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Hold the Phone: FDA to Regulate Smart Phone Health Applications

M. P. Venkatesh[1]*, Akash Dambal[2], Manish Kumar[3], T.M. Pramod Kumar[4]

[1]Pharmaceutical Regulatory Affairs Group, Department of Pharmaceutics, JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University, S.S Nagar, Mysuru – 570015, Karnataka, India
[2]M.Pharm, Pharmaceutical Regulatory Affairs, Department of Pharmaceutics, JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University, S.S Nagar, Mysuru – 570015, Karnataka, India
[3]M.Pharm, Pharmaceutical Regulatory Affairs, Department of Pharmaceutics, JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University, S.S Nagar, Mysuru – 570015, Karnataka, India
[4]Department of Pharmaceutics, JSS College of Pharmacy, Jagadguru Sri Shivarathreeshwara University, S.S Nagar, Mysuru – 570015, Karnataka, India

Abstract : As mobile platforms become more user friendly, computationally powerful, and readily available, innovators have begun to develop mobile apps of increasing complexity to leverage the portability mobile platforms can offer. Some of these new mobile apps are specifically targeted to assisting individuals in their own health and wellness management. Other mobile apps are targeted to healthcare providers as tools to improve and facilitate the delivery of patient care. Although the FDA has not issued an overarching software policy, the Agency has formally classified certain types of software applications that meet the definition of a device and, through classification, identified specific regulatory requirements that apply to these devices and their manufacturers. These software devices include products that feature one or more software components, parts, or accessories (such as electrocardiographic (ECG) systems used to monitor cardiac rhythms), as well as devices that are composed solely of software (such as laboratory information management systems).
Key words : Mobile apps, FDA, regulations, smart phone, medical devices, data systems.

Introduction[1]

Mobile health, or more commonly, mHealth, is 'the use of wireless communication devices to support public health and clinical practice'. Mobile devices are handheld in nature and include mobile phones, personal digital assistants, patient monitoring devices, and other wireless devices. mHealth applications are receiving increased attention largely due to the global penetration of mobile technologies. It is estimated that over 85% of the world's population is now covered by a commercial wireless signal, with over 5 billion mobile phone

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subscriptions. The availability of mobile technology has advanced infrastructure development in low- and middle-income countries beyond roads and electricity. Mobile medical applications range from communication between individuals and health systems (such as call centers, appointment reminders, treatment compliance) to health monitoring and surveillance (including surveys, patient monitoring devices), and access to information at the point of care (health records, decision support).

A "mobile app" is a software application that can run on a mobile platform or a web-based software application for a mobile platform that is run on a computer server. Mobile medical apps can be considered "medical devices" and subject to FDA oversight if they are "intended for use in the diagnosis or the cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body." Mobile healthcare, also known as M-health, stands to become the "biggest technology breakthrough of our time"

On 23 September, 2013, USFDA issued final guidance for developers of mobile medical applications, or apps, which are software programs that run on mobile communication devices and perform the same functions as traditional medical devices. The guidance outlines the FDA's tailored approach to mobile apps.Mobile apps have the potential to transform health care by allowing doctors to diagnose patients with potentially life-threatening conditions outside of traditional health care settings, help consumers manage their own health and wellness, and also gain access to useful information whenever and wherever they need it.

Mobile medical apps currently on the market can, for example, diagnose abnormal heart rhythms, transform smart phones into a mobile ultrasound device, or function as the "central command" for a glucose meter used by a person with insulin-dependent diabetes.

Consumers can use both mobile medical apps and mobile apps to manage their own health and wellness, such as to monitor their caloric intake for healthy weight maintenance. For example, the National Institutes of Health's LactMed app provides nursing mothers with information about the effects of medicines on breast milk and nursing infants.

Regulatory review[3]

The FDA is focusing its oversight on mobile medical apps that:

- are intended to be used as an accessory to a regulated medical device – for example, an application that allows a health care professional to make a specific diagnosis by viewing a medical image from a picture archiving and communication system (PACS) on a Smartphone or a mobile tablet; or
- Transform a mobile platform into a regulated medical device – for example, an application that turns a smart phone into an electrocardiography (ECG) machine to detect abnormal heart rhythms or determine if a patient is experiencing a heart attack.

Example- The FDA sent a letter to a firm called Bio sense, questioning the company's lack of federal regulatory clearance for uChek Urine analyzer, a kit that allows consumers to use their cell phone cameras to read colour differences on test strips designed to detect unhealthy levels of protein and other substances in urine.

The FDA strongly recommends that manufacturers of all mobile apps that may meet the definition of a device follow the Quality System 13-19 regulations (which includes good manufacturing practices) in the design and development of their mobile medical apps and initiate prompt corrections to their mobile medical apps, when appropriate, to prevent patient and user harm.

Clinicians trying to safely navigate the apps minefield have had relatively little support from regulatory agencies. The Food and Drug Administration (FDA) released their guidance only in July 2013 after a 2-year consultation period and are focusing primarily on apps that transform the mobile platform into a regulated medical device, which to date numbers approximately 100 apps. The remainder will be subject to what the FDA calls "enforcement discretion", that is, no regulation. Other regulatory agencies such as the Medicines and healthcare Products Regulatory Agency and the Therapeutic Goods Administration of Australia have offered limited guidance to health care practitioners by including apps under their existing regulations for medical devices The lack of clarity regarding when a medical app becomes a formal medical device means that many developers may not recognize that their app requires formal regulation. As a result, the vast majority of medical

apps remain without any form of regulation or safety check, and some of these may present a patient safety or other risk.

Classification of Mobile Medical App[4]

Class 1	App that connects to medical devices to control its applications • The operation of implantable medical devices or devices attached to or worn on a human body. • Examples include apps used to control infusion pumps, blood pressure cuffs, implantable neuromuscular stimulators and cochlear implants
Class 2	Apps that receive, display or transfer patient-specific information from a connected medical device • Support remote monitoring of patients by displaying or monitoring information collected by a medical device attached to a patient through a wired or wireless connection. • Examples include apps connected to bedside monitors that transfer patient data to a nearby nursing station in real-time.
Class 3	Apps that transform a mobile device or platform into a medical device • sometimes used in conjunction with sensors or electrodes that are directly attached to a host mobile device or platform to measure or display specific body functions and characteristics • Examples include app/device combinations used as an electronic stethoscope, an electrocardiograph, an audiometer

Examples of healthcare mobile applications:

1. 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. Eg-- attachment of a blood glucose strip reader to a mobile platform to function as a glucose meter, attachment of electrocardiograph (ECG) electrodes to a mobile platform to measure, store, and display
2. Mobile apps that perform sophisticated analysis or interpret data (electronically ECG signals
3. Collected or manually entered) from another medical device. E.g. Computer Aided Detection software (CAD) image processing software 15-24; and radiation therapy treatment planning software

FDA intends to exercise enforcement discretion for mobile apps that:

- Help patients (i.e., users) self-manage their disease or conditions without providing specific treatment or treatment suggestions
- Provide patients with simple tools to organize and track their health information;
- Provide easy access to information related to patients' health conditions or treatments help patients document, show, or communicate potential medical conditions to health care providers
- Automate simple tasks for health care providers

According to FDA medical applications has been divided into following annexures[5]

Annexure a: Mobile apps which are not medical devices

This Appendix provides a representative list of mobile app functionalities to illustrate the types of mobile apps that could be used in a healthcare environment, in clinical care or patient management, but are not considered medical devices. Because these mobile apps are not considered medical devices, FDA does not regulate them. The FDA understands that there may be other unique and innovative mobile apps that may not be covered in this list that may also constitute healthcare related mobile apps.

- Medical Dictionaries
- Electronic copies of medical text books
- Medical abbreviations and definitions
- Translation of medical terms across multiple languages

- Medical flashcards with medical images
- Interactive anatomy diagrams or videos
- Surgical training videos
- Medical board certification or recertification preparation apps;
- Help guide patients to ask appropriate questions to their physician relevant to their particular disease, condition, or concern;
- Find the closest medical facilities and doctors to the user's location;

Annexure b: Mobile apps for which FDA intends to exercise enforcement discretion[6]

This Appendix provides examples of mobile apps that **MAY** meet the definition of medical device but for which FDA intends to exercise enforcement discretion. These mobile apps may be intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease.

- Mobile apps that help patients with diagnosed psychiatric conditions (e.g., post-traumatic stress disorder (PTSD), depression, anxiety, obsessive compulsive disorder) maintain their behavioural coping skills
- Mobile apps that provide periodic educational information, reminders, or motivational guidance to smokers trying to quit, patients recovering from addiction, or pregnant women;
- Mobile apps that use GPS location information to alert asthmatics of environmental conditions that may cause asthma symptoms
- Mobile apps that use video and video games to motivate patients to do their physical therapy exercises at home
- Mobile apps that use patient characteristics such as age, sex, and behavioural risk factors to provide patient-specific screening, counselling and preventive recommendations from well-known and established authorities
- Mobile apps that use a checklist of common signs and symptoms to provide a list of possible medical conditions and advice on when to consult a health care provider
- Mobile apps that help asthmatics track inhaler usage, asthma episodes experienced, location of user at the time of an attack, or environmental triggers of asthma attacks
- Mobile apps that help asthmatics track inhaler usage, asthma episodes experienced, location of user at the time of an attack, or environmental triggers of asthma attacks
- Mobile apps that guide a user through a questionnaire of signs and symptoms to provide a recommendation for the type of health care facility most appropriate to their needs
- Mobile apps that record the clinical conversation a clinician has with a patient and sends it (or a link) to the patient to access after the visit;

Mobile apps that are intended to allow a user to initiate a pre-specified nurse call or emergency call using broadband or cellular phone technology

Mobile apps that aggregate and display trends in personal health incidents (e.g., hospitalization rates or alert notification rates)

Appendix c: Mobile apps that are the focus of FDA regulatory oversight (mobile medical apps)[7]

These mobile apps meet the definition of medical device in the FD&C Act and their functionality poses a risk to a patient's safety if the mobile app were to not function as intended. Each example below provides a list of possible relevant product code(s) and/or regulation number.

- Mobile apps that use a sensor or lead that is connected to a mobile platform to measure and display the electrical signal produced by the heart (electrocardiograph or ECG). Possible product code(s): DPS, MLC, OEY (21 CFR 870.2340), MLO, MWJ (21 CFR 870.280)
- Mobile apps that use a sensor or electrode attached to the mobile platform or tools within the mobile platform itself (e.g., microphone and speaker) to electronically amplify and "project sounds associated with the heart, arteries and veins and other internal organs" (i.e., an electronic stethoscope). Possible product code: DQD (21 CFR 870.1875(b))
- Mobile apps that use a sensor or electrode attached to the mobile platform or tools within the mobile platform itself (e.g., accelerometer) to measure physiological parameters during cardiopulmonary

resuscitation (CPR) and give feedback about the quality of CPR being delivered. Possible product code: LIX (21 CFR 870.5200).

- Mobile apps that use a sensor attached to the mobile platform or tools within the mobile platform itself to record, view, or analyze eye movements for use in the diagnosis of balance disorders (i.e., nystagmograph). Possible product code: GWN (21 CFR 882.1460).
- Mobile apps that use tools within the mobile platform (e.g., speaker) to produce controlled levels of test tones and signals intended for use in conducting diagnostic hearing evaluations and assisting in the diagnosis of possible otologic disorders (i.e., an audiometer). Possible product code: EWO (21 CFR 874.1050).
- Mobile apps that use an attachment to the mobile platform to measure blood oxygen saturation for diagnosis of specific disease or condition. Possible product code(s): DQA, NLF, MUD, NMD (21 CFR 870.2700) or DPZ (21 CFR 870.2710).
- Mobile apps that use an attachment to the mobile platform to measure blood glucose levels. Possible product code: NBW (21 CFR 862.1345).
- Mobile apps that use a microphone or speaker within a mobile platform to serve as a audiometer to allow healthcare providers to determine hearing loss at different frequencies. Possible product code: EWO (21 CFR 874.1050)

Appendix d: Current regulations[8]

This Appendix provides additional examples of classifications for regulated medical devices, the Class according to which they are regulated, and their regulation numbers as listed in Title 21 of the Code of Federal Regulations (CFR). This list is intended as a starting point for mobile medical app manufacturers to assist them in identifying regulated medical devices.

Appendix e: Brief description of certain device regulatory requirements[9]

This Appendix provides a high level description of certain regulatory requirements for medical devices, including mobile medical apps. The FDA has additional resources and publications online that describe these and other requirements in detail.

How a cell phone can be used like a Medical Laboratory analyzer?

The uChek app takes a picture of urine sample and analyzes it for up to 25 diseases, noted an article published by BBC news. The test kit is priced at $20 and comes with five test sticks and a special mat. The test sticks are dipped into a urine sample and then placed on the surface. The iPhone takes a photo of the colour-coded test sticks on the mat. The uChek application analyzes the image and interprets the results. Bio sense Technologies claims that uChek can detect as many as 10 parameters contained in the urine specimen, depending on the test strip used. This includes levels of:

- glucose
- proteins
- nitrates
- ketone
- specific gravity

Safety issues specific to mobile medical applications[10]

1. Connectivity

The safety and effectiveness of many mobile medical apps depends on their connection with other medical devices or other software services. However, connectivity via wired and wireless technologies can be subject to unintentional interference or service interruptions, which can impact the performance of the system or devices monitored or controlled by a mobile medical app.

2. Data integrity

Electromagnetic interference or single-event upsets can also result in the corruption of data being received or transmitted by a mobile medical app. When the integrity of data is compromised, it can potentially

lead to the display of inaccurate information to the user, incorrect operation of an attached system or device, an unintended initiation or termination of an intended operation, or the failure to initiate system operation altogether.

3. Data security

Like other modern technologies, mobile medical apps are potentially vulnerable to cyber-attack, either through malware, virus-corrupted messages or other malicious activities. Cyber-attacks can not only impact patient safety, but can also result in breaches of data security that compromises patient privacy.

4. Updating protocols and procedures

Most software products, including mobile medical apps, are subject to periodic updates to address coding errors or to provide security patches.

5. **Display size and resolution**

Mobile platforms offer displays in a variety of sizes and resolutions. Mobile medical apps that have been optimized for a specific screen configuration may unintentionally distort information displayed on a device with a different resolution or dimensions. This distortion can result in the misinterpretation of data or other vital information.

FDA regulations applicable for mobile medical applications [11]

Appendix E of the FDA's guidance document provides an overview of the regulatory requirements applicable to all medical devices, including mobile medical apps.

- Premarket submission for approval or clearance: Mobile medical apps developers must prepare and submit to the FDA a premarket submission (510(k)) application consistent with the risk classification appropriate to their app. Appendix D in the guidance document provides examples of specific medical devices and their assigned risk class.
- Quality system regulation: Developers of mobile medical apps must comply with the FDA quality system (QS) regulation, requiring them to implement systems and methods to design, produce and distribute devices that are safe and effective. Mobile medical app developers are also required to verify and validate their apps in conjunction with the relevant mobile platform
- **Product labelling:** All medical devices, including mobile medical apps, must comply with the FDA's device labeling requirements.
- **Adverse event reporting:** App developers must investigate each instance in which a mobile medical app is believed to have caused or contributed to a death or serious injury, as well as each instance in which an app has malfunctioned in such a way as to place a patient at risk of death or injury. App developers must also submit written reports to the FDA in connection with each such instance.
- **Establishment registration and medical device listing:** Medical device manufacturers, include companies that develop mobile medical apps, must register with the FDA and provide a complete list of medical devices they market. A manufacturer's registration and device listing must be updated annually[12]

Mobile apps that are NOT medical devices[13]

Specific examples of mobile apps that FDA does not consider to be devices and with no regulatory requirements under the current laws administered by FDA include:

Mobile apps that are intended to provide access to electronic "copies" (e.g., e-books, audio books) of medical textbooks or other reference materials with generic text search capabilities. These are not devices because these apps are intended to be used as reference materials and are not intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease by facilitating a health professional's assessment of a specific patient, replacing the judgment of clinical personnel, or performing any clinical assessment. Examples include mobile apps that are:

- Medical dictionaries;
- Electronic copies of medical textbooks or literature articles such as the Physician's Desk Reference or Diagnostic and Statistical Manual of Mental Disorders (DSM); Library of clinical descriptions for diseases and conditions;
- Encyclopaedia of first-aid or emergency care information;
- Medical abbreviations and definitions; Translations of medical terms across multiple languages.

Mobile apps that are intended for health care providers to use as educational tools for medical training or to reinforce training previously received. These may have more functionality than providing an electronic copy of text (e.g., videos, interactive diagrams), but are not devices because they are intended generally for user education and are not intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease by facilitating a health professional's assessment of a specific patient, replacing the judgment of clinical personnel, or performing any clinical assessment. Examples include mobile apps that are:

- Medical flash cards with medical images, pictures, graphs, etc.;
- Question/Answer quiz apps;
- Interactive anatomy diagrams or videos; o Surgical training videos; o Medical board certification or recertification preparation apps;
- Games that simulate various cardiac arrest scenarios to train health professionals in advanced CPR skills
- Mobile apps that are intended for general patient education and facilitate patient access to commonly used reference information. These apps can be patient-specific (i.e., filters information to patient-specific characteristics), but are intended for increased patient awareness, education, and empowerment, and ultimately support patient-centered health care.
- Provide information about gluten-free food products or restaurants; o Help match patients with potentially appropriate clinical trials and facilitate communication between the patient and clinical trial investigators; o Provide tutorials or training videos on how to administer first-aid or CPR;
- Allow users to input pill shape, color or imprint and displays pictures and names of pills that match this description;
- Find the closest medical facilities and doctors to the user's location;
- Provide lists of emergency hotlines and physician/nurse advice lines;

Facilitating Mobile Health Innovation

Invention has aided the development and deployment of the applications and systems described here. Those who build medical devices and develop software applications need an environment that encourages discovery and creation. This includes a culture that facilitates invention and rules that help inventors make money from their various creations.In the United States, there are also a number of issues that need to be addressed regarding government regulation of mobile medical devices. One topic is the question of whether to regulate particular products. Some devices are marketed for health and fitness monitoring and therefore are not subject to device regulation. Calorie counters or activity monitors fall within this category. As consumer items that have no discernible risks and are non-invasive in nature, there is no reason for the U.S. Food and Drug Administration (FDA) to oversee them.

Each device is assigned to one of three regulatory classes based on intended use and possible risks to patients. Stethoscopes represent an example of a Class I devices. It is subject only to general controls since they pose lower risks to patients. Class II devices such as scanners are considered higher risk and general controls alone are insufficient to provide reasonable assurance of safety and effectiveness and require premarket notification through the 510(k) review process. Brain stimulators and cardiac Improving Health Care through Mobile Medical Devices and Sensors defibrillators are examples of the highest risk devices that support or sustain human life and are of substantial importance in preventing impairment of human health represent a potential, unreasonable risk of illness or injury. Class III devices call for clinical studies demonstrating safety and effectiveness.

Medical devices are approved if "the device successfully performs as intended in a manner in which benefits outweigh expected risks." Class III devices in Europe require clinical trials, but their details are not made public and are not binding on manufacturers. Information on serious adverse events must be reported to

the relevant government authority but are not publicized to the general public. Some commentators have expressed concern that European regulators are paid directly by device sponsors and that they are focused most on whether medical tools work as intended as opposed to their impact on public health.

There now are mobile applications that aid in chronic disease management, sensors and remote devices that monitor patient physiology and electronic libraries that bring the latest knowledge to health providers around the globe. These materials represent a quantum leap forward in offering quality health care. We should work to remove barriers to adoption and make these tools much more widely available

According to the European Commission, the rapid development of the mHealth sector raises concerns about the appropriate processing of the data collected through apps or solutions since mHealth solutions and devices can collect large quantities of information. This information will be in many instances personal data since it is information relating to a natural person who is directly or indirectly identified or identifiable. In addition, the processing of data concerning health is particularly sensitive and therefore requires special protection. Personal data protection is a fundamental right in Europe, enshrined in Article 8 of the Charter of Fundamental Rights of the European Union, as well as in Article 16(1) of the Treaty on the Functioning of the European Union. Compliance with personal data protection rules, with information of the data subject, data security, and the lawful processing of personal data, including health and medical data, is therefore vital for building trust in mHealth solutions.

Medical Device Data Systems (MDDS) [14]

The FDA's mobile medical app guidance initially categorized "medical device data systems" as a type of app subject to regulation. MDDS devices display, store, or transmit patient-specific data from a medical device in its original format, or convert it according to preset specifications. MDDS devices may not be used to analyze or manipulate the data, generate signals that control another medical device, or actively monitor a patient.

In recognition that the ability to transmit data is fundamental to the digital health revolution, the FDA announced in February 2015 that MDDS devices - including the similar medical image storage devices and medical image communications devices — would be deregulated completely. This move has greatly simplified innovators' ability to develop mobile medical apps and other devices that fit within the MDDS definition.

The FDA moved quickly on this issue, following up on draft guidance it had issued only eight months earlier. This important step should encourage the industry to develop more MDDS devices, which the FDA described as the "foundation" for the inter-communication necessary to ensure the "better, more efficient patient care and improved health outcomes" offered by digital health technologies.

This is illustrated in figure 1 which shows a 2-dimensional "app-space" where an app can be located depending on its probability of harm, based on the variables above, and its complexity. According to its combined chances of harm and complexity, it will fall into one of four broad zones.

Apps in Zone A require only local inspection Zone B require a more formal risk assessment, and those in Zone C require professional review of a full safety case and the use of safety critical development methods. Zone D should meet the criteria for formal regulation and review by governmental bodies such as the FDA due to their high probability of causing harm. It is not possible to assess the proportion of medical apps in each of the risk categories of A-C given the lack of data on medical apps available. However, based on the total number of medical apps available (approximately 20,000) and the number currently regulated by the FDA (approximately 100) we calculate that the proportion of apps that currently fall into risk category D is approximately 0.5%. This classification into four broad risk zones should help app users, developers, and regulators to evaluate each app using a relevant risk assessment and management model based on the zone where the app is located. It is important to note that these zones form a spectrum rather than discrete entities, hence the gray lines at the boundaries of each zone.[15]

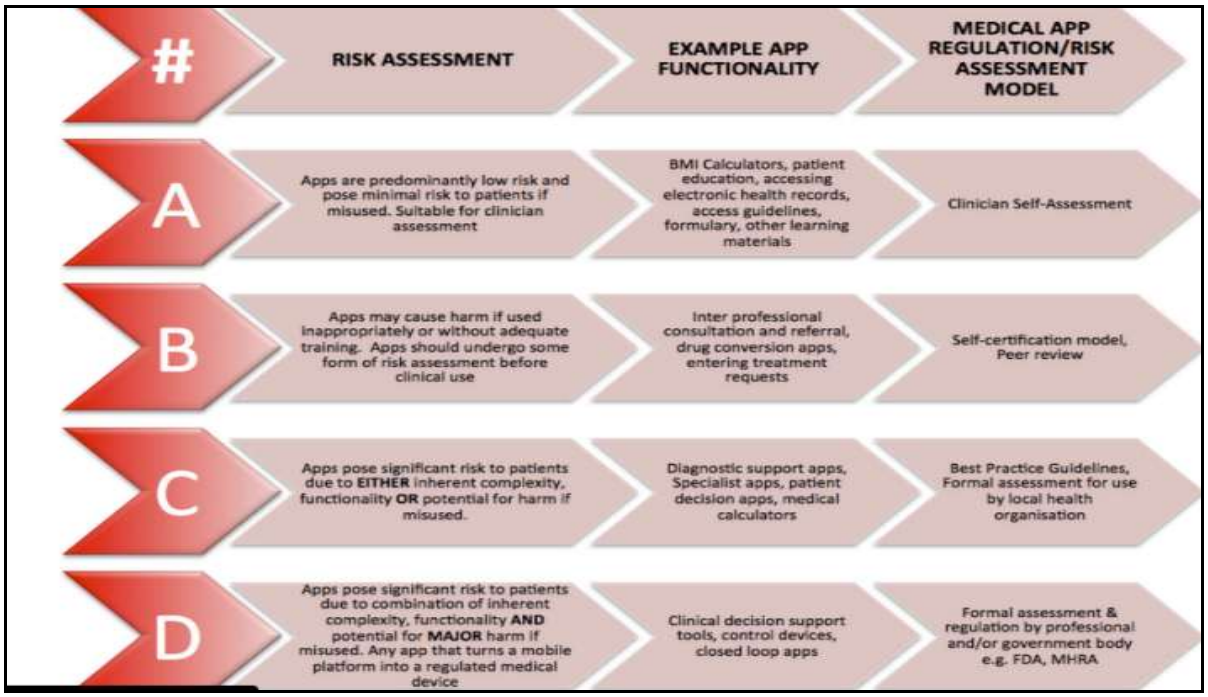

Figure 1: Dimensional "app-space" where an app can be located depending on its probability of harm, based on the variables above, and its complexity. According to its combined chances of harm and complexity, it will fall into one of four broad zones.

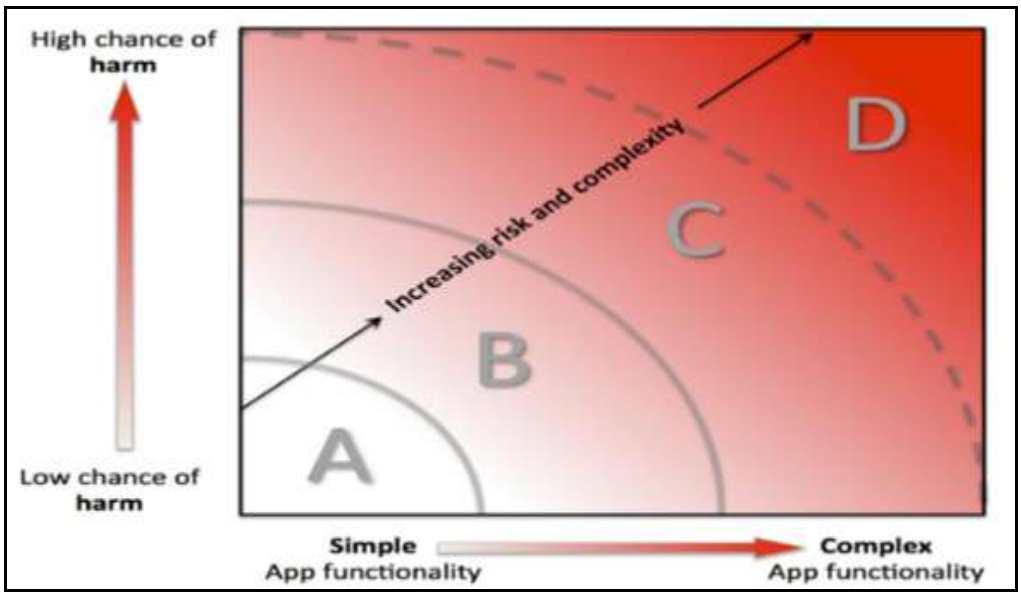

Figure 2: Two-dimensional "App-space" for risk assessment of mobile medical apps with key suggesting appropriate models for app regulation.

Conclusion

The use of mobile medical apps in the provision of healthcare services is growing rapidly, but mobile app developers may be unclear whether their products are subject to the FDA's oversight of medical devices. The FDA's recently published guidance document addressing mobile medical apps provides in-depth information on how the agency plans to regulate these products. However, it is not a substitute for an in-depth understanding of the actual regulations and requirements applicable to mobile medical apps. Developers should conduct a thorough and systematic review of their mobile apps to determine whether FDA oversight is applicable to their products, and to understand the safety risks inherent in their product's design and anticipated

use. An experience third-party can provide expert guidance that can identify potential safety issues early in the product design process and ease the regulatory approval process.

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