# Clinical Decision Support Coalition

## Citizen Petition

Date: August 16, 2016

The undersigned submits this petition under Section 701(h) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") to request the Commissioner of Food and Drugs issue what we refer to as case study guidance to answer the 26 questions provided in Appendix A.

By way of background, the Clinical Decision Support Coalition ("CDS Coalition" or the "Coalition") is a diverse group of stakeholders consisting of software providers, IT infrastructure manufacturers, healthcare providers, medical device and pharmaceutical manufacturers, trade groups and members of the clinical community. Focused on clinical decision support software, the Coalition's goal is to ensure a risk-based and clearly defined regulatory system for such software that appropriately balances the need for regulatory oversight with the need for innovation and access to new technology.

### A. Action Requested

Specifically, the undersigned requests that the Commissioner issue a guidance document providing brief answers to the 26 questions included in Appendix A, in the context of the specific use cases presented in that appendix.

### B. Statement of Grounds

1. *Importance of Digital Health Technology Innovations and Trends*

    a. The Therapeutic Benefits of Combining Pharmaceuticals with Digital Health Products

In his 2012 book, *The Creative Destruction of Medicine: How the Digital Revolution Will Create Better Health Care*, Dr. Eric Topol outlines the changes he foresees in the life sciences industry. Focusing on the future of pharmaceuticals, he offers an example of what he foresees as follows:

> Combining genomics and digital imaging, along with sensors that detect cognitive ability on a frequent or continuous basis – the sort of thing one could program to run on a smart phone – could collectively be used to identify a drug intervention with particular promise and precision for preventing or markedly delaying the onset of Alzheimer's. … The third limb of this digitized approach is confirmation or titration of the desired effects with the use of wireless sensors. We don't even have a word for that yet, but the triad package of some type of biomarker, a therapy, and a wireless sensor would be an exceptionally powerful means for catapulting medicine into the future.

That was four years ago, and the future is now. Researchers all over the world in universities, pharmaceutical companies, technology companies and provider systems are exploring the combination of digital health technologies with pharmaceuticals to achieve not just greater adherence, but better care.

Some of these joint initiatives between pharmaceutical companies and tech companies have been publicly reported. However, those in the public domain represent only the tip of the iceberg. The vast majority of this research is proprietary, and is being done behind closed doors. But the members of the

CDS Coalition can attest that this area of combined pharmaceuticals and digital health products is an area of major focus in research, and frankly, the cause for great optimism.

There are several factors driving the combination of pharmaceuticals and digital health products. Those drivers include:

- advancements in wearable sensor technology that allow sensing and electronically sharing a huge array of body signals of relevance to the treatment of patients;
- the evolution of the Healthcare Internet of Things, which allows for the stitching together of many different electronic constituent parts to allow for a more unified assessment of patient status and monitoring;
- advancements in medicine that allow us to understand the progression of disease, such that we know which body indicators and biomarkers to watch, as well as advances that help us understand the very personalized response of the body to medication; and
- advancements in pharmaceutical care that provide a better understanding of how disease progression can be studied and used to more effectively choose the timing and selection of pharmaceutical products.

All of these advancements, taken together, mean that a new model is emerging for treating disease that considers treatment strategies based on systems made up of many components, not just pills in isolation.

This is really the consequence of the elevation of systems thinking into mainstream healthcare. This sea of change has progressed to the point where one of the newest medical schools to launch – at University of Illinois in Champaign Urbana – is completely upending the traditional medical school curriculum; the school combines medicine and engineering into a single program, with systems thinking throughout in order to train a new breed of physician.[1]

    b. Three Case Studies

The members of the Coalition worked together to develop three case studies that collectively embody the issues that the industry is consistently facing in developing CDS products. These case studies involve products that show great promise in the future of pharmaceutical care, with each designed to address a critical clinical need.

    i. Adherence Enhancing Digital Health Products

In a nutshell, here's the problem:

> Medications are the primary tools used to prevent and effectively manage chronic illness; however, despite their importance and known benefit, appropriate medication use remains a challenge for both patients and providers. Patients frequently do not adhere to essential medications, resulting in poor clinical outcomes, increased cost of care, and deleterious consequences for workforce productivity and overall public health. Half of the 3.2 billion annual prescriptions dispensed in the United States are not taken as prescribed. Numerous studies have

---

[1] Carle Illinois College of Medicine, https://medicine.illinois.edu/ (last accessed June 22, 2016).

shown that patients with chronic conditions adhere only to 50-60% of medications as prescribed despite evidence that medical therapy prevents death and improves quality of life.

Estimates are that approximately 125,000 deaths per year in the United States are due to medication non-adherence and between 33 and 69 percent of medication-related hospital admissions in the U.S. are due to poor adherence. While some of the relationship between poor adherence and poor outcome is due to confounding factors, the lost opportunity for effective therapies to improve health is staggering. For example, cardiovascular medications alone are estimated to be responsible for half of the 50% reduction in mortality from coronary heart disease over the past 20 years. Yet actual achievement of these cardiovascular benefits is lost due to high rates of non-adherence in real-world settings. In fact, the true rate of non-adherence may be higher as patients with a history of non-adherence are likely underrepresented in trials outcomes research.[2]

To address the problem of non-adherence, pharmaceutical companies are partnering with digital health product developers to create a suite of products that can be packaged around pharmaceutical use to encourage greater adherence. One of the strategies for motivating greater adherence is to create a stronger connection between taking the medicine and seeing healthcare improvement. The second case study squarely addresses the issue of software and wearables woven together to help the patient see more directly the benefits of taking medicine as prescribed, with an aim toward enhancing compliance.

ii.    Disease Management Digital Health Products

The drive toward personalized medicine is well known.  Indeed, the U.S. Food and Drug Administration ("FDA" or the "Agency") itself describes the goals quite aptly in its October 2013 report on *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development*:

> The concept of personalized medicine is not new: The practice of medicine has always been about treating each individual patient, and clinicians have long observed that different patients respond differently to medical interventions. What is new is that paradigmatic developments in science and technology offer new promise for developing targeted therapeutics and tools for predicting who will respond to a medical therapy or who will suffer ill effects.[3]

Indeed, in this report, FDA shares a number of steps it is taking to clarify the pathway to market for products that seek to embody the benefits of personalized medicine.  Specifically, FDA focuses squarely on the need to clarify regulatory authorities for different products used together to achieve personalization. FDA observes:

---

[2] Hayden B. Bosworth, et al., *Medication Adherence: A Call for Action*, 162 Amer. Heart J. 412 (2011), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3947508/.

[3] U.S. Food & Drug Admin., *Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development* 4 (2013), http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PrecisionMedicine/UCM372421.pdf.

> Personalized medicine generally involves the use of two or more medical products, such as a diagnostic test to determine whether a patient may or may not benefit from a particular therapeutic intervention, and the therapeutic product itself. Often, these products are: (1) regulated under different regulatory authorities (e.g., drugs vs. devices); (2) regulated by different FDA Centers (e.g., CDER vs. CDRH); and (3) owned and manufactured by different companies.[4]

FDA describes the conundrum of digital health products used with pharmaceuticals to a tee, but then seems to focus exclusively on companion diagnostics – which are extremely important – and does nothing to identify a course of action for clarifying the pathway to market for this particular combination of products.

We need clarity for digital health products as well. The first and second case studies present these issues very concretely.

> iii.    Clinical Guideline Interpretation Products

We have long known that practicing physicians can be overwhelmed by the enormous and growing body of medical evidence that we ideally want them to understand and incorporate into their practice.[5]  In the U.S. alone, it is estimated that up to 20 percent of diagnoses are either incorrect or incomplete.[6] In addition, there are an estimated 1.5 million errors in the way medications are prescribed, delivered and taken in the U.S. every year. These mistakes could be greatly reduced if doctors had access to the latest relevant medical information. But there is so much medical data in the world that it is impossible to keep track of it all. Medical information is <u>doubling</u> every five years. Although the volume of information is rapidly increasing, we are entering an era where computers can help practicing physicians sort through all of the information they need to manage in order to arrive at the best possible decision.[7]

The third case study takes on a relatively simple aspect of this new wave of clinical decision support software aimed at helping doctors understand and apply clinical guidelines. In prescribing medication, doctors routinely need to correctly apply clinical guidelines to help them judge the need for treatment. Some clinical decision software in this area involves a rather simple and straightforward embodiment of a singular clinical guideline. But as we progress, the desire is to become more sophisticated in applying the broader body of clinical knowledge to physician decision-making. As we move in that direction, the FDA issues get more complicated. The third case study reflects a common scenario facing pharmaceutical care today.

---

[4] *Id.* at 32.

[5] *See* Richard Smith, *Information in Practice*, 313 BMJ 1062 (1996). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2352351/pdf/bmj00565-0044.pdf; Rachel Chan & Vivian Stieda, *Evaluation of Three Point-of-Care Healthcare Databases: BMJ Point-of-Care, Clin-eguide and Nursing Reference Centre*, 28 Health Information & Libraries J. 50 (2011), http://www.ncbi.nlm.nih.gov/pubmed/21314894; Eta S. Berner & Jacqueline Moss, *Informatics Challenges for the Impending Patient Information Explosion*, 12 J. Amer. Med. Information Assoc. 614 (2005), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1294032/.

[6] IBM Research*, The Doctors Are In*, http://www.research.ibm.com/articles/doctors_at_research.shtml (last accessed June 22, 2016).

[7] M.S. Kohn et al., *IBM's Health Analytics and Clinical Decision Support*, 9 Yearbook Med. Informatics 154 (2014), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4287097/.

2. *The Lack of any Clear Guidance from FDA, and the Problem that Creates for Industry and Patients*

    a.  FDA Guidance Does Not Provide a Clear Pathway for Digital Health Products Used with Pharmaceuticals

FDA's current guidance does not provide answers to basic questions about digital health products used with pharmaceuticals, including under what circumstances the software and the wearables might constitute medical devices, and under what circumstances, if they are medical devices, the marketing of these products might trigger combination product status. Relying on basic principles from the existing statutes and regulations does allow developers to piece together answers for simple scenarios. For more complex areas, however, FDA has offered no guidance.

The importance of guidance cannot be understated in terms of its impact on innovation and product development in this area. The existing uncertainty results in viable, technically sound and potentially clinically valuable projects languishing or being abandoned because the businesses considering them cannot estimate the development costs or timeline without a clear sense of the regulatory pathway.

    b.  Case-By-Case Discussion with FDA is Not the Answer

Individual companies going to FDA with every single question for digital health pharmaceutical products is not a viable solution. Some at the Agency would very genuinely say, "If you are developing software and you're having trouble figuring out the classification, please come talk to us. Perhaps we can figure something out." That will not solve the problem for several reasons.

There are of course many avenues to get information from FDA, ranging from an informal phone call to a more formal submission such as a 513(g), requests for designation, or a presubmission meeting. Let's start with the informal approach of a phone call or email.

To start with, it is important for us to all recognize that these are not simple questions. The Agency is generally very good about answering simple questions via a phone call. The issues raised in the appendix, though, are novel and complex. As a result, it would be highly unusual for anyone at FDA to want to simply give an off-the-cuff answer. But let's say we found someone at FDA willing to do that.

First, even though we are talking about a phone call, these things do not happen instantaneously. It can take a while to reach the right person at FDA. This, in turn, delays decision-making at the company level. For example, when companies meet internally as they work to develop new technologies, the regulatory affairs professional will simply not be in a position to contribute meaningfully to the discussion in any sort of real-time way. The regulatory affairs professional will need to basically end the meeting prematurely by declaring that they need to talk to someone at FDA.

Moreover, it is hard to base important company decisions purely on oral statements by FDA regulators. In these cases, there is never a written record produced. As a government agency, FDA is comprised of many people, and not surprisingly some of those people disagree with others from time to time. Oral advice from one or even a handful of FDA employees does not mean that the advice given will remain true. These decisions need to be grounded in more than just oral advice.

More fundamentally, this is not a fair system. It replaces the rule of law with the rule of people. If everything is up to the Agency in its discretion, there is very little practical oversight of the Agency.

When the Agency commits a view like the classification of a new technology to writing, stakeholders throughout government, patients, providers and industry all have a chance to express their viewpoints. Relegating these decisions to informal conversations means that sort of public oversight is lost.

In that same vein, such a system can be very unfair. It does not assure that different companies asking comparable questions are receiving harmonized answers. Among other things, the answers then tend to vary depending on which particular FDA official an industry person contacts. Further, it does not assure consistency over time. Industry needs a fair system where competitors are all treated comparably. We fully recognize that there are different answers depending on different facts. However, there should not be different answers when presented with the same facts.

For all of these reasons, a system based on "just come and ask us what we think" simply does not work.

        c.    The Formal Mechanisms for Feedback are Also Inadequate

Over the years, Congress and FDA have added formal feedback mechanisms where individual companies could petition FDA to obtain an answer to a regulatory question such as the classification of a medical device, or the regulatory category of an article that could be either a drug or a device. While in some instances those procedures can be very helpful to individual companies, in this particular case, they fall short of creating viable pathways to get the answers industry needs.

For starters, these processes all suffer from the same problem as the oral feedback route, but worse. They take a lot of time – too much time when companies are trying to develop innovative software products. Further, these processes are fairly rigid, in that the facts need to be nicely packaged at the outset, and the narrow and specific answer the company obtains from the Agency responds only to those narrow set of facts. Change any fact, and potentially, the answer changes. That means going back through the process.

But more than just the time delays, these procedures are not well suited to the questions that need to be answered. As we define the category of products in which we are interested, they all include software and pharmaceutical products. They may also include specialized hardware. For the software and hardware, one might naturally think of the 513(g) process. However, because all of these case studies involve drugs and medical devices, that means that 513(g) is not available, but rather something akin to the Request for Designation ("RFD") is necessary. Further, several in industry have had an unsatisfactory experience with this process because it can take quite a bit longer than it is supposed to, and even then not produce an answer. As a result, some in industry shy away from using this procedure.

Unfortunately, the RFD process is also inadequate. The RFD process is itself a long one, and is designed to identify the lead center. That is it. Once that lead center is identified, then we are still back in the situation of needing to get answers to the actual questions. And we are back to either calling FDA or arranging a presubmission ("pre-sub") meeting, extending the time even further.

More specifically, putting those two processes back to back – first an RFD followed by a pre-sub – means getting answers to questions like these can take four to five months at a minimum. Further, the pre-sub process is very expensive for small companies to pursue. Many of these products involve software in startups, and requiring this step in order to identify a proper classification is a major burden on these companies.

But there is a third and more fundamental reason that these processes do not solve the problem. They are a very inefficient approach to solving an industrywide need for guidance. Unfortunately for FDA, the output of these processes is considered confidential information, and so the Agency has to repeatedly answer very similar questions. In other words, at best, the RFD process only solves the issue for one company. For the industry as a whole, companies must continually ask what might amount to the exact same questions.

3. *The Challenge FDA is Facing in Developing Traditional Guidance in this Space*

As the Coalition thought about this problem, we tried to put ourselves in FDA's shoes.  Above all, we want the solution to this problem to work for the Agency as well as industry, and the public generally.

Creating guidance in this space is a difficult task for FDA. For starters, it is hard to anticipate which direction the technology will go within the general arena of software used in tandem with pharmaceutical products.  This is new territory, for us as well as for the Agency. While the new discoveries are exciting, from a policy standpoint, the lack of clarity regarding new technology creates a conundrum. Guidance that FDA issues could have unintended consequences if it is applied to scenarios that FDA has not previously thought about, because they did not exist. This risk is most exacerbated when the Agency needs to write generalized guidance to cover an entire developing technology field. That's when the risk of unintended consequences is greatest.

Moreover, to put it simply, this is hard stuff. If it was not difficult, and if it did not require judgment, industry would be able to figure out the rules based simply on the statutes and regulations. But alas, there are many difficult issues raised by these scenarios. FDA has been working on traditional guidance for clinical decision support since 2011, but has not yet issued a proposed guidance.  Again, in many ways, the difficulty comes from trying to write a broad guidance that covers a broad field. Some CDS, such as that which is used to identify possible tumors in radiological images carry with it very high risk, while a calculator used to determine an Apgar score produces little risk. Within the field of CDS, there are dozens of different subcategories of use cases influenced in some cases by subtle factors such as how medicine is practiced in a given therapeutic area.

We recognize these two challenges – the evolving nature of technology in this field and the sheer complexity and diversity of the use cases – make it very difficult for FDA to issue comprehensive guidance that addresses the range of digital health pharmaceutical products.  Accordingly, we have given considerable thought to alternatives to traditional guidance.

4. *Our Proposed Solution*

To recap, industry cannot afford the time necessary to continuously seek FDA's advice on fundamental questions of how digital health pharmaceutical products are regulated. FDA, on the other hand, faces a significant challenge in trying to write a guidance document where the technology is early and evolving, and represents a wide variety of scenarios.

What is missing, we think, is an administrative practice that FDA engaged in for decades prior to the adoption of good guidance practices – the issuance of advisory opinions. While the advisory opinion regulation is technically still on the books, FDA has not issued advisory opinions since the mid-1990s as the Agency views the practice as being inconsistent with the need to create new guidance through the guidance development process. The inconsistency that concerns FDA, we believe, is both the need to develop policy positions through a notice and comment style process, but also the recognition that

policy positions cannot be binding unless rulemaking, or a specialized procedure such as 513(g) or RFD, is employed. Unfortunately, the lack of a public advisory opinion process creates an important gap. There is no means by which FDA can provide specific guidance on regulatory questions through a mechanism that the public generally, and industry in particular, can all access.

We think FDA should develop a new, additional approach to guidance beyond the traditional lengthy and comprehensive guidance document that covers an entire field or regulatory topic. We think FDA should begin to develop guidance, using the good guidance practices, on very narrow specific questions based on a specific set of facts. For lack of a better name, we call this "case study guidance." It has the basic characteristics of an advisory opinion in the sense that it is responsive to an industry-raised topic of general concern, based on a specific set of facts, but it is developed by FDA through the guidance development process.[8]

Further, we see nothing in the good guidance practice regulations that limits FDA to only producing comprehensive guidance documents that address a broad subject matter. There is simply nothing in the regulations to limit FDA's discretion to choose the scope of a particular guidance document, or to somehow prevent the Agency from responding to issues brought to it by industry.

This process should be available whether it is an individual company that comes to FDA with what the company believes to be an issue of broad applicability, or whether, as here, a coalition of companies gets together to identify common themes and approach the government as one.

To be sure, FDA needs to be thoughtful in how it responds to these requests. Obviously, FDA needs to think about the broader implications of the decision on a case study guidance request. There is of course the possibility that industry will interpret the guidance not just for the very specific facts presented, but will extrapolate the guidance to additional facts based on what the industry can discern of the Agency's intent. But that is hardly unique to this situation. Companies are always trying to interpret and understand the Agency's position based on the gestalt of everything FDA publishes.

Indeed, this process requires FDA to go through the exact same thought process as it does when responding to a 513(g), RFD or presubmission request. FDA is routinely called upon to give opinions as to how a particular new technology is regulated. The only difference between the case study guidance and a 513(g) is that the case study guidance will be public.

In this particular case, to identify the topics where case study guidance is needed, we canvassed not only Coalition members, but also others in industry to identify common use cases that present common issues. More specifically, we contacted several pharmaceutical and medical device companies, as well as software developers, app developers, clinicians and so forth, and we developed three scenarios that typify in a very real way the issues that all of these companies are facing.

To be clear, this is not in any way an academic exercise. We are requesting a very focused response by FDA in the form of answering 26 specific questions involving three very detailed use cases in areas of tremendous importance to the industry. In this particular case, we have met with FDA to identify the facts that the Agency would need to know to be able to answer these questions. If, however, as FDA thinks about these case studies, the Agency has more questions, the Agency should feel free to add additional facts to its answers where necessary to provide clarity as to the factors it considers.

---

[8]To be clear, case study guidance would be developed under the good guidance practices (21 C.F.R. § 10.115) and would not be subject to the advisory opinion rules (21 C.F.R. § 10.85).

From a procedural standpoint, FDA will always face the question as it develops guidance as to whether that guidance is Level 1 or Level 2. Specifically, FDA will need to decide whether, under its good guidance practices, the topic may qualify for Level 2 treatment because it merely sets "forth existing practices or minor changes in interpretation or policy."[9] Sometimes case study guidance will qualify for Level 2, and sometimes it will not.

We submit that many times it will, in fact, qualify for Level 2 because by its very nature, being specific, it may well simply state what the FDA is already doing. In the case of our requested case study guidance, FDA will need to decide whether its answers to our questions are new or novel for the Agency.

In proposing this approach, we certainly cannot take credit for a new idea. Indeed, all we are requesting is what the Agency did for decades: issue public advisory opinions. We are simply proposing that the Agency do so through the established guidance development procedures. But we would also note that FDA is already headed down this path. Publishing case study guidance is very similar to the strategy FDA employed in creating a webpage for new specific mobile apps that may or may not constitute mobile medical apps.[10] Indeed, the only reason for us to not solely relying on that process is that these applications cut across drugs/biologics and medical devices. Further, that webpage is constrained to only provide brief summaries of a particular technology, and only answer the question of whether it is or is not a regulated mobile medical app. We have a few additional, but nonetheless specific and important questions.

   5.  *How this Solution Benefits FDA, Industry and Patients*

Issuing a case study guidance is a relatively simple solution to a difficult problem. It balances the industry's need for more timely guidance, with FDA's need to avoid giving broad guidance until the Agency is truly ready to do so for the whole technological/use case field.

      a.  Advantages to FDA

More specifically, this approach offers significant advantages to FDA. By focusing its case study guidance on a narrow set of facts proposed by industry, the Agency avoids committing broad answers for an entire technological field. While the Agency will certainly need to be mindful of the precedent it sets, it avoids the risk of crafting general language that is then interpreted by industry as applying to a broad field. This is particularly useful when, as here, the technology field is rapidly evolving. Indeed, if it wishes, FDA can develop boilerplate language to remind readers of case study guidance that the opinions are very specific to the facts presented.

Further, FDA will save substantial financial resources by publicly disclosing its responses to case study guidance requests, because it will not have to answer the same questions over and over again. This is extremely important in this era where all stakeholders – government and private – increasingly have to do more with less. FDA rightly has significant need for its scarce financial resources, and repetitively answering the same questions is not a good use of money. While there will always be a need for procedures like RFDs and 513(g)s to address technological innovations that are proprietary and need to be kept confidential, there will also always be areas where industry collectively is struggling with the

---

[9] 21 C.F.R. § 10.115 (2015).

[10] For example, the Agency updates its list of mobile apps that are subject to enforcement discretion. U.S. Food & Drug Admin., *Examples of Mobile Apps for which the FDA will Exercise Enforcement Discretion* (last updated Sept. 22, 2015), http://www.fda.gov/MedicalDevices/DigitalHealth/MobileMedicalApplications/ucm368744.htm.

same issue and where individual companies or coalitions can efficiently present those issues to the Agency. Indeed, in some cases, because they are narrow requests, these administrative opinions may well qualify for Level 2 guidance treatment, saving Agency resources.

b. Advantages to Industry

For industry, obviously the primary advantage of this approach is that we get our questions answered in an important therapeutic area. Digital health pharmaceutical products hold tremendous promise. These technologies help pave the way toward personalized medicine, enhance compliance and give physicians the tools necessary to stay up-to-date with the most recent medical research. Unfortunately, these technologies are being stymied by an opaque FDA regulatory process that does not lay out a clear path for combinations of digital technologies and pharmaceuticals.

Equally as important, we get our questions answered in a more timely way. As the Agency knows, we have been awaiting guidance on CDS since 2011; that is five years. In the area of software development, that is an eternity. Countless innovators have struggled to put together business plans that accurately reflect the expected regulatory path for a new piece of software, and consequently, have struggled to get funding. For more information illustrating this challenge, please review the results of the industry survey we distributed earlier this year.[11]

We cannot overstate the importance of the timeliness. To be sure, in the historical world of pharmaceutical products, we measured the product lifecycle in years, and indeed in decades. Everyone understood going into it that the process of developing a new drug, taking it through clinical trials and ultimately getting approval by FDA, was also measured in years. This new world that marries software with pharmaceutical products (and in some cases wearables as well) is fundamentally different. We no longer have the luxury of being able to wait even months to get basic regulatory questions answered regarding specific products. We cannot each go to FDA every time we have a question and are facing a blank slate. We in industry need a fundamentally different model that allows FDA to provide more timely responses, efficiently, to keep the industry as a whole moving forward.

And finally, there is a fairness issue here. Right now, FDA administers an opaque system that provides confidential answers to individual companies. That's fine; in fact, it is needed. But it also means that FDA's approach never sees the light of day, and there could be significant differences in the way FDA responds to very similar technologies advanced by different companies. A system that brings in the light of day creates greater confidence that the answers industry is receiving are substantially the same across companies.

c. Advantages to Patients

As with any FDA policy issue, we should always assess the options based on what is in the best interest of patients.

We are pursuing a more streamlined way of delivering needed therapies to patients, which breaks down some of the silos that exist both in industry and FDA. For digital health pharmaceutical products, the

---

[11] *See* CDS Coalition, *Weighing the Impact of FDA Regulatory Uncertainty on Clinical Decision Support Development* (Feb. 25, 2016), http://cdscoalition.org/wp-content/uploads/2016/02/CDS-Survey-White-Paper-Final-2016.pdf. (nearly two thirds of surveyed CDS developers reported encountering delays due to regulatory uncertainty, and one third reported that regulatory uncertainty caused them to abandon development of a CDS product).

regulatory issues span FDA's device, drug and biologics centers. Thus, as with combination products generally, we struggle to get regulatory input in this product category because FDA struggles to speak with a single voice. The guidance process is at the center of that. The RFD process by itself simply cannot propel the development of new drug/device technologies forward in a timely way that allows new innovative products to reach patients in the shortest amount of time. The RFD process is not designed to provide answers to all of our questions. It is patients that need a new approach to guidance in this space.

We also believe that patient groups would be very interested in understanding the guidance FDA is providing on how these digital health pharmaceutical products are to be regulated. The White House has placed a significant emphasis on the need for transparency. The problem with a system that relies entirely on RFDs and 513(g)s is that the broader community never really knows what is going on at FDA. It is all behind closed doors and under the veil of secrecy. The case study guidance approach makes public what FDA is already doing, but does so in a way that does not injure the competitive position of companies by revealing confidential commercial or trade secret information.

### C. Environmental Impact

Environmental impact analysis is not required for this requested action, so we claim a categorical exclusion.

### D. Economic Impact

We will supply an environmental impact analysis if the Commissioner determines that such analysis is necessary for this request.

### E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Bradley Merrill Thompson
General Counsel
CDS Coalition
1227 25<sup>th</sup> St., NW, Suite 700
Washington, DC 20037
202.861.0900

## Appendix A:
## Case Studies Involving Software that
## Guides the Use of Pharmaceuticals

For each of the case studies below, please answer the following questions as well as the questions embedded in the case study:

- Is the software described in the case study an FDA-regulated medical device?

- If the software is a medical device, how is it classified?

- 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?

- Is the software drug labeling, and therefore a component of a drug product?

- If the software product were used for investigational or commercial purposes, what types of data would be required in the investigational drug or device submission, and in any subsequent premarket submission?

Use Case 1: 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 progresses 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.

In the promotion of these technologies, Giant Silicon Valley Tech Co. makes no reference to MS, but rather promotes them generally for use in monitoring a patient's gait, sleep patterns and a variety of other biological factors, for any and all reasons someone would want to monitor those things.

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. There has not been an independent assessment of the safety or effectiveness of these wearables.  UUS is using the data outputs from these wearables at face value.

There are three different drugs for MS that are produced by three different drug companies. Based on algorithms developed by UUS, the software makes recommendations to the physician on which drugs are most appropriate at a particular stage of the disease 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.

UUS is working independently of the three drug companies as well as independently of Giant Silicon Valley Tech Co.

In promoting its MS Management System for license by physicians around the country, UUS declares that the intended use for the product is: **"An aid in a physician's clinical decision-making with regard to the management of MS, including the selection of appropriate drugs and their dosages as well as other therapies including exercise and sleep."**

As the software program is developed by medical school researchers, the recommendations regarding drugs may not always be consistent with the FDA approved drug labeling, including dosage recommendations. Further, these recommendations are built on clinical trials, but not necessarily on any consensus, professional society guidelines. The findings of these clinical trials on which these recommendations are based have been published in peer-reviewed journals. The publications identify generally the methodology used in the studies for therapy selection, but the specific algorithms and protocols remain confidential and proprietary.

Beyond the scientific foundation built around these clinical trials, the software is designed to engage in machine learning. Over time, as the algorithm considers more cases and as the outcomes are fed back into the database, the system itself is designed to improve its own performance by discerning what works best. However, while the software continues to learn, as a control, the changes do not go into effect automatically but rather are subject to periodic, new software releases by the developer.

While the software is based on published clinical trials, the software does not provide the user with explanations of the clinical evidence that determines a given recommendation. Instead, the software simply explains that its recommendations are based on published research done by UUS, and provides a bibliography of that research.

Operationally, the software analyzes large amounts of continuous data from six different sensors connected to the patient's body. The software performs calculations on a weekly basis to identify trends or changes in those measurements. The results of those calculations are provided to the physician. For example, the software might say "the patient's REM sleep decreased by 5% from the week before, and the patient's cadence in his gait (measured in steps per minute) decreased 3% from the week before." The software would then provide a high level assessment of the clinical implications of those calculations (e.g., "The patient's condition appears to be worsening"), then recommends initiation or changes in drug therapy, dosage, as well as the other possible therapeutic interventions.

Questions:

1. Is the software described in the case study an FDA-regulated medical device?

   Yes, the software is a regulated medical device. It meets the statutory definition in that it is used in the treatment of multiple sclerosis. Further, there is not sufficient transparency to the physician user with regard to how the software arrives at its recommendations.

2. If the software is a medical device, how is it classified?

There is presently no classification for the software, so by default, the software is in class III; however, it may be eligible for down-classification to a class II or class I based upon its risk through a de novo application.

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?

No, the software is not a medical device constituent part of a combination product. It does not meet the definition of a combination product, in that the drugs are not labeled for use with the device.

4. Is the software drug labeling, and therefore a component of a drug product?

No, the software is not drug labeling. It is not developed or distributed by the drug manufacturers.

5. If the software product were used for investigational or commercial purposes, what types of data would be required in the investigational drug or device submission, and in any subsequent premarket submission?

Given the prominent role of the physician in interpreting the recommendations from the software, the software would be considered nonsignificant risk and therefore an IDE would not be required for studies evaluating the software's clinical performance.

If the sponsor of the software chooses to pursue premarket approval, or if the sponsor elects to discuss the opportunity to submit a de novo reclassification petition, it is likely that the Agency would expect the software to be validated through the use of a clinical trial, given the novelty of the software algorithm. Even though it is based on clinical trials, the software algorithm needs to be clinically validated. The exact parameters of the study would need to be discussed in a presubmission meeting.

*Variations on this case study to consider*:

6. Would the answers change if the institutions were collaborating in that they share technical data and scientific insight, and then UUS pays royalties to the drug companies as well as to Giant Silicon Valley Tech Co.?

Collaboration among the institutions in the research phase would not change the answer with regard to the software, nor would simply sharing royalties. So long as UUS continues to play the role of specification developer, controlling both the specifications and the claims made about the product, the product would remain a medical device and the answers above would not change.

However, collaboration might mean that the wearables produced by Giant Silicon Valley Tech Co. may themselves become medical devices because, depending on the nature of the collaboration, such a relationship may be evidence that Giant Silicon Valley Tech Co. intends for the wearable products to be used in a manner that meets the definition of a medical device.

7. Would the answers change if one of the drug companies licensed the software from UUS and then was responsible for commercializing it?

The software would remain a medical device, and would still not be the device constituent part of a combination product unless the drug labeling was amended to reference the software. This assumes that the software already specifically references the drugs, which it would have to if it is making drug recommendations.

At the same time, in addition to being a medical device, FDA may treat the software as drug labeling if it is disseminated by the pharmaceutical company because at that point, there is evidence that the pharmaceutical company intends for the software to be used to guide decision-making around the proper administration of its drug.

8. Would the answers change if the drug recommendations will be limited to those that are within the FDA approved label?

The software would remain a medical device, but the risk profile would go down substantially. Given that a physician is involved and the recommendations are only on label and within the parameters of the drug labeling, the chance of harm or a loss of effectiveness of the drug therapy is reduced. At the same time, the software continues to meet the definition of a medical device. In this instance, FDA would entertain a de novo petition requesting that the software be placed in class I.  Such a petition would need to be accompanied by a risk analysis for the software, and some appropriate regulatory parameters around the use of the device.

9. Would the answers change if the drug recommendations will be limited to those that are within established, consensus, professional society guidelines?

The answer here is the same as number eight above. The software would remain a medical device, but the risk profile would go down substantially. Depending on a risk assessment, this software may belong in class I. The cumulative effect of the changes outlined in number eight and nine may reduce the risk such that the device belongs in enforcement discretion.

10. Would the answers change if this software were only used in a clinical trial setting as part of a drug trial to assist the physician in determining the patient's response to a drug?

If the software were used in this manner, it would have to be because the manufacturer planned to market the drug in tandem with the use of the software afterward. So the effectiveness of the drug would depend on the software being provided as well. As a result, the combination of the drug and the software would be a combination product, and so the combination product in total would be regulated as a drug because it has the primary mode of action of the drug. Consequently, it would have to be regulated under an IND/NDA.

11. What validation requirements would the FDA impose on the use of machine learning in this context?

The machine learning feature directly impacts the performance of the software, and therefore the safety and effectiveness of the software.  If the machine learning model remains the same during use and is updated via new releases, the new machine learning model would need to be validated in the same manner as the initial software release.

To the extent the software model changes during use, the software would need to be validated through a clinical evaluation that shows that the performance of the software reliably improves with the addition of the machine learning.   In this instance, the underlying algorithms used to begin with have an effect that has already been validated through clinical trials. That performance establishes the baseline, and so the subsequent clinical evaluation would need to show that the machine learning aspect produces a benefit, and that that benefit is reliable. To establish that reliability, the sample size for the clinical trial would need to be large enough to show that over time, the recommendations the software produces reliably improve as demonstrated through steadily improving clinical outcomes.

<u>Use Case 2: Relapsing MS Treatment</u>

DrugCo has developed a personal assistance companion app for its drug "LiveLonger" to treat relapsing MS.  The approval of the drug was based on an outcome measure, i.e., disability score.  The intended use of the app is **"a wellness diary and symptom tracker designed to help patients with MS see the benefits of adherence to the LiveLonger drug therapy. The app also facilitates the sharing of symptom information with the patient's physician, to aid the physician in making clinical decisions concerning the management of their patients with MS who are taking LiveLonger."**

The app includes diary functionality for the patient to use.  The collected data include wellness information on how the patient is feeling and that data is mapped in a timeline along with the dates of injections.  The patient is able to see the impact of adherence.  Further, there is an option for sharing the wellness information through social media, so friends and family can follow the patient's overall progress and offer encouragement.

In addition to that general wellness content, the app collects data on typical symptoms of the disease such as palpitations, tachycardia, vomiting, chest pain, etc. To be clear, these symptoms are selected specifically to help guide the management of an MS patient on LiveLonger. All of the data, both wellness and symptom tracking, are entered manually by the patient, except that the app also accepts data from a common activity tracker sold for general wellness purposes.  The manufacturer of the activity tracker makes no disease-related claims.

The app applies analytics that produce insights – mostly wellness trending – shared with the patient to help the patient see the progress she is making, and the correlation of improvement to taking the drug.

Further, the data are uploaded to the cloud, where software developed by DrugCo allows the physicians access so that they can manage their patients better. The physicians look at both the wellness data as well as the symptom tracking data.  For the physicians, more sophisticated analytics are used to analyze trends in the symptoms, and to make recommendations regarding changes to the drug regimen, including dosage, but also the optimal time of day for administration and so forth. The analytics are sophisticated enough that, for example, they can detect when symptoms are likely due to the fact that the medication is administered too soon after pain medications are taken, and the software can recommend that the doctor counsel the patient on waiting at least one hour after pain medications are administered.

These sophisticated analytics that perform the analysis for the physicians are embedded in software found in the cloud, where the analysis is performed. This is a separate piece of software from the app that resides on a patient's tablet or phone. There is also a piece of software that resides on a physician's desktop computer that allows the physician to review the results of the analytics. The three pieces of software must work together in a coordinated way.

The user interface for the physician software that sits on her PC does not explain the origin of its specific recommendations.  Instead, more generally, the opening screen for the software explains that the recommendations are all based on clinical trials that DrugCo performed. The software also includes a bibliography of the published discussions of those clinical trials.

Questions:

12. Is the software described in the case study an FDA-regulated medical device?

The software the patient uses on her cell phone may be a medical device, but it belongs in enforcement discretion. It is simply used to track and trend information, as well as for communication purposes, both of which FDA has determined belong in enforcement discretion. The analytics of trending do not amount to the kind of analytics that FDA regulates.

The software in the cloud as well as the software on the physician's PC are regulated medical devices. The analytical software provides recommendations that meet the statutory definition of a device in that they are used in the treatment of MS. The analytics the software performs in the cloud produce specific recommendations based on sophisticated analysis, and the software does not provide transparency to the end user by explaining the full basis for the recommendation.

13. If the software is a medical device, how is it classified?

There is no existing classification for the software, so by default, it is in class III; however, iy may be eligible for down-classification to a class II or class I based upon its risk through a de novo application.

14. 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?

If the software and drug are not cross labelled and DrugCo does not claim the drug's safety or efficacy is impacted by the use of the software, it will not be considered a constituent part of a combination product. The software will be considered labeling. See answer 15 below.

If the plan is for the drug labeling to reference the software, and the software labeling to reference the drug and for DrugCo to promote the drug safety and efficacy benefits of using the software, the software is a medical device constituent part of a combination product. The primary mode of action is that of a drug, and the drug authorities including the IND/NDA pathway would be available.

15. Is the software drug labeling, and therefore a component of a drug product?

In addition to being a medical device, the software is drug labeling and would need to be regulated as such.

16. If the software product were used for investigational or commercial purposes, what types of data would be required in the investigational drug or device submission, and in any subsequent premarket submission?

Assuming the software is a medical device constituent part of a combination product, since the software is developed after the initial development and commercialization of the drug, the task is to evaluate whether the software contributes to the safe and effective use of the drug. As such, a clinical investigation would be required to measure the incremental improvements in safety and effectiveness of the drug and software combination, over the drug alone.

17. Are the three software packages – the app that sits on the patient's phone, the software in the cloud with the sophisticated analytics, and the software that sits on the physician's PC – considered a system and regulated as one, or considered independent and regulated separately?

It is possible to keep the three software packages separate and to treat them as independent modules. As already discussed, the patient software is not a medical device, and does not need to become one simply because it provides data to the cloud. In that capacity, it is simply serving as MDDS and therefore in enforcement discretion.

At the other end, the physician PC software could be constructed so that is simply independent viewer software and therefore not part of the regulated software that operates in the cloud.

The company would need to demonstrate that the three modules operate independently enough that the function of the patient directed software and the physician PC software could not be expected to impact the safety and effectiveness of the regulated software in the cloud.

18. Since wellness was not a clinical outcome measure in the drug's approval, is DrugCo allowed to include a wellness diary?

In this scenario, DrugCo could provide a wellness diary without a supplemental NDA provided DrugCo is not claiming that use of the wellness diary impacts effectiveness of the drug.

19. Does the fact that the software accepts automatic downloads of data from an activity tracker change the regulatory status of either the software or the hardware activity tracker?

No, the automatic downloading of the data does not impact the regulatory status of any of the three software packages, nor does it impact the intended use of the hardware activity tracker. The manufacturer of the activity tracker is not participating, and there would be no evidence of a change in the activity tracker manufacturer's intended use for its product.

20. Does the name of the branded app need to be approved by CDER?

Yes, assuming the software is a medical device constituent part of a combination product, in the supplemental NDA, the name of the branded app would need to be approved. The name of the patient software would not need to be approved by CDER.

21. If the app were designed to work with multiple MS drugs and was developed and marketed by an independent third-party not connected to the drug manufacturers, does that change the regulatory treatment of the app?

It does. The cloud software would continue to be regulated as a medical device, but none of the software would be treated as drug labeling. To be drug labeling, the software needs to be marketed by the drug manufacturer. Further, if the drugs are not cross labeled to reference the software, the software would not be a device constituent part of a combination product. Thus, the software would be a standalone medical device.

*22.* If the app were offered by an independent software company, not affiliated with the pharmaceutical company, would the pharmaceutical company be required to analyze adverse events identified by the software that are associated with its own drugs and drugs from other companies to determine if it is a reportable event?

If the pharmaceutical company has no connection to the app, it does not have an affirmative obligation to review data produced by the app for possible reportable events.

*Variation on the scenario*: What if the app communicates with an autoinjector through a Bluetooth connection?  The app does not control nor transmit information to the autoinjector, but only receives injection information (e.g., device activation, dose selection) from the autoinjector.

Questions:

23. Does the Bluetooth communication with the autoinjector change the regulatory treatment of the app?

No, the fact that the consumer app collects data directly from the autoinjector does not change the regulatory classification of the consumer app.  We assume for these purposes that the autoinjector Bluetooth capability and the app are both developed by the same pharmaceutical company. But even so, merely creating an MDDS type connection between the autoinjector and the app does not transform the regulatory status of the app.

24. If the app and autoinjector are designed to communicate only with one another, as opposed to using interoperable protocols, does that change the regulatory treatment of the app or the autoinjector?

No it does not. The MDDS status of the connection does not depend on using standard interoperable protocols.

25. If the autoinjector is a device constituent part of a combination product (with the drug) approved under an NDA or BLA, is the app a device constituent part or drug constituent part of a combination product, or something else?

As already explained, the app is an independent module that is placed in enforcement discretion, and that does not change merely because of the connection to the autoinjector. Therefore, it is not a constituent part of a combination product.

26. Under what circumstances would the app be considered (a) a device constituent part of a combination product as opposed to (b) a standalone medical device?

If the app exercised any control over the autoinjector, for example, the app would become a device constituent part. If the autoinjector was in any way unusable without the use of the app (for example, the patient needs to read information on the app in order to safely use the autoinjector), the app would be a device constituent part.

Use Case 3: Gastrointestinal Stromal Tumor

Without any connection to a pharmaceutical company, GisTron, a software company, with input from a board of medical advisors, develops an app for use on an iPad that 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:

- NIH Consensus Risk Scheme for GIST;

- NCCN Risk Classification for GIST; and

- American Joint Committee on Cancer (AJCC) Staging for GIST.

The software produces a recommendation that may include drug treatment, potentially suggesting a specific drug from the available drugs.  The software may also include other recommendations like the frequency of follow-up examinations.  GisTron did not limit itself to recommending only the on-label use of approved drugs.  It is possible, for example, that the software would recommend a dose different from what FDA approved.

Under the guidance of its medical advisory board, GisTron did a large volume, retrospective analysis of clinical data to validate the performance of its algorithms.

To summarize, the intended use of the software is as **"an aid in calculating the risk of recurrence of gastrointestinal stromal tumor (GIST) by blending three commonly accepted methodologies, for the purpose of informing physician decision-making on the appropriate treatment of patients who have previously suffered GIST."**

Operationally, the physician or her assistant adds all of the information manually into the iPad program, including such factors as the size of the previously removed tumor, mitotic count, the site of the previous tumor and whether it has metastasized or spread to the lymph nodes, and the program makes its recommendation on the need for future treatment, if any.

In its user interface, the software explains that it uses a proprietary algorithm based on a combination of the three established risk classification methodologies listed above. The software does not provide the actual algorithm, including, for example, the weighting of the various factors or how they are combined. The software explains that the algorithm has been validated through a retrospective analysis of clinical data.

Questions:

27. Is the software described in the case study an FDA-regulated medical device?

Yes, the software is an FDA regulated medical device. It meets the statutory definition in that it is used in the treatment of disease, and it is not transparent enough to avoid FDA oversight. Further, the software is not merely calculating a formula provided by a consensus medical society guideline. Further, the output of the software is not merely a risk of future recurrence, but rather specific guidance on future treatment.

28. If the software is a medical device, how is it classified?

There is no existing classification for the software, so by default it is in class III; however, it may be eligible for down-classification to a class II or class I based upon its risk through a de novo application.

29. 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?

The software is not a medical device constituent part of a combination product. Under the description above, no drug product is labeled for use with the software.

30. Is the software drug labeling, and therefore a component of a drug product?

As the software is sold by an independent developer, and not by a pharmaceutical company, the software does not constitute drug labeling.

31. If the software product were used for investigational or commercial purposes, what types of data would be required in the investigational drug or device submission, and in any subsequent premarket submission?

Depending on the data set, the retrospective analysis described above could be sufficient. But the data set would have to be large enough and robust enough in order to produce a reliable analysis. If that is not the case, the software would require clinical validation because it departs from the consensus standards.

*Variations on this case study to consider*:

32. Would the regulatory classification change if the combination of the three algorithms was made transparent?

Yes, the regulatory classification may change if the formula was presented to the end-user transparently and if the clinical evidence in support of the formula was also provided, such that the physician could better evaluate for herself the merits of the recommendation. The transparency would significantly reduce the risk and may reduce the classification, even to the point where it would be unregulated.

33. Would the answer change if instead of a software company, a manufacturer of a GIST drug commercialized the app, and indeed instead of addressing all such drugs, the software only addresses when to prescribe the manufacturer's drug?

Yes, not only would the software become labeling, but assuming the drug labeling is revised to make reference to the software, the software would become a medical device constituent part of a combination product.

34. Would the answer change if the software was limited to only on label drug recommendations?

In such case, the product would remain a medical device, but the risk of the product would significantly decrease and therefore the potential classification could be lower.  Since there are no classifications, essentially this would suggest that the developer could seek class I through a de novo submission.