A primer on the regulation and development of M-Health products

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Abstract
The widespread adoption of mobile and wireless technologies, including smartphones and tablets, has given rise to the growing field of mobile health (M-Health), which is poised to revolutionise sectors of healthcare. The rapid pace of growth in M-Health presents developers with key challenges in designing and implementing new mobile solutions. The purpose of this article is to help developers navigate the development and regulation maze of M-Health products. In this paper, we discuss the definition and uses, the international regulatory environment for M-Health as medical devices – including the impact of the US 21st Century Cures Act enacted in December 2016 – and the key development constraints and product evaluation activities of M-Health technologies.

What is M-Health?

While there is no universal or standardised definition for M-Health, the term applies to the "application of mobile or wireless technologies, such as mobile phones or tablet computers, and the Internet to the delivery of healthcare". M-Health products include a wide variety of technological platforms encompassing simple standalone mobile medical applications for a smartphone up to significantly more sophisticated systems combining software components with multiple connected medical sensors or even drug delivery systems.

In addition, many traditional medical devices, including implanted ones, are connected and can transmit medical data to distant servers or the cloud to allow patients or healthcare providers to control settings, remotely monitor device or patient status, or track trends over time. Patients can receive reminders or coaching to help manage chronic conditions. Patient compliance with medication schedules can also be assessed with "smart" drug delivery systems. Data from wearable sensors can provide information regarding patient status in daily life. Finally, healthcare providers benefit from M-Health tools intended to improve the delivery of healthcare, such as clinical decision support or drug dose calculators.

With the widespread adoption of mobile technologies worldwide, M-Health strategies are appearing in many aspects of healthcare from routine doctor visits to clinical trials to telemedicine. These technologies offer to empower both patients and healthcare providers, to decentralise the delivery of healthcare, and to improve outcomes for many diseases and conditions.

How is M-Health regulated?

Intended use is the primary factor in determining whether an M-Health product will be regulated as a medical device or not. For example, products intended to promote an "overall healthy lifestyle," may be viewed by the general public or even marketed as an M-Health product, but do not necessarily have a medical purpose *per se*. However, M-Health technologies that have a medical intended use are expected to fall under the authority of the medical products regulatory agencies at least in regulatory mature international market places. Many of these regulatory agencies have been actively developing stringent frameworks and guidelines specifically for M-Health medical devices, but are not fully harmonised internationally. In such cases, these types of M-Health devices should be regarded as more than simple IT tools used for medical purposes but rather as any other medical device in terms of product development and regulatory strategy.

US

The US FDA regulates M-Health within the existing framework for medical devices (ie, 21 CFR 800 *et seq*) and has released rules and guidelines applying specific regulatory statuses to some M-Health products. A regulated medical device in the US, an M-Health product must meet the statutory definition of a device. Briefly, a medical device is 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". An FDA regulated M-Health product must also either transform the mobile platform into either a regulated medical device or an accessory to a regulated medical device.[1]

Medical devices are classified in the US by their risk and the regulatory requirements vary by class (see Table 1). The lowest risk devices, Class I, are not reviewed by the FDA and only require registration and listing in order to authorise marketing in the US. For moderate risk devices, Class II, a premarket notification often referred to as a 510(k), must be submitted and reviewed by the FDA to obtain market authorisation. The highest risk, Class III, require the submission and review of a premarket approval (PMA) application. An M-Health product potentially could fall into any of these classifications based on the intended use and risks posed by the product. Some M-Health technologies can be novel in their intended use or in their technological characteristics and are, therefore, initially considered Class III simply because they are new. However, recent decisions by the FDA demonstrate a willingness to classify novel M-Health products into lower classifications via the *de novo* pathway.

Section 3060 of the 21st Century Cures Act is intended to clarify the regulatory status of medical software by specifically excluding those that provide specific types of functionalities from the definition of a medical device, including:

Table 1: Medical device classification in the US.

Risk classification	Submission	Review standard
Class I (low risk)	None	Not reviewed (only registration and listing are required)
Class II	510(k) *de novo*	Substantial equivalence to a legally marketed predicate
Class III (high risk)	PMA	Safe and effective
Enforcement discretion	None	Not reviewed (only registration and listing are required *or* all requirements are waived)

- Electronic health records
- Administrative support of healthcare facilities
- Healthy lifestyle encouragement
- Transfer, storage, conversion, or display of laboratory or other medical device data
- Provision of information or recommendations regarding clinical management to a healthcare provider.

The FDA had previously identified types of M-Health technologies viewed as particularly low risk and has decided not to apply medical device requirements. The FDA refers to these products as being under "enforcement discretion". The Agency has acknowledged that the existing framework for M-Health product regulation will need to be updated to be consistent. Fortunately, the exclusions are largely consistent with the FDA's existing policy.

For example, medical device data systems (MDDS), which allow the electronic transfer, storage, exchange, retrieval, display and conversion of medical device data (such as recording a patient's blood pressure and transmitting the data to that patient's electronic health record) were Class I and did not require a 510(k) for market authorisation. The FDA had also applied enforcement discretion to the other medical device requirements (eg, registration and listing, the Quality System Regulation, etc) for MDDS.[2] Under the 21st Century Cures Act, MDDS would no longer meet the definition of a medical device and consequently do not fall under the FDA's regulatory authority.

The FDA also released a policy regarding mobile medical apps (MMAs), which it periodically updates with additional examples.[3] The guidance describes the types of MMA that the FDA will regulate, those under enforcement discretion, and those that are not medical devices (ie, MMAs that do not have a medical purpose). Similar to MDDS, the MMA guidance will likely be updated to reflect the exclusions from the 21st Century Cures Act. However, the types of MMA that no longer meet the definition of a medical device were already considered to be under enforcement discretion.

The one exception is the final exclusion for software that provides information or recommendations to healthcare providers. This exclusion is to remove clinical decision support (CDS) software from the definition of a medical device. The FDA had not previously issued guidance on CDS, but has indicated that a draft guidance interpreting the new provision may be issued in 2018.

Some M-Health products combine the mobile platform, or other interfaces, with a drug or biologic. The FDA views products comprising both a drug and device or a biologic and a device as a combination product. While the M-Health component, meaning the software and hardware, is a device, the entire product is regulated based on the primary mode of action.

EU

In the EU, discrepancies between the EU Directive 93/42/EEC (MDD) requirements and the national transpositions of this Directive have made regulating M-Health challenging. Implementation of the new Medical Device Regulations (MDRs) will resolve the issue as their provisions must be applied the same across all member states in Europe. The related MDRs entered into force in May 2017 and will mandatorily apply from May 2020.

To qualify as a medical device, an M-Health product shall: (1) have a medical purpose; (2) perform an action on data (other than just storage) for the medical benefit of individual patients; and (3) generate or manage personalised alerts based on monitored patients vital parameters to drive clinical management; or (4) use an algorithm to support or facilitate medical decisions by a healthcare provider.

Depending on the claimed indications and mode of actions, M-Health products can belong to various risk classes according to the MDR, with more stringent requirements for higher risk devices (see Table 2). For a low-risk device (without measuring function), Class I, no notified body (NB) intervention is required and CE marking can be accomplished via self-certification. Higher risk classes, class IIa, IIb, and III, will require certification audits and technical file/design file reviews by the NB. Such M-Health products when regulated as medical devices are considered to be active medical devices and can be regarded either as diagnostic or therapeutic devices.

Under Rule 10a, the new MDR changed the classification scheme for standalone software. In particular, software intended to provide information used in diagnostic or therapeutic decisions or to monitor physiological processes is Class IIa. The classification can be higher, based on the risks (ie, software used in decisions that could directly or indirectly cause death or an irreversible deterioration in the state of health, which in that case would be regulated as Class III). A proper risk classification of these M-Health products to be regulated as medical devices in Europe is expected from regulators, considering the intended purpose and disease type/patient condition concerned.

Worldwide

In addition to the US and EU, specific national regulatory guidelines on the topic of M-Health products have been issued by a number of major medical device agencies, including Health Canada,[4] Australia's Therapeutic Goods Administration,[5] the UK's Medicines and Healthcare products Regulatory Agency,[6] and Singapore's Health Sciences Authority.[7]

Key development and evaluation considerations

The type and level of evidence necessary to support an M-Health product is determined by the intended use and risks posed by the product. Therefore, a comprehensive and rigorous proactive

Table 2: Medical device classification in the EU.

Risk classification	Notified body intervention	Conformity assessment
Class I (low risk)	None	Self-certification
Class IIa (medium risk)	Yes	Certification audit
Class IIb (higher risk)	Yes	Certification audits Technical file reviews
Class III (high risk)	Yes	Certification audits Technical file reviews Design file reviews

risk analysis is an essential activity when developing an M-Health product, including unique M-Health aspects related to the use of distant servers, cloud storage, etc). There are commonly used voluntary standards related to risk analysis and management for medical devices. Particularly useful for M-Health products is IEC TR 80002-1, which provides information on the application of the more general ISO 14971 to medical device software.

For M-Health products that are regulated as medical devices, the corresponding requirements provide some structure for development and evaluation. Additionally, the International Medical Device Regulators Forum (IMDRF) and its predecessor, the Global Harmonisation Task Force (GHTF), have released a variety of guidelines describing common principles related to the development and manufacturing of medical devices. Because M-Health products by their very nature operate on rapidly changing technology platforms, product development and evaluation is an ongoing and iterative process. As with any medical product, the key considerations include a well-functioning quality management system, adequate safety and risk mitigation, and sufficient evidence of performance.

Quality management system

Medical devices developed or sold in the US are required to comply with the Quality System Regulation (21 CFR 820). In the EU and many other markets, adequate quality management is demonstrated by operating under ISO 13485 – Medical Device Quality Management System Requirements. IMDRF has released a document with recommendations on the application of quality management system (QMS) principles to software medical devices.[8] Central to both is the establishment of quality policies and procedures at the company level. Critical elements of a robust QMS for M-Health products at the development and evaluation stage include design controls, risk management, document/record control, and supplier management.

A robust QMS also includes policies and procedures for monitoring and addressing complaints and adverse events/vigilance incidents post-market. Because M-Health products are often connected to the internet or other mobile/cellular systems, these technologies offer the possibility of obtaining either more detailed or timelier information regarding the performance and safety of the products in the field.

Safety

Central to ensuring the safety of M-Health products is a comprehensive and well-structured software verification and validation plan. A 2012 FDA study[9] on recalls for medical devices found that 15% were due to software design failures. Such design failures often trace back to inadequate software validation and verification. The FDA has a long-standing guidance document on the principles of software validation for medical devices[10] and many similar concepts are covered in IEC 62304: Medical device software – Software lifecycle processes.

The use of mobile platforms and other computer systems in M-Health products make them vulnerable to cybersecurity threats. Vulnerabilities in M-Health products present risks to the patient (eg, direct access and manipulation of a connected device) and also to the mobile platform or any connected networks. Robust cybersecurity measures are essential throughout the lifecycle from design to deployment to maintenance of an M-Health product. The FDA has released guidance documents on cybersecurity including content of premarket submissions[11] and post-market management of cybersecurity in medical devices.[12] Additionally, standards related to the management of cybersecurity in networks and communication in general can be considered (eg, IEC 62443 – Industrial communication networks and system security). Many M-Health products include collection, storage, or transmission of sensitive information and data regarding the patient. The design and testing of such products should include adequate measures to protect this information. Such data or information may also be subject to the additional regulations in different geographic jurisdictions.

Performance/effectiveness

Although different regulatory agencies and other organisations use different terms or define them differently when discussing the acceptable performance of a medical device including software or M-Health products, generally M-Health developers need to demonstrate that a product can perform as intended without introducing unacceptable risk. The performance includes both the technical functional performance typically demonstrated with traditional software validation and verification activities (in conformance with specific standard such as ISO 62304) and the clinical effectiveness.

The level of clinical effectiveness evidence depends on the risks posed by the device when used as intended and the claimed intended medical purpose (ie, an M-Health product intended to treat or diagnose a patient versus one intended to inform clinical management). For example, an online or app version of a commonly used clinical score (eg, Glasgow Coma Scale) to be used by a healthcare professional, would likely only need to demonstrate technical functional performance (ie, the ability to accurately and reliably generate the intended output from the input data); however, a mobile app that assesses the melanoma risk of a skin lesion based on an image analysis using a novel algorithm may require a controlled clinical trial demonstrating that the output is clinically meaningful (eg, has adequate sensitivity, specificity, etc) when typically compared to a recognised reference standard.

Recently, IMDRF released a draft document regarding the clinical evidence to support software as a medical device (SaMD).[13] The FDA also released this document for comment as a draft guidance. Many M-Health products fall into the category. The document provides a useful framework for assessing the type of evidence needed to demonstrate clinical performance and effectiveness for M-Health products.

Conclusions

Advances in M-Health products promise to revolutionise healthcare from everyday healthy choices to smart drug delivery to the integration of connected devices into hospitals and clinics. Worldwide regulators are actively developing regulatory frameworks for assessing and monitoring these technologies. As such, M-Health products are not just standard IT systems used for a medical purpose and should be developed like any other medical device. In fact, M-Health products regulated as medical devices require robust development activities to ensure regulatory compliance, to deliver meaningful benefits and mitigate risks to the patient, and to facilitate their adoption by healthcare professionals in their daily practice.

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