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United States regulatory approval of medical devices and software applications enhanced by artificial intelligence ☆,☆☆

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ABSTRACT

In the United States, regulatory oversight of medical devices has evolved with the changing technology. With the introduction into routine clinical practice software applications and computer-based devices, the U.S. Food and Drug Administration (FDA) has further defined categories of risk and intended use to better uphold patient safety, while encouraging innovation in medical technology. However, as new software technologies such as artificial intelligence (AI) are developed, refined, and introduced into the healthcare sector, there will be a need for regulatory bodies to rapidly respond. In the current review, we discuss the evolution of US FDA oversight of medical devices, initially of hardware, and the present stance on medical software applications, including devices augmented with artificial intelligence.

Introduction

The impetus for the widespread adoption of health information technology (IT) in the United States began predominantly with Congressional passage of The Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 [1]. This legislation served two main purposes: 1) to encourage universal, meaningful use of electronic health record (EHR) systems for documenting patient encounters and 2) to enhance accountability of health IT security violations and breaches in protected health information (PHI). The systemic result of this and related policies has been an overall improvement in patient care and enhanced hospital efficiency in the United States [2,3]. However, at the individual provider level, results have been mixed, with some studies suggesting increased time efficiency [4,5] and conversely, others suggesting information fragmentation, increased cognitive load, and overall time inefficiency as a result of high data availability [6–8].

Concurrently, there has been a rapid commercial expansion in technology and software development over the last several decades. Advancements in consumer technologies, such as 3D bioprinting, cloud computing, artificial intelligence (AI), and blockchain, have translated to applications in the healthcare sector and require new regulatory guidelines that evolve with the rapidly changing technology. The US Food and Drug Administration (FDA) plays a critical role in facilitating the development of these emerging technologies by providing technical frameworks and guidelines, and further setting goals to improve the regulatory approval process. Recently, the FDA responded to a growing trend of 3D-bioprinted medical technologies, for which they provided a more comprehensive regulatory pathway for technologies in this area and issued new guidance advising on the technical aspects of manufacturing 3D-printed medical devices [9]. As part of this regulatory pathway, the FDA has reviewed hundreds of 3D-printed devices currently on the market for a variety of indications and has played a fundamental role in the advancement of this technology.

More recently, advancements in AI algorithms and their widespread utility suggest profound implications for healthcare and medical technology. AI has been defined as “the science and engineering of making intelligent machines, especially intelligent computer programs” [10]. Further sources distinguish between artificial narrow intelligence (ANI), which constitutes AI specially designed to perform a single task, and artificial general intelligence (AGI), which refers to AI that displays human-like intelligence and can perform any intellectual task capable by humans [11]. In general, ANI is the subtype of AI typically used for medical technologies under review by the FDA. AI-enhanced medical technologies often implement Machine Learning (ML) algorithms, which have been deployed for many years in general consumer pattern recognition and prediction and are now emerging into clinical practice as a method of automating clerical work and improving efficiency of medical decision making while minimizing human bias and error.

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Table 1
Categories of medical devices, as defined by the U.S. Food and Drug Administration (FDA).

Category	Risk	Clearance	Controls
Class I	Low	None De Novo	General
Class II	Moderate	510(k)	Based on substantial equivalent predicate
Class III	High	PMA	Device-specific safety and efficacy
HDE	~	HDE	HUD designation; institutional review board
IDE	~	IDE	Good clinical practices (GCPs)

PMA: pre-market approval; HDE: humanitarian device exemption; HUD: humanitarian use device; IDE: investigational device exemption.

With the plethora of health IT software solutions has come the need for new regulatory guidelines that evolve with the rapidly changing technology and continue to ensure patient safety. In this review, a history and evolution of the regulatory landscape for medical devices and software in the United States is described, with a specific focus on the emerging AI technologies in healthcare.

History of medical device regulation in the United States

Initial legislation regulating the safety of medical products was passed by the United States Congress in 1938, primarily as a reaction to a series of unsafe practices in pharmaceutical compounding that directly led to adverse effects in consumers. The Federal Food, Drug, and Cosmetic Act gave authority to the U.S. Food and Drug Administration (FDA) to oversee marketing and sales of products classified as drugs or medical devices [12]. In Section 201(h) of the Act, a medical device was defined as: [13]

"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
2) 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
3) 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."

Throughout 1960s, a series of adverse events linked to under-regulated medical devices led both the public and government officials to demand more stringent oversight of medical device manufacturers. Concurrently, several U.S. Supreme Court cases concluded the presence of a legislative gap around medical devices. In a 1969 statement to Congress on consumer protection, President Richard Nixon called for a set of minimum standards for medical devices, and further dictated the government take "additional authority to require premarketing clearance [14]." As a result, the Cooper Committee was established to better define and regulate this category of medical products. In their report, published in September 1970, the Committee proposed three central points: 1) definition of three classes of medical devices, 2) creation of an expert scientific review for the safety and efficacy prior to device marketing, and 3) definition of the government's role in enforcement. As recommended, the medical device classification was based on risk (Table 1): class I defined as lowest risk, generally recognized as safe and effective, and subject only to general controls; class II defined as moderate risk and regulated by specific performance standards; and class III defined as highest risk and required full premarket approval prior to clinical use [15]. The Cooper Committee also recommended establishing medical device classification panels appointed by the FDA, representing a diverse array of clinical, scientific, and engineering backgrounds. These recommendations were ultimately adopted in the Medical Device Amendments of 1976, giving the FDA direct authority to regulate the medical device industry [16].

These Amendments to the original FDA legislation further defined the pathways by which medical devices could be approved for clinical use and general marketing. Class I devices, being of lowest risk and not presenting unreasonable likelihood of illness or injury, were regulated only by the general FDA controls, ensuring high quality manufacturing, accurate labeling, proper regulatory registration, and prevention of product adulteration [17]. Class II, moderate risk devices required further data to assure reasonable safety and efficacy. Regulation of a new class II device is based on a *substantially equivalent* device with existing FDA approval, and is cleared by the FDA 510(k) pathway, which requires manufacturers to prove substantial equivalence to another predicate device. Medical devices in this category are subject to category-specific performance standards, postmarket surveillance, special labeling requirements, and more stringent product guidelines [18]. Highest risk, class III devices require an extensive premarket approval (PMA) process that relies heavily on device-specific safety and efficacy data, often generated from clinical trials. These are typically devices that are intended to support or sustain human life, or prevent impairment in human health, or for which there is no substantially equivalent predicate device.

In 1997, FDA medical device regulations were further updated with Congressional passage of the Food and Drug Administration Modernization Act, stimulated in part by the rapid advancement of digital technology and its widespread adoption in the healthcare sector. Importantly, this legislation designated a new risk category of medical devices via the *de novo* pathway. Devices classified as *de novo* are typically novel, lower risk devices for which general and special controls would reasonably assure safety and efficacy (class I/II), but for which there is no substantially equivalent device, and thus would automatically be categorized as class III [19].

The most recent regulatory effort in medical devices was passed in 2016 in the form of the 21st Century Cures Act [20], the purpose of which was to "accelerate the discovery, development, and delivery" of technologically advanced treatment modalities. The Cures Act updated FDA controls for expedited review process of novel drugs or devices, with a focus on enhancing the adoption of novel and breakthrough technologies in the healthcare sector [21]. The Act further defined and expanded the number of humanitarian device exemptions, a category provided to novel medical devices intended to treat rare diseases with fewer than 8000 patients affected. Additionally, medical devices with the potential to address unmet healthcare needs for debilitating or life-threatening diseases would be eligible for an Expedited Access Pathway (EAP) to facilitate FDA clearance.

As the first specific regulatory guidance of the 21st century, the Act defined the authority of the FDA over software used in healthcare and clarified the definition of a medical device to

Table 2
Risk-stratified classification of Software as a Medical Device (SaMD) platforms. Adapted from International Medical Device Regulators Forum: "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations[25]". Outlined in bold are the SaMD categories that hold higher importance for independent FDA review.

State of healthcare condition	Significance of information provided by SaMD to inform healthcare decision		
	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

include any software application used specifically in the diagnosis, management, treatment, or prevention of disease.

Current regulation of software for healthcare applications

Software platforms used in healthcare are currently regulated by the U.S. FDA on an intent-based classification, i.e. whether a software platform is *intended* for use in diagnosis or treatment of disease or to affect the structure or function of human anatomy or physiology [22]. Software platforms that meet the FDA's definition of a medical device are subsequently classified along the regulatory continuum (Class I, II, or III), and must follow appropriate the FDA approval guidelines (via the 510(k), PMA, or De Novo pathways). The FDA has defined several categories of medical software, with varying complexity and enforcement guidelines: Software as a Medical Device, Medical Device Data Systems, Mobile Medical Applications, and Clinical Decision Support Software (Table 3).

Software as a Medical Device (SaMD) is currently defined by the International Medical Device Regulators Forum (IMDRF), and adopted by the U.S. FDA, as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device [23]." The FDA review process for SaMD applications establishes the validity of associations between "the output of a SaMD and the targeted clinical condition" and assesses the accuracy of the software's technical and clinical output data [24]. Importantly, software incorporated into a hardware medical device does not qualify as SaMD, as this software platform would be regulated within the device clearance process. The IMDRF and FDA have further risk-stratified SaMD platforms into four categories (I-IV) depending on intended use and severity of targeted medical condition (Table 2) [25]. The FDA carries out independent review based on risk category, with preference on SaMD platforms that treat/diagnose serious and critical conditions as well as applications that drive clinical management of critical conditions. Software as a Medical Device safety principles are governed by risk management, quality management, and systems engineering according to industry best practices.

Medical Device Data Systems (MDDS) are platforms intended to provide electronic transfer or storage of medical data, conversion of medical data type, or electronic display of medical data [26]. In 2011, the FDA reclassified all MDDS as class I (low risk) medical devices, stating that general controls such as Quality System Regulations would provide reasonable assurance of safety and efficacy for this category of medical software.

According to the FDA, a Mobile Medical Applications (MMAs) is a "mobile app that meets the definition of a device in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and either is intended to be used as an accessory to a regulated medical device or to transform a mobile platform into a regulated medical device [27]." Similar to SaMDs, MMAs as medical devices are defined by their *intended* use, as illustrated by labeling claims, advertising materials, and written or oral statements by manufacturers. Based on their 2015 guidance documentation, the FDA regulates only those MMAs that act as medical devices (as defined above) and "whose functionality may pose a risk to a patient's safety if the mobile app were to not function as intended." Like hardware devices, MMAs can be categorized as Class I, II, or III, and as a result would require general controls, 510(k), or PMA, respectively, for clearance. Given the recent growth of mobile medical technologies, the FDA focuses their regulatory sights on a subset of applications that transform a mobile platform into a regulated medical device. Examples of these types of platforms include:

- Mobile apps that serve as an extension of a regulated medical device, that serve to control the device, or to be used in active patient monitoring or analyzing hardware medical device data.
- Mobile apps that transform the mobile platform into a regulated medical device by using attachments, display screens, or sensors or by including functionalities similar to those of currently regulated medical devices.
- Mobile apps that perform patient-specific analysis and provide patient-specific diagnosis or treatment recommendations [27].

Another subset of mobile medical applications that the FDA intends to exercise discretionary enforcement on a case-by-case basis includes:

- Mobile apps that facilitate supplemental care by coaching or prompting, helping patients manage their health in a daily environment.
- Mobile apps that allow patients to organize and track their personal health information.
- Mobile apps that provide access to information regarding their health condition or treatment.
- Mobile apps that facilitate communication between the patient and a healthcare provider.
- Mobile apps that connect the patient to the electronic health record.
- Mobile apps that meet the definition of a Medical Device Data System (MDDS).

Lastly, the FDA specifically defines certain medical mobile applications as non-medical devices and therefore have no regulatory oversight. These are typically general reference applications, and can include:

- Mobile apps used as a medical textbook or other reference material.
- Mobile apps used by providers as an educational tool for medical training.
- Mobile apps used for general patient education.
- Mobile apps that facilitate general office operations.

The last category of medical software that the FDA has categorized includes Clinical Decision Support Software (CDSS). As part of the 21st Century Cures Act, CDSS platforms were excluded as a medical device if the software functionality: [28]

1. Is not intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system;

Table 3
Categories of digital health technologies overseen by the U.S. Food and Drug Administration (FDA), as defined by their digital health criteria (source: https://www.fda.gov/medical-devices/digital-health/digital-health-criteria).

Category	Definition	Example
Software as a Medical Device (**SaMD**)	Intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device	Software that uses the microphone of a smart device to detect interrupted breathing during sleep and sounds a tone to rouse the sleeper
Advanced Analytics	Leverages large and complex data sets to identify and analyze information or patterns for medical purposes	An imaging system that analyzes a patient's melanoma by comparing it to a data repository from past melanoma cases and then provides a diagnosis and treatment plan for the patient
Artificial Intelligence	Imitates intelligent behavior or mimics human learning. Includes machine learning, neural networks, and natural language processing	An imaging system that uses algorithms to provide diagnostic information for malignant melanoma or skin cancer in patients
Cloud	Internet-based computing consisting of a shared pool of configurable resources that supplies data and processing resources on demand	A mobile colposcope that stores images taken on the cloud for future retrieval and review in the doctor's office
Cybersecurity	Prevents unauthorized access, modification, or misuse of information that is stored, accessed, or transferred from a medical device	User authentication (ID, password, smartcard, biometric) to limit device access
Interoperability	Exchanges or uses information through an electronic interface with another medical product	An infusion pump designed to receive patient data from any pulse oximeter and use this data to change infusion pump settings
Medical Device Data Systems (**MDDS**)	Electronic transfer, conversion, storage, or display of medical data	Software that collects output from a ventilator about a patient's CO2 level and transmits the information to a central patient data repository
Mobile Medical Applications (**MMAs**)	Accessory to a regulated medical device or to transform a mobile platform into a regulated medical device	Mobile apps that transform the mobile platform into a medical device through attachments, display screens, sensors, or additional functionalities similar to medical devices
Wireless	Uses any form of wireless communication in its function	Wi-Fi, Bluetooth, near-field communication (NFC)

2. Is intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information;
3. Is intended for the purpose of supporting or providing recommendations to a health care professional about prevention, diagnosis, or treatment of a disease or condition; and
4. Intended for the purpose of enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient

CDSS platforms that do not allow for independent review by a healthcare provider may be regulated as a medical device by the FDA, and therefore may be required to obtain the traditional regulatory clearance prior to market.

The FDA has also issued guidance on the use of off-the-shelf (OTS) software in medical devices. This specifically concerns products that utilize a conventional operating system, such as Windows or macOS, on which runs a proprietary medical software application. The FDA has determined that "a *basic* set of need-to-document items is recommended for all OTS software, and a detailed discussion is provided on additional (*special*) needs and responsibilities of the manufacturer when the severity of the hazards from OTS software failure become more significant [29]".

Digital health software precertification program (Pre-Cert)

In response to the rise of "digital health", which has been defined as "the cultural transformation of how disruptive technologies that provide digital and objective data accessible to both caregivers and patients leads to an equal level doctor-patient relationship with shared decision-making and the democratization of care" [30], the FDA launched its novel Software Precertification Pilot Program for medical software applications. This program was conceived to expedite review of and potentially replace the need for premarket submission of healthcare software platforms [31]. This program is philosophically different than the traditional FDA medical device clearance process, in that it recognizes the software or technology developer, rather than the end device, in the regulatory proceedings. In the Pre-Cert pathway, the FDA could pre-certify a digital health developer who has previously demonstrated "a culture of quality and organizational excellence based on objective criteria" and would be able to market their low-risk devices without an extensive FDA clearance process. Furthermore, for higher-risk software devices, these developers may be eligible for an expedited premarket review. In its regulatory guidance, the FDA proposes to use the end user data to feedback on the process, to facilitate transparency and allow the developer to improve its product with supervision from the FDA. Overall, the goal of this pilot program is to encourage innovation in the digital health sector and is meant to prevent undue FDA resource consumption by health applications undergoing rapid iterations.

In September 2017, the FDA selected 9 companies to participate in the Pre-Cert Pilot program, including Apple, Fitbit, Johnson & Johnson, Pear Therapeutics, Phosphorus, Roche, Samsung, Tidepool, and Verily. For qualification, these companies submitted detailed quality management protocols, collected and reported postmarket data on eligible software applications, and consented to onsite FDA visits [32].

FDA guidance on artificial intelligence (AI) applications

Currently, there exists no specific regulatory standards for the implementation of artificial intelligence in healthcare software or device applications. In April 2018, FDA Commissioner Scott Gottlieb remarked that:

> "AI holds enormous promise for the future of medicine, and we're actively developing a new regulatory framework to promote innovation in this space and support the use of AI-based technologies. So, as we apply our Pre-Cert program—where we focus on a firm's underlying quality— we'll account for one of the greatest benefits of machine learning – that it can continue to learn and improve as it is used [33]."

These comments imply a push towards specific guidelines for AI-enhanced medical software and devices in the near future. Given the present regulatory environment, however, medical devices and software applications continue to be assessed by the FDA according to the traditional standards (i.e. 510(k), PMA, or De Novo pathways). Recently, the FDA released a discussion paper describing a proposed regulatory framework for modifications to AI/ML-based SaMD that require premarket submission [34].

In February 2018, Viz LVO became the first AI-enhanced, computer-aided triage software to be cleared by the FDA via the De Novo premarket review pathway. Developed by Viz.ai (California, US), Viz LVO is a clinical decision support technology that autonomously analyzes CT angiograms for suspected large vessel embolic stroke, and automatically notifies a neurovascular specialist about positive findings via a mobile device alert. The Viz LVO software has been used to expedite identification and treatment of these stroke patients, for whom rapid treatment improves overall functional outcomes. Given its first-in-class regulatory approval via the FDA De Novo pathway, the Viz platform can now be utilized as a predicate device for future AI-enhanced technologies. As a result, 6 months later, Aidoc (Aidoc, Tel Aviv, Israel) was approved for clinical use. This system uses deep learning techniques to identify brain hemorrhages and prioritizes high acuity CT scans for radiologist review. This rapid clearance process illustrates the scalability of this model for the FDA, and may in turn facilitate further innovation in this space.

Within the last year, several clinical decision support software platforms utilizing AI algorithms have been cleared for marketing in the U.S. IDx-DR (IDx, Iowa, US), utilizes an AI algorithm to autonomously analyze images of the retina captured by a traditional retinal camera and detect evidence of diabetic retinopathy. Prior to approval, the device had been granted Breakthrough Device designation and an Expedited Access Pathway (EAP) given its potential impact on this unmet need. Another application, OsteoDetect (Imagen, New York, US) autonomously reads wrist x-rays to detect distal radius fractures and was similarly approved for clinical use via the De Novo pathway. Accipio Ix (MaxQ AI, Massachusetts, US) recently received clearance to assist in the prioritization and triage of adult patients presenting with acute intracranial hemorrhage through automated retrieval and processing of CT images. DreaMed Advisor Pro (DreaMed Diabetes, Petah Tikva, Israel) was granted De Novo approval for its algorithm that integrates data from glucose monitors and insulin pumps to determine insulin delivery for diabetics. AliveCor (California, US) has received FDA clearance for three algorithms related to smartphone-based electrocardiogram event detection. Zebra Medical Vision (Shefayim, Israel) was granted 510(k) clearance for its Coronary Calcium Scoring algorithm, which predicts coronary artery calcification scores from ECG-gated CT scans to help identify patients with high risk cardiovascular disease. In December 2018, ProFound AI (iCAD Inc., New Hampshire, US) received FDA clearance for automated detection of abnormalities on digital breast tomosynthesis, utilizing an AI algorithm.

As the FDA has done previously with emerging medical technologies, it must adapt its regulatory pathways and clearance processes to keep pacing with technical advancements. For example, the advent of AI-enhanced, data-driven clinical risk score prediction algorithms has ushered in a complex landscape of new regulatory considerations. These algorithms may potentially be used to obtain a more objective and granular genetic background for patients [35], conduct a diagnostic or risk assessment of polygenic diseases [36], and even guide the management and decision making processes for treating diseases based on predicted therapeutic efficacy from patient data [37,38]. Given the many potential applications of this technology in healthcare, the FDA's approach to regulation will likely depend on the specific roles these novel algorithms will play in the patient's care. Algorithms which simply serve as an additional source of advice to medical professionals will likely face less regulatory requirements than an algorithm intended to carry out automated decision-making processes in a healthcare setting [39].

Clearly, there has been a growing trend in AI-enhanced medical software applications. In these early stages, the software platforms approved for clinical use have been guided by the De Novo pathway, as they represent relatively lower risk devices (class I/II) but do not have a substantially equivalent device.

Conclusion

With the expansion of digital health technologies, the FDA has reacted accordingly by clearly defining the various medical software applications and set goals to improve the regulatory approval process of lower risk medical software platforms and devices. Novel concepts such as the Pre-Cert Pathway may facilitate the clearance of AI-enhanced digital health applications, given the rapid iteration that these applications must undergo for continuous algorithmic improvement. De Novo clearance of lower risk software platforms without a substantially equivalent predicate device will remain a major pathway for novel healthcare algorithms, at least during these initial stages. However, despite a rapid diaspora of AI-enhanced medical devices, it remains to be seen whether these new FDA clearance pathways contain satisfactory safety guidance to prevent patient harm. As with hardware devices, a medical practitioner should understand the risks and benefits of a software application prior to use.

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