FDA
REGULATION
OF MOBILE
HEALTH
(SECOND EDITION)
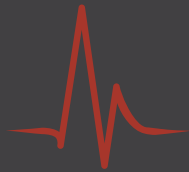
By Bradley Merrill Thompson

With a new chapter on EU regulation of mHealth

By Erik Vollebregt

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PREFACE

More than three years have passed since I wrote the first edition of this e-book, and much has changed. Among other things, FDA at last has published its final guidance on mobile medical apps. Further, the mHealth industry has morphed several times over the last couple years. Consequently, in this second edition, more than 80% of the content is new.

Not only have I updated the regulatory analysis, but I'm also covering a few new topics like FDA regulation of pharmaceutical apps. I also convinced my good friend and colleague in Amsterdam, Erik Vollebregt, to write on EU regulation of mHealth. You might recognize Erik from his popular blog, www.medicaldeviceslegal.com.

The first edition was basically a collection of posts that I had already written. In this edition, partly because of the new FDA guidance, I wanted to tell the story of FDA regulation of mHealth in a more holistic and methodical manner.

My hope is that app developers will now have the certainty they need to make business decisions about how to enter the mHealth space. To be sure, as I explain throughout the book, there are still many open issues, including how FDA ought to improve its regulatory scheme for those apps that are regulated, as opposed to just clarifying the threshold question of what FDA does regulate. Nonetheless, with this recent action by FDA, we hope and expect that mHealth technologies that address some of the greatest needs, but also with some risk, will flourish.

The mHealth Regulatory Coalition, where I serve as General Counsel, is organizing a significant educational effort in partnership with leading engineering schools to train innovators on complying with the FDA requirements. We plan to use this book as the primary text, but one objective of the meetings is to give people an opportunity to meet face-to-face and develop relationships. These engineering schools serve as regional innovation hubs, and make an ideal setting for the meetings, which will be inexpensive and open to the public. There are some mHealth entrepreneurs out there who you really should meet—pioneers who have figured out some emerging best practices in dealing with FDA regulation that they are willing to share.

While it was clearly time to write this second edition, I would also caution you that FDA regulation of mHealth will continue to evolve quickly. At the end of the book, I discuss numerous policy initiatives that are likely to produce change in 2014 and beyond. Through blog posts on MobiHealthNews, I plan to keep you up-to-date on those developments.

In the meantime, I hope you find this new edition useful and please let me know if you spot any areas where I can improve it in the future.

Bradley Merrill Thompson
October, 2013

I. Understanding Intended Use

The key to understanding what FDA regulates as a medical device is the concept of intended use. People come to me all the time and describe in loving detail every element of their widget's design and then ask me whether it's a medical device. I usually tell them I have no idea. That's because by far the biggest determinant of whether a product is a medical device is not its design, but rather the uses for which the designer intends to promote the widget.

Let me explain.

The natural place to start is with the definition of a medical device. Since it is so central to the analysis, I'm going to quote a portion the statute verbatim. Section 201(h) of the Federal Food, Drug, and Cosmetic Act defines a medical device as a device:

"...which is ... [either] intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease ... [or] intended to affect the structure or any function of the body of man or other animals."

Let's break that sentence down a bit. See the word "intended" twice in that sentence? To be a medical device, an article needs to be "intended" for a medical purpose.

But I'm going to skip the word intended for just a moment, and focus on those medical purposes before I explain the concept of intent. At a high level, there are three medical purposes you need to understand:

1. **Diagnosis**, which is listed separately because a device can diagnose either a disease or other conditions. Other conditions include things like pregnancy or genetic makeup.

2. **Treatment**, which includes a range of verbs that are interpreted pretty broadly with regard to addressing a disease.

3. **Affecting the structure or function of the body.** There had to be a category for such things as cosmetic surgery since we do plenty of things to our body not because we are sick.

Those three medical purposes are all interpreted quite broadly, so that leads us back to the concept of "intended use."

Customers routinely buy products for all sorts of uses. A statutory definition of a medical device based on whether and how customers actually use products for medical purposes would be utterly impossible to administer, and frankly unfair. The statute potentially imposes significant regulatory obligations on the seller of a product, and making those obligations depend on the whim of the customer would take compliance completely outside of the control of the seller. So instead, under the statute, it is the seller's intent with regard to how the customer should use the product that controls how the device is regulated, not how the customer actually does use the product.

Not only does the seller's intended use determine whether a device is regulated as a medical device, for those devices that are regulated, the concept of intended use also determines exactly how the product is regulated. As I will describe more below, the Medical Device Amendments do not impose one singular set of requirements on all medical devices, but rather the statute stratifies them by risk category. The intended use of a product is what determines into which of those risk categories the device is placed, and consequently the level of regulatory controls imposed. Indeed medical device manufacturers typically become very good about controlling the nuances of their intended use so as to manage the specific regulatory obligations that the manufacturer must meet.

Now you're probably thinking, how does this concept of intended use actually work? After all, in some sense, what I intend is kind of personal. To know my true intent, doesn't FDA have to read my mind?

Fortunately, no. FDA has developed a basic framework for judging the intended use of a product. The agency explains its general approach in a regulation, 21 CFR section 801.4.

Now I need to forewarn you: what I'm about to tell you is a right brain exercise. If you are an engineer, chances are pretty good you will not understand what I'm about to explain. Just kidding: my son's an engineer. But I am not kidding about the fact you need to use the side of your brain that can evaluate information holistically.

Intent is actually a pretty familiar concept in our legal system. Juries are often called upon to evaluate a person's intent, for example in connection with a crime or a civil claim for damages. If you have watched Law and Order or any other criminal justice show, you know that there are significant differences in intent between first-degree murder and manslaughter. Likewise there are significant differences between intentionally hurting someone, and mere negligence.

Let's get back to the FDA regulation. It's too long and boring to quote, but I will identify for you the key elements of the definition of intended use. Bear in mind that as I tease out the elements, I am not drawing only from the text itself but also from the myriad of enforcement actions that the federal government has brought based on its interpretation of intended use.

Really, as with any factual question, it all comes down to evidence. And the evidence one would use to determine the company's intent generally involves three different types: (1) words, (2) deeds and (3) knowledge. I will take each one separately.

1. Words.

Words are generally the most powerful and clear way to prove intent, and seem to be FDA's typical starting point. And in this case, the words that are most relevant are the words the manufacturer uses to convey to its customers the intended use of the device. So the starting point for this analysis is an examination of all of the product labeling and promotional materials the manufacturer uses to sell the product. What do all of those materials, taken together, suggest the manufacturer intends the customer to use the product for?

Now this analysis can be somewhat subtle. It includes both written words and spoken words. It includes how the sales representatives and others explain the benefits of the product. And while I am focused on the words, the pictures used also in advertising convey the intended use.

Obviously the words communicated to customers are the most powerful and the government's typical focus and starting point, but sometimes if the government has concerns and begins an investigation, they also look at internal memos and business plans to discern the intended use. Their argument is that such materials reveal the company's true intent, and also shed light on what sales representatives and others might orally say about the product.

The nice thing about a focus on words is that you can choose to be very careful, specific and clear with your customers about the use you intend. This includes being specific and clear with your customers about uses that you do not intend. Thus you can manage your intended use by including warnings and other cautionary statements directing customers away from uses for which you do not want to be held responsible.

Of course these warnings need to be sincere and effectively delivered. If you add some fine print in an area where the customer is not likely to see it, the FDA will question whether you truly intended to discourage that use.

2. Deeds.

In some cases, actions do speak louder than words. But even when they are not louder, they are typically still relevant. Here, for example, is where design decisions enter the equation. If a device has a certain design feature that can only be reasonably explained by a given intended use, the design feature will be evidence of that use.

Take an absurd example. If I make a pacemaker, and I sell it and tell my customers that it is a great paperweight, the FDA may very well disagree and say that all of the design decisions that are reflected in that pacemaker show that I intended it to be used as a pacemaker, and not a paperweight. So where design elements really only have one use, those design elements will be evidence of that intended use.

That said, there are some instances when design elements are latent, somehow not available to the customer, for example without an additional software key. Latent design elements might not be evidence of a given intended use, at least not broadly with all customers.

Other actions are relevant too. For example, if I claim that my product is only useful in urology, but my sales representatives visit cardiologists and if I do most of my advertising in the American Journal of Cardiology – I completely made that up – FDA will say that I must intend for my product to be used in cardiology, not just urology.

3. Knowledge.

This is the most controversial type of evidence to use to establish intended use. And it would be very rare for FDA to rely on this type of evidence alone. But at least in theory FDA might say that if a very large percentage of your customers are using your product a certain way, and if you are aware of that use, you must've somehow intended your customers to use the product in that way. This theory has some obvious weaknesses in it. Sometimes customers come up with new uses that you never even dreamed of, and they catch on completely outside of the manufacturer's intent. But if FDA thinks, for example, that you have been orally promoting your product for a given use, and they just haven't found specific evidence of those oral statements, they might turn to what they consider to be the end result – the customers' actual use – as evidence of your intent.

In its definition of intended use, FDA also states that it will only be interested in the objective intent of the manufacturer. In legal terms, this means that the agency will not be particularly interested in subjective explanations for why the words, deeds and knowledge should not be interpreted on face value. In the law of intent, an attorney might argue that notwithstanding the evidence, his client didn't intend something subjectively because his client, for example, suffers from a mental defect. Apparently FDA isn't interested in those sorts of subjective explanations, and intends to judge intent by a normal, objective standard. I am not sure I agree with FDA's position here.
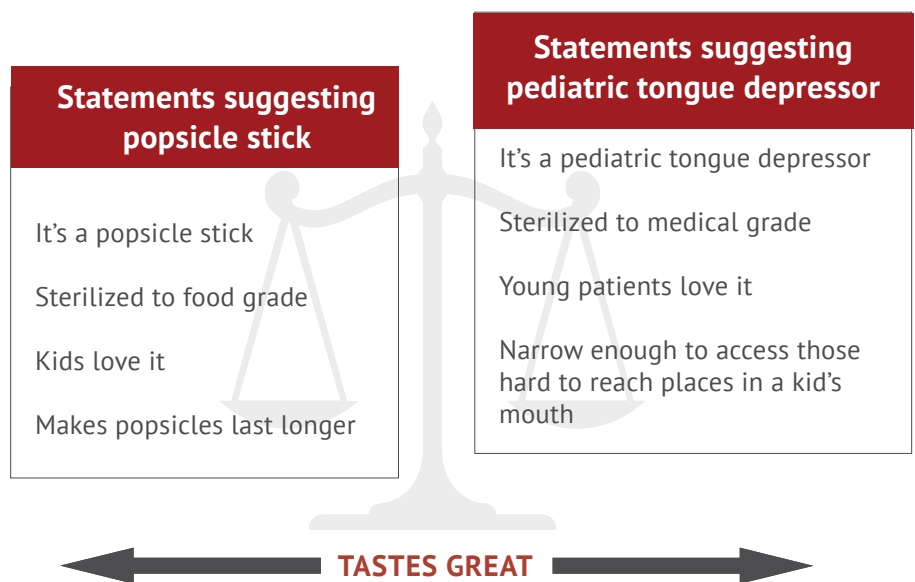
A popsicle stick example

Figuring out the actual intended use of an article depends entirely on the facts. I teach this topic occasionally at Columbia Law School, and I generally begin the session by taking out a popsicle stick. To employ the case study approach, I tell the students that I'm the CEO of a company that makes these sticks, and I want to know whether I have to comply with FDA regulations. At that point I encourage them to ask questions of me in my hypothetical role as CEO, and then ultimately to advise me.

If they have done their homework, they will start to ask me how I promote the stick. In my answers, I'm pretty coy at first, simply explaining that I sell sticks and what my customers do with them is their business. I explain that my labeling for the product merely identifies the product as a stick without going into its possible uses.

Hopefully my students have read enough to know how the regulations define "intended use" so what I say in my labeling is not the last word, but ultimately what matters is the totality of what I have done to promote the article and perhaps what I know about how my customers are using it.

Eventually my students start asking me about what trade shows I attend, what types of magazines I use to advertise the sticks, what my salesmen say to customers, and what I know about the actual usages of the sticks. And it turns out, in my hypothetical, I know that many of my customers are using them as pediatric tongue depressors, I promote them in advertisements in hospital journals, and at least some of my salesmen might encourage their use as tongue depressors. So eventually my students come to appreciate the risk that my simple popsicle sticks might in fact qualify as medical devices and be subject to FDA regulation. I use this example to teach the point that a single stick can be an FDA regulated tongue depressor or a popsicle stick depending on a whole range of factual questions quite apart from the stick itself.

Diagram 1. Determining the intended use of a stick

Statements suggesting popsicle stick	Statements suggesting pediatric tongue depressor
It's a popsicle stick	It's a pediatric tongue depressor
Sterilized to food grade	Sterilized to medical grade
Kids love it	Young patients love it
Makes popsicles last longer	Narrow enough to access those hard to reach places in a kid's mouth

TASTES GREAT

The endless flavors of intended use

If that isn't gray enough for you I'd like to add a few thoughts about all the different styles of intended use. I do so because I think it helps to understand the various options as a company is strategically trying to decide what it wants the intended use for its product to be. Deciding how to characterize the intended use is a bit of marketing and regulatory strategy, and a bit of art.

General versus specific

Among other variables, I can describe the intended use for a mobile app at a very high level of generality, or very specifically. Let's look at a few examples that could be used with regard to an app that allows you to record what you eat, how much exercise you get, how much sleep you get and perhaps a self-evaluation of the amount of stress you are under.

"This app will help you manage your life."

This is a general purpose claim, and it literally covers the waterfront from health to just general lifestyle management. FDA would not regulate this type of intended use because it is not specific even to health/disease.

"This app will help you manage your health and certain chronic diseases."

We have gone from the general purpose claim, to now a general health claim. We have mentioned that it is intended for use with regard to disease, but have not specified the disease. Literally this type of claim may meet the definition of a medical device, but as we will see below FDA seems to be indicating that this type of claim might well be excluded from active FDA regulation.

"This app will help manage your diabetes."

More specific yet, not all diseases but specifically diabetes. This pretty clearly meets the statutory definition of a medical device, but might also be in a category that FDA would exempt from active regulation because it is low risk. We will explore that below.

"This app will help you better control your blood glucose so as to better control your diabetes and reduce the risk of diabetic retinopathy, stroke and heart attack."

Not only would this claim meet the definition of a medical device, but now we're into territory that FDA likely regulates.

The possible variations from general to specific are virtually endless, but hopefully you get the point regarding the latitude that you have and the implications of the intended use specificity.

Functionality vs clinical utility

There's another dimension in which intended uses tend to vary. Among other choices, an intended use can be framed either to explain the technical how or the clinical how for the device. The technical how is generally referred to as a tool type claim. Some examples might help.

The classic example is a scalpel. If a scalpel has any directions for use at all, those directions may simply indicate that the scalpel is for cutting tissue. From that, the user may deduce that the scalpel can be used generally for surgery, or wherever a sharp blade is needed. The promotion might be limited to a description of the shape of the blade or its sharpness or its materials and its ability to hold a sharp edge or be cleaned. But all of the claims focus on the functionality of the tool, rather than saying, for example, this scalpel is perfect for an appendectomy or a tonsillectomy. I prefaced this by suggesting that the directions may not say anything, and certain tools are so basic that FDA does not require they be labeled at all, because their uses are commonly understood. But generally tool type claims are assumed to have very broad general health purpose intended uses.

Now let's get closer to home. Let's talk about the mobile app from my hypothetical above for tracking daily living, but now this time let's look at functionality claims versus clinical utility claims.

"This app allows you to track every morsel of food you eat during the day efficiently through its simple yet elegant user interface that allows you to type in the general name of the food you ate, the quantity, and then answer certain basic questions that allow the software to calculate with great accuracy the amount of fat and calories in everything you eat."

This is a classic functionality or tool type claim. With this sort of claim, FDA would assume a general purpose diet management intended use. As such, under the rules that I will identify below, FDA would probably agree that this is not a medical device.

Functionality vs clinical utility *(continued...)*

"If you suffer from diabetes, this app allows you to track every morsel of food you eat during the day efficiently through its simple yet elegant user interface."

So here I have identified the relevant disease and connected the use of the device to that disease, but I'm still principally focused on how the tool works in general terms without connecting it to a specific outcome. So this is a tool type claim blended with a disease specific claim but without a clinical outcome.

"This app, by empowering a patient to carefully monitor their fat and calorie intake, guides the patient through the steps necessary to substantially reduce the risk of diabetic retinopathy, heart attack and stroke that often accompany diabetes."

This is a clinical utility type claim that expressly declares how the device can help the patient achieve a certain clinical outcome in the context of a disease. FDA regulates these products closely.

Obviously, I could go on. The basic point is that there are at least two dimensions on which these intended uses can be arrayed, general versus specific and claims that focus on function versus claims that focus on the clinical purpose or outcome. People who work in the FDA regulated space become very adept to creating the perfect intended use statement that maximizes marketing potential while it minimizes the regulatory obligations. It's important in this industry to learn that calculus.

The meaning of disease

I have left out a couple of key definitions, including the meaning of the word "disease." I did so because in most respects the word disease is not terribly ambiguous, but also because the design of the statute is not to rely too heavily on the word disease. For example, as I've already pointed out, the statute says "disease or other condition." Further, something can be a medical device if it is used to affect the structure or function of the body. So disease is only one among several elements that might trigger medical device status.

But the word "disease" does have at least one important role, and that is to distinguish those devices that merit regulation from those that are used in general health or wellness that do not merit FDA regulation. Over the years, FDA has reaffirmed that products used to support a healthy lifestyle in general are not regulated. This means that a product designed generally, for example, to help a healthy person get or stay physically fit is not regulated. A common treadmill, therefore, with claims that it will help you improve your cardio functioning is unregulated by FDA. But if the manufacturer of those treadmills instead made claims about the treadmill being useful in conducting a stress test to evaluate your cardiac health, it might be regulated. Same product, different outcome because of different intended use.

If you don't think this dichotomy causes real problems, talk to the Chairman of the Board of General Mills. In 2009, he received a warning letter from FDA because the marketing people at General Mills had gotten, at least in FDA's eyes, too aggressive in drawing a connection between eating Cheerios for breakfast and managing your cholesterol. In various advertising and promotions, the company had shared evidence from studies showing that eating Cheerios regularly for breakfast reduced your cholesterol. FDA said: those claims make Cheerios into a drug. The definition of a drug is very similar to the definition of a device, with regard to relying on the concept of intended use. This issue comes up often with regard to food as food marketers try to tie the consumption of certain food to overall improvements in health, and specific improvements with regard to conditions like high cholesterol.

This dichotomy is incredibly important for products in the mHealth space. Much of mHealth is about integrating information into our lives in a way that it can help us make healthier choices. There are tens of thousands of apps designed to let consumers better manage their general fitness and health by giving them access to important information at the point where it can be most useful – where they work, play and live. The mHealth revolution has come about because of two separate revolutions – the technology revolution that allow us to gain easy access to information on the go, and the wellness revolution that helps us understand how daily choices like diet, exercise, sleep and so forth can have a dramatic impact on our health in general and our risk of certain diseases specifically.

It is that last bit that causes the regulatory confusion. Now that we understand more fully the risk factors for many diseases, the desire obviously is to help people manage those risk factors to reduce the risk of the disease. Further, psychologists and other experts will tell you that explaining the connection between those risk factors and disease is an important step in motivating people to take better care of themselves. But technically, the mere mention of a disease arguably trips the line into FDA regulated territory. This is because the FDA definition of a medical device is not a risk-based definition, but an intended use based definition. If an intended use meets the literal terms of the statute, it can be a medical device. So then it falls to FDA to use its enforcement discretion to exempt out those intended uses which are low enough risk that they do not merit FDA oversight.

The meaning of disease *(continued...)*

Take, for example, as before the app that monitors and tracks a user's daily exercise. This developer might claim that using the app can reduce the risk of heart disease or diabetes or help treat obesity. You might recall that just a couple of months ago obesity was officially classified as a disease. Technically the app would be a medical device.

If the developer instead claims that the same app can be used to monitor daily activity, manage your health, or improve the user's physical condition, the FDA would likely not regulate the app. Those simple variations in claims can potentially impact its FDA regulatory status in a very concrete way. We talk about this much more below.

The meaning of device

Under the statute, a device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part or accessory." Frankly, I generally don't spend much time analyzing that, because it's so wide-open it normally is not very useful in determining whether an article is a regulated medical device. This definition was written in the mid-1970s, and so from a technology standpoint tends to use some old-fashioned terms. But over the last several decades, FDA has interpreted this definition broadly, and for example has interpreted the term contrivance to include software, so long as the software is on computer media. If I wrote code on a simple piece of paper, that would not be a contrivance and therefore not a medical device. But once I load the code onto computer readable media, according to FDA, it now qualifies as a device and might be a medical device if it meets the intended use element of the definition.

That doesn't mean the device element of the definition is irrelevant. One situation where the definition is important is the distinction between selling a thing, and providing a service. Selling a device is regulated and providing a service is not. So those of you in the software business immediately start to think about different models where software can be a service. But don't get too excited.

Fully distinguishing the sale of software from the sale of services is well beyond the scope of this book. But in a nutshell, the difference between selling a thing and selling a service is the human element. At least in this context, services are provided by people, not software. FDA does not regulate the practice of medicine, but the practice of medicine is done by doctors, not by software developed by doctors. Further, FDA could care less what the nature of the financial transaction is. You could give the software away for free and FDA would still regulate it. You could rent the software, and FDA would still regulate it. But if what you are selling is truly a human service, as opposed to access to software, that's where we draw the line of FDA jurisdiction.

Conclusion

As FDA says, it all comes down to function, which is a more vernacular term for intended use. FDA jurisdiction often really has little to do with the technology, unless the technology reveals something of the intended use. The technology always changes and will continue to change. The FDA statute is not specific to a technology, but instead focuses on how the seller of that technology intends for the user to make use of it. If the technology has one of the medical purposes outlined above, it's a medical device. In the next chapter, were going to take this general rule on intended use and FDA's recent guidance, and start parsing exactly which apps fall within FDA jurisdiction.

Most normal people would expect this chapter to be about putting mobile apps into two buckets—(1) those FDA regulates and (2) those it does not. But alas, the world is not so simple.

There are actually three buckets, including (1) those FDA regulates, (2) those it does not and (3) those FDA could regulate but which the agency has decided at least temporarily not to regulate. Good grief. I have a headache already.

Why is it so complicated? Well, Congress, in its wisdom, came up with a statutory definition of a medical device that is too all-encompassing. Heck, if you read the statute carefully, you realize that even an ambulance is a medical device. I'm not talking about all the crap in the back, but the actual vehicle itself including the engine and the driver's seat and the headlights and so forth. The vehicle itself is used in the treatment of people with diseases or other conditions. Indeed, if the ambulance breaks down and can't get to the hospital, the patient could suffer.

Fortunately, FDA is supposed to use its judgment and limit the scope of medical devices to those that truly need to be regulated, even though the statutory definition is not expressly based on any risk criteria. And FDA does this through a legal concept called enforcement discretion.

Generally enforcement discretion is the power that an agency has to limit the scope of its own regulatory requirements when it deems that broader regulation is not necessary to serve the purposes of the statute. Once in a while you hear about prosecutors deciding not to prosecute a case when they do not feel that it meets the spirit or intent of the statute, even if literally they could. Same thing here. FDA can decide to limit its regulatory reach so as not to waste private or governmental resources.

As a result, I am going to describe for you each of the three buckets. And I like to borrow FDA's visual depiction of these three buckets as layers of a triangle. FDA uses this visual aid to make the point that the smallest category, and the one logically shown as the top of the triangle, includes the apps FDA regulates.

Regulated apps

It is useful to start at the top with the apps FDA regulates because to some extent the other two categories are defined as the universe of health-related apps minus those that FDA regulates. By far the greatest precision comes in defining what FDA does regulate because it is defined by law, and the other two categories are at least partly defined as excluding what FDA regulates.

For those who are new to FDA regulation of medical devices, figuring out which mobile apps FDA regulates may feel foreign and difficult to understand. But the reality of it is that figuring out what FDA regulates is actually very simple and can be explained in a nutshell. Quite simply, the agency regulates the same stuff it has regulated for the last few decades.

What gets regulated?

Regulated mobile medical apps

Mobile apps subject to enforcement discretion

Unregulated mobile apps
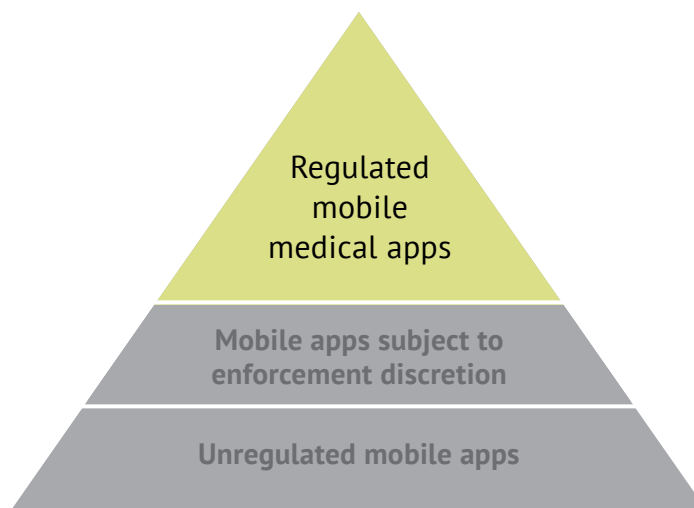
Regulated Apps *(continued...)*

In its final guidance, FDA repeatedly says that it is the functionality, not the platform, that determines whether FDA regulates the app. So, to use an example from FDA's past enforcement in the mobile app space, if an app is used for urinalysis, and if FDA has traditionally regulated urinalysis machines, the app would be regulated because it does the same thing as a traditionally regulated machine. It is the intended use of urinalysis that determines FDA regulation, not the machine on which the urinalysis is performed.

To me, that actually makes the dividing line between regulated and unregulated apps fairly clear, but I also recognize that someone who has not been studying the scope of FDA regulation for decades may find that explanation unhelpful. But bear with me. Figuring out whether FDA regulates a given functionality is probably easier than it sounds. The FDA website provides in searchable form a database of all those medical devices that the agency has approved or cleared over the years. So if you find a machine that FDA has cleared the does substantially what your app does, that's pretty clear evidence that FDA will regulate your app.

You need to be careful to remember, however, that FDA regulates some medical devices without requiring that they go through any sort of clearance or approval. These are referred to as class I medical devices, and they usually are subject to FDA quality system requirements and adverse event reporting requirements. These you can find by searching the FDA classification database. By regulation, FDA has classified most of the typical functionalities that it regulates. FDA has included a list of some of the more common classifications as Appendix D to the final mobile medical app guidance.

Admittedly, these searches are not foolproof. For one thing, some of the classifications are defined in a very strange way, not using the words necessarily that you would expect to describe the functionality. So, if you don't find anything after searching, you might use one of the vehicles for asking FDA this type of question. In connection with the mobile medical app guidance, FDA has created an email address you can use to ask whether your app is regulated. For cases where you think you fall into a gray area and you want a more certain answer, there is a process for filing what is referred to as a 513(g) submission that gives you a more definitive answer. It takes about 60 days for FDA to respond typically, but they have been running longer than that recently.

What the guidance says

Beyond looking to see if FDA has regulated the same functionality previously, there is a more conceptual way to determine whether your app is regulated. In the final mobile medical app guidance document, FDA lays out three different categories of regulated apps. I will describe each one in turn.

Accessories to medical devices

As already explained, FDA classifies medical devices according to risk, and the regulatory requirements are tailored to each of those risk levels. In the FDA's vocabulary, the classification scheme looks like the following:

There has been a basic and fundamental rule at FDA with regard to classification that any product that accessorizes a medical device is regulated in the same manner, meaning in the same class, as the medical device it accessorizes. Often that's pretty simple to figure out. If I sell an ultrasound machine, and someone else sells the transducer that is used to send the sound waves into the body and record the returning waves and transmit them to the ultrasound machine, it makes sense that that transducer would be placed in the same classification as the medical device it accessorizes, namely the ultrasound machine. If the transducer doesn't work, the patient is potentially at risk for the same safety and effectiveness issues as when the ultrasound machine itself doesn't work.

Figure 1. Three different categories of regulated apps

Class	Risk	Regulatory requirements
Class I	Low	Typically, mostly observance of the quality system and reporting of adverse events.
Class II	Medium	The class I requirements plus often an obligation to seek FDA clearance before marketing. FDA clearance involves showing that your product is substantially equivalent to others in the market, and often involves 90 or more days of FDA review.
Class III	High	The class I requirements plus an obligation to seek FDA approval before marketing. Approval, in contrast to clearance, involves showing fundamentally that the product is safe and effective. Often this requires clinical studies and takes much longer in terms of FDA review.

Accessories to medical devices *(continued...)*

So here's where mobile apps come in. Some of the mobile apps that are being developed would seem to fit the accessory category. They are being promoted with a specific intended use to accompany, and indeed to accessorize, a recognized medical device. Examples abound, including apps that are designed to take data from a blood glucose meter and trend it to help the person with diabetes better manage their glucose levels. Some mobile apps are even being used to control the medical device, for example they might be paired with a blood pressure cuff. The app is used to inflate the cuff and then measure the blood pressure.

Now, having suggested that it's actually pretty simple to figure this out, unfortunately like many rules, this can lead to overregulation. There are relatively simple accessories that do not engender much risk of failure, but if they are paired with a high risk device, this accessory can find itself in the same high risk classification. That has significant practical implications because anytime the vendor of the accessory wants to make changes, the vendor will find itself having to jump through extra hoops at FDA.

As a practical matter, FDA is supposed to avoid that overregulation by publishing specific classifications for low risk accessories. The problem is, that process requires a rather elaborate form of rulemaking, and FDA in the present environment of budget challenges is not inclined to create those classifications. A couple of years ago FDA created a new classification for software accessories that they called medical device data systems, or MDDS, and the development of that classification took years. So instead of pursuing new classifications, to save money, FDA does not promulgate these accessory classifications very often and instead favors less formal routes that are not always available. Unfortunately, as a consequence, many types of software that play relatively benign accessory roles get up classified and overregulated.

FDA recognizes the problem, and in the guidance indicates that they will be developing a separate guidance providing some general rules designed to minimize the effect of this up classification. Presumably they will come up with descriptions for categories of accessories that they will treat as low risk, notwithstanding the accessory status. I have to admit, to me that is a Band-Aid approach because by law the agency is supposed to adopt classifications and it's very awkward to do all of this by guidance. But, so far, no one has offered to make me King so I can't just tell FDA what to do. Being King really would be handy though.

As a consequence of all of that, FDA is trying to articulate at least a general definition for when it believes that a mobile app will accessorize a medical device, while avoiding the use of the term accessory. It's funny how politics and budget issues can cause an agency to behave in such a way.

In the mobile medical app guidance, FDA declares that it will regulate apps that are an "extension" of a medical device. To be an extension, the app must be connected to the medical device, and must do one of two things:

1. Control the medical device or
2. Display, store, analyze or transmit patient specific medical device data.

To my simple way of thinking, these two subcategories relate to information sent to the device and information taken from the device.

I assume most people agree that the first category makes eminent sense. If a medical device is regulated, and if an app is used to control that medical device, it surely seems reasonable that FDA would regulate the app that's doing the controlling. So if a blood pressure cuff is regulated, and if an app is controlling inflation of the cuff and the taking of the blood pressure reading, FDA should regulate the app. If the app doesn't work, the device doesn't work. Many of the safety or effectiveness issues associated with the medical device could potentially be implicated by the controller of the device. Footnote 23 of the final guidance says that controlling the device includes controlling the intended use, function, modes or energy source of the connected medical device. It's a pretty broad category.

Upon reading the second prong of the accessory category, that is apps that "display, store, analyze or transmit patient specific medical device data," in a burst of excitement the reader might say: hey that's a medical device data system. But that reader would be wrong. Sorry.

To be sure, medical device data systems are included within the scope of that section, but the new language goes much further. A medical device data system is a piece of software that displays, stores, converts (through limited preset parameters) or transmits patient specific medical device data.

Accessories to Medical Devices *(continued...)*

One of the key differences between those two categories is "analysis." MDDS software cannot analyze data. If a piece of software analyzes data, it does not qualify for MDDS class I treatment. Software that analyzes the data from the medical device is considered much higher risk than merely the much dumber functions of just moving data around. FDA considers analysis to be an inherently riskier activity, and therefore is much more likely to classify software which analyzes medical device data into the same class as the medical device that generated the data.

In this section, FDA does not define what "analyzing" means. Later in the guidance, in the enforcement discretion bucket, apps that "trend" blood pressure measurements and share that data with healthcare providers are subject to enforcement discretion. Therefore, I would gather that analyzing means something more than merely trending. But where exactly does FDA draw the line between relatively benign analysis like trending and more rigorous analysis that would be subject to FDA regulation?

I would note, too, that there is a big difference between the displaying of data permitted in MDDS and the displaying of data that might cause a mobile app to be an accessory to a medical device. MDDS software may only display data in its original form from the medical device. So if, for example, a blood glucose meter produces data on blood glucose values and time, MDDS may only present that data as ordered pairs. The software may not, for example, produce a linear graph. FDA believes that a linear graph is actually an interpretation of the data, suggesting a linear relationship between data points.

My point is simply this: The scope of this accessory category is broader than MDDS. A mobile medical app that functions as MDDS is certainly regulated, but so too is an app that interprets medical device data by analyzing it or even just displaying it in a different format than was generated by the medical device.

Freestanding medical device apps

Some of the more innovative and frankly cool medical apps are those which don't simply connect to an existing medical device, but transform a mobile phone into a medical device itself. So what does FDA include in this category?

Apps can do a whole lot more than simply supplement another, otherwise independent medical device. Apps can be so sophisticated, and the range of potential accessories to the mobile phone so diverse and so powerful, that it's actually easy to turn a mobile phone into a medical device. Typically this is done in one of three ways.

First, you can use the phone's built-in functionality like the accelerometer, microphone or camera that comes almost standard with a smart phone to make a device. Just about any of those built-in sensors can be turned into some sort of medical device. For example, an app can make use of the built-in

microphone to turn the mobile phone into an electronic stethoscope. With this app, just put the microphone up to your chest and listen to your heart beat. Or, use the camera to read a urinalysis test strip, and you can turn the phone into a urinalysis instrument. This category includes the rather substantial category of apps that allow the display of radiological images. Mobile phones and tablets have become quite popular in serving as a class II picture archiving and communication system, or so-called PACS. In this way, these mobile phone systems replace common viewers that physicians used to use for displaying these radiological images.

Second, you can connect the mobile phone to a common attachment of some sort, like a general-purpose heart rate monitor, and with a special app turn the phone into a medical device used to monitor the heart for diagnostic or therapeutic purposes. This is a combination of technology with medical device-type promotional claims of the kind discussed in the chapter 1.

And third, you can connect a mobile phone to specialized attachments such as a blood glucose strip reader and turn the mobile phone into a blood glucose meter. This is an area that would seem ripe for future growth as more and more specialized attachments are created that take advantage of the computing power and sophistication of modern smartphones.

In Appendix C to FDA's mobile medical app guidance, on pages 26 through 27, FDA lists almost a dozen different kinds of medical devices that you could create either using the internal sensors or simple attachments.

In analyzing these possible scenarios, FDA offers up the basic standard already discussed: does the resulting configuration of software and hardware serve the same function as a traditional medical device previously regulated? If it does, FDA regulates the app.

Clinical decision support software, but called something else

Here's another section of the guidance that does not come across as clearly as it could because of politics. FDA has publicly promised they will examine the issue of clinical decision support software through a separate public process, and indeed consult with FCC and ONC on this topic as a part drafting the FDASIA report due in January 2014. I will talk more about that later, but my point here is the agency doesn't want to get ahead of that process by defining clinical decision support in this mobile medical app guidance document.

However, here's the conundrum. FDA really can't define the universe of mobile medical apps without talking about one of the key categories, clinical decision support software. So they go ahead and describe it, but don't use the proper name. Just between you and me, we both know that it is clinical decision support software, or CDS.

In defining this third category, FDA says they regulate apps that:

1. **Perform patient specific analysis and**
2. **Provide patient specific diagnosis or treatment recommendations**

That should be a dead giveaway that we're talking about CDS. The definition lines up very closely with what FDA has used in the past to define CDS.

But after providing a very general definition, FDA provides only a couple of examples in the guidance itself of apps that the agency intends to regulate. The archetypal example is computer aided detection software, or CAD. This software, and other examples like radiation therapy treatment planning and imaging processing software, do not use any specialized hardware other than the computing power of the mobile phone or tablet. Nonetheless, in FDA's views, these types of software meet the definition of a medical device because they are, and I am paraphrasing, a contrivance used in the diagnosis or treatment of a disease or other condition.

Even though the topic is given very shallow treatment in the final mobile medical app guidance, this category of CDS deserves more attention and so I dedicate a whole chapter below. What's important to understand is that even though FDA has not fully defined CDS, they are already, and in fact have been for quite some time, regulating the higher risk products in this category.
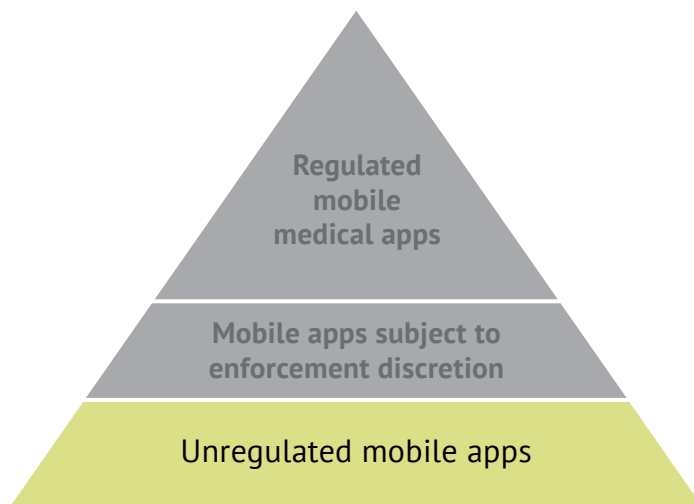
Unregulated mobile apps

Having defined what FDA regulates, it becomes easier to understand what the agency doesn't regulate, principally by subtracting the regulated apps.

But FDA goes further and gives specific guidance as to things which in the agency's mind do not constitute medical devices. The list is nowhere near comprehensive, because there would be an endless list of apps that do not qualify as medical devices. But the agency picked a few that perhaps they have received questions regarding to use as examples. FDA provides five major categories of apps they do not regulate.

1. Electronic copies of medical reference materials

FDA does not regulate electronic copies of medical reference materials. This would include such things as electronic medical dictionaries, electronic medical textbooks, and Physicians' Desk Reference materials. On the one hand you might say, of course they don't. But think about how broadly the statute is written. Does an electronic textbook meet the device component of the statute? Well it probably does. Does it meet the intended use requirement? Well, in a sense, it is used in the diagnosis or treatment of disease. A doctor might consult an electronic textbook in making a diagnosis. So it is a good thing FDA states it has no intention of regulating these articles?

Unregulated mobile apps

Pyramid diagram from top to bottom: Regulated mobile medical apps; Mobile apps subject to enforcement discretion; Unregulated mobile apps

Unregulated mobile apps *(continued...)*

For each of these exclusions I think it's important to understand why FDA is excluding them from the medical device category, because often it is not simply a literal interpretation of the statute. Rather, FDA considers other factors not expressly stated in the statute. If you understand the reasoning as to why these five categories are not medical devices, you will be able to make better judgments about other products.

The reason that electronic medical textbooks are not medical devices is the generality of the information. Information in a medical reference is not customized to a particular patient. In that sense, it serves a different function from CDS or any other software that provides specific information about a specific patient to aid in a specific decision making process. It's the generality that makes these reference materials not medical devices. So any software that provides truly general – not patient specific – information should not constitute a medical device.

2. Educational tools

FDA does not regulate educational tools. This category includes, for example, medical flashcards, medical quiz apps, interactive anatomy diagrams, surgical training videos and so forth. FDA excludes this category for the same reason as the medical reference materials – the information is quite general and not patient specific.

3. Apps that a patient might use to get medical information

FDA does not regulate apps that a patient might use to get medical information. This is a huge and diverse category. In fact, it probably would be helpful to break it down into a few major subcategories. As I look at the list of items that the agency provides as examples, I would group them in the following subcategories.

   a. Educational materials. Here the defining characteristic would be the generality of the information, much like the category above for professional reference materials. These are not patient specific, and these apps simply allow patients to do with they might do using a search engine – find general information out there relevant to their interest. Think about all the websites like WebMD and Mayo that provide general information to patients. Further, think about apps that help patients learn things like CPR. FDA does not treat these as medical devices.

   b. Apps that help consumers find medical care. Several of the examples FDA offers fit into this category, including apps that help patients find relevant clinical trials and apps that help patients find the closest medical facilities or emergency care hotlines.

   c. Apps that help consumers shop, for example to compare drug costs.

In explaining the scope of this unregulated category, FDA emphasizes that it is not meant to include apps that provide clinical decision support. More specifically, FDA explains that this category does not include apps that "facilitate a health professional's assessment of a specific patient, replace the judgment of the health professional or perform any clinical assessment." So the hallmark of this category appears to be again the generality of the information, but also a focus on assisted shopping. Apparently you can use an app as a patient to find health professionals and products, but not to figure out at least specifically why you might need them.

4. Automate general office functions

FDA does not regulate apps that automate general office functions. Like the others, this one is probably obvious because this category does not impact patient care. These functions do not in any way diagnose or treat patients, but rather simply provide the office infrastructure. So any software that limits itself to these office functions, such as billing and insurance, accounting, or scheduling, is safely outside of FDA's purview.

5. General-purpose products

FDA does not regulate general-purpose products, and this category is one of the reasons I covered the intended use concept in such detail in chapter 1. If the intended use of a product is general enough to include significant nonmedical uses as well as potentially medical uses, FDA does not regulate that product. FDA does not regulate a test tube, just because some uses of a test tube could be clinical. Likewise, FDA does not regulate an app used to record diet and exercise, just because some health professionals might adopt that app for use with patients with diabetes.

If the developer of the app legitimately keeps the descriptions of the app to such a high level that they have both medical and nonmedical uses, and if those nonmedical uses are material and not fictional or hypothetical, FDA will not regulate the app. FDA gives as examples apps that can be used as a generic magnifying glass, recording audio or notetaking,

email and maps. All of those things could be used in a medical context, but have obvious nonmedical uses as well. Typically the promotion of these products must remain at a high level of generality, but under certain circumstances the developer can explain specific uses so long as the developer does not raise any new issues of safety or effectiveness in providing specific examples. New issues might be raised, for example, by a developer promoting a general purpose magnifying glass as a great way to find life-threatening melanoma.

Enforcement discretion

Now we get to tackle arguably the hardest of the three categories – the middle category – enforcement discretion.

I wish I could say that these are simply apps that fall within the statutory definition of a medical device, but FDA has decided to exempt because they are low risk. That's close, but not completely accurate. There are two inaccuracies in that statement.

First, not everything in this category clearly belongs in the statutory definition of a medical device. While I would agree that some of them are medical devices, some of them are not. Basically FDA is saying, let's not quibble about the apps in the definitional gray area; we will just treat them as subject to enforcement discretion. Okay, I can live with that.

But second, and arguably more importantly, FDA is not simply saying that these devices are exempted from FDA requirements. Here's where FDA really muddies the waters. Instead of a simple exemption, I believe the following are all bundled up in FDA's creation of this enforcement discretion category.

1. This grant of enforcement discretion is not permanent and unconditional. FDA explicitly says that they will monitor the situation and periodically reevaluate their position. In other words, they could decide to regulate these apps in the future.

2. FDA recommends that apps in this category be developed under an FDA compliant quality system. About now you're probably thinking, what the hell does that mean? What does it mean for a federal agency to "recommend" compliance with a set of regulations? More specifically,

   a. What will happen to us if we do not follow that recommendation? Can we get in legal trouble if we do not? I would say probably not. I know it's not completely reassuring when an attorney inserts the word "probably" in his opinion, but that's the best I can do here. As a lawyer, when an agency simply recommends something, I would say it's not binding and that means you cannot get into trouble for declining the recommendation. But the document isn't especially clear.

   b. Can they come and inspect us? Well I'm not entirely sure what the law would permit, but as a practical matter I do not think they plan to conduct inspections of apps developed under enforcement discretion. However, …

3. There are incentives for following the quality system. Actually, I can think of three or four.

   a. As I said above, FDA plans to monitor the situation and may change its view on enforcement discretion in the future. If FDA gets the sense that companies in this category are not making use of the quality system (and I'm not offhand sure how they would know), this could be a reason that FDA would shift to actively regulating these apps. In other words, industry is being given a chance to do the right thing by itself without a regulatory requirement, but if industry fails to do with the agency thinks it should do, a requirement might be in our future. Long-term I'm sure that FDA would love to collect data to assess whether adoption of a quality system for mobile apps enhances quality and reduces adverse events, but under the current scheme I'm honestly not sure how they would collect such data.

   b. Given the risk that FDA might require a quality system in the future, it may be economically advantageous to employ a quality system now so that you don't need to go back and remediate the quality of your app later. It's a whole lot cheaper to build it right the first time, than to try to go back and re-create under a quality system what you've already done.

   c. Here's a bit of a downer. Now that FDA has made this recommendation, if a company does not adopt a quality system for one of the products in the enforcement discretion category, and someone does end up getting hurt, I can well imagine a plaintiff's lawyer in a product liability suit arguing that the company was negligent by not employing a quality system recommended by a federal agency. I really don't think FDA contemplated that when they made the recommendation.

   d. Actually, data do show that using a quality system improves the quality of your product, which leads to increased value in the hands of your customers. In other words, quality is good.

Enforcement discretion *(continued...)*

4. Although it's not clearly stated, I believe that products in the enforcement discretion category will not be subjected to other FDA requirements like adverse event reporting. At the same time, I know there is a movement afoot among policymakers responsible for health information technology to devise a better and broader system for collecting adverse event information associated with any HIT. So perhaps FDA is not requiring these enforcement discretion apps to comply with the FDA adverse event reporting process, but at the same time is anticipating that these apps might get swept into whatever new adverse event reporting mechanism might ultimately be adopted.

As I said, it's not as simple as a general exemption from FDA regulation. That would be too easy. As you can probably tell, these ambiguities are brought about by FDA facing the hardest task for any regulatory agency – letting go. Regulators find it very hard to just completely exempt out anything. When it's your job to regulate, deregulating makes you very nervous. And so this is what we have.

But let's move on to discussing what exactly is in this enforcement discretion category. And here I applaud FDA for extending enforcement discretion to some pretty important categories of apps. There are six subcategories within enforcement discretion, and each of them has a policy basis for existing.

1. Patient self-management

There has been quite a bit of social science research into what motivates people to take better care of themselves. Now much of that research is finding expression in mobile apps. That's the beauty of a technology that follows us all day long, to work, to play and at home. Many people even reportedly sleep with their mobile phones. So this mobile technology becomes an ideal platform for helping us change our habits, our lifestyles. Through creating messages our mobile phones can prompt us to do certain things like exercise or take our medicine, offer us encouragement to do things like stop smoking and lecture us on the consequences of eating that third éclair. Actually, it sounds kind of annoying to me, but some people apparently like it.

One of the keys to understanding this category is to recognize that the app must stop short of "providing specific treatment or treatment suggestions." Unfortunately, the guidance provides no explanation beyond that. But there does seem to be a distinction between coaching and reminding on the one hand, and diagnosis and treatment on the other. Presumably an app that allows the consumer to enter a list of symptoms and be told that she has a migraine is outside of simple coaching and reminding. However, I imagine a gray area where an app wants to amplify its message by not just reminding me, but cautioning me that my behavior might lead to a certain disease such as hypertension.

Mobile apps subject to enforcement

Regulated mobile medical apps

Mobile apps subject to enforcement discretion

Unregulated mobile apps
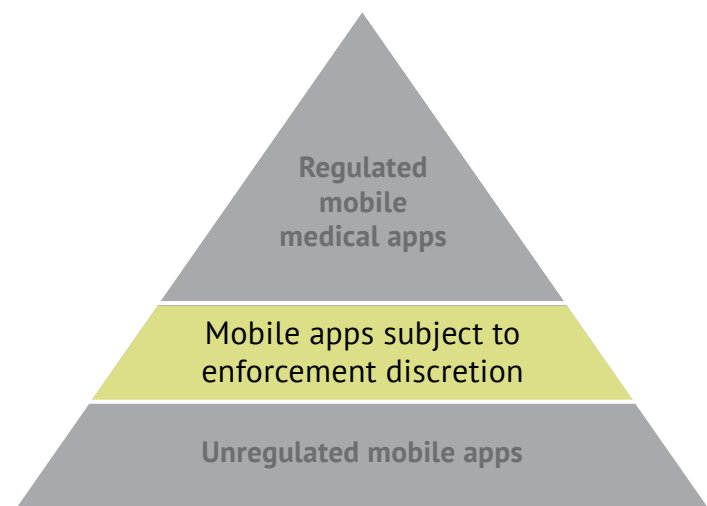
Enforcement discretion *(continued...)*

2. Patient trackers

We need data to make decisions, so I truly believe that apps that allow us to collect data on ourselves during the day allow us to make much more effective decisions about future behavior. For example, people who carefully manage their budgets, keeping track of all of their expenses, often seem to make better purchasing decisions down the road. Likewise, people who track what they eat, how much exercise they get, how much sleep they get and so forth can make better decisions down the road.

But this goes beyond simple lifestyle decisions. People who track their blood pressure, weight, drug intake times, stress and other factors can do a better job both in making their own general health decisions, but also in communicating more accurately with their doctors.

As always, there is a limit to this category. In this particular case, FDA wants to make sure that such apps don't drift into "providing recommendations to alter or change your previously prescribed treatment or therapy." So this category involves mostly passive data collection, and presumably display in useful formats like graphing and trending. But what these apps should not do is take a step further and recommend changes to therapy.

This limitation is somewhat difficult to manage because it's hard to know whether a given patient would be following a doctor's treatment plan. The limitation seems to turn on something that the developer not only doesn't control but doesn't even know: whether the patient has received specific advice from a doctor. I suppose one way to address this is to constantly inform the patient through reminders that they should always follow the doctor's orders over the software. A more conservative route would be to not make recommendations at all, but that would seem overly conservative. This is an ambiguity that will need to be worked out as we go forward.

3. Access to contextually relevant information

Hopefully you remember that one of the categories of nonmedical devices discussed above was those apps used for accessing general information such as the kind provided by WebMD. or the Mayo Clinic. There also was a similar category for professional information that exempted such things as providing electronic copies of medical reference books.

This subcategory in the enforcement discretion category is different, indeed, closer to the border, in that this category is focused on apps that allow a patient or a doctor to get more focused, more specific information relevant to the health needs of a particular patient. This subcategory starts to butt up against what FDA would call CDS, because it begins to be more specialized, less general.

FDA defines this category as an app that allows the user to find "contextually-relevant information ... by matching patient-specific information ... to reference information routinely used in clinical practice ... to facilitate a user's assessment of a specific patient." That's really complicated, and FDA actually spends very little time explaining it. Again, this is because of politics. This particular category is an element of CDS, and as FDA has said, it's keeping its powder dry with regard to CDS for the moment while it works with the other federal agencies – ONC and FCC. So instead they lay out the basic framework, but then don't explain it. That's a pity.

I will try to tease this definition apart somewhat because it is very important. For simplicity, I deleted portions of the sentence to make it more understandable, but let's go back and fill in some of the details I omitted.

First, patient specific information apparently means "diagnosis, treatments, allergies, signs or symptoms." That's pretty broad, and indeed those are only examples and not meant to limit the scope of patient specific information. So apparently we're talking about nearly any type of medical information that is specific to a given patient.

Second, reference information routinely used in clinical practice apparently means such things as practice guidelines.

So we start to see what FDA intends to include in this category. They would include an app that takes that patient specific information, and through algorithms, identifies specific relevant medical guidelines that the doctor or patient should consult. So these apps are more tailored and in a sense more valuable than an app that simply allows you to pull up specific reference material that you probably already have read. This app specializes in making the association between the patient information and the clinical guidelines. Indeed, one of the two examples FDA provides is an app that uses a patient's diagnosis to provide a clinician with best practice treatment guidelines for common illnesses like influenza.

This is significant, and welcomed. There is a movement in healthcare to help doctors by pulling up relevant clinical guidelines to ensure that the doctors can employ best practices at the point of their decision-making. This has tremendous implications for improving the quality of healthcare, and I must congratulate FDA for wanting to encourage this trend.

Enforcement discretion *(continued...)*

4. Patient communication and telemedicine

For various reasons not the least of which is reimbursement, communication with doctors has been largely stuck in the dark ages. But that is starting to change, and FDA clearly does not want to stand in the way of that change.

Telemedicine is evolving into a much broader concept than it was 20 years ago. In the old days it was primarily focused on simply helping people in rural areas get access to specialists hundreds of miles away. It also emphasized peer-to-peer collaboration over geographical differences. Now telemedicine means use of different models for physician patient encounters, where patients don't need to be physically present with their physician for many routine matters.

FDA's posture is designed to facilitate this larger use of telemedicine that ultimately will improve care by encouraging more consultations with doctors. This, in turn, will increase patient compliance and enhance early and preventative care in particular, while perhaps simultaneously reducing the cost of care overall by making the encounters more efficient.

In this area, there have been some nagging regulatory questions about the use of some very basic technology such as cameras, for example, to allow for remote viewing by a doctor of skin lesions or wounds, and for video to help a doctor in an overall assessment of the patient. Claims that technology could be used in this manner ran a substantial risk of making the technologies subject to FDA requirements.

In this new position, FDA seems to be liberating much of this technology from active FDA regulation. FDA seems to be saying that so long as these technologies are simply used in general communication, albeit in a medical context, that the agency will consider them to be in enforcement discretion.

There is, however, an important limitation to this. FDA expressly says that the promotional materials for these technologies cannot promote the technologies for a medical use. I really wish FDA had been clearer here. On the one hand, isn't promoting a camera or video capability for use in a medical encounter a "medical use"? I'm afraid we have to do a fair amount of reading between the lines here.

I would say that claims of specific utility to clinical conditions may make the product regulated. Maybe an example would help explain the difference.

With this app, a patient can use the camera on her mobile phone to take pictures of her skin to share with her dermatologist as part of a virtual examination, thereby making health care more convenient for the patient.	Enforcement discretion
With this app, a patient can use the camera on her mobile phone to take pictures of her skin to share with her dermatologist, so that her dermotologist can assess any lesions for possible melanoma.	FDA regulated

The difference is that the second of those two claims draws a specific connection between the use of the camera and a specific outcome, appropriate diagnosis of possible melanoma. I think FDA is saying, apropos to our discussion of intended uses above, that they will allow general telemedicine claims, e.g. the use of technology in communicating in a medical context, but that specific clinical claims will still trigger FDA regulation. This is another area where we will have to watch to see how FDA interprets this category over time.

Over time, we will also need to sort out how this enforcement discretion category butts up against the MDDS category. One of the new areas for apps is using the camera function basically is a scanner to capture medical device data and transmit it to physicians. Obviously of a general purpose smartphone is used for this, there is no issue because the smart phone has a very general intended use. But let's say a developer creates a specific app that makes use of the camera to transmit medical device data as a part of a system especially designed for that purpose. Does this enforcement discretion category create a loophole in the MDDS classification?

Enforcement discretion *(continued...)*

5. Simple, professional calculators

In defining the scope of calculators that FDA will treat under the enforcement discretion category, FDA repeatedly uses the word "simple". I have to admit, while I understand the logic and the intent, I think the use of the word "simple" is a bit too subjective. What might seem simple to you might seem extremely complex to me.

FDA does try to define the term with respect to two objective criteria. Specifically, FDA says that an app is simple if it is (1) taught in medical schools and (2) routinely used in clinical practice. Okay, that helps some.

At their heart, these calculators are like any other calculators used in math and science. While they are expressed in the clinical context, the heart of the technology is the execution of a mathematical formula. So the intent of these apps is merely to help the user avoid a mathematical mistake. These do not really bring any additional intelligence to the clinical decision-making process other than the avoidance of math errors.

When I talk to people about this, it seems the most effective explanation FDA provided is the numerous examples that illustrate what they intend to include. The examples are:

- Body mass index
- Total body water/urea volume of distribution
- Mean arterial pressure
- Glascow coma scale score
- APGAR score
- NIH stroke scale
- Delivery date estimator

Most people, by the time we get to the examples, feel like they understand at least generally what FDA intends. But, if you have a calculator that is on the bubble, you can always consult FDA through their email system especially set up for this enforcement discretion category.

6. Connections to EHRs

The federal government has spent billions of dollars over the last few years trying to encourage healthcare providers to make meaningful use of electronic health records. The last thing FDA wants to do is stand in the way of that progress. The benefits of greater adoption of electronic health records are so substantial that imposing FDA regulation as an obstacle to that enhanced use would be a bad policy choice. FDA recognizes that.

So while FDA has repeatedly said that it is presently putting electronic health records in the enforcement discretion category, now they have expanded that to software apps used to access the information in the EHR. That's a logical extension.

At the same time, FDA seems pretty clear that they are limiting this enforcement discretion to apps which "allow individuals to view or download EHR data." That's a pretty passive use. It should not be confused, for example, for an app that analyzes the data. As I have said before, display and analysis are fundamentally different and have fundamentally different risk profiles. So this extension of the enforcement discretion must be understood to apply to those apps that engage in passive display without analysis.

Summary of the enforcement discretion category

At an even higher level, several of those enforcement discretion categories involved in patient empowerment. There is widespread recognition across the federal government that one of the best ways to really help improve the health of Americans is to empower them to do a better job of managing their own health. We face epidemics of chronic disease, and we need to find a new model that will be more effective in stemming those epidemics. Patient empowerment seems to offer great promise, and the FDA does not want to stand in the way of this movement.

At that same high level, the first, third and fifth categories are all flavors of CDS. The fact that all three of these categories are in enforcement discretion reveals an intent at FDA to tread lightly in this broad category. This is good news indeed.

Resolving the ambiguities

FDA recognizes that it is hard to be very precise and comprehensive in its explanation of what is included in this enforcement discretion category in a static guidance. Innovators will continue to come up with new ideas for how to create apps that add value in ways that we haven't previously contemplated. So to its credit, FDA has not only included a liberal number of examples throughout the guidance document, but also created a mechanism for innovators to get hopefully timely feedback on whether new apps fall within or without the enforcement discretion category.

Specifically, FDA has mechanism for contacting the agency via email or by phone to discuss new ideas for apps and how they might be categorized. To ensure a level playing field and transparency, the agency has also indicated that it will continuously update a webpage with new examples of apps that are placed in this enforcement discretion category.

Resolving the Ambiguities *(continued...)*

This is a useful and fair way to handle this issue, but companies need to understand the open public nature of this process. If you have some clever new idea for an app and you consult FDA and they give you a decision on whether it's in the enforcement discretion category are not, that app may be summarized on their webpage. Thus it creates an interesting dilemma regarding the optimal timing of consulting the agency. If you consult them very early you can potentially save yourself a lot of time and hassle depending on the answer. But you may also be telegraphing to your competitors a potentially clever idea for a new app.

There is an opportunity for a more private assessment. FDA has a process called a 513(g) submission where you can get a concrete answer to your question privately. Unfortunately, it takes FDA typically 60 days and even more to respond to such a request.

From the FDA's vantage point, they obviously want to keep the playing field as level as possible by treating everyone in the same and by sharing important information about how they are applying the rules.

Questions left open

I don't think anyone expected the final mobile medical app guidance to answer every question related to mobile health. In part that's because the questions are constantly changing, but it's also because FDA did not try to answer every question in this one document. Even so, I thought it might be useful here to summarize some of the larger open questions that remain to be addressed.

1. Clinical Decision Support Software

I have noted throughout the course of this chapter that one of the big open questions, by design, is the scope of FDA regulation of clinical decision support software. And indeed, I think it's such a big topic that I have written an entire chapter below on it.

2. Hardware

FDA was very clear in the scope of this guidance document that it was focusing on the apps. But obviously many people are interested in the hardware associated with mobile health. So I dedicated the next chapter on this topic.

3. Wellness versus disease

In chapter 1 on intended use, I explained that the statute focuses on disease, and does not regulate intended use claims that relate to wellness. I further explained that this is a terribly important issue for mHealth, because a huge number of apps relate to wellness rather than health. But alas, the dividing line between wellness and disease is not a clear one. So much so, that FDA has announced plans to develop a separate guidance on this topic.

Fortunately, while we wait for FDA to develop its new guidance on wellness versus disease, the final mobile medical app guidance did provide some insight into this topic. The insight isn't found in the explanations of what FDA regulates, but rather in the appendices where FDA provides examples. FDA has an entire section on examples of wellness related apps that would not be regulated.

Those examples focus on one particular functionality associated with wellness, that is tracking important information to help people maintain healthier lives. According to appendix B which lists the apps found in the enforcement discretion category, tracking the following information renders an app in the enforcement discretion category:

- Provide tools to promote or encourage healthy eating, exercise, weight loss or other activities generally related to a healthy lifestyle or wellness;
- Provide dietary logs, calorie counters or make dietary suggestions;
- Provide meal planners and recipes;
- Track general daily activities or make exercise or posture suggestions;
- Track a normal baby's sleeping and feeding habits;
- Actively monitor and trend exercise activity;
- Help healthy people track the quantity or quality of their normal sleep patterns;
- Provide and track scores from mind-challenging games or generic "brain age" tests;
- Provide daily motivational tips (e.g., via text or other types of messaging) to reduce stress and promote a positive mental outlook;
- Use social gaming to encourage healthy lifestyle habits;
- Calculate calories burned in a workout.

Well, that's a start. But it's important to recognize that the functionality permitted in enforcement discretion is simply tracking; appendix B says nothing about analysis or making recommendations for how to live a healthier life. So there is much work to be done in getting FDA clarification.

Questions left open *(continued...)*

4. The interplay between the new guidance and old regulations like MDDS

Most people know how to play the game rock, paper, scissors. The game works and is understandable because there are clear rules about what beats what: rock beats scissors, scissors beats paper, and paper beats rock. If we didn't have those rules, the game wouldn't make any sense.

I'm afraid FDA's use of guidance to address these issues of mobile health has created a bit of a conundrum with regard to interpreting these rules. In law school, they teach you that the Constitution is supreme, below that are congressional statutes, below those are agency regulations, and at the bottom of the heap is agency guidance which is purely educational in nature. The problem is that FDA seems to be using guidance in effect to overrule regulations. I'm not going to complain because I like the outcome. So please don't tell this to FDA, but the guidance can't be used to overrule a regulation.

At a practical level this insistence on using the easier to create guidance in preference over the more difficult to create regulations means that we have a bit of a challenge in interpreting the law. For example, medication reminders which are identified by a specific product code – NXQ – and covered by a specific regulation found at 21 CFR 890.5050 are now placed in enforcement discretion, contrary to the regulation. I love what FDA is trying to do, but just wish they would update the regulations. Trying to accomplish this through guidance is really not the right way to do it.

At least in that example the FDA intent to overrule the regulation is clear. So in that sense, it's unambiguous, although a court would certainly have trouble figuring out which to follow. But on a deeper level I'm concerned that FDA is effectively updating a lot of different regulations without being nearly so clear. For example, I'm concerned that not all of the guidance is consistent with the MDDS regulation. The MDDS regulation indicates that trending would fall outside of MDDS and would be considered a higher risk feature, potentially class II. However the guidance (enforcement discretion, category #2) indicates that trending would be subject to enforcement discretion. How do we reconcile these two approaches? More generally, where the FDA's intent to overrule a regulation is not clear, FDA's strategy makes it particularly difficult to put your faith merely in the guidance over the regulation.

5. Drawing the line between software modules, regulated versus unregulated

Sophisticated software often consists of independent modules that function separately and as part of overall software programs. In fact, the Federal Aviation Administration (FAA) currently approves reusable software modules or reusable software components (RSC), allowing for reuse of a GPS software module, for example. The FAA has used this approach in all types of aviation systems, including those in the highest risk classification. According to the FAA, if properly planned and packaged, software life cycle data (including software code) can be reused from one project to the next, with minimal rework.

Mobile applications similarly are made up of distinct modules from a variety of sources, but FDA does not have a policy of allowing easy mixing and matching of modules, some regulated and some not.

The European Commission recently distinguished between modules that have a medical purpose and those that do not and acknowledged that non-medical device modules are not subject to the medical devices requirements. The guidance requires the manufacturer to identify the boundaries between the medical and non-medical use modules based on the module's intended use.

In contrast, the FDA regulates medical device software programs or apps as a single product. It views software as one system and applies the highest applicable regulatory classification to all modules included in software.

The current regulatory approach does not stratify functionality within a software app based on the risk associated with specific functional modules. This creates a significant regulatory burden and restricts the use of reusable modules in innovative software designs.

For example, an app could include a module to facilitate the download of information from a medical device (e.g. blood pressure cuff or blood glucose monitor). The app could also include a module to generate graphical reports to show the data received over time and a database module to store the information. The app could also incorporate a calendar module, allowing the user to add reminders for appointments, when tests were taken, etc. From a software design perspective, the modules can be designed with logical separation to compartmentalize risks within each module; only communication linkages are exposed to the other modules. The design establishes confidence that the risks are mitigated for information shared between modules.

## Questions left open *(continued...)*

Under the current regulatory framework, if one of the modules in the example of the blood glucose app is classified as Class II, the other modules such as the calendar might also be classified as Class II. In my opinion, that's overkill. It means that any time the developer of that calendar module wants to update it, for example to make it work with Facebook, they may need to get FDA clearance.

I am hopeful that this is an issue that FDA will tackle in the future.

Conclusion

I'd like to go back to where I started with this category. Fundamentally, it's pretty simple. FDA regulates mobile apps that do the same thing as medical devices the agency has always regulated. Ever since the 1976 Medical Device Amendments, FDA has regulated blood-pressure cuffs, EEG machines, urinalysis equipment, and devices for viewing radiological images. Now that all of those things can be done on a mobile phone or tablet, FDA regulates the software used to accomplish those functions.

To be sure, there are some new functionalities – capabilities that have never existed before. The scope of FDA regulation with regard to those new capabilities will be discerned by applying the basic statutory principles to determine whether the article involves an intended use of the kind described in the statute. But in addition to the analysis, developers may wish to confirm their assessments using the FDA's new dynamic guidance approach. I for one intend to watch the FDA webpage closely to see what new apps the agency puts in the enforcement discretion category.
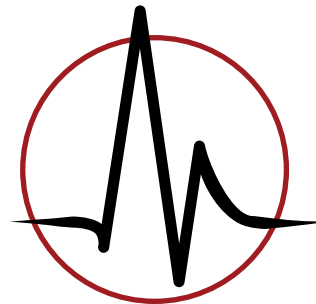
The scope of the final mobile medical app guidance is exactly that: mobile medical apps. The guidance was never intended to address hardware. Perhaps someday FDA will put out a guidance on hardware, but I wouldn't count on it anytime soon. So we need to make the best of what we have.

Fortunately, the guidance does give us several clues as to how FDA approaches hardware. I'd like to break this discussion down into two general categories (1) mobile phones and other mobile devices and (2) accessories that might connect with the mobile phones.

Mobile phones and other mobile devices

After having just said that FDA does not address hardware in its guidance, there is a single sentence that is very important. On page 8 of the guidance, FDA explains: "Under this guidance, FDA would not regulate the sale or general/conventional consumer use of smartphones or tablets." That's an extremely important statement by FDA, but not to be a party pooper, I need to explain what that statement actually means, including its limits. That statement means FDA will not regulate mobile phones, usually. Don't you just hate that word "usually." Broadly speaking, there are three circumstances when FDA would regulate a mobile phone.

1. Medical device claims

Recall in chapter 1 where I explained that whether something constitutes a medical device turns principally on its intended use. Remember also that I explained that nearly anything, including a popsicle stick or my shoe for that matter, can become a medical device if the seller promotes it for use, loosely speaking, in the diagnosis, cure, mitigation or treatment of disease or other conditions.

In its statement regarding mobile phones, FDA is saying that merely having an intended use to host a mobile medical app will not make the mobile phone an FDA regulated medical device, at least in the hands of the mobile phone seller. That's a useful statement. Getting that clarity really helps mobile phone manufacturers.

But that is not an unqualified statement that a mobile phone will never be a medical device. If the mobile phone manufacturer decides to promote its mobile phones somehow directly for use in diagnosing or treating disease, the mobile phone company may cross the line into regulated territory. FDA just said that the mere use by customers with mobile medical apps does not transform the phone into a medical device as sold by its manufacturer.

Intended use is incredibly important to understand for this chapter on hardware. In particular, I would direct you to the end of chapter 1 where I discuss the different types of intended uses. One of the areas where mobile phone manufacturers could run amok and find themselves regulated is if they depart from the general intended uses of communicating and computing power, and dive too deeply and too specifically into medical applications. Even if the mobile phone has no particular features that are uniquely medical, if the mobile phone manufacturer through its promotion makes claims about the utility of its mobile phone as somehow especially well-suited for some medical purpose, it could cross the line into regulated territory. The mobile phone manufacturers need to remember to keep their claims general, encompassing a wide variety of uses both medical and nonmedical.

2. Design features

It isn't just marketing claims that might get a mobile phone manufacturer into regulated territory. Design decisions could also cause a phone to become regulated. I'll offer a few possibilities here.

First, it's possible that a mobile phone manufacturer, wanting to pursue a business strategy of excluding competitors from certain software products, would design both a mobile app and a mobile phone handset to be intertwined in a proprietary way. If a mobile medical app is basically designed to work with only one phone, the associated integration might indicate that the phone and the app are inseparable and therefore the mobile phone too would be regulated.

Second, right now mobile phones come with certain typical hardware built-in such as a camera, a microphone and an accelerometer. But let's say a mobile phone manufacturer became enamored of the medical market and started to add certain accessories that really only had a medical purpose. That would cause the handset to become itself a regulated medical device.

Mobile phones and other mobile devices *(continued...)*

Third, it's possible that either hardware or the operating system would be designed in such a way so as to meet specialized medical standards. The features of the mobile phone added to comply with those special medical device standards evidence at least some intent for the product to be used as a medical device specifically. There isn't a theory by which you look at all the different functionalities of a mobile phone and the majority rule. If you add a single medical device functionality to a mobile phone that single functionality gets regulated. That said, I'm hoping that someday FDA issues guidance to the effect that merely complying with certain medical standards does not cause a product to be regulated. I think FDA should take that direction under enforcement discretion, but FDA has not clearly stated it yet.

Fourth, consider what would happen if a mobile phone manufacturer promotes its phones for use in the diagnosis or treatment of disease because they contain certain hardware or software features that make the phones especially suitable for hosting certain kinds of mobile medical apps. They might get away with that without making the phone a medical device, but it's not clear. On the one hand, they are specifically claiming some sort of special compatibility with medical apps, but on the other hand it still fairly general claim. I could see FDA looking the other way under enforcement discretion but they haven't said that yet.

These are just a few of the examples of scenarios where the mobile phone could indeed be regulated through design choices. The bottom line is, if you give the mobile phone a uniquely medical function, even if it retains all of its other functionality, you have arguably made the phone into a medical device.

3. Mobile phone as component

In the previous two discussions, I've talked about whether the mobile phone might be a medical device as it leaves the hands of the manufacturer. But there is an additional question: Is the mobile phone considered a component of a medical device in the hands of the customer?

In its guidance, FDA says: "When mobile medical apps are run on a mobile platform, the mobile platform is treated as a component of the mobile medical app's intended use." I am really not even sure what that says, but if it suggests that the phone is a component, I disagree. Of course you need to also understand that I don't make the rules, but that is my opinion for what it's worth. Something can only be a component when it is added to other components to ultimately produce a finished medical device in the hands of a manufacturer. When a customer joins two articles, that is not manufacturing and it doesn't make either article into a component. Typically when a customer joins two things, that's the definition of an accessory, but FDA's conundrum is that calling the phone an accessory would mean that the phone was regulated at the time it left the mobile phone manufacturer's hands. FDA obviously doesn't want to call a mobile phone a medical device when it leaves the manufacturer's hands (and I agree that it's not an accessory). But at the same time, FDA seems to really want to call the phone regulated in the hands of the customer. So they misuse of the term component and call the phone a component.

In my analysis (and I feel pretty comfortable with this), the mobile medical app would be a medical device and the mobile phone on which it operates would simply be part of the environment in which the medical device operates. As such, the mobile medical app manufacturer is obligated to make sure that its app will operate in the environments which it recommends or that can reasonably be anticipated. In this case, that environment would be a combination of hardware and software (for example, the operating system). The app manufacturer needs to test and validate the app as working in the recommended and anticipated environments.

I'm not sure that my disagreement with FDA matters very much, because the agency concedes that: "the mobile platform manufacturer is exempt from the Quality System regulation and registration and listing requirements." But it still concerns me that for some reason FDA feels inclined to call the mobile phone and the operating system "components" of a medical device.

Attachments to mobile phones

What do we know about the regulatory status of the stuff that plugs into the phone? Unfortunately, the final MMA guidance does not provide much insight into when and how attachments might be regulated. FDA declared such issues to be out of scope for this guidance document. In speeches, FDA has explained that they are developing a separate guidance document to cover these accessories, but that could take some time. So I will have to draw upon other guidance documents and regulatory pronouncements to see what we can learn.

I'd like to start this part of the analysis by discussing a bit deeper the statutory difference between an accessory and a component.

In the area of mobile health technology, it's important to understand that both an accessory and a component of a medical device are themselves regulated medical devices. Further, the difference between an accessory and a component is who buys it. End-users buy accessories, while manufacturers buy components. Thus the exact same piece of equipment could be either an accessory or a component depending on the target purchaser.

Attachments to mobile phones *(continued...)*

Deciding whether something is an accessory or a component makes a big difference in terms of applicable regulatory requirements. Components are exempt from most FDA regulatory requirements, with the regulatory burdens being borne by the finished device manufacturer. Accessories, on the other hand, since they go right to the end user, must meet the FDA requirements before they leave the hands of the accessory manufacturer. These differences are summarized in the figure below.

The level of regulation imposed by FDA on an accessory or component is determined by the parent device to which it relates. So if the accessory relates to a high risk device, say an implantable cardiac defibrillator, it will be subject to a high level of regulation even if the accessory is relatively benign in and of itself.

This approach would seem to regulate accessories once removed, twice removed—indeed, the whole family tree – at the same level as the "parent" device. The agency's theory is simply: if an accessory breaks, the risk to the patient would be the same as if the parent medical device broke.

Let's take as an example: headphones. Headphones obviously have a very generic use, listening to sound from a player of some sort. But let's say that headphones are specifically promoted to be used together with a mobile medical app. Let's say the mobile medical app uses sounds as therapy for treating individuals with disorders including autism. In the face of specific promotion of the headphones for that medical use, the headphones would be regulated to the same level as the underlying app.

With that as general background on accessory regulation, let's analyze the potential range of hardware that can attach to a mobile phone, and look at what the likely regulatory status of those attachments will be. I have come up with at least three different categories of attachments.

1. Attachments with specific medical functionality.

There is a growing market of specialized medical attachments that can plug into a phone that to make it function as a medical device. We discussed these accessories in chapter 2 in relation to the associated apps, but here we focus on the hardware. Examples would be attachments like a blood glucose strip reader or ECG electrodes.

Based on the description of this category, I hope by now you can guess that these devices will be regulated. That should be pretty obvious.

I would predict that some of the medical attachments will fall into the MDDS category because they will be used in the display, transfer or storage of medical device data. Most people think of MDDS as software, but the classification also covers hardware. In the FDA system, such devices are class I, exempt from premarket notification but subject to the quality system requirements.

Falling outside the MDDS classification has two potentially opposite consequences. On the one hand, falling outside might mean that the product is not regulated by FDA at all. Perhaps it's because the accessory is a generic accessory of the type described in the next section. On the other hand, falling outside the MDDS classification might mean that the product is a class II or III medical device, a very different outcome. This would be because, for example, the accessory provides functionality beyond merely transmitting, displaying or storing medical device data.

Figure 1. Types of devices

Element of device definition	Finished stand alone parent device	Accessory	Component
Definition	A medical device in finished form, ready to use perhaps with accessories, intended for sale to the end user	An article intended for use in or with a finished medical device, intended for use by the end user	An article intended for use in or with a finished medical device, intended for use by a manufacturer
FDA clearance required?	Yes, unless exept from clearance	Yes, unless exempt from clearance	No
GMPs required?	Yes, unless exempt from GMPs	Yes, unless exempt from GMPs	No, but quality must be assured to the satisfaction of the finished device manufacturer

2. Generic accessories.

By now you're probably getting pretty sick of me talking about the difference between general versus a specific intended uses. But that concept is important to the hardware that attaches to a phone. If I attach a general-purpose, supplemental display unit, FDA does not regulate the attachment so long as I only make those general claims. If I claim that the display unit is especially suited, for example, because of resolution or some other feature to show ultrasound images, I have just made it into a medical device.

In the preceding section, I discussed the likelihood that certain accessories would qualify as MDDS because they would be intended for use in the storage, transfer or display of medical device data. But if you think about it, if I sell a common cable perhaps with a USB connector on one end and an Apple Lightning connector on the other, and I just say it's for connecting stuff to your iPhone, that cable will not be MDDS because I have not claimed any specific medical function. So it's possible that by staying at a high enough level of generality many accessories can escape regulation altogether.
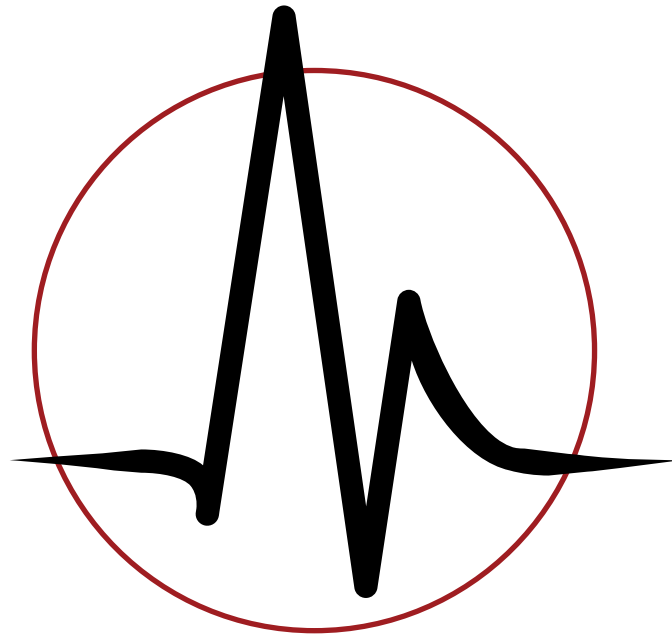
3. Wellness sensors like heart rate and weight scales

For decades, FDA has permitted electronics companies to produce and sell various kinds of sensors used by people to manage their health and wellness. Examples include a common bathroom scale, heart rate monitor used by athletes during training, and an activity or sleep tracker. These sensors are easily and cheaply available through retailers.

Let's say a mobile medical app developer sells an app that requires the customer to go out and buy one of these sensors and use it in tandem with the app. By definition, because I use the term mobile medical app, I'm referring to the variety of apps that FDA regulates, so it must have an intended use in the cure, mitigation, treatment or diagnosis of disease or other conditions (loosely stated).

If the app maker does that unilaterally with no involvement of the sensor manufacturer, the intended use of the sensor does not change in the hands of the sensor manufacturer when it sells the sensor to the customer. The sensor manufacturer intends the generic wellness use for its sensor. Just as I argued for the mobile phone scenario above, I would say that the sensor is not even an accessory or a component of a medical device. Rather it is just part of the environment in which the mobile medical app will operate. For its part, the developer of the mobile medical app needs to prove that the app will perform safely and effectively using a generic, off-the-shelf sensor.

Even if the mobile medical app developer goes so far as to specify a specific brand of sensor to use, when the sensor manufacturer sells that specific sensor it is still not a medical device. It is the sensor manufacturer's intended use for its sensor it sells that matters, at least while the sensor is still in the sensor manufacturer's hands.

But let's say the sensor manufacturer and the app manufacturer collaborate in some way, first maybe to test to make sure that the sensor and the app work well together, and then likewise engage in some level of joint promotion for the use of the two articles together. Boom. The line has been crossed. The sensor is now an accessory to the mobile medical app, and regulated in the same manner.

I told you the concept of intended use is important.

Unfortunately, there is an enormous hole in FDA's final mobile medical app guidance document. That hole is the definition of clinical decision support software. There isn't one.

That's a problem, because CDS is one of only three flavors of FDA regulated mobile apps, and may yet prove to be the biggest of the three. FDA goes through a lot of verbal maneuvering on the one hand to explain that there is this category of clinical decision support software, but on the other hand not define it.

I explained in Chapter 1 why the FDA felt it necessary to omit the key definition. CDS has been long undefined in FDA land, and in 2011 FDA announced its intention to develop a guidance document defining the types of CDS that FDA regulates. Indeed, in September 2011, when FDA held its hearing on mobile medical apps, the agency tacked on an extra morning to cover CDS specifically. And we have been waiting ever since to see the proposed guidance.

Since then, in the summer of 2012 Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA). In section 618 of that legislation, Congress directed FDA to work with ONC and FCC to write a comprehensive regulatory strategy for all health information technology, including mobile medical apps. That report is due to Congress by January 2014.

At a recent meeting, Dr. Jeff Shuren, the Director of the Center for Devices and Radiological Health of FDA, was asked how the agency plans to address the CDS issue. He explained that the agency's intention is to collaborate with ONC and FCC to analyze the CDS issue as a part of drafting the FDASIA section 618 report. He explained that in addition to the report to Congress, which will talk about CDS but only as one element of an overall HIT strategy, FDA may publish a CDS proposal or perhaps just a concept paper after January 2014 to get public input.

While I am disappointed by the delay, this approach makes sense because CDS, in contrast to most of the others things FDA regulates, is often directly interwoven with the electronic health record. Thus ONC, and to a lesser extent FCC, have an interest in CDS. Ensuring that federal policy is as coordinated as possible among the agencies will certainly help industry.

In the meantime, there's this darn hole in the mobile medical app guidance document. And even come January, we are not likely to get definitive answers but only perhaps more questions from the agency. So what do we do in the meantime, before FDA speaks more definitively of its regulatory approach to CDS?

Current FDA policy on CDS

What do we know in advance of FDA's January report? Turns out, we know quite a bit. Consider the following four sources of intelligence.

1. The statute

Okay, there's honestly not a whole lot we can glean from the statute itself, other than the fact that FDA has authority to regulate software that is intended for use in the diagnosis or treatment of diseases or other conditions. I'm paraphrasing a bit, but I've covered that several times already.

At a very fundamental level, though, it is important to appreciate that as with mobile medical apps, this is a case of FDA needing to clarify its existing regulatory policy, as opposed to a new area the FDA is thinking about regulating. Indeed, as I show below, FDA has regulated several categories of CDS since 1976.

In contrast with mobile medical apps, though, this is different because FDA's regulation of this category has never been clear for very many forms of CDS. In the case of mobile medical apps, really all FDA is saying is that they regulate apps that function the same as a traditional medical device. So if an app performs urinalysis and if FDA traditionally regulated the machines that did urinalysis, FDA will regulate the app. That's a pretty modest revelation.

In the case of CDS, for decades industry has been asking FDA to clarify the types of software FDA regulates, and the agency has utterly failed to do it except in a few very narrow categories such as calculators and computer-aided diagnosis. So there's no simple explanation here; rather FDA truly is articulating new interpretive rules.

2. FDA comments: September 2011 hearing.

As I mentioned above, FDA held a half day hearing on the topic of CDS in September 2011. If you are interested in this topic, I highly recommend you go to the FDA website and read the transcript. There was quite a bit of discussion. At the risk of oversimplifying things, I'd like to present a couple of takeaways that I got out of the hearing.

First, at least one FDA speaker seem to suggest that CDS was characterized by a three-step process.

Step one is the collection of data, quite frankly nearly any data. FDA did not seem to care too much whether it was medical device data, environmental data, demographic data or any other data that might be relevant to inform clinical decision-making. I do think that logically there has to be two different types of data used. One type of data would relate to the patient, and the other type of data would relate to medical learning of some sort. Clearly this sort of medical data might be simply inherent or embedded in the analysis that comes in step two. But the whole point of CDS is to take patient specific information and then apply more generalized medical knowledge.

Step two is the analysis of that data. Here again FDA didn't seem too particular about what kind of analysis might be performed. Whether it's simple database lookups or more elaborate algorithms, FDA seemed to sweep it all into this category of CDS.

Step three was the production of a patient-specific, actionable recommendation. Now there are finally some words that limit the scope of this category. Patient specific is probably self-evident, but to me it distinguishes this type of software from software that might, for example, make population-based recommendations for public health officials. Actionable, as I understood that term, means specific enough in the form of the recommendation to prompt action. If the output of the software is simply a laundry list of possibilities and the software leaves everything to the human decision-maker, such output would not be actionable.

Thus, as I gather it, the FDA's concept of CDS in general is that it has to produce a recommendation that might say something like, Mr. Thompson, you probably have a migraine. Or Mr. Thompson, take two aspirin and call a doctor in the morning. But in any event, the output would be a specific recommendation for the specific patient.

To be clear, FDA wasn't suggesting that this is the definition of what FDA should regulate, but rather the starting point of the definition for CDS. As in MMA, FDA has said that it only wishes to regulate the riskiest, and not to impede the development of low risk software.

Diagrammatically, I visualized the FDA definition of CDS in illustration #1 below.

Illustration 1. What do we know today on CDS?
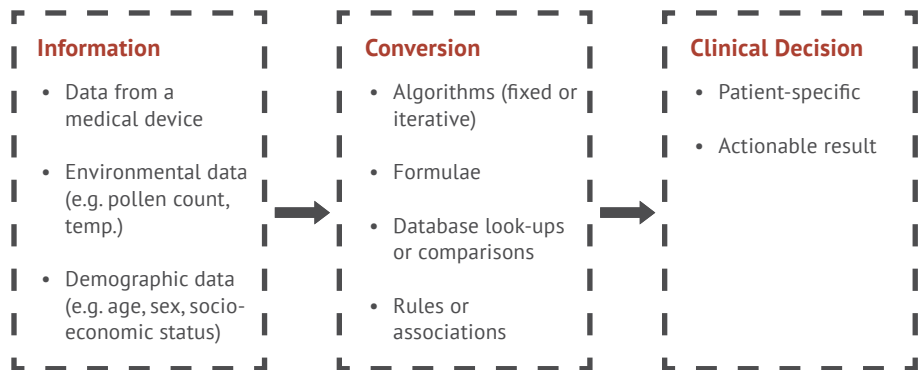
September 2011 preliminary definition of CDS

After FDA presented its basic framework on what it thought CDS meant, the agency then provided some examples as in illustration #2 below. Further, the agency wanted to make the point that CDS exists along a rather wide risk continuum, and that some CDS is much riskier than others. The following are the examples I heard presented at the September 2011 hearing.

Illustration 2. Examples of CDS software
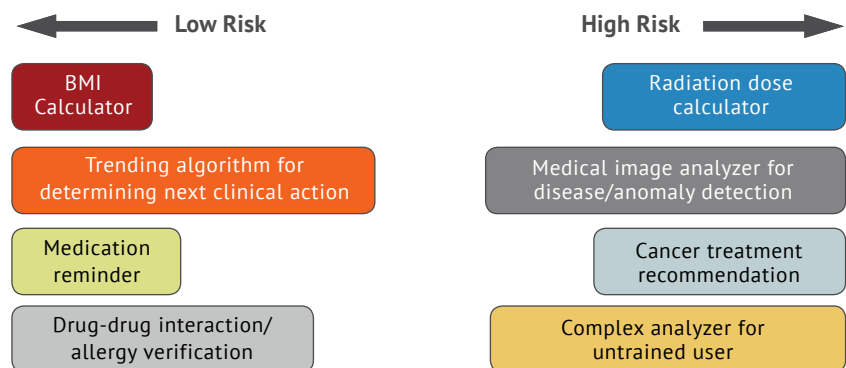
Current FDA policy on CDS *(continued…)*

While this information is now over two years old, from everything I've heard FDA would continue to regard these materials as accurate on these basic concepts. I find it very interesting that out of the examples given in September 2011, the MMA guidance just released placed the BMI calculator and medication reminder in the enforcement discretion category. More on that below.

3. FDA classification regulations

As I said in the context of the statutory discussion above, FDA does have existing statutory authority to regulate at least certain categories of CDS. Indeed, they long have. There are several different FDA classifications for software that would fall into the CDS category. I picked just one, calculators, and ran a search to see how many different calculators FDA has already classified. The results are in the following illustration.

Other common forms of CDS that FDA has actively regulated for a long time include such area as computer-aided diagnosis. That's software a radiologist uses to help her evaluate a digital medical image to see where potential tumors and other abnormalities might be found. The software scans the image and then perhaps uses color to highlight the abnormalities, drawing the attention of the radiologist.

So, if you have an app that serves as a medical calculator or helps to evaluate a digital image or frankly any other type of CDS, you might invest some time looking at the existing categories of FDA regulation to determine whether FDA already regulates your app.

4. September 2013 MMA guidance

Throughout chapter 2, as I was looking at each of the categories of mobile apps, including those that are regulated, those that are not and those that are in enforcement discretion, I made note of where FDA addressed CDS even if they didn't call it that by name. I don't want to repeat all of that here, but rather I will direct your attention to the following.

Medical devices

With regard to apps FDA regulates, the guidance specifically calls out the CDS category, although unfortunately not by name, as a type of app the agency does indeed regulate. The agency included a very brief high level definition of CDS, and then gave the example of computer-aided diagnosis.

Nonmedical devices

With regard to apps FDA does not regulate, in the third category regarding apps that facilitate patient access to information, I pointed out that FDA was careful to distinguish this category from CDS.

Enforcement discretion

With regard to apps that FDA places in enforcement discretion, I pointed out that the first, third and fifth categories all related to CDS. Further, in this same vein, Appendix B which is a list of apps subject to enforcement discretion includes numerous examples of CDS.

Actually, for a guidance document which professes not to address CDS, the final guidance sure does provide a lot of information about it.

Summary of what we've learned

Let's take a look at all of this together: what does it tell us?

First, obviously, it gives us some specific software types that FDA considers within its regulatory oversight. This includes things like computer-aided design and radiation dosage calculators.

Summary of what we've learned *(continued...)*

Second, we know that FDA's inclined to put in enforcement discretion a variety of low risk CDS including routine drug reminders and simple calculators for such things as BMI. Likewise, FDA's inclined to put in enforcement discretion those apps which are really more about motivating people than actually diagnosing or treating people. Further, FDA is inclined to put in enforcement discretion apps that simply pull up contextually relevant information like treatment guidelines associated with the patient's particular disease.

Third, a bit more broadly, we see FDA focusing on software that gives specific recommendations for specific patients, as opposed to accessing general information even if the software selected the information because it's relevant to a specific patient.

Fourth, we see a sensitivity to replacing the physician as opposed to aiding the patient or a physician more generally. This FDA concern comes into play particularly with consumer directed apps where a patient might rely on the software rather than seek a medical professional.

Fifth, we see the concept of simplicity, where FDA calls out very basic calculations that are taught in medical school and that use well-accepted content. Software that merely facilitates calculations or access to such information seems to get much more relaxed treatment from FDA.

Sixth, studying what FDA puts in enforcement discretion is revealing both for what they include, but also for what they do not include. To my surprise, FDA does not include straight up software that makes recommendations to physicians in low risk areas other than basic calculators and apps that pull-up clinical guidelines. If that means such software that makes recommendations to physicians beyond simple calculations or accessing guidelines is indeed subject to FDA regulation, that will be a problem.

I am hoping that is not what it means, but rather FDA is simply keeping its powder dry while they go through the collaborative process with the other agencies.

While we have those general principles, obviously those create as many questions as they answer, so I suspect many people will be interested to see what FDA comes up with in January.

CDS coalition proposal

During this time when the agencies are considering options for regulatory approaches to CDS, a coalition I represent, cleverly called the CDS Coalition, has spent almost 2 years developing ideas around ways to draw the line between regulated and unregulated CDS. Thus, to be transparent, I must acknowledge a self-interest in what I'm about to share.

Through that work, we have come up with some ideas for ways that we recommend FDA go beyond merely considering the risk associated with the disease at issue and the role that software plays in diagnosing or making treatment recommendations with regard to that disease. We believe, and have communicated to FDA, that the agency ought to also examine closely the relationship between the software and the user. In a phrase, we believe that only software that creates "substantial dependence" on the software by the user merits FDA regulation. If the user is not substantially dependent on the software, FDA regulation would seem to be overkill.

Conceived another way, this is the difference between (1) on the one hand mere information that a person could get from the library or other source, and (2) on the other hand a medical device that directly plays a role in diagnosis or treatment. Dependence on the software is the difference.

So our proposed definition of "regulated CDS" is CDS that causes the user to be substantially dependent. Now you might be wondering why the heck it took us two years to figure that out. Actually most of that time we spent writing proposed guidelines to determine whether the user is substantially dependent on the software. These guidelines focus on three criteria. If CDS software meets these three criteria, the user is not substantially dependent on the software and therefore the software should not be regulated.

1. The software is transparent. This refers to how easy it is for the user to understand the basis for the software recommendation. Does the software in a meaningful way reveal the underlying data it considered, the source of its clinical analysis, and the context and clinical logic of its recommendation?

2. The user is competent to make the clinical decision. Is the user qualified – through training or professional experience – to understand and critically evaluate the software recommendations and make the decision?

3. The user has time to reflect. Does the user have enough time to reflect and/or challenge the software recommendation?

So if those three conditions exist, the user is not substantially dependent on the software and the software is not acting as a medical device and under our proposal should not be regulated.

Below the coalition gives a little bit more description and context for these three factors. This is a summary of about 30 pages of guidelines.

1. Transparency of CDS Software

Transparency requires clarity with regard to four types of information.

a. The intended use

Software should explain its role in the decision making process, situations where software should not be used, who should use it – doctor, nurse, consumer, etc. – and where it should be used – hospital, home, etc.

b. Information that is entered into the software

Either manually or automatically, the user enters information about the patient into the software. The software must also contain clinical information of some sort, for example clinical guidelines or algorithms based on clinical knowledge. The software must reveal to the user at least in general terms the information, both patient specific and clinical, on which its recommendation is based.

c. Recommendation

The software should reveal its full recommendation regarding what the diagnosis or treatment should be. Sometimes the patient specific inputs or clinical knowledge do not lead to a single recommendation with much certainty, so the software has to be able to communicate the limits of its recommendations.

d. The rationale

The software should explain how it reached its recommendation. What's important is the clinical thought process, not the mechanics of the software. In this way, the software ought to roughly mimic how colleagues would consult with each other, offering the clinical rationale for their conclusions not just the conclusions.

2. Competent human intervention

Competent human intervention means the intended user (healthcare professional or consumer) is competent to use the software. More specifically, it means that the intended user is competent to make the underlying clinical decision. If the end-user is fully trained and experienced in the type of decision that needs to be made, the software acts merely as a convenient aid to synthesize the relevant information. Thus there can be CDS that supports decisions made by consumers as well as CDS that supports the decisions of expert physicians. The key is making sure that the intended user is well-qualified to make the decision.

3. Time to reflect

Adequate time to reflect means the CDS software is intended to be used in a setting that allows the user sufficient time to evaluate and consider the CDS recommendation before making the particular decision. To determine whether adequate time for reflection exists, we need to consider two different factors.

The first is the amount of time available in the anticipated care setting, with the anticipated clinical condition. Treatment of a gunshot wound in an emergency department allows less time to reflect than a visit with a patient with diabetes in the doctor's office.

The other factor is the complexity of the decision to be made. The clinical decision can be simple, moderate or complex. This complexity depends on how many elements the user must consider in order to make the decision.

So in determining overall the adequacy of the time for reflection, we must consider the complexity of the decision in light of the anticipated available time. An "adequate" amount of time means that the anticipated time for reflection is indeed sufficient, given the complexity of the decision, for the competent human described above to make a confident decision with the aid of the software, but allowing needed time for appropriate challenge to the software.

Conclusion

CDS is potentially a big category. There are many apps that do not connect with any special hardware but instead simply use the computing power of the mobile phone to do remarkable things with data. This is one of the more exciting areas of mobile medical apps, so we will be watching with great interest to see what FDA does in January 2014.

At the same time, we do know quite a bit already about how FDA regulates certain categories of CDS. The agency has clearly signaled that some of the low risk categories belong in the enforcement discretion category. What we are less sure about is medium risk CDS. The high risk CDS is already classified in most cases as a medical device.

Many of the stakeholders hope that FDA broadens its thinking with regard to factors that should determine whether CDS gets regulated by FDA. Speaking on behalf of the CDS Coalition, we hope FDA considers whether the software creates substantial dependence in its users. If a user isn't substantially dependent on the software, the software becomes like any other knowledge base, simply another learning aid in the quiver of the caregiver.

V. Who Does FDA Regulate?

I'm going to keep this chapter short and sweet, in large part because I intend to reserve two of the more interesting questions for subsequent chapters. In this chapter, I'm going to cover what the MMA guidance says about which organizations will be regulated, and which will not. But I'm going to reserve for subsequent chapters (1) the circumstances under which FDA will regulate a healthcare provider and (2) how to shift the regulatory burden on to someone else.

App developers get regulated

The primary FDA regulatory obligations will typically fall on the app developer. I realize that's an ambiguous sentence because in this virtual world many apps are developed by a group of organizations working together.

I could torture you with a long and complex analysis of all of the terms in the statutes and regulations in order to show you how all of this fits together, but I'm old and impatient, so I thought I would just cut to the chase. The primary FDA regulations will fall on the organization that:

1. **Controls the product specifications, and**

2. **Controls the marketing claims made about the product**

In FDA's terminology that organization goes by various names, including manufacturer and specification developer. But you don't need to remember any of that. Just figure out who does those two things, and that's the organization responsible for FDA compliance.

Perhaps you're wondering why that is the rule, why those two things? It's because those two activities are the focal point of the regulatory requirements. Controlling the product specifications means that your organization is at the top of the heap from a product production standpoint. It means you're the boss of the manufacturing. You control what FDA cares most about from the standpoint of assuring safety and effectiveness, and the most important element from the standpoint of a quality system.

Controlling the claims made about the product is of equal importance, because as I've said probably 50 times so far in this book, intended use is the key to the level of regulatory requirements imposed, and a key determinant of the safety and effectiveness of the product. In a very real sense, FDA regulates the intended use, so whoever controls that intended use is squarely in FDA's sites.

Perhaps some Smart Alec out there is thinking, well Brad, what happens if two different organizations control those two different things? To that question I would respond, I really hope not. How could one organization control the marketing claims, but not have control over the nature of the product they are marketing? It would be utterly dysfunctional for one organization to monkey around with what the product is, while a separate organization working independently decides what claims to make about the product's performance. Product specifications and product claims are inextricably tied, so it darn well better be the same organization controlling both. Maybe in reality it is a partnership of two where they decide together, but my corporate law background tells me that a partnership is in fact one organization. So take that any Smart Alecs. (Sorry, I've been writing for five straight days.)

Organizations getting a free pass

I have to say that as I read the final MMA guidance, FDA is being pretty practical in limiting the obligations of other potentially responsible parties. Let's look at a few discussed in the guidance.

App stores

Call them distributors or call them retailers, these are typically virtual stores that sell the apps. Think "Google play," "iTunes store," and "BlackBerry App World". FDA shows an intent to tread lightly here.

Before discussing the app stores specifically, I'd like to give you some background on what the statute authorizes FDA to do with respect to distributors and retailers. Under the statute, FDA has authority to regulate any organization in interstate commerce that deals in regulated articles such as medical devices. As a practical matter, FDA generally doesn't pay too much attention to the folks low down in the chain of distribution, except that they expect two things out of these organizations.

First, they expect them to use what are generally referred to as good distribution practices. You won't find these practices in any regulation, but rather these concepts are more folklore. But the point is that FDA expects a distributor to handle regulated articles in a way that does not cause them to be, to use the technical statutory terms, "adulterated or misbranded."

Typically adulteration means that somehow the product has been rendered unfit. With food and drugs, you can imagine that these requirements involve a certain level of cleanliness as well as perhaps control over temperature and humidity. If a distributor is dealing with a medical device that is sensitive to the environment, the medical device distributor would likewise need to store the product in a way that does not cause it to become less safe or effective.

Typically misbranded refers to the way products are promoted. If a distributor or retailer buys products for resale, and then changes the claims made about the products, the distributor or retailer is responsible for those new claims. That means they are responsible to FDA for ensuring any regulatory compliance necessary for those new claims.

The second thing that distributors and retailers are responsible for is helping to facilitate a recall or corrective action when necessary to protect the public health. So if a product is found to be flawed, and evidence suggests that the flaw could be putting people at risk, the distributors and retailers are expected to cooperate with the manufacturer in correcting the problem, however that is best done. Sometimes it's by recalling the product, but sometimes it's by fixing the product in the hands of the customer. In the case of software, this might mean ensuring the distribution of an appropriate patch for the software.

With that as background, let's return to what the guidance says about app distributors. In the final guidance, FDA says: "FDA does not consider entities that exclusively distribute mobile medical apps, such as the owners and operators of the "iTunes App store" or the "Android market," to be medical device manufacturers." Well of course not.

To go back to the first section, these app distributors do not control the product specifications or the marketing claims. While they might have terms of use that limit what can be said through the site and what products can be sold, that's not the same as controlling how an individual product is designed or marketed. That is just setting up parameters for who can participate on the site.

I would note that in the relevant passage FDA uses the word "exclusively" to modify the term "distributing." By adding that word, FDA is leaving the door open to regulating an organization that goes beyond mere distribution into controlling specifications and the claims associated with the product. I would further point out that FDA is merely stating the obvious, that these organizations are not manufacturers. But as I explained above, they are distributors and distributors do have obligations under the statute.

Mobile phone Manufacturers

In chapter 3, I discuss FDA regulation of hardware, and in particular the mobile phone itself. Most of the time the mobile phone will not be regulated so long as the mobile phone manufacturer maintains an intended use that is general, for example all of the uses for which a smart phone typically is suitable without any special emphasis on specific medical applications.

Assuming the manufacturer maintains that general intended use, the mobile phone is not regulated and thus the mobile phone manufacturer need not comply with such things as the quality system requirements.

Mobile operators and other internet service providers

FDA makes it quite clear that they have no plans to regulate those who provide the communications connectivity only. Again, this is because those organizations have an intended use for their products that is very general including all communication needs. They are not promoting their services as somehow uniquely tailored or suitable for the purposes listed in the statutory definition of a medical device. Nothing shocking here.

IT tool providers

FDA also calls out a wide variety of other providers of general IT services and tools, including providers of:

1. General purpose computer or information technology

2. Web hosting services for content or software application

3. Customer support services

4. Data center hosting services

5. Cloud hosting services

6. Application hosting services

7. Software development kits

The key element in all of these cases is a general intended use that covers a broad range of IT applications, only one of which is health. However, it is important that even within the general use, the providers do not make specific claims associated with the uses that would trigger the medical device definition. The ability to make a general claim is not a license to make a wide variety of specific medical claims.

FDA has a somewhat outdated guidance on general versus specific claims which explains that the ability to make a general claim does not necessarily mean a company can make any specific claim that logically fits within it. The policy reason behind that position is that specific claims often raise specific issues of safety and effectiveness that may not have been evaluated as a part of the decision-making regarding the general claim.

An example would probably make that more understandable. I may be authorized by FDA to sell a scalpel, with the general claim that it cuts tissue. However, being able to make that general claim that it cuts tissue does not give me authority to claim that the scalpel is ideally suited for a certain kind of open heart surgery, and then provide details as to how to use the scalpel in that open-heart surgery. That more specific use raises many additional safety and effectiveness issues which would not have been evaluated and validated as a part of preparing to make a general claim that the scalpel cuts tissue. Bottom line, the ability to make a general claim does not automatically authorize you to make any specific claims that fall logically within it.

Mobile apps seem all the rage in the pharmaceutical industry. There are presently over 200 of them publicly available. Based on what I'm hearing from pharmaceutical companies, that's only a small number compared to the apps in development.

There's been a debate going on in the UK about whether pharmaceutical apps are medical devices under EU law. A consulting firm called Bluelight & d4 suggested in a January 2012 report that many health-related apps are indeed medical devices. Specific to pharmaceutical apps, the report suggests that at least in the UK "if your app will be associated with, contributes to or makes a clinical decision, assume that it will be classified as a medical device...." The report stirred quite a controversy among champions of innovation and free speech.

In the US, pharmaceutical companies have begun to focus on these issues for a couple reasons. First, FDA held a public hearing in March 2012 to take testimony on whether greater reliance on patient decision support software could allow certain drugs to switch from prescription status to over-the-counter. That prompted companies to wonder how such software would be regulated.

And second, given the technology trends and the opportunities to enhance patient care, pharmaceutical companies and healthcare providers alike have been interested in identifying all the possible uses for mobile apps in connection with drug therapy. Much creativity and energy is going into identifying the best uses for pharmaceutical mobile apps.

Strangely, though, FDA's final guidance on mobile medical apps says little about apps used for pharmaceuticals. Substantively, in the entire document, drug-related apps are only mentioned a handful of times, mostly in passing or in minor examples.

In the first several chapters, I laid out the basics of FDA regulation of mHealth. Given how little discussion there is of pharmaceuticals in the final guidance, we have to use reasoning to discern how FDA regulates pharmaceutical apps. I'm hoping that FDA adds clarification in this area as time goes by.

Regulatory categories

The starting point is to understand the four different possible regulatory categories into which pharmaceutical apps might fit. Those categories are:

1. Heaven on earth, a.k.a. unregulated apps.

Just about everyone wants their app to be unregulated. And Utopia it is. But, not to be a downer, I need to be clear that this just means unregulated by FDA. Most apps would still be regulated by the Federal Trade Commission, and indeed it was the FTC that brought one of the first enforcement actions against a mobile app developer. Further, nearly all apps would be subject to state regulators, Lanham Act challenges by competitors, and tort law if they hurt somebody. So it's probably still a good idea if app developers exempt from FDA nonetheless test their apps to make sure they work.

2. Drug labeling.

FDA law makes it clear that information provided by a pharmaceutical company in support of its drugs qualifies as a regulated drug labeling even if it is not physically near the drug itself. Generally there are two kinds of labeling:

a. Prescribing information, which also is sometimes referred to as product labeling or a package insert, provides carefully crafted information regarding instructions for use. This information is highly regulated, and for new prescription drugs is the subject of much negotiation between the manufacturer and the agency.

2. Drug labeling. *(continued...)*

b. **Promotional labeling,** which is used to help sell the drug. This kind of labeling comes in all different shapes and sizes from brochures and booklets, videotapes, refrigerator magnets, cups and other giveaways to virtually anything else where a pharmaceutical company tries to convey a message about its drugs. There are different levels of promotional labeling, and for example a reminder advertisement is intended merely to convey the brand name. A full discussion of the contours and scope of promotional labeling is well beyond on this book, but suffice it to say that apps and other software used to convey information about a prescription drug will typically be at least regulated as drug labeling. As such, it will be regulated, which may include, at a minimum, providing full prescribing information and perhaps need to be filed with FDA at time of first use.

3. Medical device.

Yes, I said a medical device. In chapter 2, I explained the medical device definition ad nauseum, and I don't want to go through all that again. Basically software, if intended for a medical purpose in the treatment or diagnosis of disease, can be a medical device. Let's look at the three basic categories covered in chapter 2.

a. **FDA regulated.** The main possibility for FDA regulation would seem to come in the category of CDS. I say this because many of the pharmaceutical apps with which I am familiar exist in order to give either professionals or patients a better understanding of how to determine if, when, how and in what dosage to take the drugs. I will get into this more below.

b. **Enforcement discretion.** Here the guidance contains some good news with regard to three different kinds of pharmaceutical apps.

   i. **Medication reminders.** Even though medication reminders have been explicitly regulated for quite some time, the guidance seems to overrule 21 CFR section 890.5050 to declare that the medication reminder intended to help the patient adhere to a predetermined medication dosage schedule would fall in the enforcement discretion category.

   ii. **Medication trackers.** FDA also indicates that an app used by a patient to track drug intake times would likewise fall within enforcement discretion.

   iii. **Drug interaction lookup tools.** Similarly, FDA indicates that apps used for drug-drug interaction or drug-allergy lookup tools likewise fall in enforcement discretion.

c. **Unregulated.** In this category, FDA put apps used for shopping for drugs – apps that might help with price comparisons and pharmacy location.

Further, on May 18, 2012 Dr. Shuren of FDA gave a speech at a Capitol Hill briefing where he revealed a little bit of their thinking. In his speech, Dr. Shuren explained that certain low risk CDS would likely not be regulated, and in addition to some of the items already mentioned, he included IV drug dose calculators (e.g., for calculating drip rates). Because it was a speech, we don't have much detail on specifically the scope of those categories. I'm wondering whether the IV calculator was not included in the MMA guidance because it will be addressed in the upcoming CDS guidance.

4. Combination products.

This category only applies if the app first is a medical device. If that's true, and if the app cross-references a drug to be used with the app, and if likewise the drug cross-references the app to be used together, that creates what is called a combination product. Below I'll give some examples of combination products, but for the moment it is simply important to understand that if an app and the drug together constitute a combination product, that means the FDA regulatory process gets a bit more complex. Literally it means that two different centers at FDA get involved in regulating the product, the drug people and the device people. FDA has put in place some procedures for trying to improve the coordination of the reviews between those two centers, but it is not without its challenges.

Okay, that's the background. Now let's get to the interesting stuff: the apps. The easiest way to organize this part of the discussion is to divide the apps between those for professionals and those for patients.

Apps for healthcare professionals

There are a ton of different apps for professionals that relate to pharmaceuticals, and I thought I would just pick a few of the more common categories to discuss.

1. Drug labeling

I'll go out on a limb and say that a drug labeling app ordinarily would fall into the regulatory category for "drug labeling." If an app is an electronic version of the approved drug labeling, the FDA requirements for drug labeling apply, including, for certain products, submission to FDA that the time of first use, and all the other rules around the content itself. For the most part, FDA doesn't allow manufacturers to mess around with the package insert, and there are many, many restrictions on promotional labeling. The good news is drug labeling apps generally should not be medical devices. The final MMA guidance says FDA does not regulate mobile apps that are electronic "copies" of medical textbooks, teaching aids or reference materials. These types of apps do not contain any patient-specific information. So as long as the drug labeling app doesn't add functionality like a dosage calculator or decision support, it's just drug labeling.

2. Drug dosage calculators

Here I wish I had better insight to offer you. The only thing I really know is that not all drug dosage calculators are created equally. On the one hand, Dr. Shuren in his speech called out IV drug dose calculators as likely to be unregulated. That's terrific, but the topic was conspicuously omitted from the final guidance. Further, in September 2011, in a speech on clinical decision support software, the agency identified radiation dose calculators and software used to determine chemotherapy as high risk CDS. Further, as stated in the draft MMA guidance, "the FDA has previously classified software that calculates a drug dose based on a patients height, weight, mass, and other patient-specific information as a "Drug Dose Calculator" under 21 CFR 868.1890." That

Diagram 1. Possible Regulatory Categories for Patient Apps

Function	Description	Regulatory Implications
Communication	Apps allow parties to: • Communicate at will • Synch and transmit data and documentation (CRFs, drug logs, etc.) • Share notes and calendars • Schedule appointments	Electronic Records, Electronic Signatures (21 CFR Part 11) Investigator record keeping and record retention (21 CFR Part 312.62) Protection of Human Subjects (21 CFR Part 50)
Management	Apps can provide monitors and investigators with: • To-do lists and other guides to trial rules and management • Audit trails through data and time stamping	Electronic Records, Electronic Signatures Investigator record keeping and record retention
Tracking	Apps can assist investigators in tracking tasks by: • Creating forms (e.g., screening and enrollment, drug regimens, ordering supplies, etc.) • Printing labels and handling information for biological samples	Electronic Records, Electronic Signatures Protection of Human Subjects cGMP (21 CFR Parts 210 and 211)
Data Collection	Apps prompt patients to record required clinical data and information in prescribed, common, electronic formats. • Enables quick, timely and easy transmission of data to central repository for analysis, reaction and trial adjustment. • Can fulfill compliance req.	Electronic Records, Electronic Signatures Protection of Human Subjects
Storage	Store a variety of trial documents on investigators' mobile devices for easy reference, including: • Protocols and potential violations • Clinical practice tutorials • Rules for sample handling • Inclusion/exclusion criteria • Annotated CRF templates	Electronic Records, Electronic Signatures Investigator record keeping and record retention

classification includes mostly insulin calculators, and places them in class II, which is for moderate risk devices that typically require premarket clearance from FDA. But in the final guidance, the topic was completely omitted. So basically I don't know what to tell you except some are regulated and some aren't. Hopefully the CDS guidance will address this issue.

3. Drug/drug interactions

The final guidance explains that most apps or other software that look for drug/drug interactions will not be regulated under the agency's enforcement discretion. We do not have a lot of details on that, so we will have to play that one by ear.

4. Decision support apps

In chapter 3 I explain FDA's approach to decision support software. We need to wait and see what FDA publishes as a draft hopefully in January 2014. All indications point to FDA taking a similar approach to the one they took with mobile apps where they stratified the types of software based on risk and proposed only to regulate the riskiest. As to where they draw that line, that will be the interesting part.

5. Clinical trial management

As I understand it, there are a whole slew of apps being developed for many different functionalities for drug clinical trials. To create the chart featured on the previou spage, I borrowed the categorization of these apps that was developed in, "Opportunities: Advancing The Pharmaceutical Industry Through Mobile Technologies, An ArcStream Solutions Whitepaper." Frankly, all of the functionalities have potentially applicable FDA requirements. FDA does offer a specific bit of insight in its recent mobile medical app guidance. In particular, FDA observes "Mobile apps used for data collection in clinical studies (such as electronic Patient Reported Outcomes (ePRO) apps) are not considered on its own a mobile medical app. However, manufacturers and users of this type of mobile app should see FDA's draft guidance related to use of computers in clinical trials, 'Electronic Source Data in Clinical Investigations,' 44 issued on November 20, 2012."

6. Adverse event data management

Frankly, no one should accuse FDA of not being hip. Not only are they making major forays into social media – you can look at their Flickr page and see pictures of all the lovely items that are being recalled – but they've also developed their own app. In April 2013, FDA announced the availability of its new MedWatcher Mobile App. MedWatcher "allows individuals to submit voluntary reports of serious medical device problems to the FDA using a smart phone or tablet. The app makes it easier and faster for healthcare professionals, patients and caregivers to send voluntary reports of medical device problems to the FDA, compared to the traditional reporting methods - mail, phone or online. The MedWatcher app allows users to upload photographs of medical devices, which can help identify visible problems with the device, such as breakage or corrosion." Actually that sounds pretty cool. I wonder if it's a medical device. Makes you wonder who would regulate it?

7. EHR functionality

FDA has said over and over again that it is using its enforcement discretion to not regulate EHRs. In the final guidance, FDA goes a step further to say that they will not regulate those apps that allow access to EHRs. That seems clear. The ambiguities arise when an app goes beyond the functionality of merely storing and retrieving data entered manually based on a healthcare professional's observations. For example, a software app that stores data from a medical device is itself a medical device, and goes under the name of medical device data system, or MDDS. Further, functionality that goes beyond mere storage and retrieval to add an analytical piece can be CDS. So in the future it will be interesting to see how broadly or narrowly FDA interprets this category.

It's hard to make any generalities regarding these apps to be used by healthcare professionals, but certainly some of them address uses that carry with them much risk, but on the other hand by definition they involve a healthcare professional trained in the subject matter. This area should be significantly clarified when FDA publishes its guidance on CDS, perhaps early in 2014.

Apps for patients

Usually apps for patients address less important subjects, but on the other hand involve people who may have very little training or expertise in the task at hand. Balancing those out, it seems as though these apps present a wide range of risk. Some of the apps discussed above can be targeted at patients, for example CDS apps that help patients make self-diagnosis or therapeutic decisions. I won't repeat any of those topics here. Instead I'll go through a few apps that are uniquely tailored to patients.

1. Public toilet finders

I'm over 50, so I really like the sound of this app. Pfizer cleverly developed this app where the user community can note the location of bathrooms and rate them based on cleanliness and other factors. Pfizer launched the app for Israel, where I understand it can be very difficult to find a public restroom. Why Pfizer? I suppose it might have something to do with the fact that they have a drug for overactive bladder. So if this app were introduced into the United States, which it was not, the question would be whether the app constituted promotional labeling for the associated drug. Sometimes the connection between the drug and the supposed labeling can be pretty remote.

2. Drug reminders

There are many different apps that provide drug reminder functionality, and the functionality can be based on different technologies. Some can be just a manual programming an app to alarm at a given time, while others might be reminders sent by the health professional. In any event, if they're like an alarm clock that simply reminds you that it's time to do something, that's pretty low risk, and as explained above, the final guidance put these in the enforcement discretion category if they simply alert the user to take medicine at a preset time. If the app is branded to work with a particular drug, it's pretty easy to fall into the drug labeling category.

3. Drug tracking logs

Compliance with medication regimens is a big issue for a lot of patients, and doctors want as much objective evidence as they can obtain. So it can be quite useful for patients to keep track of what drugs they take and when. As explained above, simple apps used for recording when drugs are taken fall into the enforcement discretion category. If the apps get more elaborate than that, we are into a gray area.

4. Smart Pill Apps

By now most people are well aware of the ability to use technology to very precisely measure the exact time a pill is ingested, for purposes of tracking drug compliance. It should come as no surprise that the software used to manage that technology will at least be a medical device, if not also in some cases part of a combination product.

5. Apps That Are a Condition of Drug Sale

Public health officials have long been trying to figure out ways to improve medication adherence. For a variety of reasons, people just don't take their medicine. Sometimes it's because the regimen for taking the medicine is pretty darn complicated, and sometimes it's because people just don't want the hassle and the cost of getting the prescription in the first place. FDA believes apps can help with that. Apps that use what would amount to CDS functionality can help people decide whether they need medications for certain common and chronic diseases such as high cholesterol or high blood pressure. Further, as discussed above, apps can help instruct people on how to properly take their medications. There is so much potential here that FDA is actually thinking about switching certain common medications for chronic diseases from prescription status to over-the-counter,

Diagram 2. Possible Regulatory Categories for Patient Apps

Patient Apps	Unregulated	Enforcement Discretion	Drug Labeling	Medical Device	Combination Product
Public toilet finders	✓		✓		
Drug labeling			✓		
Drug dosage calculators		✓	✓	✓	
Drug reminders		✓	✓		
Drug tracking logs		✓	✓		
Drug compliance measures				✓	✓
Decision support apps, condition of drug sales			✓	✓	✓

but on the condition that the patient makes use of the software. In FDA's early thinking, the software might be available at the pharmacy or through some other means. FDA held a hearing on this topic on March 22, 2012, and sought comments. From a regulatory standpoint, software used in this manner may very well constitute either drug labeling or a medical device, for example CDS. If it is CDS, it's quite likely that the drug and device pair would be considered a combination product.

This is a lot of information, so I thought I would summarize it in the following chart showing the possible regulatory categories for these types of patient apps.

Conclusion

The possibilities for using apps to improve the delivery of pharmaceutical care seems almost endless. The mobile medical app guidance was a positive step forward in that it clearly placed in enforcement discretion several popular categories of pharmaceutical apps. Unfortunately, some of the more important uses of apps were not addressed, and hopefully will be the focus of the CDS proposal yet to come from FDA.

Up to this point in the book, I've mostly focused on whether or not an app or a piece of hardware is regulated by FDA. Now I'm going to shift gears and start to address, for software and hardware that is regulated, the FDA requirements that would apply. At a high level, those requirements include getting clearance or approval from FDA, manufacturing the product according to the quality system requirements, reporting adverse events, and registering your manufacturing facility. I'll take those one by one.

Premarket clearance or approval

In contrast to components that are simply sold to another manufacturer, medical devices and accessories sold to end users may require some form of premarket clearance or approval. Once you know you have an FDA-regulated device (software or hardware) or an accessory, here's how you figure out if clearance is required:

Step one

Figure out the most appropriate classification for your product.

There is a bit of both art and science to this. FDA has published about 1,700 classification regulations. Each of those regulations has a description or "identification" of the types of devices covered by that regulation. FDA has a searchable database of these regulations accessible through their website. Some hardware and software are so important that FDA has separately classified them, and you can find them directly through searching. The regulations are organized by clinical application so all of the orthopedic devices, for example, are in one part of the regulations. You might get lucky and find one that directly describes your product. A quick search of the regulations revealed that the word "computer" appears in 225 regulations, "software" in 431 and "network" in 43. There is, for example, a classification for remote medication management systems in 21 CFR 880.6315.

As of the publication of this book, FDA has cleared over 100 apps. I keep a list of them, and if you are in this industry, you ought to as well. FDA has started keeping a webpage with example mobile apps the agency has cleared, but their list is incomplete. It's just examples. Knowing the range of what FDA is clearing is important because if someone else has already gotten the clearance for a similar type app, that will give you a roadmap for how to classify your product.

If you can't find a classification that directly describes your product, perhaps it's because FDA considers your product to be merely an accessory to a "parent" device. I'll give you an example. In 2009 FDA cleared an updated version of the Polytel glucose meter accessory, which is a small module that plugs into the port of a glucose meter, receives data from the meter and transfers it wirelessly to an Internet capable communication device like a mobile phone or an APT. In clearing the device, FDA agreed with its classification in 21 CFR 862.1345, which covers all glucose test systems, including the "parent" glucose meters.

Step two

Read the second half of the classification regulation to see how FDA regulates that particular article.

FDA assigns each product into one of three classifications, cleverly called class I, II and III. Class I devices represent the least risk, while class III represent the greatest. Associated with those classifications are specific regulatory requirements. Many class I devices will be exempt from premarket clearance, and some products will be exempt from other regulatory requirements that I'll describe in a minute. Some class I and most class II devices require filing a premarket notification (or 510(k)) with FDA. These submissions are manageable documents that compare the new device to those lawfully on the market. The specific data requirements are discussed below.

The highest risk devices – class III – usually require premarket approval (PMA) from FDA, which can cost hundreds of thousands of dollars if not millions. Most apps will not be in that classification, unless they are an accessory to a high risk device. If your device is classified as an accessory, it is subject to all of the regulatory requirements applicable to the parent device.

Step three

Research the requirements.

FDA has published scads of guidance documents on its website that cover many different aspects of the technologies they regulate. It's important you find all of these so-called "special controls" because you'll need to make sure that your product complies with those technical standards.

A few examples include:

- Guidance for Industry – Wireless Medical Telemetry Risks and Recommendations

- Guidance for Industry, FDA Reviewers and Compliance on Off-The-Shelf Software Use in Medical Devices

- General Principles of Software Validation; Final Guidance for Industry and FDA Staff

- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices

- Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software

- Device-specific guidance (e.g. glucose monitors)

**Step four**

Consider your options.

Even once you know how a device is classified and the specific regulatory requirements, you may well have options for how you get marketing clearance. Let's say your device is in class II, and some sort of premarket notification or so-called 510(k) is required. 510(k)s come in lots of different flavors, including traditional, special and abbreviated. For some, as an alternative to filing at the FDA, you can seek to have your device reviewed by an independent third-party who then certifies its review to the FDA. Going through each of those options is beyond the scope of this article, but it's important to understand that you have options. I have tried to illustrate the major options in Diagram 1 below.

Step five

Determine the type of evidence needed for FDA clearance.

Even more choices need to be made here. The amount and type of data needed to secure clearance depends directly on the types of claims you want to make. In many cases, as explained in chapter 1, you might have the option to merely make a "tool" claim: a claim that your product simply does a specific function. In the accessory example I gave above regarding the Polytel product, the company makes a tool claim that its article merely connects one medical device to the Internet.

Diagram 1. Some major pathways to market for IT devices
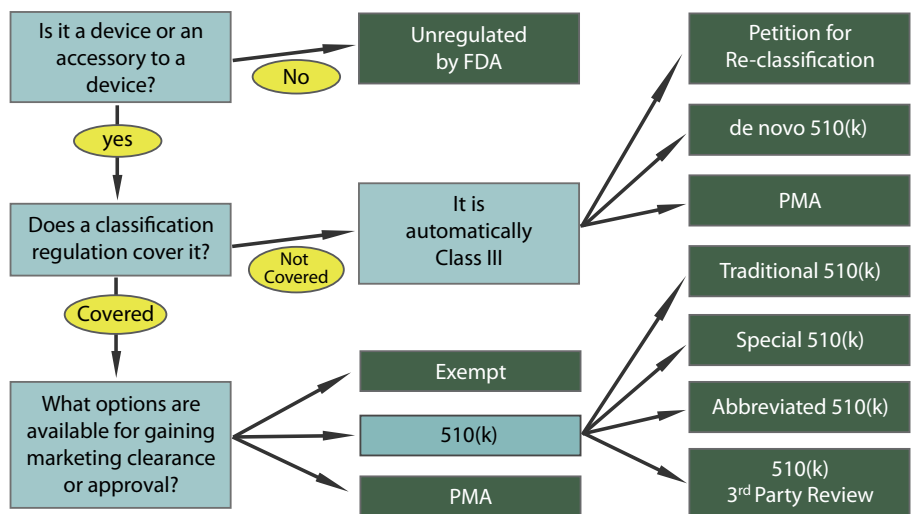
You might prefer to make an outcome type claim: a claim that your device will help treat or diagnose a specific disease or condition. For example: "Using this device to transmit your blood glucose readings to your physician typically allows for better control of diabetes and will help you wean yourself of dependency on insulin."

The types of data you need to provide FDA will depend on which type of claim you make and indeed on the exact wording of the claim. Typically, you could support a tool type claim with bench testing or other non-clinical evaluation. Basically you need to prove that your tool works. If you choose to make outcome based claims, you'll need to prove that the device indeed achieves those outcomes. That's much harder, and requires testing in a clinical setting.

If you are following the 510(k) pathway, the fundamental standard is whether your device is substantially equivalent to other lawful devices. So most submissions follow a comparative format where the submitter compares his device to others in the marketplace.

With regard to the type of evidence required, there are many open questions at this point. For example, what does an app developer need to show with regard to the suitability of the underlying mobile platform?

Apps where the classification is not clear

Let's say you try to use my five-step process above, but you get stuck on the very first step. You are stuck because there does not seem to be clear FDA classification for your software. What do you do? Unfortunately, you are in a gray area, and you are not alone.

The FDA's final mobile medical app guidance starts us well down the path of understanding which apps are regulated, and which are not. But it doesn't address, even slightly, the question of when a particular app subject to FDA oversight must be cleared prior to marketing. I'm afraid we will have to wait further for the answer to that.

What are software companies supposed to do in the meantime? What fits within this regulated but exempt from premarket notification category? The best anyone can do right now is look at a variety of risk factors to figure out which side of the premarket clearance line again an app falls. Based on FDA comments and actions over the last 20 years, I would propose the following list of factors be considered:

- Whether the app is intended or designed to provide any real time, active, or online patient monitoring functions.

- The capability to display, create, or detect alarm conditions, or actually sound an alarm, or the capability to create alarms that are not already present from the connected medical devices.

- The seriousness of the particular disease or condition which the app is intended to diagnose, cure, mitigate, treat or prevent and how the software contributes to the user's decision-making for diagnosis or clinical management of the patient. Example: Is the app designed to call attention to imminent hazard conditions or does the app provide long-term storage for diagnostic information?

- The amount of time available before using the information provided by the app, i.e., the time until a therapeutic or additional diagnostic intervention must be implemented by the health care provider after the results of the software have been provided. Example: app provides an EKG reading and analysis package whose output is "SHOCK NOW" or does it provide a proposed reading with notation that the rhythm itself should be checked?

- Whether the data output is provided or manipulated in a novel or non-traditional manner, or whether decision trees within the app depart from customary use. Example: Does the app's algorithms, parameters, internal decision trees, or other output manipulations depart from customary use or traditional data presentation?

- Whether the app provides individualized patient care recommendations, e.g., whether app suggests or recommends specific treatment for a specific patient. Example: How specific is the app's output with regard to particular patients? Is the app providing general advice or information, like a library, article, or textbook, or is the app designed to provide a specific recommendation for a specific patient whose individual data have been entered as input?

Apps where the classification is not clear *(continued...)*

- Whether the mechanism by which the app arrives at a decision is hidden or transparent, i.e., does the product use undisclosed parameters or internal decision trees or other mechanisms that are not available for review by the health care professional. Example: How transparent is the app's manipulation to the intended user community? Included in transparency is the extent to which limitations on the process are made known to the user, such as data contraction, deletion, editing, or simplification. Also, how are comparisons made to normative databases and how are normative databases created?

In the past, I have validated that with people at FDA. That said, this is an evolving area and we will have to continue to watch FDA to see what they do in the absence of written guidance. My hope is that we might get written guidance, but I wouldn't count on it very soon.

Apps requiring validation

A 510(k) submission for an app will need to be based on an appropriate level of validation for the software. If the app is an accessory, the parent device determines the level of validation required. If not an accessory, to determine the validation required, you will need to figure out whether FDA classifies the software as "major", "moderate" or "minor" "level of concern."

- It's major if the software directly affects the patient or anyone else such that a failure could result in death or serious injury

- It's moderate if the injuries would be nonserious

- An app's risk and the associated "level" determine:

    - the depth and degree of hazard analysis and mitigation that is expected

    - the depth and degree of documentation

    - what needs to be submitted vs. merely documented

    - the rigor applied to the verification and validation of the software

    - the degree to which the device manufacturer's software development process is scrutinized

In addition to the premarket clearance or approval question, devices must comply with other FDA requirements, as described in the next section.

Quality system requirements

The other big hurdle is ensuring compliance with the quality system regulations. As the name suggests, these requirements are focused on ensuring manufacturers produce quality products commensurate with the risks associated with using the device. So the exact nature of the quality system will depend on the intended use of the article. For companies that are ISO 13485 certified, becoming compliant with the quality system regulations is mostly a matter of creating documentation systems so that you can prove your compliance. More substantial changes are required if the company is only ISO 9001 certified.

In its final mobile medical app guidance, FDA asserts that the majority of the quality system requirements "are consistent with commonly used and accepted good software development practices, such as those from the Institute of Electrical and Electronics Engineers' (IEEE), Software Engineering Body of Knowledge (SWEBOK), and Carnegie Mellon Software Engineering Institute's Capability Maturity Model Integration (CMMI) methods."

One of the most frequent questions I get is how to comply with the full range of quality system requirements when some of them seem applicable to hardware but not software. In its final guidance, FDA agrees that "Certain portions of the QS regulation that apply to medical device hardware (such as the production and process controls outlined in 21 CFR 820.70) may not clearly apply to mobile medical apps." In these cases, a company need only comply with the requirements that apply to the particular operations in which the company engages. Section 820.1 of the quality system regulations states that "if a manufacturer engages in only some operations subject to the requirements in this part, and not in others, that manufacturer need only comply with those requirements applicable to the operations in which it is engaged."

Quality systems requirements *(continued...)*

These quality system regulations apply cradle-to-grave, so the minute you begin the design process, the design controls must be observed. Design controls specify the process used and the records to be created during the design, development, and manufacturing scaleup of a device. They extend all the way to postmarket issues such as complaint handling, risk management, and failure analysis and feedback to the design and manufacturing organizations.

In the medical device world, component suppliers are exempt from these regulatory requirements.

Being exempt from the requirements doesn't mean the components need not be high quality, but rather it means that the finished device manufacturer has the regulatory burden of assuring the quality of the components it uses. While this could mean incoming inspections of raw materials, components and subassemblies, it more often means that a device manufacturer must apply the necessary controls on a supplier-by-supplier basis to make sure that any controls the supplier is missing, the device manufacturer provides.

Reporting adverse events and product fixes

As kind of a belt and suspenders, in addition to requiring premarket review of the product and imposing quality system requirements, FDA expects companies to be vigilant for reports of people getting hurt or products malfunctioning. In some cases those incidents might rise to the level of needing to be reported to FDA. These so-called Medical Device Reports are time sensitive (an assessment is due in a matter of days or weeks), and require the company to have in place systems for reviewing all relevant incoming information to assess the potential of each report to be categorized as an Adverse Event.

The basic trigger for the obligation to file the report is "whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device they market may have caused or contributed to a death or serious injury, or has malfunctioned and the device or a similar device that they market would be likely to cause or contribute to a reportable death or serious injury if the malfunction were to recur." Unfortunately, that broad standard requires a lot of interpretation by the manufacturer.

If the company decides to take corrective action, in some cases the company needs to notify FDA. According to the mobile medical app guidance, "mobile medical app manufacturers are required to promptly report, within 10 working days from the time the correction is initiated, to the FDA certain actions concerning device corrections and removals for the mobile medical app. Specifically, mobile medical app manufacturers are required to report to FDA any corrections made to a mobile medical app to reduce a risk to health posed by the mobile medical app or to remedy a violation of the FD&C Act caused by the mobile medical app which may present a risk to health.

The reporting requirement does not extend to all modifications to mobile medical apps. For example, certain actions that would improve the quality of a mobile medical app but that would not reduce a risk to health posed by the mobile medical app or remedy a violation of the FD&C Act are not required to be reported under 21 CFR 806.1(b)39. If there is not a "risk to health" involved, a report to FDA is not required, but the mobile medical app manufacturer must keep a record of the correction. An example of such action taken by the manufacturer could be changes made to correct a defect that creates a nuisance for the user but does not present a risk to the health of the user or patient."

It all sounds kind of painful, and it does require having a process in place and training your people to follow it. Once it's in place, however, most companies find it to be manageable.

Testing your app to make sure it works

It's quite common in the app world for developers to release early, beta versions of their apps in order to get feedback from users. That makes sense, and it's a very worthwhile exercise. But in the world of medical devices, releasing a regulated app for user experience creates risk. By definition, FDA only regulates apps that serve a medical purpose, where if the app doesn't work someone could get hurt or at least suffer from an ineffective product.

That's why the FDA has specific requirements for investigating whether early versions of medical devices work properly. These requirements can be found in FDA's Investigational Device Exemption regulations. If an app is what FDA would refer to as "a nonsignificant risk device" (and most apps will indeed fall into that category), the requirements are fairly modest. The two biggest requirements are that you conduct your evaluation under the oversight of a healthcare institution's Institutional Review Board, or IRB, and that you ensure that you have informed consent from any patient whose information might be involved in the study (subject to a few exceptions).

Other regulatory requirements

FDA has a variety of other requirements that may apply, including such things as registering manufacturing facilities, listing the products manufactured, export and import restrictions, and labeling and advertising requirements. FDA also has a variety of requirements that apply to post-market distribution to ensure that products can be identified and traced back. These requirements are pretty boring and also typically fairly straightforward, so I would refer you to the FDA's website for the details.

Conclusion

Those are the basic FDA requirements that apply to bringing an app to market in the mHealth field. Undoubtedly, to those not accustomed to the FDA regulated world, those hurdles might seem high. In the next chapter, we'll tackle the benefits and burdens of going through those admittedly rigorous FDA requirements from a business standpoint. In particular we'll focus on the competitive advantages that can be derived from entering the regulated space, weighed against the cost of achieving those advantages.

There is no doubt that these requirements can be quite burdensome. But to state the obvious, thousands of companies have found it possible and worthwhile to enter the medical device realm.
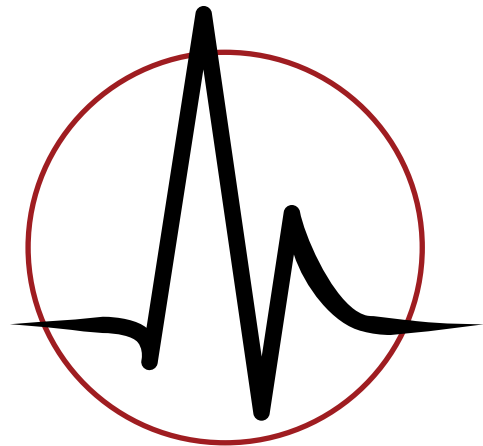
At the risk of insulting my new friends in Silicon Valley, I submit that traditionally-unregulated IT companies may want to adopt a different view of federal regulation. Over the last couple years, I've had the opportunity to observe firsthand the culture clash as free-spirited, libertarian Silicon Valley meets Rockville, Maryland, the home of the decidedly more buttoned-down U.S. Food & Drug Administration. Rather than fleeing in fear of the federal bureaucracy, I would argue that at least some IT companies should consider embracing federal regulators. Well, maybe start with at least shaking hands.

With the basic framework behind us, in this chapter we will explore the burdens and benefits of entering FDA regulated territory. Yes, I said benefits.

It's okay to consider the benefits of federal regulation limiting competition

As I've learned recently working with Silicon Valley companies, IT companies generally seem to love nothing more than a good, competitive, bare-knuckled fight with their competitors, and abhor the first hint of artificial restraints on competition, especially those from the government. In the IT industry, cooperation around the development of industry standards sets the rules of engagement for the market, and then everyone competes intensely based on those rules and execution of their business plan. Innovation can flourish, with upstarts appearing and challenging big, established companies' dominance of any particular portion of the business. The big companies accept it because they are moving aggressively too; adjacent markets can be pretty attractive if it appears there is money to be made by offering a faster, better, cheaper alternative to the current market leaders. The goal of unrestricted competition is great, and undoubtedly benefits customers in terms of producing products that they want at the best possible prices.

However, as IT companies consider entering the health market, they need to appreciate the differences. In traditional IT and telecommunications markets, if a product doesn't work, such as a server crashing, people can become really annoyed when they can't check their email from their mobile phone every second. Inconvenient and somewhat costly, for sure, but all might be forgiven once the server is back up and running. If it happens with any frequency, the company that produced the technology will get a reputation for poor reliability, and may go out of business.

But companies in the health space that produce medical devices, using many of the same components as what goes into the email server, face a much different problem set. If their product doesn't work consistently and reliably, they can hurt people, or even cause their deaths. So we don't, and can't, rely simply on competition to weed out the good from the bad. Instead, the government regulates them.

That's more than just a legal framework: that's a philosophy for how the marketplace in health works. You can think of federal regulation as just a bunch of health and safety laws that prescriptively require that you do this and not do that, but it's more accurate to think about federal regulation as saying we only want companies willing to invest the significant resources required to get the product right the first time they enter the market, and to take the risk of failure to meet high standards of safety and effectiveness.
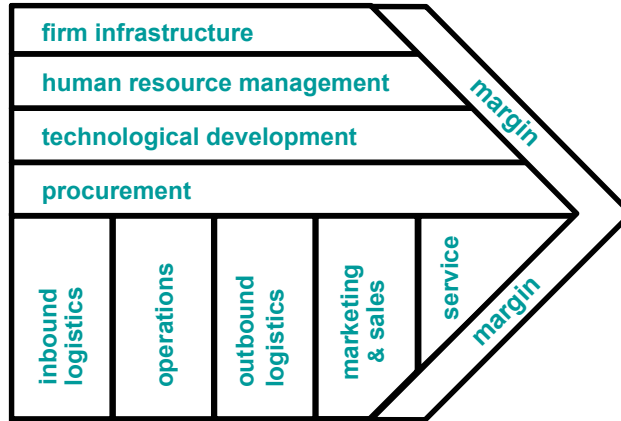
To put it in business school terms, federal regulation amounts to a significant barrier to entry for the health markets. And that is quite deliberate. FDA law means "don't enter this business unless you're willing to do it right." And, as classic economic theory suggests, companies that are willing and able to invest the additional resources required and take greater risk get rewarded with greater return. That's as it should be, to protect the public from unsafe protects and to further the public health by encouraging companies to invest in medical innovation. In that later regard, FDA law rewards innovation in a manner similar to the patent laws. We simply do not want all companies to be able to make health care products. We choose to impose much higher standards in that field, and for companies willing and able to meet those standards we allow them to earn a potentially higher return.

Benefits and Burdens of FDA Regulation

Let's bring it down from the 100,000 ft. view and get more specific about how entering FDA-regulated space affects both the company's cost structure and opportunities to earn a higher return. For a specific company, this would require a fairly detailed analysis, but let me provide you with an overview here. To conduct this analysis, I've chosen the competitive strategy framework developed by Prof. Michael Porter at the Harvard Business School. It's familiar to many and reasonably well-suited to assessing the impact of a regulatory scheme on a business. In a pair of roughly 500 page books, Prof. Porter details an entire methodology for considering a company's strategic options in light of the markets and business environment in which they operate. I'll focus on two tools he uses in his analysis.

FDA regulatory impact on the value chain

In his value chain tool, Prof. Porter focuses on the individual firm, and how the firm creates value. In Diagram 1 below, Prof. Porter shows conceptually along the bottom the sequence of steps necessary to produce a product, and in the rows at the top the overhead necessary for the firm to function.

The specific activities that the company selects to engage in directly determine its profit margin. Certain activities are high-value and produce higher margins, while others not surprisingly are lower. A firm's competitive advantage derives from its ability to select and execute the most highly value-added functions.

Much more could be said, but let's move on to look at how FDA regulation impacts the value chain. To convey this impact at a high-level, I've drawn the intensity map included as Diagram 2 below. To understand an intensity map, think National Geographic magazine and a map showing population density through colors. I've borrowed that approach here to show the intensity of FDA regulation on each of the different elements of the value chain analysis.

This is a bit subjective, so others might disagree. I also made an assumption that the company has a basic ISO 9001 type quality system already.

Here's how I came up with the intensities depicted.

Diagram 1. Value Chain Activities

source: Michael Porter, competitive advantage

FDA requirements will be very similar to ISO systems

FDA requirements will be more stringent

FDA requirements will be far more demanding than ISO

Diagram 2. FDA Impact on Value Chain Activities

FDA Approval. One of the most challenging steps of FDA regulation is securing premarket clearance or approval; there is no "beta testing" allowed in healthcare. You can't offer someone the chance to sign up for a discount if they help you test the product first to see if it works as you intended. For an innovative device, that requires substantial effort to design and then test the device to ensure that it meets its intended use safely and effectively, and perhaps highly regulated clinical trials. In the diagram, I suggest that the effects of this requirement are felt as a part of validation and design controls, as well as in the regulation of the claims that can be made.

Marketing Regulation. In addition to FDA rules regarding securing approval of specific claims, other federal and state regulators impose stringent requirements on the marketing function. Thus federal regulation is perhaps most intensely felt in the marketing function of the company. Again, this will feel quite foreign in Silicon Valley, where battles between "Marketectures" wage almost daily.

FDA regulatory impact on the value chain *(continued...)*

In the post-market servicing function, companies in the medical device field must adopt systems designed to vigilantly watch for and report any problems, and take perhaps significant corrective action when problems arise.

In the quality system area, companies that are certified to ISO standards will have the most new work to do in the design control and validation areas.

In the modest impact category, the quality system requirements will require that the device manufacturer take greater measures to assure the quality of inputs being supplied. This will include periodic auditing of suppliers to ensure their systems are robust enough. The wide spread decision to outsource and off-shore customer service functions, prevalent in IT, would have to be considered in light of these requirements. They could still be done, but doing so could take longer, be more involved, and actually end up costing more than keeping it in-house.

The changes necessary in the actual production of the products are perhaps least burdensome for a company that is ISO compliant. In general, all of those measures:

- Impose added cost.

- Lengthen lead times in product development.

- Add complexity.

- Can be difficult to implement from a cultural standpoint for a company unaccustomed to that environment because they require discipline and rigor.

- And of course multiply the paperwork.

In their analysis of the opportunity health markets present, many companies go no further than this. But this is exactly where some companies should persevere in their assessments, and consider the dynamics of the medical device market place.

FDA regulatory impact on competitive forces

In Diagram 3 below, Prof. Porter depicts the five forces that in his model drive the industry dynamics. Those five forces include:

1. **Threat that new companies will enter the market**

2. **Threat that new products will become substitutes for marketed products**

3. **Bargaining power of suppliers**

4. **Bargaining power of customers**

5. **Competitive rivalry within the industry itself**

**Diagram 3. Five forces: impact of FDA regulation**

FDA regulatory impact on competitive forces *(continued...)*

The degrees of those threats and powers determine the ability of the company to earn a profit. With regard to the threat that new companies will enter the market, Prof. Porter identifies several barriers to entry, and one of them is government policy or regulation.

Assessing the five competitive forces, in some cases the analysis reveals some interesting opportunities. In diagram 3, again using an intensity map where darker yellow represents more competition, I suggest where I perceive the greatest sources of competition to reside for the medical device industry generally.

In the industries regulated by FDA, the greatest competition tends to be from established firms in the same industry. This is true for the simple reason that entering the regulated industry often requires a very significant investment to create the innovations and establish the manufacturing systems necessary to produce them, as well as considerable lead time to get through the FDA clearance or approval process. Thus the threat of new entrants is lower than the competition created by existing firms that have well-established systems in place for bringing new regulated products to market. Indeed a company's ability to cope with the regulated environment becomes a key asset, determining competitive advantage.

There is an important limitation to this, however. Companies that follow the premarket clearance route, if they don't have patent or other intellectual property protection for their products, might find that other established device companies can quickly follow them through the FDA clearance process. This is sometimes referred to as a first mover disadvantage. Further, the laws administered by the FDA do not create any private cause of action that an individual company can use to force competitors to abide by the law. FDA is solely responsible for enforcement of its laws, and if the agency isn't paying attention or simply doesn't have the needed resources, less reputable competitors might get away with taking shortcuts.
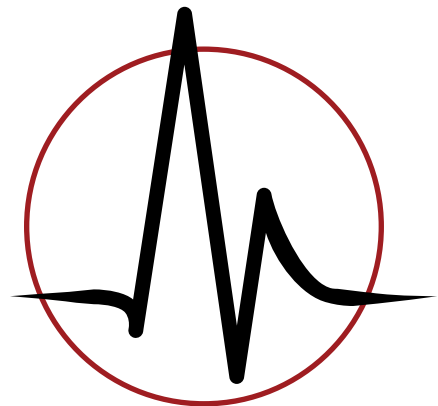
Most people know the difference between tax avoidance and tax evasion. Tax avoidance is the lawful planning of such things as charitable contributions to minimize taxes, while tax evasion is the unlawful and usually deceitful actions taken to hide income. In this chapter, I will share some tips for the avoidance of FDA regulation, not the evasion of FDA regulation.
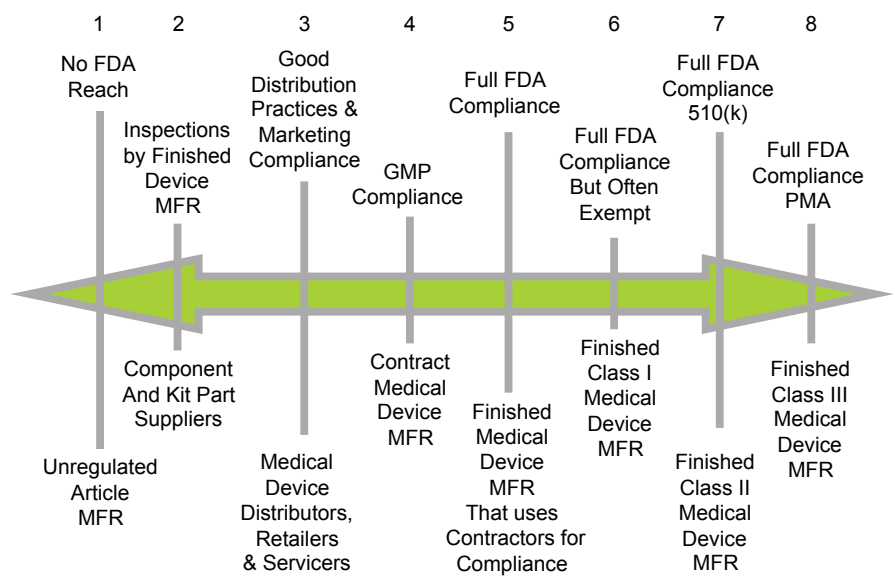
The first several chapters in this report dealt with understanding the scope and nature of FDA regulation for mHealth, and the last chapter advanced the notion that IT companies wanting to make money in health ought to consider entering the FDA-regulated zone. Nonetheless, subjecting your company to FDA regulation is not for everyone, so this chapter is designed to help those who have decided to stay out of the production of FDA-regulated apps. In particular, I explain four ways to connect to health markets, and the pluses and minuses of each such approach.

The binary misunderstanding

Some IT companies new to the health field seem to misunderstand the nature of FDA regulation, and think of it as all or nothing. In other words, a company is either a manufacturer of medical devices and subject to the full panoply of FDA requirements, or they're not and likewise are not subject to any FDA restrictions. But that's not an accurate depiction.

Instead, companies should think of FDA regulation as a continuum. Diagram 1 illustrates the two extremes and a few of the cases in between.

On the far right side, the diagram depicts the traditional manufacturer of finished medical devices that is indeed subject to

all of the FDA requirements for medical devices. Even here, though, there are different levels of FDA requirements depending on the novelty and risk associated with a particular device. As outlined in the second chapter, devices are classified into three different classifications, and the types and burdens of FDA regulations vary considerably. Class III medical devices include such things as pacemakers, embody the greatest risk and thus must meet the most demanding requirements. Class I devices include such things as tongue depressors and have very minimal FDA requirements. Indeed, most class I devices do not even need to be approved by FDA, and the quality system requirements might be very basic. Many mobile medical apps might fall into class I or class II. All of this was covered in much greater detail in the second chapter.

On the far left side, the diagram includes unregulated articles such as personal computers that contain no medical references at all and over which FDA has no regulatory authority. It's the stuff in the middle that is interesting for mHealth purposes.

The cases in the middle include, for example, companies that merely make components for others to use in manufacturing medical devices, distributors of finished product that have no control over the promotional claims or the design specifications of the device, and contract manufacturers that make finished medical devices at the direction of another company. These different functional responsibilities all have narrower sets of FDA requirements that apply to them, directly or indirectly. It's important to understand the range of possible relationships before talking about ways to reduce or avoid FDA requirements, and exactly what that means.

Diagram 1. Continuum of potential involvement in the device industry

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Four ways to connect to the health market while reducing or avoiding FDA requirements

Before I go through the four strategies, it probably goes without saying that each one is predicated on the company implementing the strategy in good faith. Anything less potentially becomes FDA law evasion, rather than avoidance.

Okay, so here they are:

Strategy 1: avoid medical devices and their accessories.

About now you're wondering whether this chapter is worth reading, but stick with me for a second, there's a more subtle and profound observation to be made. In your mind, go back to chapter 1 on intended use. I went through an example of a stick, and how it could be either a popsicle stick or a pediatric tongue depressor, depending on what claims the company chooses to make. My point is that in many cases, the design of the product does not determine its regulatory status, but rather the promotional claims determine its status. So if your company can reach its commercial objectives without medical claims, and if the product has legitimate and material nonmedical uses, you might be able to avoid FDA regulation by avoiding medical claims, for example by making very general claims.

The mobile phone itself is an example. A mobile phone can be promoted merely as a mobile phone, and no FDA compliance issues will arise. But as explained in Chapter 3 if the manufacturer of the mobile phone starts to make claims that the phone is suitable specifically for healthcare applications, the mobile phone manufacturer runs the very real risk of turning its simple phone into a regulated medical device.

Remember from the first chapter that the manufacturer might get into trouble making claims that its product is specifically intended to accompany a medical device. That may very well make the product an accessory to the medical device, which makes it a regulated device. Again, claims are pivotal in determining whether something is an accessory or not.

In the last couple years as I've been watching what's coming out of Silicon Valley, I'm seeing a tremendous number of hardware and software products that probably could be sold as unregulated articles, but where the manufacturer, possibly quite inadvertently, is making claims that would cause FDA to regulate them. FDA is stretched pretty thin these days, so they aren't watching everything coming out of the IT industry, but someday I suspect FDA will get more active in this space.

There are limits to this strategy. As I explained in the first chapter, I can't make a pacemaker, for example, and try to pass it off as a simple, generic piece of electrical equipment. In designing the pacemaker, I've done too much to make the design specific to a medical use to later disclaim that use. Remember intended use is judged by words, actions, and in some cases, inaction. If you're interested in this strategy, you ought to go back and review the first chapter of this report.

A number of startups in mHealth have come up with very innovative business plans that put them squarely in the gray area between medical and nonmedical intended uses. For example, there are companies developing strategies for remote monitoring of people, rather than their disease or condition. There are gray areas between wellness programs and disease programs where FDA needs to give industry clearer guidance. Obesity, as a disease, is often difficult to distinguish from general physical conditioning. Unfortunately, I suspect we will all need to feel our way along in the dark for the time being until the FDA releases new guidance on disease versus wellness.

Finally, to employ this strategy, the maker of the equipment must be duly diligent in avoiding making medical claims. My emphasis in that sentence is on the word diligence. That means the company needs to have some level of compliance and training systems in place to ensure, for example, that sales representatives do not go rogue. Even unauthorized sales activity can come back to haunt the company if the government decides that the company wasn't careful enough in managing its people.

Strategy 2: avoid controlling the product specifications and the claims made.

In the chapter on who FDA regulates, I explained the essence of manufacturing as controlling the specifications and controlling the claims. Most FDA requirements, including the need to obtain FDA clearance or approval and the responsibility for reporting adverse experiences, fall on the company that owns and controls the product specifications and the claims made. Because most of the risk of a medical device stems from its design and the claims made about it, whoever controls those two features has most of the FDA compliance responsibilities. So, if you don't want those responsibilities, don't own or control those two features of the device.

Some examples probably would help. In most cases, a contract manufacturer does not control the product specifications or the claims made about the product. That's true even if the contract manufacturer produces finished product and drop ships it to the ultimate purchaser on behalf of the

place supplier controls sufficient to ensure the quality of the components it uses. These controls might include, for example, periodic inspections of suppliers.

Another strategy is to supply finished medical devices to a firm that will co-package its own device with yours. From a regulatory standpoint, this is essentially the same as the component supplier scenario just discussed. Even though the article is a finished one, if it is bundled together with another product before it is sold to the end user, the company that does the bundling has responsibility for ensuring that each product in the bundle has the requisite regulatory compliance. Sometimes the supplier for the article to be bundled will undertake compliance with the FDA requirements itself, and sometimes the bundler takes that job. But because the bundler is considered to own the specifications of the bundle and whatever claims are made for the bundle, it generally has the ultimate regulatory responsibility.

Let's take, for example, again a common mobile phone, hypothetically call it a mePhone. If the mobile phone manufacturer makes no medical claims about it, the mobile phone manufacturer will have no direct FDA responsibilities. But let's say a blood glucose meter manufacturer claims, in promotional materials, "our meter will pair with the mePhone to download data for analysis on our special app." As I pointed out earlier, in FDA's eyes arguably the blood glucose meter manufacturer has made the mePhone and the app into components of its medical device system. (Personally, I think the mobile phone is just part of the environment, but that's just me.) So the blood glucose meter manufacturer may, for example, either need to prove through a risk assessment that mePhones available in the market place will remain suitable for that intended use, or need to enter into an agreement with the mePhone maker such that the two companies, through

cooperation and control, will ensure the future compatibility of the two devices. I've kept this simple but in real life these facts are usually much more complex.

I want to underscore something I said earlier: almost none of the organizations in this section are completely outside of FDA's jurisdiction. They all have some, albeit perhaps minor, FDA responsibilities. Even distributors and retailers have to ensure their promotion remains consistent with the approved labeling, and their facilities appropriately safeguard the integrity of the products. They must also cooperate in a recall. Components suppliers, while technically exempt from the quality system regulations, often must nonetheless ensure that they are not selling adulterated components for use in medical equipment.

Over the last several years, I have read a dizzying array of corporate agreements that provide for various kinds of collaborations like these between companies. Some of them are fashioned as supply agreements, while others look like contract manufacturing agreements, and yet others look like intellectual property license agreements.

As a regulatory lawyer, when I read these agreements, often I'm asked to make a judgment as to who has the FDA regulatory responsibilities. And sometimes, honestly, it just isn't clear. I've read agreements where all the specifications and promotional claims have to be mutually agreed upon between two parties. In other cases, one party maintains a general level of control over the specifications and claims, while the other party is able to exercise wide latitude within certain limits.

In those cases, where it is genuinely unclear which party has the FDA responsibilities under the regulations, I believe FDA permits the parties to specify in the agreement who has those responsibilities, so long as that division is reasonable to resolve

the gray area. So my advice: have your regulatory lawyer work closely with your corporate lawyer to make sure that your various collaboration agreements specify a reasonable – and your intended – division of labor on the regulatory compliance side.

Strategy 3: contract out the hard stuff.

Even if your company markets what is admittedly a medical device and controls the specifications and the promotional claims so that your company is clearly regulated by FDA, that doesn't mean your company itself must do the hard stuff. The regulatory work can generally be contracted out, even if the regulatory responsibility has to remain with the specification owner.

It probably won't surprise anyone to know that there are whole industries designed to conduct various responsibilities of medical device specification owners in compliance with FDA requirements. For example, there are clinical research organizations that can do all of the clinical research, soup to nuts, and one of their main selling points invariably is that they take responsibility for the FDA compliance for that function. There are regulatory consultants who can quite ably prepare premarket submissions. There are contract manufacturers who specialize in producing product under FDA quality system requirements, and there are other consultants who can help bring the specification owners' facilities up to code, so to speak. There are design organizations well-versed in conducting the design process in compliance with FDA design controls. Bottom line: if there's some feature of FDA regulatory compliance that makes you nervous, there's probably a whole industry out there quite willing to help you do it.

That said, it bears repeating that you can contract out the work but not the responsibility. If your organization is the one that controls the specifications and

the claims, it will bear ultimate responsibility for FDA compliance. As a practical matter, if you choose to contract out any of that work, it means you have the obligation to be duly diligent in selecting the right qualified firm to help you do the work, and providing reasonable oversight for the function. So the handoff isn't complete.

Strategy 4: sell a service or be a user, not a product producer.

This strategy is sometimes risky, but sometimes it can work. FDA's jurisdiction is very clear: the agency regulates products. Earlier, I discussed the need for a physical product that is the subject of FDA regulation. FDA does not regulate services, nor do they regulate the practice of medicine.

That circumstance has led some medical professionals to be able to do things that product manufacturers and sellers cannot. For example, clinical laboratories routinely develop their own clinical tests that they use with their own customers. For decades, FDA has taken a nearly hands-off approach to that practice, saying that clinical labs are sufficiently regulated under a different piece of legislation, the Clinical Laboratory Improvement Amendments of 1988. Likewise, pharmacists who are regulated under state pharmacy laws have a certain latitude to compound drugs. In these cases, FDA has decided that these are professional service businesses rather (already regulated by others) than the sellers of devices or drugs.

Conceptually, it may be possible to position certain healthcare services as services, rather than the sale of products. But be mindful that this is not simply converting outright sales to rentals, or selling software as a service. That makes no difference to FDA. Instead, the difference between a service and a product is the predominance of the human element. Services are performed by humans, whereas FDA regulates products and machinery no matter how they are provided. Further, as you might guess, if a particular operation starts to look too much like manufacturing, FDA will regulate it. My only point is that healthcare professionals have a certain latitude to provide services to their patients without FDA intrusion. We will discuss in much greater depth in chapter 11 the latitude that doctors have to provide services with apps they make for themselves.

The trade-offs

As Milton Freidman observed, there ain't no such thing as a free lunch. Each of these strategies involves trade-offs, and I've tried to depict those at a high-level in Diagram 2 below.

As with some of my other diagrams, this one reflects subjective judgments concerning the magnitude of the benefits and burdens associated with a few of the strategies. I've used blue stars to depict features where more is better, and I've used black stars to indicate attributes where less is better.

So, if we look in the column for FDA regulated articles (#8 for class III), we see my assessment that the potential profit margins are the greatest and the product life cycle length is the longest and barriers to entry are the greatest, but on the negative side internal overhead costs are the greatest. I chose to characterize product lifecycle length as good simply because it means the company has a longer time in which to recoup its investment. I realize some IT companies like the short product lifecycles because they consider speedy new product innovation to be a competitive advantage for the firm.

On the other end of the spectrum, I indicate that unregulated articles normally have much lower profit margins and shorter product lifecycles and fewer barriers to entry, but lower overhead

Diagram 2. Trade-offs

	FDA Regulated 8	Contract out tasks 5	Component supplier 2	Not regulated 1
Profit margins	★★★★★	★★★★	★★★	★★
Product life cycle length	★★★★★	★★★★★	★★★	★★
Internal over head costs	★★★★★	★★★	★★	★
Barriers to entry	★★★★★	★★★★★	★	★

The trade-offs *(continued...)*

costs. However, I'm sure everyone can think of examples where that's not true. In some cases companies are able to develop patent protection around truly novel technologies and earn tremendous profit margins over the full length of the patent life. Further, the development of those innovative products might be a tremendously high cost. But I'm treating those as the exception, not the rule. Perhaps I'm wrong, but in the consumer electronics area, it seems as though competition is fierce and technologies quickly become commoditized despite whatever patent protections might be available.

In the middle you find compromises between those two extremes. In scenario 5 where the company simply contracts out certain difficult tasks, the profit margins go down correspondingly as the costs of contracting go up, but the company still benefits from some barriers to entry and earns a comparatively better profit margin than the far right side of that table. Likewise, component suppliers often enjoy fewer barriers to entry and have comparably lower profit margins to the finished medical device manufacturers, but they also face a lower cost structure.

There is a quantitative basis for this judgment that bears noting. According to Thomson Reuters, medical equipment manufacturers enjoy an average five-year gross margin of 59%, compared with 45.8% for the S&P500. Research coming from the Deloitte Center for the Edge, which has studied the business climate for US industries over the past forty years, calculates the average return on assets (ROA) for the entire U.S. economy had fallen to almost one-quarter of its 1965 levels by 2008, while performance in the Health Care industry has run contrary to the trend. That occurred while the ROA in healthcare rose from 1.7 percent in the early 1970s to 3.8 percent in the same period, nearly doubling.

Choosing a strategy is a very complicated exercise that involves looking at these issues, plus most of the competitive issues discussed in the prior chapter. The dynamics of the marketplace and the competitive strengths of the firm itself will play major roles in any assessment of the optimal strategy. My only point here is that each strategy has its own rewards and risks.

Conclusion

This chapter is meant to give you a high-level understanding of some broad strategies for avoiding or at least reducing your company's FDA compliance obligations. Within each of these broad strategies are multiple variations that raise complexities well beyond the scope of this chapter. The last strategy, selling services or being a user of products, is complicated enough that it deserves its own chapter below.

Some technology companies are sitting on the sidelines, or just dipping their toes in the mHealth waters, out of fear of the unknown. Does FDA regulate this particular app? If we get into healthcare, will we get sued if someone breaks a finger nail using our app? Will the FTC come after us if we don't have a bunch of clinical trials to support every claim we make? Will a patient come after us if personal health information somehow gets into the wrong hands? What about the company's reputation if something goes wrong? And don't get me started if your product triggers Medicare reimbursement. In many ways, the healthcare field seems scary at first, just based on the headlines we all read concerning regulatory and legal landmines.

Equally troubling, some technology companies are diving in without understanding the risks or having a plan to mitigate them. Indeed some just seem to be in a state of denial, as if not thinking about these issues makes them go away. Something akin to don't ask, don't tell. Others figure that as long as they don't intend any harm, nothing bad can happen to them.

Both approaches are equally misguided. Instead of those approaches, I suggest you deal with the risks upfront – understand and address them. This isn't rocket science. I promise you can handle this, and make money doing so if your idea is good.

I am not going to do a treatise and describe all of the obscure legal and regulatory risks. If you like reading statutes and regulations, you're in the wrong place. I'm not even going to paraphrase the law most of the time. My goal is simply to give you practical guidelines for how to navigate these uncertain waters.

I'm also not going to cover the myriad of legal and regulatory risks including product liability, HIPAA compliance, fraud and abuse, and the FTC. Instead I'm going to focus on FDA, partly because it's representative of the other risks, and partly because it's the area I know best. If your product doesn't work well and someone gets hurt, you will have to both deal with FDA and face product liability.

At its heart, FDA regulatory risk is fairly intuitive because you only need to remember one thing: it's all about putting the patient first. Every FDA requirement can be explained by reference to what's necessary to protect the patient. And that includes protecting the patient from misleading information, not just physical harm.

A technology company new to the potentially regulated mHealth space needs to start by understanding: (1) the regulatory risk – its sources, nature, magnitude and likelihood and then (2) more importantly, the primary risk mitigation strategies – how to avoid getting in trouble with FDA. I will tackle the issues in that order.

Root cause of regulatory risk

I've been doing this stuff nearly 30 years, and it's been my observation that companies get in trouble for one of three reasons:

1. FDA has not spelled out the regulatory requirements clearly enough so you know what to do.

Fortunately, we do have FDA's recently released final guidance. But as you can tell from reading this book, there are still numerous ambiguities. In the case of extreme ambiguity, this could even be a defense, because criminal statutes are supposed to be clear enough that a person knows what they need to do to comply. As a practical matter, out of fairness, FDA is usually reluctant to proceed with enforcement if the rules are not clear. Indeed, FDA has been very slow to enforce the rules in the mobile app space since they haven't yet published their guidance, frankly even when the violations appear reasonably clear.

2. You don't know what you don't know.

It's possible that the FDA requirements are clearly specified somewhere, for example, on the agency's website, but you don't know what those requirements are out of simple ignorance. As probably everyone in America knows, though, ignorance of the law is no excuse. So this represents one of the most dangerous pitfalls.

3. You screw up the execution.

Here, I'm assuming the law is clear and that you know what it was, but in a big organization sometimes the left hand doesn't know what the right is doing, or you simply do a poor job of complying. These can be hard cases to defend if the violation itself is clear. It all comes down to the facts and what you did or didn't do.

So these basically are the ultimate sources of regulatory enforcement risk, and I want you to keep these in mind as you go through this chapter. That's because, if I've done this right, the mitigation strategies all relate back to these three fundamental risks.

FDA's fairness in practice

FDA for the most part is pretty fair and practical. I think a lot of people outside the device industry fear that FDA is arbitrary and unreasonable, but that's not been my experience. These industry people fear that if they make an innocent mistake, FDA will come down on them with a sledgehammer. But that's a myth. Instead, FDA approaches enforcement in a common sense way, where they start with the least aggressive action first to see if they can bring about compliance. They do this both because it's fair, and because it is more cost-effective than getting too aggressive too early. The following tends to be the escalating steps FDA would take to bring a company into compliance.

1. Private communication.

Sometimes in the form of a letter, FDA may simply talk to you about your compliance, or suggest the need to address some deficiency. They will do this for what might be minor violations. FDA recently did this last spring when they sent a letter to Biosense explaining that it has "come to our attention" the company was selling an app for urinalysis. The letter raised concerns over the marketing of the app without clearance. It was a very gently worded letter. And, the only reason FDA published this particular letter was that I had been very public in raising the issue in testimony before a congressional committee and in the media. I was making the point, which I will explain more in a subsequent chapter, that enforcement needs to be evenhanded. So FDA posted the letter to its website. But I would not expect them to continue posting such letters as a matter of general practice. Normally, they are much more private.

2. Warning letter.

This is an official correspondence that routinely gets posted on the FDA's website. The warning letter is directed at a more significant deficiency that requires immediate attention.

3. Administrative or judicial enforcement action.

An administrative enforcement action is one that the agency has the power to do without involving the court. An example in the medical device realm is "administrative detention" where they can literally quarantine your products for up to 20 days. Most of the other really severe enforcement steps require the involvement of the court. This includes actions like seizures, injunctions and criminal penalties.

In practice, when FDA is really concerned about the conduct of a company, FDA has two additional very powerful weapons up its sleeve that do not require the direct involvement of a court.

The first is adverse publicity. FDA has the power to talk to the media where, for example, they believe the public is at risk. In my observation, FDA has been using this more and more to get their point across, and there's no question that it has a punitive effect on the companies that are the target of FDA's wrath. From a legal standpoint this is a bit scary because there are very few legal controls over what FDA can do.

The second is recalls and other field corrections. Technically this is not a punishment, but it sure feels like one sometimes. FDA can push companies into very expensive recalls – both in terms of out-of-pocket but also reputational. Ostensibly necessary to correct the violation, I do believe that FDA also uses them occasionally to make a point. At the same time, to the agency's credit, I believe they only pursue these when they are genuinely very concerned about the conduct of the company and the public health risk.

Types of regulatory risk

So, you screwed up. The question is, what can they do to you? I hate it when someone asks me that because essentially they're asking the question broadly of what are all the possibilities. The honest answer is offhand "I'm not sure what they can't do to you." For example, they can:

1. Detain your product. I'm not exactly sure how they would do that in the case of software, but I would guess they would think of something.

2. Seek to impose criminal sanctions, either on the company as a whole or the responsible officers.

3. Go to court and get an order for you to do or not to something.

4. Seek fines.

5. They can shoot you, bury you, dig you up, shoot you again, and your mother too.

If you are debating whether to intentionally violate the law based on the magnitude of the regulatory risk, you might want to comply.

At the same time, for fair balance, I don't want to leave you with the impression that if you screw up they will throw you in jail. It depends very much on nature of the screw up and your intentions. In fact, the phrase screwup suggests an innocent mistake, and for those types of mistakes you ordinarily simply get a warning and an opportunity to do the right thing.

What triggers these risks?

I will bypass the technical, mumbo-jumbo about jurisdiction. Basically if you are doing business in the U.S. and you are putting a medical device in commerce, you are subject to FDA regulation.

But regulatory liability comes into play when you fail to meet the standards that apply to a given activity associated with bringing a medical device to market. The following table illustrates some of the more common requirements and the activities to which they relate.

Diagram 1. What triggers these risks?

Activity	Requirement
Development	Good clinical practices
Manufacturing	Good manufacturing practices
Promotion	Good promotional practices

If the requirement applies, the responsibility for meeting it can't simply be contracted away, generally speaking. However, you can shift the whole activity and with it much of the day-to-day work. But typically, if you control (1) the specifications for the product and (2) the marketing strategy for the product, as I have explained before, you will possess ultimate responsibility for regulatory compliance.

Intent: what it's not and what it is

As I explained in the first chapter, anyone who has watched Law and Order knows that intent plays a very important role in the American justice system. But what you would not get from the show is the relevance of intent to a regulatory violation of the Federal Food, Drug and Cosmetic Act. It's different. Boy is it different.

For starters, for a low level violation, it doesn't matter whether you intended the violation or not, the conduct is still a violation. For example, to establish a violation, no one cares whether you had specific intent to do something you knew was wrong, or whether you were even directly involved in the wrongdoing. Further, no one really cares if you feel good about yourself or have a clear conscience. And certainly no one gives a darn whether you think your conduct is legal.

Diagram 2. Intent: What it tends to be

	Company	Individual
Civil remedies (e.g. warning letter, injunction, recall)	None, FDA just needs to establish the product is violative	None, but rarely individual consequences
Civil monetary penalties	Tipically for repeat offenders or egregious cases	Typically personal involvement in the activity
Criminal penalties *misdemeanor*	Did the company fail to be duly diligent, proactively controlling its people	**Did the person have:** (1) Power to fix the problem (2) Responsibility for the function where the problem existed
Criminal Penalties *felony*	Same as misdemeanor plus intentional conduct	Same as misdemeanor plus intentional conduct

Intent: What it's not and what it is *(continued...)*

Intent does come into play in that it is the distinction between a felony and misdemeanor. But if we're talking felonies and misdemeanors, you probably ought to be reading something more scholarly than this article. For the rest of you, the chart on the previous page depicts very broadly and imprecisely the role of intent in the various levels of FDA enforcement. I don't want any comments from attorneys asking me where in the statute this language appears. It doesn't. Instead, this is based on my observation of FDA practice.

For me, the key take away from the chart is the very first row where the chart explains you do not need any intent at all for the vast majority of FDA enforcement actions. It's not about blaming someone, but rather simply the existence of a violation. If the device is broken, it needs to be fixed, whether anyone is blame worthy or not. The second take away is that traditional intent really doesn't come into play until you arrive at the last row, where we are talking about criminal felonies. For the stuff in the middle, the issue is more about whether the company fulfilled its obligation to be duly diligent in controlling its people, and whether an individual had the power to do something to avoid the violation, and the responsibility to act.

Statistically, well more than 99.99% (pure estimation) of people in the medical device industry will never have to worry about whether they had the requisite intent for a felony. Those prosecutions are very rare. But there is an aspect of intent that is much more relevant to developers of mHealth apps. A few folks have asked me over the last couple of years what I would expect the FDA response would be to a software developer that produces a medical app without complying with FDA requirements, if it turns out they are indeed required. My response is to describe two different scenarios that involve two different types of intent.

1. The first is a true borderline case where it is unclear, based on all the different sources of FDA guidance (and there are many beyond the draft mobile apps guidance), that the app is FDA regulated and the developer truly believed that they had a reasonable case for deciding that it is not. I would also include in this category a situation where there is reasonable ignorance of the law. You've always heard that ignorance of the law is no excuse, but in practical terms FDA is willing to cut some slack to very small businesses that don't have many resources. The larger the business, the more sophistication FDA expects. In these cases, I would expect FDA to respond with either a private or public warning directing the company to come into compliance. If it was truly a reasonable interpretation and low public health risk, I would imagine FDA would try as hard as it could to allow for a reasonable transition to regulatory compliance without disrupting patients and the delivery of healthcare.

2. A different scenario would be where the company took a more reckless or arrogant or sneaky position where it really was clear that the FDA requirements applied, and maybe the company was just gambling on flying under the radar or simply felt that it wanted to wait until FDA got serious. In that instance, I would expect FDA to respond with a more public warning but also to be much less willing to accommodate a smooth transition. Among other things, FDA might demand (a) that the product be taken off the market until compliance is achieved, (b) that the existing products on the market be recalled, and (c) public warnings be issued. If you add to the scenario that the public was put at risk by the noncompliance, which is frankly more often than not because every FDA requirement is there to protect the public, or more extreme sneakiness or indifference you might also see the agency pursue the penalties described in the next section.

Magnitude and likelihood of regulatory risk

If someone casually picks up the statute to read about the penalties (okay I have no idea why anyone might do that), that person might be surprised to see that the basic misdemeanor violation of the act is punishable by no more than one year in prison and a fine of not more than $1,000. That doesn't seem so bad. The problem is, that's for each violation, and each widget sold in violation of the act is a separate violation. So if you sell thousand adulterated widgets, that means the maximum penalty is 1,000 years in prison and 1 million bucks. Actually, in that case, calculating the prison term is more complicated, but you get the idea – it multiplies. In practice, FDA has quite a bit of discretion, and the penalties they seek are generally proportionate to the blameworthiness of the conduct as they see it.

The likelihood of facing FDA penalties is really hard to predict. In chapter 12 below, I explain that FDA enforcement has been rather uneven lately. I've seen in many cases blatantly unlawful conduct to which at least publicly FDA does not respond. In this area of mobile apps, FDA has not yet developed, let alone publicly articulated, an enforcement strategy to deal with the torrent of new mobile apps. They've talked about doing things almost like class actions, where they would send a raft of warning letters to a bunch of companies all doing the same thing, as they did with the pharmaceutical companies over the issue of sponsored links. I'm hoping they don't go too far down that road because at the end of the day this is America. They need to take appropriate steps to document a violation first. I hope we don't see ready, fire, aim.

That said, traditionally the likelihood of FDA enforcement depends on five factors, as follows:

Magnitude and likelihood of regulatory risk *(continued...)*

1. Visibility of the conduct.

Obviously visibility doesn't mean some conduct is actually worse than others, it just means that in practical terms when an agency is strapped for resources, if you go and stand in front of their offices in Silver Spring, Maryland and shout about all sorts of off label uses for your product, it seems more likely they will pursue you. That's obviously hyperbole, and a more realistic example would be an app that makes a big splash in the media or on the Internet. FDA loves to surf the Internet because they can do that very inexpensively. They also love to go to large trade shows because they can walk up and down the aisles and see what everyone is doing all in one visit.

2. Disgruntled employees.

Statistically, a very large portion of the complaints FDA receives about the conduct of companies comes from the company's own employees. This tends to be one of two scenarios. The first is where an employee is pissed off at a company for any number of reasons, including being laid off or simply not getting the pay raise they were expecting. But the other kind is the conscientious employee who is bothered by the conduct of her employer. Particularly in the quality field, those jobs attract people who are personally very invested in the safety and quality of their products, and are bothered in their souls when the company decides to cut corners. In either case, the FDA is only a phone call away, and they use it.

3. Competitor dynamics.

An even bigger percentage of the complaints FDA receives are from competitors. While the reason is obvious, there are some more subtle predictors that you want to watch. One is if your competitor has gone to the trouble and expense of complying with the FDA requirements, you know darn well that they will expect you do the same.

4. Public health consequences.

In reality, FDA lets a lot of minor stuff slide simply because they don't have the time to do anything about it. But what will galvanize FDA most quickly is if they believe the consumer is at risk. If your conduct even arguably puts people at risk, your regulatory risk goes up substantially.

5. Clarity.

Here I am referring both to the clarity of the FDA rules as well as the clarity of your conduct. When pursuing an enforcement action, FDA always has to think about how well it can prove its case, and the clarity of the lines that were crossed and the documented conduct by the manufacturer get scrutinized carefully before FDA proceeds. The government doesn't like to invest in enforcement cases they might lose.

So there you have it. That's what I see in terms of the regulatory risk of entering, or skirting the edges of, the medical device industry. The reason for going through all of that to lay the foundation for discussion about all about ways to minimize the risk of those regulatory consequences. We've covered the painful part; I promise the next part will be more uplifting.

Risk mitigation strategies

So that's all the nasty stuff that can happen if you enter mHealth and your app or your hardware ends up FDA regulated, but you don't comply. That discussion was ugly, but it had to be done, because it laid the groundwork for this portion. Now I'd like to share the good news that there is plenty you can do to mitigate your risk of FDA enforcement. As usual, I think in lists. The following is my checklist.

1. Check your attitude.

As I've said I've been doing this for almost 30 years now, and I can generally tell which companies will succeed and which will fail when it comes to FDA compliance. There is one very clear hallmark of the companies that succeed: In their attitude they are able to embrace the FDA and put patient safety first. If you can do that, you've won easily half the battle. It sounds almost silly, but it goes to the very DNA of the organization. If the organization views FDA as a stakeholder that needs to be kept happy, they will organize their business partly around pleasing that stakeholder, in addition to customers, shareholders, employees and others. These companies make it part of their mission to learn the rules and play by them. If you can't do that, my advice is simple. Stay out of this space.

2. It's all about intended use.

In chapter 1, I tried to explain the concept of intended use. As you might recall, intended use is the manufacturer's objective intent with regard to how its customers will use its product. This concept is the linchpin of FDA regulation. It determines everything, including (1) whether or not FDA regulates your product, and (2) if it's regulated, to what level. Intended use is therefore by far the single biggest determinant of regulatory risk, and companies that figure that out put in place robust systems for managing the intended use of their products. That means they carefully manage how they promote the products and what design features they add. They tightly control all of the things which ultimately determine the company's intended use for their product, so that it stays exactly where they wanted it to stay.

Risk mitigation strategies *(continued...)*

3. Aim as low as you can.

To reduce regulatory risk, focus on the lowest risk conditions and the least claims you can make. The risk associated with the health conditions you target partly determines the regulatory category (it's an element of the intended use), and the claims you make about your product need to be proven to FDA's satisfaction. So I say, aim as low as you can. I can almost hear the marketing people screaming. Okay, I get it – you need to be bold in business to make money. So what I'm really saying is pick a happy medium between the "our product will save the world" claims the marketing people want to make, and selling an inert paperweight. Carefully pick whatever the least is that can accomplish your sales goals. Less can definitely be more. Further, many companies not traditionally in the healthcare space confuse "common" with "low" risk. Diabetes is quite common these days, but not low risk. Similarly, claims of real time monitoring of patients with serious conditions are not low risk. Learn the difference.

4. Pursue a generic intended use.

I covered this in chapter 1. You don't always have to tell people exactly how to use something. I can make and sell test tubes without regulatory oversight so long as I'm just making a glass tube and the claims I make relate, for example, to the quality of the glass and its cleanliness. I can make a network router that is just a router. Where I tend to get put in the regulatory soup is when I start to make specific medical claims that, for example, my router is especially good because of its design for some specific medical application. For the generic intended use strategy to be legitimate, there have to be legitimate nonmedical uses, which for test tubes and routers is not a problem. Please remember, though, how broad the concept of intended use is, in that it encompasses, for example, (1) the words I use to describe the product, (2) any special design features I might add that have only medical uses, as well as (3) uniquely medical channels of distribution I choose to pursue.

5. Take a more nuanced approach.

It's not all in or all out. There are many different roles the company can play in the industry. Companies can avoid many of the regulatory obligations by limiting their role to serving as a contract manufacturer. Or a design firm can collaborate with the manufacturer without taking on all of the regulatory obligations. Or you can just be a distributor if someone else's willing to be the manufacturer. There are lots of roles to play, they aren't all equally risky. I explained that in excruciating detail in chapter 9.

6. Manage your supply chain well.

The most successful folks I know in the medical device industry would put this at the top of their list, as a matter of general business practice. It makes my list with regard to ensuring regulatory compliance for several specific reasons. Companies should get accustomed to using supplier contracting to share the burdens of regulatory compliance—asking their suppliers to shoulder some of the obligations. At a minimum, contracts should specify the regulatory obligations rather than leave the issues unaddressed. Warranties are important, and there is even a so-called "pure food and drug warranty" in the FDA regulations which if you use that wording you can shift regulatory risk upstream. There also are whole tasks that can be outsourced, notably the clinical research function to a Clinical Research Organization. This is a little bit controversial in the device area; there's an express provision on the drug side of FDA that allows this but not so on the device side. Even so, using a CRO typically can help reduce the risk.

7. Build a robust compliance infrastructure.

You're probably thinking, wow, what great insight he has. Well, I couldn't exactly leave it off the list even if it's perfectly obvious. And frankly I don't want to attempt to thoroughly cover the compliance process—whole books have been written on that. Instead, let me just say that compliance tends to depend very heavily on having written procedures, documenting compliance, and training your people. It requires a continued investment to control your organization that includes in equal measure auditing to find noncompliance and fixing what you find. It's funny – some companies are really good at auditing and not very good at fixing. Other companies are not so great auditing but they do fix what they find. Frankly it takes both, in a sustained way.

8. Control your communications.

Once companies figure out that intended use impacts regulatory risk, and that they need a very proactive compliance program, they generally implement an intense program to control communications. At many science-based non-medical companies, the scientists are encouraged to engage in discussions rather freely. That doesn't work very well in the medical device space. But even more importantly than the scientists, companies target communications that create impressions in the marketplace with regard to the intended use of their products. In this regard, companies learn that what they put on their website really matters, because in this era of limited resources, FDA makes disproportionate use of visiting websites to gather evidence for enforcement. Equally so, companies control what they say at trade shows because FDA attends those shows to efficiently learn what everyone in industry is saying. Further, emails can be rather dramatic evidence of a company's intended use for its products. So companies train their people to stay within fixed parameters when describing intended use in email, just as in any other communication. When you are regulated by FDA, what you say really matters.

9. Run a tight ship.

Operations plays a big role in regulatory compliance, particular because product quality is such a central focus of FDA regulation. The companies I've seen that have been most successful aspired to meet very high quality standards. I want you to understand that I chose the word "aspire" very carefully just then. I selected it instead of, say "set" high quality standards, because a company should not self-impose through policies an extremely high quality standard beyond what FDA would require. The reason is simple – you can hang yourself by not meeting your own standard. So companies that document reasonable standards and then push their people to always in practice aspire to the highest quality do the best. After all, high-quality products generally mean you won't have customers complaining or people getting hurt, and therefore you are less likely to have FDA knocking at your door. The practical reality is that FDA goes after public health risk, so if you don't create a public health risk, you stand a better chance of avoiding FDA enforcement. In addition, documenting what you do should become part of the DNA of the company. In FDA's view, if it's not documented, it didn't happen. So the practice of documenting actions has to get woven into every day operations in an efficient and effective way.

10. Invest in recall preparedness.

Sorry to be the bearer of bad news, but if you end up in FDA regulated space, you need to be prepared for recall. It will happen. They are a common fact of life. If you put regulated software or hardware out onto the market and it doesn't work the way it should, FDA's going to expect you to recall it. The good news is that there are techniques you use in your operations that will make it far easier to efficiently identify and quarantine the scope of what needs to be recalled, and then recall it efficiently. But it takes prior planning. There are many consultants and vendors out there who can help companies put in place systems to make recalls less painful. Recalls will never be pain free, but with prior planning the pain can at least be minimized.

11. Consider setting up a separate health business.

Without trying to be pejorative, think of FDA regulation as a virus that needs to be contained. Then think through how best you can use corporate structures to limit the scope of FDA regulation on your operations. In tandem with creating separate corporate forms, you will need a relatively clear delineation between those operations subject to the quality system, and those that are not. In addition to limiting regulatory risk, this separation might also be an opportunity to limit reputational risk to your brand. In the table below I have sought to outline some of the pros and cons of creating a separate corporate structure to own and operate the medical device operations.

Pros & Cons of Separation

Pros	Cons
• Might be able to limit exposure	• Cost and complexity
• Facilitates separate branding to protect franchise name	• May not be completely effective if company remains closely connected operationally
• Can give focus to the operation	
• Can save money by limiting the scope of compliance	

If you decide to pursue this, though, be aware that separation might prove to be complicated. One of the most heavily regulated aspects under the quality system is the design control process, but figuring out how to separate R&D in a meaningful way might be difficult. Generally, the research side would not need to be separated, but the development side would. Further, just like any divorce, you have to separate the assets including the plant, equipment, intellectual property and records. All of the records associated with the quality system must belong to the medical device corporation. In addition to assets, the actual manufacturing processes will need to be separated. It is possible though, to use one company as a contract manufacturer for the other, but that means the contract manufacturer is subject to the quality system. People and governance need to be separated, keeping control at the strategic level without destroying the separation. If the separation is not sufficient, the regulatory requirements could carry over to the mother ship.

12. Get good help.

Well, duh. This has always been a rule of business, but it is particularly important here. You need to get good advisors and vendors with regard to medical device compliance matters including submissions to the FDA and any clinical testing that you need to do, among other things. You can also reduce your risk by getting second opinions by outside attorneys and consultants, but you need to realize that those opinions do not constitute a get out of jail free card. You still have ultimate responsibility. All the opinions do is make it more likely that FDA will respond to you with at least some sympathy. The companies you partner with, including critical areas like the design process and manufacturing, can have a big impact on your regulatory risk if you are the entity that bears that risk. So get good help, and use appropriate due diligence to make sure that all of your advisors and partners can perform to the levels needed.

13. Work with FDA.

The very first item on this list was to challenge you to critically self-assess whether you can treat FDA as a strategic partner. So assuming you can do that, you need to start building a relationship with the agency and lines of communication. If you find yourself involved in advocacy, make sure that you're advocating policies that are sensible for patients as well as innovation. Remember, everything we do is about the patient. Generally, if you plan to consult FDA, consider doing it early when you have the most flexibility to adapt and to give them time to think about it. Also, seek clarity, but not too much. Some people just can't stand ambiguity, so they will over communicate with FDA to try to pin down even the smallest details. I don't recommend that. When you do that, you have to realize you will get the most conservative advice each time, plus eventually they will get annoyed. They are not your consultants – they are too busy to field every question. Sometimes taking a good faith, informed position is the best in the face of ambiguity. If FDA raises questions about your compliance, treat them right. Always be respectful, be prepared for surprise inspections and take any warning you receive seriously. It's really not that hard, but it needs to be part of your DNA.

14. Watch out.

Vigilance in this industry is essential. Watch your competitors. If they go through the FDA compliance process, you can be darn sure they will expect you to, and will complain to FDA if you don't. Watch out for changes in the law, regulations and FDA sentiments. This is an area that changes constantly. Subscribe to the right journals, monitor the right websites and attend the right meetings. It's terribly important to stay up-to-date on the regulatory environment.

15. Be proactive.

Indeed, this is the main point I'm trying to make. Confront the issues directly and intelligently, rather than just hoping they go away. Don't just assume that compliance will happen so long as you're a good person. It's doesn't work that way. It takes a lot of affirmative effort.

This probably sounds scary, and it is a bit. But realize that there are roughly 20,000 companies registered with FDA as medical device manufacturers, and about 80% of them qualify as small manufacturers. If they can do it, you probably can too, if you really want to. Often the rewards are well worth it. But it's up to you.
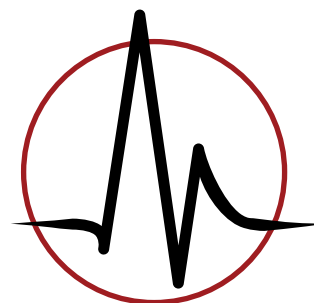
XI. Does FDA Regulate mHealth Care Providers?

At mHealth meetings, I keep hearing representatives from hospitals and other healthcare providers say they don't believe FDA regulations extend to them. They seem to believe that an institution must have a smokestack and an assembly line before it needs to worry about FDA regulation beyond clinical research. But that's just not true. FDA can and frequently does regulate even those engaged in the practice of medicine, if they are also engaged in FDA-regulated activities.

FDA tackles the issue squarely in its final MMA guidance. Given how directly FDA addresses this issue, I'll quote the guidance at length. FDA says the following is not a medical device manufacturer:

> Licensed practitioners, including physicians, dentists, and optometrists, who manufacture a mobile medical app or alter a mobile medical app solely for use in their professional practice and do not label or promote their mobile medical apps to be generally used by other licensed practitioners or other individuals. For example, if Dr. XYZ, a licensed practitioner, creates a mobile medical app called the "XYZ-recorder" which enables attaching an ECG electrode to a smartphone, and provides the "XYZ-recorder" to his/her patient to use it to record the patient's electrocardiographic readings for 24 hours, Dr. XYZ is not considered a mobile medical app manufacturer. If Dr. XYZ is in a group practice (including a telehealth network) and permits other physicians in the practice to provide the XYZ-recorder to their patients, Dr. XYZ is not considered a mobile medical apps manufacturer. However, if Dr. XYZ, the licensed practitioner, distributes the "XYZ-recorder" and, through labeling or promotion intends to make it generally available to or to be generally used by other physicians (or other specially qualified persons), Dr. XYZ would be considered a mobile medical app manufacturer (emphasis added);

When I read that passage, I immediately think of two questions:

1. What does FDA mean when they talk about doctors "who manufacture a mobile medical app"? How literally do I need to read that? Does that mean the doctor, obviously trained in medicine, also knows enough about computer coding to actually create the app with his own hands (and computer)? What if a doctor pairs with a computer scientist to jointly create the app? Does it matter if the computer scientist works full-time for the clinic, or does the work on a contract basis? I'll tell you why I ask these questions. In similar circumstances FDA reads the language surprisingly narrowly. For example, FDA has said that it will allow clinical laboratories under enforcement discretion to create diagnostic tests for their own purposes. But in conversations I've had with the agency, they've asserted that the statement is quite literal, meaning that the lab cannot use outside vendors to assist it with that process and remain within enforcement discretion. Notice that is squarely at odds with the definition of the manufacturer discussed in chapter 3, where I observed that a manufacturer is the one who controls the specifications and controls the claims. So apparently in these matters of enforcement discretion, FDA may mean something much narrower when they say manufacturing. They may mean that the doctor has to do it with his own two hands himself. I don't know.

2. What does "group practice" mean? I am no expert, but my partners in the healthcare side of our law practice routinely create a dizzying array of medical practices, some of them loosely affiliated confederations and others tightly-knit, centrally-controlled organizations. An HMO is a group practice, but as you know some HMOs are huge. One of the largest has 9000 physicians. Does that mean that a large enterprise can use an app that they develop internally? Going back to my first question, what if this large organization has a whole bunch of doctors and a whole bunch of computer programmers. Can they all collaborate to create an app that can be used internally within this large organization on millions of patients?

In the context of enforcement discretion, FDA has a habit of being vague, and sometimes it drives me crazy. They deliberately choose to be vague in order to not limit their discretion in the future. But the Federal Food, Drug and Cosmetic Act is a criminal statute, and American citizens have a right to a clear explanation of the scope of a criminal statute. We should not be left guessing like this.

In the face of the ambiguity, the best we can do is go back to the statute and regulations to try to figure out the scope of FDA oversight.

Background: The law

In this section, I review examples of where FDA has regulated caregivers to identify the factors that lead the agency in that direction, and provide a high-level overview of the relevant law. With that as background, I also examine some mHealth care provider practices that might end up FDA regulated, and offer suggestions for how care providers can avoid FDA regulation if that prospect doesn't excite them.

FDA care provider regulation examples

If, as an example, a large hospital were to buy a medical device company, FDA would not all of a sudden lose authority over the products the medical device company sells. In fact, it's actually somewhat common for FDA to regulate activities of healthcare providers and professionals who wade into product waters. I'll give four examples.

First, over the last couple of decades, in FDA's view some pharmacies went beyond the traditional practice of pharmacy services into the production of new drugs. Pharmacies have always compounded drugs, which can include mixing various ingredients to make them taste better or easier to digest. But according to FDA, in some cases pharmacies started to basically make their own versions of commercially-available drugs. Apparently some of those pharmacies also did so in advance of receiving a prescription, and in large quantities unrelated to any one patient. So FDA adopted an enforcement policy declaring those activities to be regulated drug manufacturing. Actually, they did that even before the recent outbreaks of contamination brought this issue into the public eye. Unfortunately, not all of the pharmacies had been following the FDA requirements.

Second, as already mentioned, some clinical laboratories develop their own chemical reagents and software for conducting tests on blood and other specimens. FDA declared it has the right to regulate those chemical products just as if they were made by commercial manufacturers. Indeed, FDA has proposed to regulate a subset of laboratory-developed tests that combine multiple variables (e.g. gender, age, and weight) using an interpretation function (i.e. algorithm) to generate a patient specific result.

Third, physicians and other clinicians sometimes directly sell drugs to, or use medical devices on, patients. When they do so, these clinicians also might promote their services. If they promote uses the FDA has not approved for the products, FDA may enforce its regulatory requirement on the caregivers. In the 1960s and 70s, FDA took several clinics to court that were hawking various remedies for cancer and all sorts of other maladies. A few years ago, FDA went after a clinic that was offering hyperbaric chambers to treat conditions like stroke, coma, and multiple sclerosis. When the clinicians stand to directly gain financially and use aggressive promotion beyond the cleared label, FDA tends to get involved.

Fourth, and perhaps most analogous to mHealth, FDA regulates the hospital reprocessing and reusing of "single use devices." Manufacturers of disposable products do not validate cleaning and re-sterilization of their products. So when hospitals decide, as a matter of saving money, to reuse devices intended to be thrown away, FDA says in industry guidance that the reuse is a new use beyond what the original clearance contemplated. As the promoter of the new use, the hospital needs to satisfy FDA regulatory requirements just as any other manufacturer, securing approval and following good manufacturing practices.

The point of these examples is FDA has shown no reluctance to impose its requirements on any type of healthcare organization that engages in what the agency believes to be manufacturing. Smokestacks are not required.

Legal overview

A warning to lawyers: this is not a law review article. These issues are complicated, but I'd like to distill these complex laws down to an executive summary.

Being a math nut, I developed the formula on the following page to describe how FDA jurisdiction is established.

In its simplest terms, FDA regulates medical devices that have an adequate connection to commerce. As already mentioned, in the first chapter I described what it takes to be a medical device. The definition includes both a tangible device such as software and an intended use for a medical purpose.

Legal overview *(continued...)*

So the question becomes whether these articles in the hands of hospitals and other providers satisfy the connection to commerce necessary for FDA jurisdiction. One piece of that required connection is the interstate element. While I won't bore you with a dissertation on interstate commerce, most lawyers realize that almost any commerce now is connected enough to interstate commerce to give the federal government jurisdiction. Indeed, in medical device law, that connection is presumed.

The Federal Food, Drug and Cosmetic Act says that if an organization, when holding a device for sale, does anything to cause it to be "adulterated or misbranded", including promoting for an unapproved use, the organization has committed a prohibited act. So in this case the issue really comes down to whether an article is "held for sale." Broadly speaking, there are a variety of judicial cases over the last 40 years which suggest that healthcare providers may be holding devices for sale if they resell or otherwise provide the device to the patient, or even use the device on a patient. When enforcing this particular provision, FDA seems to look for instances where the caregiver is in the distribution chain and engaged in promotion.

Upon learning this, many doctors will quickly point out that they are engaged in the practice of medicine and section 906 of the Act says that FDA will not regulate that. That is true. But there is a line the doctors can cross leaving the practice of medicine behind and entering the business of selling devices. The statute contemplates giving freedom to those who are regulated by state boards of medicine under professional standards, with regard to the activities traditionally within that realm. The statute does not contemplate giving freedom to software engineers working away from patients, developing software and hardware configurations, even if they are hired by and collaborating with doctors.

Diagram 1. Formula for FDA jurisdiction
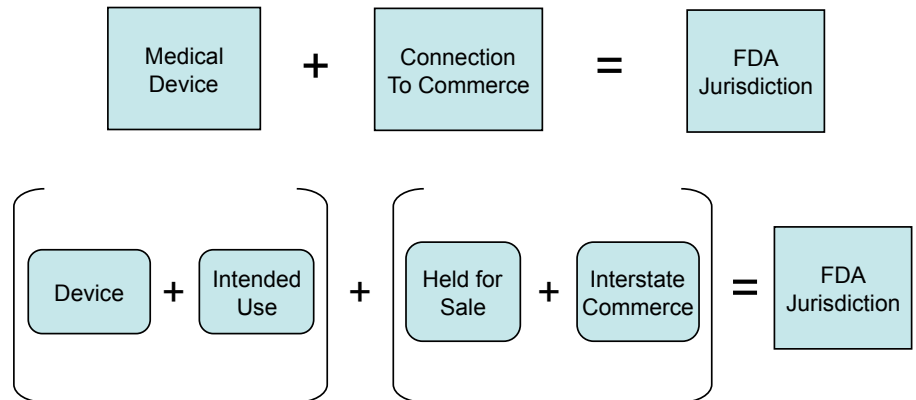
It is also true that manufacturing custom devices falls within an exemption from most FDA regulations. While the exact scope of that exemption has been the subject of much debate and was modified in 2012 by FDASIA, most agree the custom device exemption is directed to the practice of tinkering with approved devices to make them suitable for individual patients or individual doctors or other professionals. It does not contemplate producing HIT systems used by multiple patients or multiple caregivers.

The bottom line is that the Act can quite comfortably be read as applying to hospitals and other caregivers engaged in the development and production of software and hardware configurations that support mHealth.

Implicated hospital activities

So what mHealth hospital activities might fall within FDA regulation? The following are just hypothetical and broad categories of activities that under certain circumstances FDA might decide to regulate. Let's say a hospital wants to use mHealth to better manage the care of people with diabetes. Let's also say there are commercially available apps that allow people with diabetes to download their glucose readings into the app on their smart phones. As I've explained before, that app is quite likely to be FDA-regulated itself. Let's further say the plan is for that app to transmit the data back to a hospital.

Now here is where it gets interesting. What if the hospital wants to develop its own proprietary system that sits on its own servers to collect the data from patients using apps and manage a database into which physicians can tap using an app that the hospital develops? Let's say the hospital pursues this route because either it's simply not satisfied with the commercially-available software products, or there's some need to develop a better, more integrated approach that fits the hospital's legacy systems.

That hospital developed proprietary system might be FDA-regulated. Even though the system is one-of-a-kind, in this hypothetical it is used for each and every patient enrolled in the program. If that system hiccups and switches the identities

Implicated hospital activities *(continued...)*

of two patients, care can be affected. Compounding this, hospitals are apparently starting to sell access to their own HIT systems to smaller hospitals and physician practices. In these cases, the hospitals risk even more likely becoming resellers of the software. That practice frankly makes it easier for FDA to assert jurisdiction.

Under the final mobile medical app guidance, it would also be hard to characterize most hospitals as a physician group practice. Legally, they are just not structured that way.

Avoiding FDA regulation of care providers

As before, I'm not giving advice on the evasion of detection, but rather on staying outside of the regulated territory. The following is merely my personal list of eight factors that may keep FDA from deciding to regulate a hospital's software or hardware development.

First, it would help if some regulatory authority stepped in and oversaw this area of hospital activity. In the examples above, FDA was most likely to stay away from regulating a given activity if the agency felt another agency already was doing the job. FDA avoids duplicating the efforts of the state boards of pharmacy, state boards of medicine, and federal and state regulators of clinical laboratories. If hospitals work with an accrediting organization or some other body that could oversee this activity, they may well keep FDA from getting involved. However, it's unlikely the current CCHIT certification is demanding enough to give FDA much comfort.

Second, these hospitals and clinics may wish to avoid mHealth apps that involve too much public health risk. That includes the disease or condition being treated (cancer compared to sinus infections) and the clinical role of the technology, as well as the novelty of the apps. FDA is much less likely to regulate apps that merely embody tried and true algorithms than those that advance novel approaches. Further, the more proactive a hospital is in conducting quality assurance of the kind a manufacturer would pursue, the less likely FDA will regulate.

Third, the hospital should stay as far away as possible from the actual parent medical device. FDA is more likely to regulate software or hardware that more directly accessorizes a blood glucose meter or other traditional medical device. Further, the less tailored the software or hardware is to the particular medical device, the less likely FDA will regulate. These factors all revolve around close functionality, not the physical proximity of the hardware or software to the medical device.

Fourth, FDA will be less likely to regulate hospitals if the hospital is filling an important void. If there are already commercially-available products and the hospital is making its own either to save money or because of some other idiosyncratic preference, FDA may view the activity as trying to skirt its authority. In a fast-moving area like mHealth, the question is not only whether there already is a product available commercially, but whether there could be a commercial product. FDA would not want to see hospitals jump in simply because they are impatient with commercial manufacturers conducting a more diligent but time-consuming development process.

Fifth, in all of the examples above where FDA chose to regulate, the agency was responding to aggressive promotion. The more aggressive the promotion and the more outside of traditional FDA clearances, the more likely FDA is to regulate.

Sixth, scale is a big factor. In nearly all of the examples above, FDA only got interested when the practices grew big. That's a practical factor in the sense the technology starts to affect more patients, and commercial manufacturers could actually supply that need.

Seventh, sharing the hardware and software with others makes it easier for FDA to assert the hospital is in the business of reselling.

Eighth, and perhaps most obviously, if the hospital is engaged in modification of commercial systems, staying within any existing FDA clearance avoids FDA interest. Obviously "modification" can encompass a wide range of activities from life-critical changes to changes in the user interface, and configuration changes to hardware and network design and support. The regulatory risk of each type of change needs to be considered on a case-by-case basis.

Conclusions

At the end of January 2010, FDA held a public meeting on the interoperability of medical devices. At that meeting, many of the speakers talked about the need for systems integrators. The favorite analogy was the aircraft industry where two primary manufacturers are big enough to set specifications for individual component suppliers to assure interoperability. By analogy, some people at the meeting suggested hospitals and other end-users play that role with medical devices.

For mHealth, that's problematic if neither the systems integrator nor the individual component suppliers secure the necessary FDA clearance for the system as a whole. FDA regulates systems. So if the individual component companies don't take on the responsibility of FDA compliance for the system, it's up to the integrator.

Perhaps some hospitals want to take on that role and secure the necessary clearance from FDA. That could make some sense. But frankly it seems far more likely that an independent third party would play the systems integrator role, securing FDA clearance, and then selling that system to multiple hospitals and other caregivers. Either way, FDA will want to make sure the systems are safe and effective.

Over the last few years, the mobile medical apps community has been living in the Wild West. In the absence of a clear articulation of the scope of FDA regulation with regard to mobile medical apps, the agency has held back on enforcement. Instead, the Federal Trade Commission picked up the mantel and pursued a couple of different app developers over their claims regarding the treatment of acne. In fact, recently FTC announced that it plans to continue to focus on health-related mobile apps.

Now that FDA has published the final guidance, many observers expect FDA to begin enforcing its requirements. For its part, the agency has taken a measured approach in their public statements, saying that they are not out for scalps – my word not theirs – but rather want to work with innovators to help them come into compliance. They clearly do not want to scare innovators away, and I applaud them for that.

At the same time, FDA will need to level the playing field. We've been seeing a growing issue among developers of mobile medical apps where a considerable number of them seem to be flouting even the clear FDA requirements. This creates an enormous challenge for responsible medical device manufacturers that want to obey the law. Some app developers come out with $.99 apps that, they claim, are as effective as any other app out there, but at a fraction of the development cost because they don't worry about a quality system, let alone FDA premarket notification. That puts the app developers who are trying to do things right in compliance with FDA requirements at a substantial disadvantage.

Frankly I'm hoping to start a conversation around this issue, because companies are really struggling to do the right thing.

Unevenness of the past few years

Some app developers already follow FDA's regulation, and implement appropriate quality systems, registration, and adverse event reporting processes in order to ensure compliance with the regulatory requirements. But some are not.

Biosense case

In the spring of 2013, a company called Biosense made a big splash with a Ted talk regarding an innovative app that allows you to do urinalysis with your iPhone. The company website presented the app as able to help patients understand and manage diseases like diabetes, urinary tract infections and pre-eclampsia, a high blood pressure pregnancy complication.

You do the test mostly the old-fashioned way of collecting urine in a cup and then inserting a test strip. The app objectively reads the results using the camera on the phone.

The company launched the product through iTunes and sold a kit consisting of a color mat to calibrate the app plus 5 sample urine dipsticks for $19.99 through the company's website.

But here is the problem—this app falls within longstanding FDA regulation for urinalysis. When I first heard about it, it

seemed to me that the company must be aware of the potential for FDA regulation, because on its home page, at the very bottom, after extolling the clinical uses of its product to monitor disease, the company tried to simply disclaim FDA medical device status.

Significantly, the company's website was also full of statements suggesting that people use their kit in lieu of the FDA regulated instruments used for urinalysis. It stated the smart phone app "can help you analyse, interpret and trend your urinalysis data to help you understand and manage diseases like diabetes, ... urinary tract infections and pre-eclampsia."

Further, it couldn't have been any clearer that instruments used for urinalysis are indeed medical devices. The device classification regulation, 21 CFR Sec. 862.2900 Automated urinalysis system, clearly establishes that FDA regulates urinalysis systems:

"An automated urinalysis system is a device intended to measure certain of the physical properties and chemical constituents of urine by procedures that duplicate manual urinalysis systems. This device is used in conjunction with certain materials to measure a variety of urinary analytes."

Moreover, measurement of blood glucose and occult blood actually raises the profile of the device to class II requiring premarket notification. Indeed, a search of FDA's databases reveals that the other devices that measure those analytes had gone through the FDA premarket notification process.

Biosense case *(continued...)*

Here's the problem. There are all sorts of companies out there trying to do this kind of stuff right. They follow the rules, and that costs money. In the case of the class I device that means using a quality system to make sure the device actually does what it's supposed to do. For class II, they must file a premarket notification with FDA. It would appear that this company wished to avoid using the quality system, registering, reporting adverse events and doing all the other things that bona fide medical device companies do.

This app kit sold for about 20 bucks. Companies that employ a quality system probably have to charge more than that to make a decent return. How can a company lawfully compete with those that are willing to try to avoid FDA regulation with a simple disclaimer?

So I raised this issue, first in a blog post, and then in testimony before a congressional subcommittee. My goal was to put on the table the need to level the playing field so that all companies are treated equally.

On the one hand, it might seem like I am picking on this company. But frankly, it is simply typical of what we are seeing day in and day out show up in the various app stores.

At the end of the day, these rules are there for a reason. People get hurt when medical devices do not possess the quality they need to reliably perform their functions. If this urinalysis test, for example, under-reports or over-reports an analyte, a person might be lulled into believing they do not have a medical condition when in fact they do. For diseases like diabetes, that can have deadly consequences. Of course, if FDA regulation is no longer necessary for urinalysis, I am sure everyone in that business would appreciate FDA rescinding that regulation.

For a regulated industry, one of the worst things that can happen is to have a law on the books that is not enforced. That puts every ethical company in a dilemma – do you sink to the level of your competition that seems to be getting away with flouting the laws, or do you stick to your ethical guns.

FDA agreed with me, at least with regard to this particular app. In May 2013, FDA sent a letter to Biosense explaining that it had come to the agency's attention that the company was selling the app for urinalysis, and FDA records did not show that they had filed a premarket notification. Overall, it was a very gently worded letter, and I think that's exactly the right approach to take. FDA should not charge in and treat people like criminals. I thought they took a very professional approach to this matter. The agency did take the unusual step of publishing the letter to their website, a step they normally reserved only for warning letters. But I gather they did that because I had so publicly raised the issue they felt they needed to bring closure to it.

Over the summer of 2013, I saw communications from Biosense suggesting that they were indeed going to seek FDA clearance for an expanded app. However, some of the same communications explained that they needed money, so they were taking orders for the app in advance of the FDA clearance in order to fund the work to obtain the FDA clearance.

Good grief. I really wish these guys would get experienced FDA counsel, rather than trying to just wing it. The law is quite clear that companies may not presell medical devices in the hopes of obtaining FDA clearance later. That's been the law for decades. Making matters worse, after they did that, I saw some other app developers do the same thing. I assume FDA will communicate with them, but they will probably do so privately this time.

Plan going forward

FDA faces very serious challenges in coming up with an enforcement strategy for mobile apps. On the one hand, we are awash in a sea of apps, and developing a carefully constructed factual case to support enforcement is quite resource intensive. On the other hand, FDA simply cannot take enforcement lightly and proceed without the needed evidence.

One strategy that FDA might be thinking about is the strategy they deployed when it came to pharmaceutical companies using sponsored links to promote description drugs. The FDA sent a raft of 14 so-called untitled letters in a single day to 14 different pharmaceutical companies that made use of sponsored links. I'm not sure that sending the letters all at once necessarily was more efficient for FDA, but rather I think it was designed to send the industry as a whole a message regarding how serious the agency was, as well as a way of showing that FDA wanted to be fair and evenhanded in their treatment of the issue.

I'm not sure that's quite the right approach because you still have to make sure that every company in fact deserves to receive such a letter. Enforcement includes at least three elements, and each element presents its own challenges:

Plan going forward *(continued...)*

1. Finding the companies that are violating the law

Actually, this first element is probably the easiest of the three. It's actually a bit like shooting fish in a barrel. An FDA enforcement official can sit at his or her desk and surf the Internet, going to app stores and looking at the claims being made. Indeed, the agency could hire pretty inexpensively a few college students and train them to find the offending apps. In that way, without even leaving the office, the agency could probably find as a rough estimate 80% of the apps that should be subject to FDA review but are not. Given that so few apps have as of yet been approved or cleared by FDA, it's not difficult for FDA to check its own files.

2. Building the factual case regarding the violation

One of the primary violations at issue, selling an app without having submitted a premarket notification, will depend mostly on assessing the app's intended use. An initial pass at that evaluation can be done simply by looking at the information that's available at the App Store, and linking to the company's promotional website. To be sure, that doesn't answer all the questions around intended use as frankly many websites are quite ambiguous, incomplete and out of date.

For those apps that look to be intended for a medical device use, the agency then needs to double check its own database to make sure that a premarket notification has not in fact been filed. Sometimes ambiguities around corporate names and so forth make it difficult to be confident of the search, but in some cases it's easy.

For class I medical devices where premarket clearance is not required, instead of checking the premarket notification database the agency would simply check the facility registration database. Here too ambiguities can arise with regard to corporate names.

Because the fact checking in many cases cannot be certain, I would be in favor of FDA adopting the process of sending an informal inquiry to a company to get the facts before FDA decides to send a more formal enforcement letter. At FDA, this is known as the "it has come to our attention letter." It seems to me that this is a prudent step to ensure that the agency has the facts before chastising the company publicly.

3. Pursuing the companies through some sort of enforcement

For a huge percentage of companies, receiving either an untitled enforcement letter from FDA is enough to cause them to come into compliance. I don't have the exact numbers, but it seems to be an application of the 80/20 rule, where 80% of companies will come into compliance and 20% will drag their feet. From a resource standpoint, it's clearly the 20% that cause concern for FDA.

As a matter of policy, the agency doesn't want to send warning letters out unless they are prepared to back them up with the full power of the federal government. Otherwise the agency would gain a reputation as a toothless tiger.

So that's really the conundrum. For the 20% who might not come into compliance upon receiving a letter from the agency, with all of the budget cuts and other limitations on resources, how can FDA be confident that it can fully pursue and achieve compliance among those who don't go there voluntarily?

I certainly understand that FDA can't make a threat unless it is prepared to follow through, and they're simply not sure they can follow through with a high-volume of threats. On the other hand, I'm not sure that FDA fully appreciates how self-regulating the healthcare market can be when it has good information. If FDA ends up sending a public warning letter to an app developer, I believe that many customers and partners of the app developer will back away from the developer, even if the developer itself is slow to respond. Doctors, hospitals and others in the healthcare environment are sensitive to product liability and malpractice, and usually careful not to use products where FDA has raised the concern about safety, effectiveness and regulatory compliance. So even if FDA does not have the resources to pursue those 20% of companies that do not come into compliance on their own, the receipt of a warning letter can still be a very important and impactful step.

But I truly do understand that FDA cannot send out warnings without being prepared to enforce them, even if customers and others can be counted on to apply pressure to the recalcitrant developer. I don't have the answer here, but I want to start a conversation to try to find some approach that keeps ethical companies from getting hurt while trying to do the right thing.

Bottom Line: Enforce it or get rid of it

Let me be clear: what I'm objecting to is unenforced requirements. Unenforced requirements that clearly apply mean that a reputable company has a choice:

1. Comply when others are not, at great expense and competitive disadvantage; or

2. Don't comply and presumably violate the company's own code of conduct mandating compliance with all relevant laws.

Notice that that's far more than an ethical conundrum. If a company starts ignoring legal requirements, the company has a very difficult time imposing legal requirements on its own people. The system starts to look arbitrary, based not on whether there is a requirement but rather based on the likelihood of getting caught for a violation. It has extremely corrosive effects on an organization's overall compliance.

Both of those choices stink. Obviously the government has two different ways of solving the dilemma. The government can either:

1. Enforce the law; or

2. Remove the regulatory requirement

Which they choose of course depends on whether there remains a safety issue that needs to be regulated. But if there is indeed a safety issue, the government needs to regulate in an evenhanded manner.

Conclusion

I expect we will slowly start to see the government's strategy for enforcing the mobile medical app guidance. I do not expect a dramatic shift. I imagine the government will spend the next six months or so trying to educate everyone about the guidance, and then gradually thereafter start to get sterner in its communications. I also expect that they will favor those companies that come to the agency to try to work out a compliance plan, over those that the agency has to take to task. If a company comes proactively to FDA, and if there's no evidence of a safety issue, the agency may well allow the company to remain on the market while the company comes into compliance.

As should be obvious from the prior chapters, FDA is not done with regard to policy making in the area of mHealth. Through publishing the final mobile medical app guidance, the agency has addressed numerous questions, but has created additional questions and left some questions unanswered. One of the largest gaps, as explained above, is the scope of FDA regulation of clinical decision support software. So what does the future of policymaking in this area look like? For that, we have to consider a couple of different forums.

FDA

Notwithstanding pressure from some IT trade groups, I think FDA will continue to regulate mobile apps that do the same thing as traditional medical devices, like the urinalysis app and apps used to read ultrasound images. At the same time, there will be much discussion around apps that are more peripheral to those core medical device functionalities.

The current forum for these policy discussions is the collaborative working group created by the three agencies – FDA, the Office of the National Coordinator and the Federal Communications Commission – to develop an overall strategic plan for regulating health information technology, including mobile medical apps. As I write this book, in the fall of 2013, as soon as the agencies come back from their furlough, they will work intensely on drafting that report. Under section 618 FDASIA, the report is due to Congress in January 2014.

I obviously have no clue what the report will say. However, I do think that the agencies will seriously consider the input of the advisory committee they put together as a part of this process. In the spring of 2013, under guidelines established by FDASIA, the agencies pulled together 29 individuals from a wide variety of sectors involved in HIT. I had the opportunity to serve, and was asked to cochair the Regulations Subgroup.

Over the course of the summer of 2013, the advisory committee worked intensely, sometimes having up to three conference calls a week, to develop a comprehensive set of inputs for the agency's deliberations. To be clear, we were not called to develop a draft regulatory strategy, but rather to identify important aspects of that strategy that were needed to balance safety, with innovation. The advisory committee completed its work by the first week of September, and made a public presentation before ONC's HIT Policy Committee. If you are interested in the report, both the written work product and an audio recording are available on the ONC website by going to the section on the HIT Policy Committee.

Of particular relevance to the mHealth segment, the advisory committee recommended that FDA clarify several areas including (1) the definition of clinical decision support software, (2) the scope of FDA regulation over accessories, (3) the dichotomy between health and wellness, and (4) FDA regulation of software modules. We also made several recommendations to improve the FDA regulatory process, including (1) identifying ways to help industry understand the requirements

better through more educational outreach, and (2) use of enforcement discretion to exercise a light touch in areas where the risk was very low and the opportunity for innovation great. In addition, the working group recommended that FDA clarify how its existing requirements would apply to mobile apps, including premarket requirements as well as post-market reporting obligations. Further, the working group favored exemptions from the quality system for the lowest risk software products.

All three agencies have a tradition of trying, wherever possible, to accept the input of their advisory committees, so it's my hope that the agencies will take these various recommendations seriously as they develop their strategy. I guess we will see in January 2014, although I must also say that the agencies do not always meet their deadlines, especially when being shut down by Congress for a sizable amount of time.

Congress

While FDA has been developing its regulatory strategies for mobile health, Congress has been interested in the same topic and suggesting that it may legislate in this area. In March 2013, the House Energy and Commerce Committee, through two subcommittees, held three days of hearings on the regulation of mobile health. I had the opportunity to testify at that hearing.

Much of the hearing focused on the medical device tax, and frankly those on the Republican side expressed some

Congress *(continued...)*

outrage that innovative mobile apps would be taxed. While I wholeheartedly support the repeal of the tax, in this particular case it was a bit distracting because the tax actually exempts mobile apps sold at retail. So apps purchased by consumers through iTunes, for example, would not be subject to the tax.

But the tax issue aside, it seems that most people in the room wanted to figure out a way to ensure that innovation in mHealth continues to flourish. Throughout the summer of 2013, various Congressmen and their staff were discussing different approaches to legislation. Representative Mike Honda (D−CA) has an interest in creating a separate office at FDA to take responsibility for wireless health generally, including mHealth. The theory being that by giving mobile health more attention and more focus, the agency could develop better policy more quickly. Representative Marsha Blackburn (R−Tenn.) wants to take on the definition of a medical device, and separate out software type devices from traditional physical medical devices. Among other things, that would remove mobile medical apps from the medical device tax.

All of those legislative efforts are relatively early on in their development, and I would anticipate that Congress will wait until the agencies have come up with their strategy under FDASIA section 618 to see what it says. Nonetheless, I do anticipate that 2014 will be an interesting year for mHealth on Capitol Hill and at the agencies.

How FDA can avoid unduly treading on mHealth innovation

As Congress and the federal agencies work this fall to assess how they can improve FDA regulation with regard to mHealth, I think it's important for all involved to start a discussion around what it would take to encourage innovation in mHealth. Under section 618 of FDASIA, in formulating the government's strategy, the agencies are supposed to encourage continued innovation as much as possible. The question is, how should they do that?

It seems to me they ought to start by understanding the factors that drive innovation in mHealth. So what are those factors, beyond the availability of pizza?

In this chapter, I'm going to share what I think are some best practices that support innovation. Here we are not talking about macroeconomics and policy such as the availability of venture capital and good IP protection, but rather microeconomics and company conditions that need to exist for innovation to thrive.

The nature of innovation in mHealth

I divide the universe of factors important to innovation into two broad categories, specifically (1) the act and process of innovating and (2) the business model for supporting innovation.

The act and process of innovating

I have tried to collect best practices from leading companies in mHealth to discern how they succeed in innovation. I'm sure this is only a partial list, but hopefully it represents a good start in identifying what needs to be protected and allowed to flourish.

- Collaboration among app developers, clinicians, medical device developers and scientists of many sorts. Collaboration is the wellspring of innovation. Perhaps in some areas of technology, innovation can occur from a lone, brilliant scientist tinkering late at night in his own lab. But in the area of mHealth, true innovation uniformly comes from collaboration among very disparate sets of expertise. After all, mHealth often is about connecting the patient to this data, and often to his caregiver.

- Finding talent wherever it might be. In a sense, this is a continuation of the collaboration need, but here I am focused on the fact that the needed experts might be dispersed around the world. In other areas of technology development, it's more traditional to bring everyone together under one roof to facilitate the development process. In IT, it's quite common not to bring everyone together physically but to let them interact virtually throughout the United States and the world.

- Tinkering and experimentation, with feedback loops. Any form of engineering requires the development of prototypes, but software development in particular involves the development of beta versions that can be tested in real world situations in order to obtain feedback and strengthen the technology. Consequently, to make real progress in mHealth, we need to ensure that that tinkering and experimentation can continue in some appropriate way.

The act and process of innovating *(continued...)*

- Major breakthroughs followed by many, many incremental improvements. The pace of innovation is uneven. Certainly there are inspirations in which new technologies are created, or new uses for existing technology are identified. But those breakthroughs typically are followed by a significant number of incremental enhancements over sometimes a prolonged period.

- Nonlinear process. Creative minds tend to zig and zag. If you add to that collaboration where many people are working together, innovation tends to happen here and there, not necessarily according to some linear process. Regulatory restrictions, for example, in the name of a quality system that attempt to make development a purely linear process are doomed to cause confusion and unnecessary burden.

- Short product lifecycles. Indeed, this is simply the other side of the coin from the rapid progress in mHealth technology. But it's important also to understand and appreciate the cultural impact that the short lifecycles have on the developers themselves. Developers thrive in an environment in which change is constant, and progress is something that can be made virtually every day. Fundamentally changing that culture and environment by imposing regulatory obligations that would dramatically lengthen the product lifecycles would have a tremendous stifling impact on the exciting cultures that exist in these technology developers' organizations.

- Sensible technology standards driven by industry. The promise of mHealth depends tremendously on the interoperability of medical devices and IT systems. Thus, for mHealth to flourish, the developers of these technologies need to agree upon common standards to be used. While this in a sense constrains innovation, industry organizations are in a position to develop the standards in a way that balances the need for innovation with the need for standardization.

- Modularization of software. It never makes sense to reinvent the wheel. Software development is no exception. Over the last few decades hundreds of thousands of software developers have created literally millions of software programs that accomplish a mind-boggling range of tasks. It simply doesn't make sense to ignore those existing software modules when developing new programs. So instead, developers stitch together existing programs and then add a new innovative coding to do whatever is new or different that the developer wants to accomplish. Sometimes this is done by drawing those modules together into a single program, and sometimes it is effectively accomplished by a software program being designed to interact with other software on a given platform, such as a mobile phone. A simple example is a software application on a mobile phone making use of the existing program that tracks date and time. Any regulation needs to appreciate this fundamental design dynamic.

The business model for supporting innovation

mHealth innovators must live in the real world, and that real world has economic issues as well. The following are at least a few of the economic factors that need to be considered as we look to preserving and enhancing innovation in mHealth.

- Small companies. Fortunately for everyone, mHealth in particular is not a capital-intensive business, so small companies can engage in innovation and product development. This is good news, because it means that we can open up to a broader group the opportunity to develop innovative products. The bad news is that these companies tend to have less capital, and also tend to need more assistance from government regulators in understanding and navigating complex regulatory systems.

- Venture capital and angel investment. These small companies, because they often lack sufficient capital from the founders, need to seek out and obtain venture capital and angel investments. Okay, that's a macroeconomic factor but I use it to lead into a microeconomic factor. To access that capital, the innovators need to be able to put together business plans that identify clearly the regulatory demands and the timetables associated with bringing their products to market. Thus, clarity in the regulatory pathway becomes extremely important.

- Access to markets in a reasonable time. There's no getting around that mHealth is a business. While we all certainly have a focus on the patient and protecting the patient, healthcare doesn't work in this country if those engaged in it can't make a living. Thus, when determining the appropriate level of regulation, we need to keep in mind that the healthcare system cannot succeed in caring for patients if those working in it cannot operate a viable business and cannot bring their products to the market in a reasonable time. Again, this is partly because the innovators are often small, and may not have a diverse portfolio of products.

**The business model for supporting innovation** *(continued...)*

- Joint ventures and other deals between parts of the mHealth ecosystem. Because we are focused on technology networks, we need to appreciate that this will mean many different forms of business agreements among vendors supplying various components of those systems and their customers. These deals will impact the intended use of the various components of these mHealth systems. Regulators such as FDA focus on a product's intended use, so the regulatory framework will need to be flexible to accommodate these innovative joint ventures that will undoubtedly impact the intended use.

- Reasonable and clear regulatory risk. Above we talk about the need for a relatively clear regulatory pathway to market, but here we are focused on regulatory liabilities associated with marketed products. For innovative businesses to attract capital, the regulatory risks need to be reasonable and quantifiable. These regulatory risks include such post-market obligations as adverse event reporting and conducting recalls. In a networked environment, presently these obligations are anything but clear.

Ambiguity and the entrepreneur

I have just suggested that clarity is often desirable in regulatory requirements. But it is important to be precise in where clarity is desirable. In fact, depending on the particular regulatory requirement, ambiguity can be either good or bad in its impact on innovation.

- Ambiguity can be good when it creates the opportunity for flexibility in compliance. It's actually okay for many regulatory standards to be written in a general way. The quality system regulations are written at a high level, which in a sense makes them ambiguous with regard to what they require. But that form of ambiguity is good in that it allows flexibility and innovation on the part of the manufacturer in determining how it will come into compliance.

- Ambiguity tends to be bad when it relates to the scope of a regulatory requirement. Industry needs to know whether a particular requirement applies or not. Knowing whether a given piece of software is subject to FDA regulation can make a big difference in the cost and timeline associated with bringing that software to market, so the developer of that software needs a fairly clear and certain understanding of the scope of FDA regulation. Likewise, knowing the classification of a medical device is critical to determining what types of regulatory requirements apply. Ambiguity there is not helpful.

So that's my assessment of important conditions at the individual company level that allow creative people to innovate in mHealth. My hope is that we can begin a discussion about what the agencies should take into account as they are developing their approach to mHealth for the future regulation.
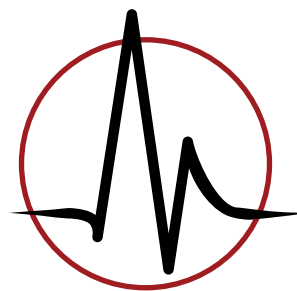
I've always found the saying, "Be careful what you wish for; you might just get it" to be rather condescending. In a way it suggests that we are too stupid to manage our own affairs. But like any popular saying, it probably has a kernel of truth.

Frankly, I'm a little nervous about a request made by industry for international medical device regulators to focus on standalone software, including mobile medical apps. At the request of an international trade group, on March 21, 2013, the International Medical Device Regulators Forum (IMDRF) decided to pursue harmonization of the regulatory approach to standalone medical device software. Standalone software in healthcare, as most people use that term, would include mobile medical apps, clinical decision support software, electronic health records and any other software used in healthcare that does not drive a medical device (hence it stands alone.)

Many of the industrialized and developing nations around the world established IMDRF in 2011 to provide a forum to discuss future directions in medical device regulation, and harmonization at an international level. The IMDRF builds upon the work of the Global Harmonization Task Force.

IMDRF membership includes regulators from Australia, Brazil, Canada, China, European Union, Japan and the United States, as well as the World Health Organization (WHO). In the US, for example, FDA is the participant, and in the EU the representative is the European Commission Directorate – General Health and Consumers. The recent IMDRF meeting that examined software took place in Nice (France) from 19th to the 21st of March 2013.

The IMDRF manages its agenda by formally adopting so-called work items. These work items then become the focus of activities between the full, semi-annual gatherings of the Forum. In 2012, at the fall meeting in Sydney, the DITTA (Global Diagnostic Imaging, Healthcare IT and Radiation Therapy Trade Association) recommended the creation of a work item dedicated to medical software. In an October 29, 2012 letter to IMDRF, DITTA wrote:

> DITTA greatly appreciates the Management Committee's further consideration during their session on 27 September of our proposal for a possible future IMDRF work item on medical software. Reasons which justified our suggested work item to IMDRF are that medical software is playing an increasingly greater role in medical technology in product-embedded software applications or in stand-alone software solutions. This includes but is not limited to aspects of software vulnerability with potential impact on patient safety. Therefore global harmonization of regulations and standards governing medical software is critical for patient safety as well as to the future innovation and prosperity of our industry.

Selecting standalone software as a work item is a big step as the 2-year-old forum only maintains about a half-dozen work items. Indeed, the most recent meeting only produced two new ones.

This is either a tremendous opportunity or a tremendous threat depending on whether you are an optimist or pessimist. I frankly don't know what it is. Subject to what region you're from, international harmonization can either raise the tide or lower it. Some folks worry that when regulators get together to compare notes on an issue the hurdles typically go up, kind of a regulatory arms race, but the positive side is that harmonization can be very helpful to international businesses.

Certainly there is a lot going on in the US with regard to mHealth regulation, but most people in the space can't afford to simply ignore the rest of the world. Indeed, even if you're only involved in US, this Forum has the potential to influence US regulation. Industry needs to be actively involved in all of these discussions to ensure the resulting regulation is sensible, and accommodates innovation. I just hope we like what we asked for.

by Erik Vollebregt

mHealth is a hot topic in the EU, and the EU has firmly embedded mHealth policy in its overarching healthcare goals in its digital policy: "ICT can be our most powerful ally for good and affordable health care.", the European Commission says. Especially mHealth plays a pivotal role in this, because it empowers people to easily take control of their own health; the Commission is working on a Green Paper, which will launch a public debate on that issue and a guidance document on the legal framework applicable to health and wellbeing apps. Both of these documents are scheduled for end of 2013.

Also, with 28 different member states working on different things, interoperability is an important issue. That's why the EU is planning to propose an eHealth Interoperability Framework by 2015.

The EU is further working on a regulation on eIdentification, of which the timing is not clear yet, but may impact mHealth services as well.

Internationally the EU will likely work on the harmonization further to the Memorandum of Understanding signed with the FDA in 2010, and in the TTIP negotiations.

The EU regulates mHealth in a number of ways: by means of medical devices regulation, regulation of personal health data, reimbursement of healthcare rules and product liability. This chapter focuses on medical devices regulation, as the previous chapters have done. You can find a convenient if not a little dry overview of other regulations applicable to mHealth regulation at the EU level in the European Commission's Staff Working Paper on Telemedicine. The overall policy goals are in the eHealth Action Plan, adopted in December 2012, which looks ahead until 2020.

In the EU there is no integrated health regulation framework with a single FDA as in the US. mHealth as a service is not regulated at the EU level but the software to provide the service is. Individual member states may pose constraints on the provision of healthcare services via mHealth, or may choose to reimburse it or not. However, like in the US states cannot just hinder interstate commerce without good reason: if member states enact rules that hinder the provision of services from another member state they must be able to justify them. They must show that the rules indeed serve to achieve a goal of protection of public health or another ground of public policy that the EU Court has held to be a valid justification. They must further show that the restrictions are proportionate in light of the goal and do not go further than necessary.

While this chapter is not the exhaustive word on software regulation under EU medical devices rules, it provides a lot of information to start from. You can find a lot more detail and how-to materials on my blog at http://medicaldeviceslegal.com. If you want an overview of the political initiatives in the EU, the ENVI committee's workshop on eHealth of 24 September 2013 is a good start.

mHealth as medical device

Under the EU medical devices directive the software used to provide mHealth services may constitute a medical device under the Medical Devices Directive. Software made available to the user over the internet (directly or via download) or via in vitro diagnostic commercial services, which is qualified as a medical device, is subject to the medical devices directives.

mHealth as a service is also covered by the e-Commerce Directive, like general Software as a Service ("SaaS"). This directive harmonises the EU member states' laws with respect to the provision of online services to end-users. These laws are also controlled by EU general supervision over the free provision of services. The European Court has recently ruled that member states have a lot less freedom than they thought they had in regulating the provision of mHealth. At least, that is my reading of the Ker-Optika judgment from 2012.

Don't forget that the data that the software collects, processes, and/or sends on to be processed elsewhere likely constitutes 'personal data' in the meaning of the EU Personal Data Directive. Mind you, the EU probably has the strictest regime in the world for controlling the processing of personal data and regulates 'data concerning health' under the strictest rules of this regime. If you deploy software to collect and process health data of EU citizens, personal data regulation should be top of mind, if only because of the privacy by design requirements. This means that you have to design your software in a way that it can be compliant with these rules, and preferably already is in its default settings. A good point to start is the helpful guidance on processing of personal data by smart apps. You should keep in mind that the EU is currently revising the personal data rules to make them not only stricter but also make them significantly more unattractive to contravene by proposing a 2% of worldwide turnover penalty on breaking them. Following the adoption of the new rules, the so-called General Data Protection Regulation, the Commission plans to issue additional guidance on the application of EU data protection law in the field of eHealth. We don't know where this regulation will land as a result of the EU discovering the degree to which the NSA is able to access personal data across the world. This has put a serious dent in the EU's trust in US companies being able to manage sensitive personal data in the way they promise, and has led the European Parliament to call for more controls on the export of personal data to the US.

If the software is used to interpret data derived from an in vitro diagnostic medical device, the software could constitute an in vitro diagnostic medical device under the In Vitro Diagnostics Directive ("IVDD") . This is a subcategory of medical devices with its own directive to regulate in vitro diagnostic medical devices, including apps and other standalone software that has IVD functionality.

Like in the US, EU law divides software into two categories: (1) standalone software and (2) accessories. Software that comes pre-installed on the device when the device is placed on the market is not regulated as a separate medical device. Unlike in the US, there is no enforcement discretion for the medical devices authorities. Either something is a medical device and they have enforcement power, or it is not and some other authority has power to oversee this.

Accessories

Accessories are software that whilst not being standalone software (a device as such) is intended specifically by the manufacturer of the accessory to be used together with a device (which can be standalone software) of another manufacturer to enable it to be used in accordance with the use of the device intended by the manufacturer of the device.

Understanding that framework is important because it determines the regulatory requirements that apply to a given piece of software. If the software is designed, for example, to analyze data downloaded from a blood glucose meter, the software is an accessory and will be regulated in the same manner as the blood glucose meter. The classification and most of the EU regulatory requirements will be dictated by how the parent medical device is regulated. Standalone software, in contrast, is regulated or not on its own merits, without regard to another medical device.

Categories, MDD or IVD?

If you are sure of the regulatory category in which your app falls, you can determine its regulatory status. Typically that would be one of the following three options:

1. Software that does NOT meet the legal definition of a device and is not regulated under the EU MDD;

2. Software that DOES meet the legal definition of a device and can be self-certified before it may be placed on the market or put into service; and

3. Software that DOES meet the definition of a device and needs to be certified by a notified body before it may be placed on the market or put into service.

Software that does not meet the legal definition of a medical device would be, for example, a system that would not serve any of the intended purposes set out in the definition of device in the MDD :

- Diagnosis, prevention, monitoring, treatment or alleviation of disease;

- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;

- Investigation, replacement, or modification of the anatomy or of a physiological process; and

- Control of conception.

Categories, MDD or IVD? *(continued...)*

Software that does not meet this definition is typically software that may be used in a medical context or may contain medical data, but which does not have a medical purpose itself, such as scheduling software or documents containing medical reference tables. See below under "Unregulated software" for more detail.

If the software falls within the scope of the MDD, the manufacturer must take another step to determine as what specific medical device the software is regulated: as a 'general' medical device or as and in-vitro diagnostic medical device. The latter category is regulated under yet another EU directive, the EU In-Vitro Diagnostic Devices Directive ("IVDD") . The IVDD regulates software that qualifies as medical device in the above definition and is moreover intended to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

- concerning a physiological or pathological state, or

- concerning a congenital abnormality, or

- to determine the safety and compatibility with potential recipients, or

- to monitor therapeutic measures.

With apps specifically in mind: software that is intended to create or modify medical information might be qualified as a medical device. If such alterations are made to facilitate the perceptual and/or interpretative tasks performed by the healthcare professionals when reviewing medical information, (e.g. when searching the image for findings that support a clinical hypothesis as to the diagnosis or evolution of therapy) the software could be a medical device.

Unregulated software

Software that is outside the scope of the MDD is not regulated. This typically concerns "software for general purposes when used in a healthcare setting" . However, all software "when specifically intended by the manufacturer to be used for one or more of the medical purposes set out in the definition of a medical device, is a medical device". So, software that is not specifically intended by the manufacturer as medical device is not covered, even if it is used in a medical context (like a medical reference book in an iPad app). That would for example be general database software, reference materials and spreadsheet software. Generally speaking, if the software does not perform an action on data, or performs an action limited to storage, archival, communication, 'simple search' or lossless compression (i.e. using a compression procedure that allows the exact reconstruction of the original data) it is not a medical device.

There is some difference in opinion between EU member states about the scope of the concept of 'medical device' in relation to software. Sweden, for example, tends to interpret the scope of this concept in relation of software very widely.

Software that can be self-certified

The certification system for medical devices in the EU is set up in the way that the devices falling in class I, the lowest risk class, are not subject to review by a third party but may be self certified by the manufacturer. As stated above, all SOFTWARE is by default in class I, so capable of self-certification, unless an exception applies (see below).

Self-certification involves composition of a technical file and design of a quality system, for example in conformity with ISO 13485, the standard for medical devices quality systems accepted by the EU as state of the art.

Design controls

Building the technical file involves checking your software against all of the 'essential requirements' in the MDD or IVDD. These design requirements for software are incorporated in the MDD and for IVDs in the IVDD, and are further implemented by means of harmonized standards that relate to a particular essential requirement. While the essential requirement often gives a general description of what is required, the harmonized standard will give you a lot more detail. Meeting the requirements of the relevant harmonized standard entitles you to a presumption of conformity with the essential requirement concerned.

The process of checking involves usability requirements with respect to your GUI, for example. Also, your software must be validated according to the state of the art taking into account the principles of development lifecycle, risk management, validation and verification. This requirement involves application of the EN 62304:2006 standard, the EU harmonized version of the ISO 62304 standard for this particular essential requirement. A very good FAQ document on the application of the EN 62304 standard was recently released by Team NB, the association of notified bodies. Making sure that you document your development process in the logic of the EN 62304 process is probably one of the biggest favours you can do yourself as a developer. My experience is that EU authorities and notified bodies otherwise find it very difficult (and time consuming) to make sense of whether your software meets the essential requirements.

When does software need to be certified by a third party?

All apps that are medical devices will fall in MDD risk class I by default, except if a classification rule applies that bumps it up in risk class to class IIa or IIb, because the software's risk profile changes. An example would be that the software can influence or control high risk devices. If the software has functionality that allows it to drive a device or influences the use of a device, it falls automatically in the same class as that device. An example of this would be an app that can implement the recommend action by exercising control over another device that is in class IIa or higher, e.g. an iPad app that assists a cardiologist in interpreting data read out from a patient's pacemaker at a distance via WiFi, and then after having obtained the cardiologist's OK on a suggested reconfiguration, implements the reconfiguration of the patient's pacemaker at a distance.

The Standalone Software MEDDEV

The most relevant EU guidance document for apps is MEDDEV 2.1/6. This document provides for guidance in the application of the above criteria and to determine if an app is a, (in vitro diagnostic) medical device or not. It further provides for guidance on design documentation, many useful examples and guidance with respect to modularization of software.

The MEDDEV contains two flow charts, one for deciding if an app is a medical device and one to be applied subsequently to determine if the medical device is an in vitro diagnostic medical device.

MDD flowchart for apps

So, you want to determine if your app is a medical device - the medical devices flow chart directly to the right.

Diagram 1. MDD Flowchart for Apps

MDD flowchart for apps *(continued...)*

Step 1: computer program?

Software is regulated under the MDD as a so-called 'active device', which means it has to be able to act autonomously to an extent. For software this translates to the criterion that it must be able to execute, as opposed to documents that only contain information.

Step 2: embedded or standalone?

Software that is embedded on the device and comes pre-installed is regulated together with the device. It does not need to be certified separately from the device. Any updates will also be seen as updates to the device on which the device runs.

Step 3: does it create or modify medical information?

If the software does not perform an action on data, or performs an action limited to storage, archival, communication, 'simple search' or lossless compression (i.e. using a compression procedure that allows the exact reconstruction of the original data) it is not a medical device. 'Simple search' refers to the retrieval of records by matching record metadata against record search criteria, e.g. library functions. Simple search does not include software which provides interpretative search results, e.g. to identify medical findings in health records or on medical images.

If the software makes alterations to medical information like measurement readings to facilitate the perceptual and/or interpretative tasks performed by the healthcare professionals when reviewing medical information, (e.g. when searching the image for findings that support a clinical hypothesis as to the diagnosis or evolution of therapy) the software is likely a medical device. The MEDDEV mentions as examples of alterations that would be regulated:

- reconstruction,
- lossy compression,
- filtering,
- pattern recognition,
- modelling,
- interpolation,
- transformation,
- classification (e.g. scoring of tumors against specific criteria),
- segmentation,
- registration (e.g. mapping a data set to a model or atlas or to another data set, e.g. registering an MRI image on a CT image),
- calculations,
- quantification,
- qualification (e.g. comparison of data against references),
- rendering,
- visualisation, and
- interpretation.

For example: plotting data points over time against a bandwidth of (un)healthy values would typically be regulated functionality.

Step 4:

is the software for the benefit of individual patients?

This step is to determine if the data provides actionable information relating to one or more specific patients. Examples of software that are not considered as being
for the benefit of individual patients are those which aggregate population data, provide generic diagnostic or treatment pathways, scientific literature, medical atlases, models and templates as well as software for epidemiologic studies or registers.

Step 5:

is the functionality within the scope of the definition of medical device?

This step requires application of the definition of 'medical device' i.e. is the software intended for either of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease;

- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;

- Investigation, replacement, or modification of the anatomy or of a physiological process; or

- Control of conception.

Step 6:

if it is not a device, is it an accessory to a device?

Apps may also be intended to enable medical devices to function according to their intended use, for example an app that allows controlling IV pumps in a hospital ward at a distance.

IVD flowchart for apps

The IVD flowchart looks as follows:

Step 1: Medical device?

Determine if the app is a medical device by means of the flowchart for medical devices. If the app is not a medical device or an accessory to a medical device, it may (theoretically) still be an accessory to an IVD (see below in step 5).

Step 2: In vitro diagnostic medical device?

Determine is the app is intended to function as a stand alone software with expert function, by providing information on e.g. differential diagnosis, prediction of the risks of developing a disease, prediction of the percentage of efficiency or failure (e.g. of a treatment), or identifying species of bacteria.

Step 3: Data from IVD?

If the information that is the input for the expert system is provided by an IVD device (e.g. a blood glucose meter) the software containing the expert system is an IVD as well.

Step 4: Data from only from MDD?

If the information provided by the software is based on data obtained from medical devices only, the software would be a medical device.

Step 5/6: Accessory?

These steps are identical and serve to determine if the app is an accessory under the IVDD. The accessory criterion under the MDD is identical to the accessory criterion under the IVDD, see above under Accessories.

Diagram 2. IVD Flowchart for Apps

Revision of the MDD and IVDD and other developments

EU medical devices law with respect to apps is currently very much in flux:

- Both the MDD and IVDD are currently under revision and the legislative proposals contain both more detail on software and stricter requirements:

  - A much expanded definition of 'medical device' which includes software for 'indirect medical purposes'. The EU Parliament's ENVI Committee has voted that this decision should be adopted, even if nobody has a clue of how broad the scope of 'indirect medical purpose' is. Would that include apps that make sure that you move enough during the day to stay at a healthy weight? Nobody knows at this stage and the definition may still change further along in the legislative procedure.

- A much expanded definition of 'accessory', which includes also devices that 'assist' a medical device in its intended purpose. The concept of 'assist' was already included in the GHTF's definition of medical device , but the EU will now implement this. The EU Parliament's ENVI Committee has voted that this decision should be adopted.
  o Rules for the provision of medical devices and IVD functionality at a distance as service, so-called medical device as service.

- Design requirements for software that runs on 'mobile computing platforms'.

- Risk management measures regarding 'the risk associated with the possible negative interaction between software and the environment within which it operates and interacts'.

- Clinical data requirements with respect to software validation and verification.

- MEDDEV 2.1/6 on standalone software is under revision and may be influenced by the Swedish lobby for a wider scope of regulation of software.

- The EN 62304 standard is getting old and there are initiatives at ISO level to update it with the IEC 82304-1 "Health Software" standard. This International Standard applies to the safety of health software that is designed to operate on general purpose IT platforms and intended to be placed on the market (or be made available) without a specific hardware. In other words, this standard has mHealth written all over it. This standard could well be harmonized under the EU MDD and IVDD in the near future.

All of this means that if you are currently developing apps or have them on the market in the EU, you must closely monitor these developments. Especially with respect to the new medical devices and IVD regulations the process is technically complex with a lot of policy involved. Either the regulations are finished in early 2014, well before the EU parliamentary elections in May 2014 and they enter into force in 2014, or they will be delayed by the elections and may be put on the agenda again after the elections in a new political constellation and will probably not enter into force before 2015/2016.
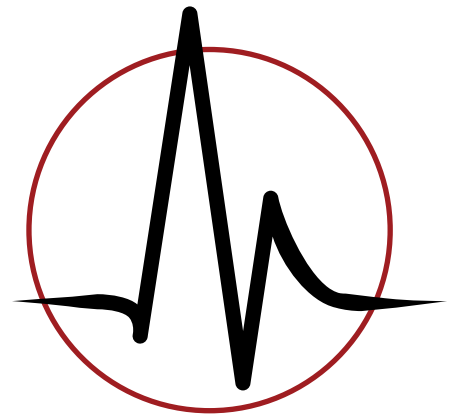
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