the 510(k) pathway. While most high-risk class III devices required PMA based on evaluation of their safety and effectiveness prior to use in clinical practice[16] (similar to drugs[17,18,19]), devices for which PMA was not required could utilize the 510(k) pathway,[20] discussed in more detail below.

Continued Framing of FDA Oversight

In 1982, the Center for Devices and Radiological Health (CDRH) was formed within the FDA to regulate devices and radiation-emitting products.[21] The Safe Medical Devices Act (SMDA)[22] of 1990 defined *substantial equivalence* to a predicate device (a device already on the market) as a standard for clearing devices utilizing the 510(k) pathway. A 510(k)-cleared device must (1) have the same intended use as a predicate device and (2) have the same technical characteristics or, if different, not raise questions about safety and effectiveness and demonstrate comparable safety and effectiveness to the predicate device through performance data submitted to the FDA.[20] In addition, the SMDA introduced postmarket surveillance requirements for manufacturers, mandated adverse event reporting for medical facilities, established penalties for violations, and granted the FDA recall authority.[22] Three recall categories (I, II, III) based on health hazard risk were created, with class I considered the highest risk.[22] Subsequent legislation included requirements to establish a unique device identification system and to include devices in the Sentinel System of postmarket safety surveillance.[23,24,25]

As requirements became more stringent, however, concerns arose that regulation could stifle innovation and deprive patients of timely access to lifesaving devices.[10,26] Subsequent legislation introduced a "least burdensome" approach to premarket review,[27] the De Novo program for novel low- to moderate-risk devices,[24] and reduction of the PMA cost burden for small business manufacturers.[28] More efficient and flexible approaches were outlined in 2016, with the 21st Century Cures Act[29] providing support for breakthrough devices and expanding criteria for humanitarian-use devices.

Pre- and Postmarket Oversight

Despite increased regulatory oversight by the FDA and expansion of device use in patient care, safety concerns can evolve over the lifespan of some devices. Recalls of cardioverter-defibrillator leads[30] and metal-on-metal hip implants,[31] complications with urogynecologic surgical mesh[32] and a permanent implantable contraceptive device,[33] anaplastic large cell lymphoma association with breast implants,[34] and potential mortality associated with paclitaxel-containing devices[35,36] all reinforce the FDA's critical ongoing role in public protection.

The 510(k) pathway, particularly the substantial equivalence standard, has faced criticism. For devices cleared or approved between 1992 and 2012, 510(k)-cleared devices were 11.5 times more likely to face recalls than devices approved through the more stringent PMA process.[37] The percentage of devices utilizing clinical evidence to support substantial equivalence on the basis of safety and effectiveness was 27% for otolaryngologic devices cleared between 1997 and 2016.[38] Additionally, manufacturers of just 16% of devices in a sample of 510(k)-implanted devices cleared from 2008 to 2012 offered publicly available documentation of scientific evidence used to establish substantial equivalence, despite FDA requirements to do so.[39]

Furthermore, devices or materials have been cleared based on their substantial equivalence to predicates that were recalled due to adverse events, as was the case for 16% of surgical meshes cleared between 2013 and 2015.[40] A 2011 Institute of Medicine report concluded that, with some exceptions, "the 510(k) clearance process is not intended to evaluate the safety and effectiveness of medical devices" but rather to assess substantial equivalence to predicate devices.[17] Such concerns are clinically and ethically important, as premarket notification continues to be the primary regulatory pathway for many devices. In 2017, 3173 devices—82% of the total FDA-approved or cleared devices that year—entered the market via the 510(k) pathway.[41]

Postmarket surveillance, a combination of active and passive surveillance, has also faced criticism as being too narrowly focused or hampered by incomplete data. Although possible causal relationships between adverse events and a device have been successfully detected during postmarket surveillance, there is currently no comprehensive system for the FDA to field robust, reliable postmarket data.[42,43]

Comparisons have been made between the safety and performance requirements for devices and drugs. Drug approval includes demonstration of "substantial evidence" of safety and efficacy through clinical trials.[17,18,19] Moreover, for drugs, the FDA Sentinel Initiative[25,44] utilizes well-coordinated, standardized database distribution and data collection structures with multiple partners and has been a robust part of FDA active postmarket surveillance.[45,46]

Strengthening and Modernizing

Establishing a robust system of medical device postmarket surveillance and evaluation is a critical policy need that has been a major focus of the FDA, along with strengthening and modernizing premarket regulatory processes. This effort includes a focus on the 510(k) pathway, a unique device identification (UDI) system, use of real-world data (RWD) and real-world evidence (RWE), and, in collaboration with other stakeholders, the development of the National Evaluation System for Health Technology (NEST).[46]

510(k) pathway. Throughout the last decade, the FDA has standardized device review procedures,[41] introduced a "refuse-to-accept" policy based on submission completeness,[47] and added substantial equivalence documentation requirements for 510(k) clearance.[48] The FDA's Safety and Performance Based Pathway offers manufacturers of well-understood device types an option to use FDA-identified performance criteria to demonstrate safety and effectiveness.[49,50] To more fully address safety concerns stemming from use of recalled or high-risk predicates, nearly 1500 devices have been eliminated for use as predicates in 510(k) submissions since 2012.[41] Use of the 510(k) pathway has also been curtailed for new high-risk devices,[51,52] with no class III devices cleared for market via premarket notification in

2018.[41] Recommendations have also been made that the Safety and Performance Based Pathway become mandatory for eligible devices, commonly recalled device types, and possibly all 510(k) devices.[50,53]

UDI system. Development of a UDI system was prompted by the FDA's Unique Device Identification System Rule of 2013,[54] which required manufacturers to assign UDIs to devices. This requirement has facilitated development of a standard for electronic health record (EHR) documentation of device implants in patients,[55] adverse event reporting, and recall notification. UDI availability and use also supports improved aggregation of postmarket data from EHRs, payer claims, and clinical registries, enabling more robust postmarket surveillance.[56] A UDI implementation roadmap for implantable devices for health care organizations has been created,[57] and research has demonstrated successful UDI transmission via claims to payers.[58] One ongoing challenge is that, while moderate- and high-risk devices now have UDIs as mandated by the Unique Device Identification System Rule,[54] there is no requirement for UDI documentation during the course of clinical care, which is critical for broad UDI availability and use. Although some organizations are documenting UDIs without a mandate, policy updates will be required to advance broader applications.

RWD and RWE. Use of RWD and RWE in regulatory decision making and postmarket surveillance of devices has been an ongoing FDA priority, prompting the FDA to issue guidance[59] and convene an expert workshop in 2017.[60] Expanded UDI utilization would support the FDA's focus on RWD, which includes patient characteristics and health outcomes from multiple sources (EHRs, claims databases, and clinical registries).[61] Use and analysis of RWD from clinical trials and observational studies can be used to generate RWE, the clinical information needed to determine device use risks and benefits.[61] One historical limitation of RWD and RWE, however, has been data quality and analysis validity; both are current foci of the NEST Coordinating Center (NESTcc),[62] the FDA's RWE program,[63] and collaborative efforts.[64]

NESTcc. Establishing a national evaluation system for health technology was included in the CDRH's *2016-17 Strategic Priorities*.[65] NESTcc is a public-private organization consisting of multiple partners (health systems, academia, payers, registries, and research networks).[66] NESTcc is advancing the use of RWD and RWE in research projects,[67,68,69] with the goal of informing device evaluation and regulation.[70]

Conclusion

As the Dalkon Shield case illuminates, patient harm has been a driver of change in device oversight and regulation. This historical overview has summarized key strengths and weaknesses of the federal legislative response, which has attempted to protect patient safety while fostering innovation. Ongoing efforts by the FDA to strengthen and modernize pre- and postmarket regulatory processes aim to advance device safety and enhance patient outcomes.

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