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Postmarket Surveillance in a Digital Health Solution World: Challenges and Opportunities for an Evolving Industry

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This article discusses the challenges and opportunities within the digital health technology postmarketing safety and surveillance arena faced by many manufactures. The authors discuss the opportunities and challenges these devices and technologies may present, compared to the traditional healthcare products in the regulated arena.



Introduction

The term digital health solution is used to categorize technology available through a multitude of devices which provide information to their end user, aimed at improving healthcare and outcomes. Healthcare providers, patients and consumers are using these solutions on a variety of platforms such as smart phones, social networks and internet applications and may not realize that these products fall under FDA's regulatory oversight to protect the end users. The varying levels of adverse outcomes the user could experience, including serious injury and/or death, impact the solutions regulatory status under FDA.

Digital health solutions are becoming more prevalent as society becomes more

technologically driven and dependent on these radical advancements in the way we obtain information. Pharmaceutical organizations, technology vendors and medical device organizations are creating health solutions for adherence, patient engagement, behavior modification and companion solutions for treatment. While these advancements in technology are continuously evolving, they share the common goal of assisting healthcare professionals and patients with the ability to further diagnose, treat, access information and educate. The accessibility, convenience and mobility of digital health solutions have created a cultural shift in the way we think about and provide healthcare.¹ However, traditional pharmaceutical, biologic and medical device organizations have realized through their experience in product development that postmarketing surveillance is a critical ongoing phase that may identify opportunities or risks that were not considered prior to product entry. This inherent challenge associated with any of these products beg the following questions:

- What happens when my application has a software bug that miscalculates a dose?
- How can that be reported?
- What types of digital applications require reporting (regulated versus nonregulated)?
- How can I perform a field correction or recall on a digital product that's marketed?

It is well understood that many products have different types of inherent risks as well as benefits and digital health solutions are not free from these considerations.

Background

The legislative enactment of the *21st Century Cures Act* redefined what constitutes a medical device and clarified software applications which could be excluded.² While this seemed to increase transparency surrounding the classification of medical devices and digital health solutions, this presented challenges companies' compliance with postmarketing surveillance reporting requirements.

At a high level, if the intended use of the software function is related to the diagnosis, cure, mitigation, prevention or treatment of a disease or condition, the product falls within the definition of a medical device and thus becomes a regulated product. General wellness products' intended use relates to helping people manage their health and wellness, promote healthy living and gain access to useful information when and where they need it.³ However, FDA states that device regulations will not be applied to the general wellness products.

Digital health incorporates technology and therapeutics to provide accessible tools such as

mobile Health (mHealth), health Information Technology (IT), wearable devices, telehealth/telemedicine and personalized medicine. These are utilized by healthcare providers and others to reduce inefficiencies, improve access, reduce costs, increase quality and provide more personalized medicine. Patients can use digital technology to track and manage disease states.⁴ A spectrum of intended use and expected outcomes exists due to the variety of end-users of the digital solution. Digital health solutions' spectrum of intended use and expected outcomes is further complicated by the increased accessibility of these products to the end-user. The expanding consumer base introduces risks which vary in type and impact to its end-user.

While it is understood that medical devices and all products have inherent risks, it cannot be overlooked that new technology driven solutions may create a different approach to how we traditionally think about postmarketing activities for medical devices. Digital health solutions present a variety of unique challenges compared to traditional medical devices, drugs and biologics. The novel technology has unique attributes that need to be considered (i.e., cybersecurity). Drugs, biologics and medical devices have clearly defined classifications describing the level of impact the event may or have had, which provides an appropriate path and subsequent actions forward for the responsible personnel. For example, medical device reporting is one of the postmarketing surveillance tools used to monitor device performance, detect potential safety issues and provide input for benefit-risk assessments of these products. According to *21 CFR 803*, there are mandatory reporting requirements for manufacturers, importers and device user facilities and voluntary reporting from healthcare professionals, patients and consumers. Manufacturers and importers of medical devices are required to submit reports to FDA whenever they are aware of information which suggests that a marketed device may have directly caused or contributed to a patient's serious injury and/or death.⁵ Often, patients will report any issues to the manufacturer rather than directly to FDA, so it is the manufacturer's responsibility to convey such information to FDA.

Some of the challenges that could be facing digital solution postmarketing surveillance, including interoperability and reporting responsibilities, field corrections and recalls and how real-world evidence can be captured will be discussed.

Interoperability and Reporting Responsibilities

Interoperability occurs when medical devices and digital health solutions interact with one another. As interoperability becomes more prevalent, safety of the patient and operator is an important consideration. For example, a dosing calculator (digital solution) transmits weight in kg, but the receiving device (medical device) assumes measurements in pounds.

This can result in delivering the wrong dosing of a medication to a patient which could potentially result in serious injury and/or death. The challenge lies in determining which party is responsible for reporting the adverse event. It is no longer as straight forward as traditional medical device reporting because now there are multiple components involved. Appropriate safety considerations during initial device design can prevent unforeseen safety issues from occurring.⁶ Alignment between medical devices and digital health solutions in the interoperability space is critical, especially on decisions regarding which party would be responsible for adverse event reporting.

Field Correction and Recalls

There is a big challenge of recalling a digital solution. Users download the application onto their mobile devices, so if there is an issue with it, how do we make sure that the software is not used anymore or removed? Importantly, there needs to be announcements of the issue and advisory of removal of the application. Using social media such as Twitter or Facebook can be effective. It's possible to pull the application from the store and upload a new one, but that presents challenges for users that already downloaded the initial faulty application. In that case, using push messages over a smartphone to notify the user to delete the application can be considered. Ultimately, no matter which route is taken, it's important to resolve the issue quickly to protect the patient.^{7,8}

Collection, Monitoring and Real-World Evidence

The collection and monitoring of pharmacovigilance data is imperative to understanding the associated risks and benefits of a product whether it be a drug, device, or even digital solution. Adverse event reports undergo extensive review and are utilized by both FDA and manufacturers to aid in regulatory decisions and enhance safety measures, together achieving better patient outcomes. An inherent challenge which prevents digital health solutions from being reported stems from unawareness from the end-users such as patients and healthcare professionals that these products are regulated. Combination products, such as insulin pens, that have drug and device components seem to carry more risk to individuals compared to a phone application that calculates antibiotic dosing regimens. Due to the nature of ambiguity of necessity to report, education must be provided to end-users so that they know to report adverse events associated with the application.

FDA developed the MedWatcher Mobile App to ameliorate the voluntary reporting process and increase accessibility.⁹ The intent is to encourage patients and/or providers to report via the app on their mobile device, as compared to the traditional, cumbersome

methods of mail, telephone or computer. This app does not replace the mandatory medical device reporting requirements for manufacturers.

In addition to the MedWatcher app, FDA announced a new mobile technology to improve the collection of real-world evidence from the patient's mobile device.¹⁰ Real-world evidence is collected from a variety of platforms and populations, allowing for an enhanced understanding of the product's role in therapy. This potentially could eliminate variability in patient self-reporting, as well as the need to conduct continued safety monitoring via postmarketing studies. The MyStudies app was developed to expand the diversity of health information available for trials and studies as well as capturing patient perspective and experiences.¹¹ The app will be adaptable to sponsors for their specific monitoring needs, as well as increase compliance with data authenticity, integrity and confidentiality. Enabling sponsors to customize the app to capture additional data through questionnaires, symptom scales, etc., will provide a comprehensive approach to safety monitoring.¹² As the app becomes more widely used and robust, there may be an opportunity to eliminate manufacturer responsibility of reporting by simply bypassing the manufacturer, the adverse event is captured in FDA's system, thus ensuring compliance through removing human error.

Conclusion

As we are in the age where many people are engulfed in modern technology and are grasping this idea to not only use this technology for things such as social media, but also to live a healthier lifestyle, we must consider the responsibilities that come with digital health solutions. Due diligence must be taken upon manufacturers to allow digital health solutions to be a part of people's lives and wellness, but also assist the digital manufacturers with their need for safety and efficacy, thus a win-win for everyone involved.

In contrast to drugs, biologics and medical devices that have standardizations on how to deal with postmarketing surveillance, digital health solutions present many unique challenges. Issues with interoperability and deciding which party is responsible to report a safety concern becomes more prevalent because software and device now interact together. Field corrections and recalls become more challenging because the digital solution is in the user's hands after it is downloaded. However, good also can come from digital health solutions as they can be used as a means of collecting real-world data to drive safer advancements in the future.

Digital health solutions may have lower risks at face-value compared to Clinical Decision Software (CDS) and Software as a Medical Device (SaMD); therefore, industry should look

toward the application of the FDA's general stance as illustrated within the 2016 draft SaMD Guidance, thus allowing the establishment of robust internal processes to the standard that SaMD is currently held to.^{13,14}

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