CDS Coalition Pharmaceutical Use Cases

There are several types of decisions in relation to the proper use of pharmaceuticals that standalone software can support:

1. Is the patient a candidate for the drug, and will the patient likely respond to the drug?
2. How can I select a particular drug from an approved class of drugs with the same mechanism of action?
3. What is the evolving post-marketing safety profile of the drug and how can I select/change therapy based on this information?
4. How should the drug be administered, including dosage calculations?

The CDS Coalition is dedicated to clarifying the FDA oversight of all clinical decision support software, including that which is used to support decision-making around the use of pharmaceuticals. As a result, the coalition is vitally interested in how FDA regulates, if at all, CDS used for those purposes.

The CDS Coalition assembled a list of pharmaceutical use cases in order to engage in a dialogue – all at the same time – with the Office of Combination Products, the Center for Devices and Radiological Health as well as the Center for Drug Evaluation and Research at FDA. The purpose of the dialogue is to get some clarity on the regulatory treatment of these software products, although we well recognize that the first meeting may be more about better defining the questions and a subsequent meeting might then focus on the answers.

Assume in each of the following cases that the user is substantially dependent on the software because, for example, the software is not transparent or the user is not sophisticated enough to independently make the decision.

Questions

While we also have individual questions following certain case studies below, as a general matter in each of these case studies we are struggling to understand:

1. Is the software described in the case study an FDA- regulated medical device?
2. Is the software drug labeling, and therefore a component of a drug product?
3. If the software is a medical device, is it a medical device constituent part of a combination product? If so, what is the primary mode of action and what is the regulatory pathway?
4. If the software is a medical device, how is it classified?

Use Cases

Multiple Sclerosis Treatment

Two patients with similar MS symptoms today could have very different lives in a few years, with one in a wheelchair and one playing daily games of tennis. Fortunately, researchers have discovered new, more precise ways to understand how the disease affects individuals over time.

Previously, information was only available through physician observation during office visits or self-reporting by the patient. But now, Giant Silicon Valley Tech Co. has developed a set of wearables that constantly records information regarding a patient's gait, sleep patterns and a variety of other subtle biological changes that can guide physicians in both the selection and titration of three different drug treatments for MS produced by three different drug companies.

The University of the United States (UUS) has now developed clinical decision support software that performs calculations based on the data gathered through those wearable sensors and, based on algorithms developed by UUS, makes recommendations to the physician on which drugs are most appropriate and in what dosages. Based on its clinical trials, UUS claims that its MS Management System can arrest the progress of MS by up to 10 years in some patients.

Relapsing MS Treatment

DrugCo has developed a personal assistance app for their drug "LiveLonger" to treat relapsing MS. The approval of the product was based on an outcome measure i.e. disability score.

DrugCo wants to include wellness diary functionality in the app that the patient could use. The wellness data would include very general terminology on how well the patient is feeling and that data would be mapped in a timeline along with the dates of injections. The patient would be able to see the impact of adherence. Part of the diary in the app would also collect data on typical symptoms of the disease such as palpitations, tachycardia, vomiting, chest pain etc.

DrugCo applies big data analytics that produces insights shared with the patient to help the patient manage her disease. Further, the data are uploaded to the cloud, allowing the physicians access so that they can manage their patients better.

Questions presented:

1. Since wellness was not a clinical outcome measure in the drug's approval, is DrugCo allowed to include a wellness diary?
2. Does this somehow result in off-label promotion implications for the use of the drug if the drug approval is not updated to reflect the use of the app?

3. The composite disability score is based on evaluating a variety of negative outcomes such as palpitations, vomiting, and chest pain. Does the collection of the individual negative outcome measure require AE reporting?
4. Does the name of the branded app need to be approved by CDER?
5. If the app is only designed to work with one MS drug does that change the classification, regulation or potential enforcement discretion as provided in the CDHR guidance?
6. Does this relationship make the app a drug constituent part of a combination product because it communicates with the autoinjector (even if the drug labeling does not specify the use of the app)?

Variation on the scenario tangential to its CDS status: What if the app communicates with the autoinjector through a Bluetooth connection? The app does not control nor transmit information to the autoinjector, but only receives injection information from the autoinjector.

Questions:

1. Does the Bluetooth communication with the autoinjector change the classification, regulation or potential enforcement discretions as provided in the CDHR guidance?
2. If the autoinjector is a device constituent part of a combination product (with the drug) approved under and NDA or BLA, is the app a drug constituent part of a combination product because it communicates with the autoinjector (even if the drug labeling and the autoinjector IFU do not specify the use of the app)?
3. Does the fact that the autoinjector is a device constituent part of a combination product (with the drug) approved under and NDA or BLA change the classification, regulation or potential enforcement discretions as provided in the CDHR guidance?

Oncology Therapy

Advanced data analytics in a software program called eSaveMe can mine electronic medical records, including diagnostic results, medication history, genomic, proteolytic and gene expression data to identify candidates for a new cancer drug called SaveMe. DrugCo – the maker of SaveMe and eSaveMe – wants to provide the software free of charge to hospitals and oncology treatment centers. When the software finds a match, it produces a detailed treatment program customized for the particular patient based on all the medical information reviewed.

Cardiac Radionuclide Imaging

This free app helps guide physicians through the process of determining whether cardiac radionuclide imaging (RNI) is appropriate for a patient, based on the 2009 Appropriate Use Criteria, a report of the American College of Cardiology Foundation. Through collecting information on a series of questions, the app will make a recommendation as follows:

- Score 7–9; Appropriate test for specific indication (test is generally acceptable and is a reasonable approach for the indication).
- Score 4–6; Uncertain for specific indication (test may be generally acceptable and may be a reasonable approach for the indication). (Uncertainty also implies that more research and/or patient information is needed to classify the indication definitively.)
- Score 1–3; Inappropriate test for that indication (test is not generally acceptable and is not a reasonable approach for the indication).

The app tracks the consensus recommendations fairly closely, but not exactly. There were areas that in order to program this into an algorithm, additional medical input was required. In most cases, this was to address ambiguity in the appropriate use criteria, and in some cases the modifications were simply a function of needing to translate medical concepts into computer algorithms or a need to update the criteria based on more recent medical evidence.

Gastrointestinal Stromal Tumor

An interactive activity designed for use on an iPad, this program estimates the risk of recurrence in gastrointestinal stromal tumor (GIST)—a GI cancer—using various assessment methodologies and helps the physician to decide if the patient should receive additional preventive pharmaceutical care. The software combines elements of the:

1. NIH Consensus Risk Scheme for GIST;
2. NCCN Risk Classification for GIST; and
3. American Joint Committee on Cancer (AJCC) Staging for GIST

The software produces a recommendation that may include drug treatment, potentially suggesting a specific recommended drug out of the range of available drugs.

Glaucoma

Targeting optometrists, the Scoring Tool for Assessing Risk calculator is available as an iPhone App. Early detection of glaucoma is crucial to prevent further visual impairment, and this 5-year risk assessment tool is a flexible, easy way to help determine risk. The app requires the following information:

1. Age
2. Vertical cup/disc ratio by contour
3. IOP (3 measurements per eye measured using Goldmann applanation tonometry)
4. Central corneal thickness using an ultrasound pachymeter (3 measurements per eye)
5. Pattern standard deviation using any of the following (2 measurements per eye):
   a. Humphrey full threshold 30-2 or 24-2

b. SITA standard 30-2 or 24-2
c. Loss variance from Octopus 32-2

The app then uses two different calculations based on the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study (EGPS), and through proprietary algorithmic analysis combines them into one output, namely a recommendation regarding whether the patient should be put on preventative drug therapy.

Drug dosage for patients with reduced renal function

This App is designed specifically to give healthcare professionals the tools to perform two calculations needed to adjust drug dosage. In order to adjust the dose of renally excreted drugs in response to reduced renal function, it is necessary to make a quantitative estimate of the glomerular filtration rate (GFR) of the patient. Traditionally this has been done with the use of the Cockcroft and Gault equation or a measured creatinine clearance. More recently the Modification of Diet in Renal Disease (MDRD) formula has become available, providing an estimate of GFR readily available on routine pathology reports.

The presence of these different methods of assessing renal function has created some confusion for healthcare workers as to the best approach. The calculation aids in this app show the formulas so an HCP can check her work, offer guidance on comparing and contrasting the two different formulas, and recommend a singular reconciliation of the differences for use in a drug dosage calculation. Thus the app gives the physician confidence on a singular path forward in the face of two different calculations.

High Cholesterol Drug Prescribing App

The app provides a set of questions that the patient needs to answer to assess whether the patient has high cholesterol and is a candidate for the drug, HiChol. If the patient wants the drug, the app sends the results to a pharmacist who then fills the order.

For background, see FDA's request for comments on "Using Innovative Technologies and Other Conditions of Safe Use To Expand Which Drug Products Can Be Considered Nonprescription," Docket No. FDA–2012–N–0171.

> FDA is considering whether medications for certain diseases or conditions that would otherwise be available only by prescription could be made available without a prescription with certain conditions of safe use. For example, some conditions of safe use could be designed to assist patients in self-selection of an appropriate medication or provide for followup monitoring during continued use. The conditions of use could include requiring pharmacist intervention to

ensure appropriate nonprescription use. Additionally, conditions of safe use could involve the use of innovative technologies, such as diagnostics approved or cleared by FDA for use in the pharmacy or other setting.

FDA is aware that industry is developing new technologies that consumers could use to self-screen for a particular disease or condition and determine whether a particular medication is appropriate for them. For example, kiosks or other technological aids in pharmacies or on the Internet could lead consumers through an algorithm for a particular drug product. Such an algorithm could consist of a series of questions that help consumers properly self-diagnose certain medical conditions, or determine whether specific medication warnings contraindicate their use of a drug product. In addition, for some drug products that require an initial prescription, the product could be made available as a nonprescription product with a condition of safe use for the purpose of product refills.

Stroke or Heart Disease

An app that uses data from individuals for predicting risk score for developing stroke or heart disease for creating prevention or interventional strategies, including once a day aspirin as well as higher risk drugs.

Insulin Dosing

An app that helps diabetic patients by calculating bolus insulin dose based on carbohydrate intake, pre-meal blood glucose, and reported anticipated physical activity to adjust carbohydrate ratio and basal insulin.

Asthma Management

An app that collects data from peak-flow meter and symptom diaries, sends alerts regarding an anticipated occurrence of an asthma episode, and recommends preventative inhaler drug treatment.

Doctor Visit App

This app allows the patient to thoroughly describe what is ailing the patient in response to a structured questionnaire, in lieu of a visit to the doctor. If, based on the algorithms in the app, the app can determine the likely disease or condition, and if over-the-counter medication is the best, first-line course of action, the app will direct the patient to go to the drugstore to purchase the necessary medication instead of visiting the doctor. If the symptoms persist, the app will recommend a doctor visit.

Addendum A

Non-CDS Use Cases Involving Pharmaceuticals

While this paper is focused on CDS, we recognize that FDA might be interested in other digital health applications that relate to pharmaceuticals – that are not CDS – including such things as:

1. Monitoring a patient's reaction to a pharmaceutical by collecting and analyzing data from sensors and other medical devices in such a way as to make it an accessory to a medical device
2. Adjunctive treatment meant to enhance the overall therapeutic benefit beyond what the pharmaceutical can do by itself
3. Encouraging the adherence of the patient to the prescribed pharmaceutical regimen, including patient reminders that address the behavioral impediments, as well as smart pills that offer more reliable information on the adherence.

Because the focus of the CDS Coalition is obviously on CDS, above we only address the CDS type questions. The Combination Product Coalition will address the instances where the software is used beyond a CDS use case to produce a potential companion diagnostic (not limited to a laboratory medicine sense) or adjunctive therapy.

Specific Use Cases

<u>Asthma Therapy</u>

DrugCo offers a mobile inhaler to deliver its drugs for asthma. E-inhaler™ tracks every time the preventer and reliever medications are taken. E-inhaler™ communicates via Bluetooth to a smart phone. Information is uploaded to the cloud through the E-inhaler™ Electronic Health Record. If the user forgets to take the prescribed medication in the morning or evening, the E-inhaler™ provides a reminder.

The technology is used to monitor patients' use of therapy and provide personalized advice to patients based on their conditions and medication use and also to provide objective evidence for physicians. Through a partnership with a tech company, DrugCo also offers additional sensors designed to monitor a patient's condition and the environment around the patient and assess a patient's personalized risk factors.

Fewer than 50% of asthma patients adhere to their prescribed preventative medications. The addition of an E-inhaler™ has been clinically proven to increase adherence by up to 70% in adults and 200% in children with asthma (when it is electronically connected to the mother's

smart phone). In adults, clinical evidence also shows that using E-inhaler can reduce severe episodes by 65%.

AFib Treatment

As a class project, students at the University of the United States College of Engineering developed an app that guides users who have been prescribed oral anticoagulation therapy for AFib, a hard-to-detect irregular heartbeat that can cause a stroke if left untreated. The app coaches patients on how to take their medication, and also creates feedback loops that help doctors create proper care management plans. The patient records a variety of information including:

- Unpleasant palpitations or irregularity of the heart beat
- Mild chest discomfort (sensation of tightness) or pain
- A sense of the heart racing
- Lightheadedness
- Difficulty breathing
- Fainting, or near fainting, due to a reduction in blood flow to the brain
- Confusion
- Fatigue

The oral anticoagulation therapy is made by DrugCo. DrugCo provided a variety of research data to the University of Illinois to facilitate the student's research and the development of the app, but has no commercial relationship with University.

StartupCo received FDA clearance for an algorithm that detects AFib, and plans to include this technology in a wearable monitor that would give users – and their caregivers – access to a real-time ECG recording.

Doctors are now using the UUS app, together with the ECG recordings, to recommend changes in anticoagulation therapy between office visits. This approach has been put into guidelines by the American College for Afib Doctors. The College has been training doctors on the application of its guidelines through CME, supported in part by an unrestricted grant from DrugCo.

Opioid Addiction Therapy

A specialty pharmaceutical company NoOpio released an app to help support recovering opioid addicts. The app, called MyFriend, is designed to work with the NoOpio's drug OpioFree.

The OpioFree website explains:

> MyFriend is a support program embodied in a mobile app to help opioid-dependent patients manage their opioid addiction with medication, reliable information, tools for caregivers, and practical advice to keep patients on track.

The OpioFree website then provides a link to the MyFriend website, which explains:

> The MyFriend app helps you identify your personal goals and monitor your progress as well as keep track of your moods, your emotions, your personal triggers and your medication. The MyFriend app also includes a program developed by psychiatrists to help assess the severity of the cravings, using commercially available wearable sensors that measure temperature, of a type used by athletes. Doctors can use this data to gauge progress in the patient's treatment.

The MyFriend website does not refer back to the OpioFree website.

In promotional literature directed to doctors, NoOpio touts the combined program of the drug and the app as increasing the effectiveness in the five-year treatment of addicts by 70% over the drug alone.