STRATEGIES FOR DEVELOPING MOBILE MEDICAL APPS FOR PATIENT-INTERACTIVE MEDICAL DEVICES AND SIMPLIFYING THE CLINICAL PATH TO MARKET APPROVAL

Prithul Bom, MBA, RAC, ASQ-CSQE
Senior Director, Scientific Affairs, TA Leader for Medical Device & Diagnostics

Lisa Moore, PhD, RN
Senior Director, Scientific Affairs, TA Leader for Cardiovascular

Randy Anderson, PhD
Senior Vice President, Scientific Affairs, TA Leader for Endocrinology and Metabolism
INTRODUCTION
To manage chronic medical conditions, real-time monitoring of disease-specific physiologic metrics is becoming an important part of standard of care, and smartphone technology is making it possible. Existing smartphone interfacing devices now record health parameters and metrics on diseases such as diabetes, cancer, respiratory diseases, heart failure, sleep disorders and more. Even microscopic sensors are emerging, with bioengineering innovations for continuous blood glucose monitoring and for detection of gastric and other cancers. The environment in which these medical monitoring systems work has been referred to as the mobile ecosystem and includes the medical device developers, medical devices, smartphone interfaces, operating systems and software, wireless service providers and most importantly, the end users.

The complexity of this environment mandates an understanding of the regulatory considerations not only for the medical device, but also the smartphone interface with the end user. That interface includes the smartphone software, known as a mobile medical application (MMA). Human factors and usability engineering are critical parts of the product development and evaluation process, and as a result, there are a number of recently updated regulatory guidance documents. In this paper, we explore the concept-to-market product development pathway for medical devices with MMAs, using the following as examples:

- A Class 3 continuous glucose monitor (CGM) system with an MMA interface, indicated for insulin-dependent diabetes
- A Class 2 MMA diabetes management device that offers pharmacy and reimbursement benefits

This paper will explore at a high level the regulatory guidance documents for the device system and MMA interface development, and will support a smooth progression through concept, development and market approval.

BACKGROUND
Patients with diabetes mellitus utilize a variety of devices to monitor and manage blood glucose and insulin administration. Examples include handheld portable blood glucose meter systems, continuous subcutaneous insulin infusion pump systems and continuous glucose monitoring systems (CGM).

A CGM system has a glucose sensor that is inserted into the subcutaneous tissue. The sensor measures a glucose-sensitive electrical gradient in the interstitial fluid and then transmits data to a custom receiver or smartphone MMA, which processes and summarizes the data quantitatively and graphically as interstitial glucose concentration changes over time.

Upon approval, patients will be able to use glucose trending information to make decisions regarding insulin administration around meals, exercise and physical activities. The Dexcom® G5 Mobile CGM (G5 CGM), with a patient-interfacing companion software application (app), provides an example where the MMA serves as an integral component to the device system.
In contrast, BlueStar®, an FDA-approved app for the management of Type 2 diabetes, serves as an example of a Class 2 MMA. BlueStar® is an example of an MMA that offers personalized behavioral intervention for blood glucose control. While BlueStar® did not require clinical study data to establish its safety and efficacy profile to achieve clearance in 2011, it did need to prove its value to payers in order to prove a pharmacy benefit. To fulfill the need for reimbursement, BlueStar® was investigated in a cluster-randomized clinical trial and the results demonstrated a clear benefit to patients. Benefits to patients translated into payers appreciating the value of this MMA. The MMA’s clinical trial data effectively demonstrated the value of the app to payers and enabled patients to fill the BlueStar® prescription as they would fill any other medication prescription.

**IS AN APP A MEDICAL DEVICE OR NOT?**

Mobile apps that meet the FDA definition of a medical device are regulated as mobile medical applications. A medical device is defined as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which 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.”

Mobile medical apps are defined as “medical devices that are mobile apps, meet the definition of medical device and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device.” Mobile apps are defined as software programs that run on smartphones and other mobile communication devices. They can also be accessories that attach to a smartphone or other mobile communication devices, or a combination of accessories and software. Apps can serve as interfaces between a wearable accessory and a smartphone or other mobile communication devices. Apps such as those used to track fitness or manage diet, do not meet the definition of a medical device, and therefore are not considered mobile medical applications.

The BlueStar® app is an example in which the MMA itself is considered a Class 2 medical device. The Dexcom G5 CGM is an example where the app serves as a component to a complex Class 3 device system. Both operate within the mobile ecosystem per the manufacturer’s intended use.

**CGM DEVICE DEVELOPMENT**

The development pathway for the G5 CGM system illustrates the complexity of the development pathway for a Class 3 medical device with an MMA. The first question to consider is how to classify the MMA. The FDA released an updated guidance document in February 2015 to assist manufacturers and developers with this process. In general, mobile medical apps will fall into three categories: 1) those that will not be regulated, 2) those that require regulation and 3) those that will be regulated by discretion. Given that there are more than 165,000 medical and health care apps reported...
to be on the market, only a very small number are regulated as Class 3 devices (the FDA’s highest risk classification). The majority of the other apps (65 percent) are fitness, diet and lifestyle related applications requiring no regulation at all. 

In this paper we focus on MMAs that require FDA regulation and the process to market these devices. The product design and development pathway aimed at meeting clinical endpoints for a Class 2 or Class 3 implantable, diabetes management device system, for example, can take several years. Numerous guidance documents and standards exist to help understand and navigate each development phase in the pathway efficiently. Each phase can conclude successfully only after meeting the safety and functional requirement goals of that phase in the development continuum. Should validation fail at any phase, developers would need to go through an iterative process to ensure their device passes validation and performance considerations before moving on to the next stage.

**MOBILE MEDICAL APP DEVELOPMENT**
The CGM mobile medical app component follows its own design and development pathway, which is rigorous and contains iterative steps within the overall development pathway of the system. App development is conducted in conjunction with CGM development and validation activities being conducted together in an iterative fashion until the whole system functions as intended, to serve patient needs. Manufacturers should not wait until the last minute to work on the mobile medical app. We have provided a depiction of the pathway below.

**SOFTWARE APPLICATION DEVELOPMENT**

In the next section, we will discuss the guidance documents and standards most relevant to our example devices. These recommendations are not comprehensive but aim to draw attention to the most important considerations.

**PART I: RECOMMENDATIONS SPECIFIC TO A CLASS 3 COMPLEX DEVICE OF WHICH MMA IS AN ACCESSORY**

**BENEFITS-RISK ASSESSMENT**
The starting point of any device development process would be a critical evaluation of the value that it brings to the patient. Questions such as the ones presented below will help the manufacturer determine the device’s benefit-risk profile conceptually.

- What are the conceptual components and functionality of the system?
- What unmet need(s) will the device fulfill?
- Will the design be safe and effective?
- How is the device superior to those already existing in the marketplace?
- What types of preclinical and clinical testing do we need to conduct?
Guidance documents and engineering standards that can help the manufacturer through the development pathway include:

- **Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications.** The FDA provides guidance on safety and effectiveness related concepts applicable to the medical device development process from concept to market. These concepts tie closely with those expressed in ANSI/AAMI/ISO 14971, Medical Devices – Application of risk management to medical devices aiming at weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use. Key recommendations include submitting valid scientific evidence, including preclinical and clinical investigations to support that the device functions per manufacturer’s intended use. Preclinical investigations utilized to support valid scientific evidence may include, for example for the CGM device, bench performance tests to validate device safety, reliability and characterization, human factors and usability engineering (HFE/UE) under simulated conditions of use, animal model- and cell-based investigations, and computer simulations. Clinical investigations utilized to support valid scientific evidence may include randomized clinical trials in appropriate target patient populations, controlled, partially controlled or case-controlled studies led by qualified principal investigators.

We recommend evaluating the benefit-risk profile of the device in parallel against the two guidance documents cited above. Because ISO 14971 is an FDA-recognized standard, following its described processes to systematically manage device risk, hazard to patient, care providers, property — the mobile ecosystem — will help ensure the manufacturer conforms to design validation requirements of Design Controls, part of the FDA’s regulations governing quality systems requirements.

One of the most important considerations for benefit-risk determinations is to identify the critical step factor described more fully in the human factors section. Examples of bench performance tests for the CGM device conducted to ensure the device would continue to function normally, i.e., as intended by the manufacturer, include storage conditions, chemical/fluid compatibility, liquid ingress, drop test, connector cycling, and last but not least, battery life. Battery life is a key consideration in MMA development in these regulated devices.

If there is a pump, such as one that might interface with an MMA such as the Dexcom® G5 CGM, this component would also be tested to confirm emissions are within acceptable ranges and continue to function normally in the presence of other electromagnetic signals. Examples of tests relevant to the CGM electromagnetic compatibility include direct and indirect electrostatic discharge sensitivity, radiated emissions, radiofrequency field immunity, power frequency magnetic field immunity, electronic article surveillance equipment immunity, cell phone immunity, metal detector immunity, X-ray immunity and wireless coexistence immunity. Another FDA guidance document that may be important to the function of the MMA and its associated devices is the *Radio Frequency Wireless Technology in Medical Devices Guidance for Industry and FDA Staff* issued in 2013.

**QUALITY MANAGEMENT SYSTEMS – REGULATORY REQUIREMENTS**

- **ISO 13485 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes** is a standard providing the requirements for a quality management system (QMS) for the design and development, production, installation and servicing of a medical device. For most countries around the world, including the EU, Australia and Canada, the preferred method to prove conformity with regulatory requirements is the certification of a manufacturer’s QMS to ISO 13485. A manufacturer wishing to distribute its device in the US, however, is required to establish and maintain a quality system that meets the Quality System Regulation (QSR) in the US Code of Federal Regulations, Title 21 CFR Part 820 that includes current Good Manufacturing Practices (cGMP). The 21 CFR Part 820 is generally consistent with ISO 13485. Due to the few requirements that differ, there is a gap and the manufacturer must take care to address all aspects of both the QSR and ISO 13485 when marketing globally.
BIOLOGICAL EVALUATION
The FDA guidance document that provides information useful for justification for a precedent or predicate device is the following:

• Use of International Standard ISO 10993-1 – Biological evaluation of medical device – Part 1: Evaluation and testing within a risk management process. The FDA discusses in detail device risk identification, assessment and management in a systematic manner to ensure mitigation of risks associated with cytotoxicity, sensitization, hemocompatibility, pyrogenicity, implantation, genotoxicity, carcinogenicity, reproductive and development toxicity, and degradation. Existence of acceptable justification set by a precedence device may obviate the need for new test data for certain risks. Acceptable justification means the CGM device would share the same material formulation, geometry and physico-chemical properties, body/fluid contact, method and dosing and follow the same manufacturing, sterilization processes as the currently marketed device, if one exists.

STERILIZATION, PACKAGING AND SHIPPING
All sterile components of any device similar to the CGM device system, which requires an interface with an implantable sensor, would be tested and validated per requirements of the following documents:

• EN/ISO 11137 – Sterilization of health care products. The FDA provides guidance via means of Content and Format of Premarket Notification [510(k)] Submissions for Liquid Chemical Sterilants/High Level Disinfectants. The guidance document discusses differences between thermal and liquid chemical sterilization helping the manufacturer determine the method most suitable for their device.
• The packaging of sterile device components would be validated per requirements of ISO 11607 Packaging for terminally sterilized devices – Parts 1 & 2, ASTM D4169 Standard Practice for Performance Testing of Shipping Containers and Systems and ASTM D642-00 Standard Test Method for Determining Compressive Resistance of Shipping Containers, Components, and Unit Loads.
• Shipping distribution testing for relevant components of the device system would be conducted per requirements of ASTM D4169-09 Standard Practice for Performance Testing of Shipping Containers and Systems.

HUMAN FACTORS, USABILITY ENGINEERING AND USABILITY TESTING
The FDA provides extensive guidance on human factors (HFE) and usability engineering (UE) and has recently issued an updated document in 2016:

• Applying Human Factors and Usability Engineering to Optimize Medical Device Design. The guidance document should be evaluated in parallel with ISO/IEC 62366:2007 Medical Devices – Application of Usability Engineering to Medical Devices. For a device that is planned for clearance in multiple markets, the UK’s Medicines and Healthcare products Regulatory Agency (MHRA) has also released a new HF and UE document in June 2016.

HFE/UE is an integral part of device design and development and constitutes the basis for several recalls of MMA devices. HFE/UE and testing are conducted to reduce or eliminate risks and to ensure performance of the device according to its intended use.

Human factors engineering involves the interaction of human abilities, expectations and limitations with work environments and system design. Usability is defined as the characteristic of the user interface that establishes effectiveness, efficiency, ease of user learning (training) and user satisfaction. The major goal of applying human factors to devices is to ensure that the device system is designed such that risks to users are minimized and that the device meets safety and effectiveness performance requirements. Considerations for the user interface include the need for the device and the risk associated with use error or failure and the potential for harm.
The three major input components in HFE/UE are those of the mobile ecosystem — device use environment, device user and device user interface. The interactions among these three components in a mobile ecosystem can result in two possible outcomes: correct use or use error. Use error translates into unsafe or ineffective use of the device and requires reducing or eliminating any design-related problems that contribute to unsafe or ineffective use. Use error is why HFE/UE and the risk management process described above are intrinsically intertwined.

The FDA’s Clinical Chemistry and Clinical Toxicology Device Panel meeting held in July 2016 to discuss a new indication for G5 CGM use to replace fingerstick blood glucose testing for diabetes treatment decisions can serve to exemplify the critical importance the FDA places on HFE/UE. In its presentation, the FDA confirmed that its human factors assessment would include:

- How CGM information will be used when making treatment decisions
- Design to mitigate risk
- Testing

The FDA indicated it wanted to ensure interactions between the device use environment, device user and device user interface would result in correct use of the device and that HFE/UE testing was a useful tool for highlighting and mitigating device user behavior associated risks. In the particular study design geared to satisfy the new indication, risks assessed included:

- Users not responding to alerts
- Using CGM information to make a treatment decision when only incomplete information is available
- Inappropriately trusting CGM information over symptoms when making treatment decisions

Test participants, representative of real-world device users, included those with diabetes managed with insulin and comprised the following demographics:

- Self-managing adults
- Self-managing children and adolescents
- Caregivers managing therapy for children with diabetes

And finally, training comprised of:

- One-on-one with the manufacturer trainer and the device’s ‘getting started’ guide
- Self-training, or interactive computer based training (CBT)
- No training

The above study design elements implemented in the testing reported that training was among the factors that reduced some risks, taking into consideration people with declining auditory, tactile or visual capacity due to their disease and age, as well as other co-morbidities such as cognitive changes or arthritis that may impact their decision-making or ability to interface with the device.

The presentation of benefit-risk data associated with the indication — as well as a discussion whether end users would safely incorporate G5 CGM glucose trend and rate of change information when making insulin dosing decisions — led the FDA panel to conclude that the labeling provided with the device, along with additional training material, would be sufficient information for safe and effective use of the device. HFE/UE and testing supported the positive decision by the panel.
PART II: RECOMMENDATIONS SPECIFIC TO MMAS

The development process for an app includes a critical evaluation of the value, the app as an accessory, brings to the patient. Questions such as the ones presented below will help the manufacturer determine the device’s benefit-risk profile conceptually.

- What unmet need(s) will our app fulfill?
- How will the patient use the app?
- What level of training will the user need?
- Will the use of the app be safe?
- How can we design the app to make the device system additionally effective?

LEVEL OF CONCERN

*Content of Premarket Submissions for Software Contained in Medical Devices*¹⁷ provides a pathway for development and documentation of the software development life cycle for a medical app. As with any software medical device, the first responsibility of the manufacturer is to determine the app’s level of concern (LoC). LoC is measured as major, moderate and minor and is based on how the software app directly or indirectly affects the patient or operator. Hypothetically, a mobile app, such as one displaying radiological images on a mobile device such as an iPad, will have a moderate LoC. In comparison, an app that is used in conjunction with a facility for blood components such as the computer software intended for use in the manufacture of blood and blood components that supports key decisions regarding donor/recipient sensitization, suitability of donor and release of blood or blood components for transfusion or further manufacture would have a higher LoC.

The companion app utilized by a system such as the G5 CGM would be a major LoC, not only by virtue of its association with a complex, Class 3 diagnostic device, but for several other reasons. For example, because its glucose readings would be used for insulin treatment decisions, and being that insulin overdose is one of the major risks in diabetes management, the app’s failure to calculate or display a correct result could pose serious injury or be fatal to the patient. In the software guidance, serious injury is described as one that is:

- Life threatening
- Results in permanent impairment of a body function or permanent damage to a body structure; or
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

The app would reside on a mobile platform and therefore operate on an off-the-shelf operating system native to the platform. *The Guidance for Off-the-Shelf Software Use in Medical Devices*¹⁸ provides recommendations for considerations applicable to such a situation.
RISK MANAGEMENT AND HAZARD ANALYSIS

Like the full CGM system, the MMA component needs its own risk analysis. Unlike heat or electrical energy, an app itself is not a hazard; contact with an app cannot cause injury. However, an app may cause a patient, caregiver or provider to be exposed to a hazard, contributing to a hazardous situation and leading to harm (serious injury or death). Again, the G5 CGM app exemplifies such indirect injury risk, since the system is designed to display interstitial glucose trending, which the patient may use to make treatment decisions. Relevant guidance documents include:

- ANSI/AAMI/ISO 14971, Medical Devices – Application of risk management to medical devices, in conjunction with the technical report IEC/TR 80002-1: Guidance on the Application of ISO 14971 to Medical Device Software, is aimed at risk management of devices containing software. While these reports don’t specifically call out risk management of apps, recommendations therein are applicable to software medical devices, and apps, after all, are software.

HUMAN FACTORS, USABILITY ENGINEERING AND USABILITY TESTING

Determination of the risk associated with an MMA and the classification of the device must take into account the risks associated with app failure, user error and failure of system components controlled by the MMA. Consideration of the target user’s capabilities, familiarity with smartphone use and any sensory (dis)abilities are key to the successful use of the medical device. Answers to the following questions must be critically evaluated:

- Who is the end user and what environment will it be used in? There will be a very different set of considerations if the end users are professionals such as clinicians than would be the case if the end users are patients or family caregivers in a home setting. The requirements for use in an emergency field situation also will differ greatly from a controlled hospital setting or a home environment.
- Will end users have special needs arising from age or impaired cognition?
- Will end users be accustomed to smartphone technology?
- How will end users be able to master the complexities of the system?
- Will the end users have the ability to interpret the health data?
- Does the user interface design facilitate appropriate medical decisions and limit risks of inappropriate and/or harmful decisions, relative to a patient’s disease self-management without the MMA?

The three major mobile ecosystem components described above — device use environment, device user and device user interface — remain consistent when considering HFE/UE in MMAs. Of key importance is identification of the critical step. The critical step is a step in which a mistake in choice by the user with the app interface impacts the safety or effectiveness of the device in a negative way. Important to the MMA success is whether there is built-in technology for error reversal to prevent an error from occurring. In the example of the CGM, potential errors in treatment decisions based on the user understanding and interaction with the user interface need to be understood and tested. The graphic below depicts some of the key features that are important to the safety of an MMA.
HFE/UE and usability testing recommended in the aforementioned guidance documents and standards can mitigate or entirely eliminate use errors that result in unsafe or ineffective use of the MMA.

Another consideration for HFE and UE is how the testing is conducted. The FDA requires that the testing be conducted in the actual user group. Again, we will use the Dexcom G5 GCM as an example in which testing was iterative at different stages of the development and approval process. During clinical testing the sponsor was able to reduce the number of actual subjects required for demonstrating effective use by incorporating model simulations. These simulations were run for a variety of test conditions that included mealtime dosing, hypoglycemia and hyperglycemia. Thousands of virtual subject simulations were accomplished in this manner resulting in the need for a smaller sample size, which greatly reduced cost and time to submission.

**CONCLUSION**

Using an MMA as a component of a device system in a clinical research setting can help the manufacturer realize the potential of mobile ecosystem by delivering the intended value to the end user. Detailed attention to steps throughout the device design and development, preclinical and clinical research are categorically important to achieve approval. Application of HFE/UE considerations is critical for the effectiveness and safety of the device and is necessary for approval and to ensure market adoption.

Chiltern, in collaboration with our strategic alliance, published our first paper, Mobile Medical Applications, in May of 2015 introducing the context, history, design/development, reimbursement, clinical research and basic regulatory frameworks with examples. We presented an educational webinar titled *Embracing a Mobile Medical App in a Clinical Development Strategy to Improve Clinical Outcomes, Increase ROI and Lower Costs* in June 2015. The webinar, evoked deeper questions on design/development, reimbursement, clinical research and regulatory topics. Chiltern followed with an in-depth discussion of a total MMA product life cycle approach, in *Applied Clinical Trials* in September 2015. The paper provided considerations for reimbursement and health economic outcomes, design and development, and clinical research operations. Based upon Chiltern current experiences utilizing MMAs in more complex clinical research settings, this installment in our series of white papers discusses the regulatory considerations for the mobile ecosystem in the clinical path to market.
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