ASK THE EXPERTS

Unleashing the potential: Unveiling the regulatory drivers of the SaMD market in the US and EU

Speaker Profiles
Moderator - Christophe Amiel – Senior Director, Medical Devices & Digital Life Sciences

Christophe is an accomplished HealthTech professional with more than 25 years of experience in regulatory science from concept to market in start-up and international company environment. He has assisted more than 300 Medtech/Digital companies for placing on EU and US markets of their disruptive technologies by establishing and implementing their regulatory strategies for their disruptive health technologies including AI/ML based SaMD, Expert Systems, Connected Devices, Drug delivery systems and Digital biomarkers.

Andromachi Kaltampani, M.Eng., M.Sc - Director, Medical Devices
Andromachi holds over 10 years of experience in the medical devices industry, working with active device manufacturers of different regulatory maturity and product risk profile with particular focus on software devices. She has worked with regulators in Europe and North America. She has been instrumental in the transition of Technical Files from MDD to MDR, along with SaMD product up-classification. Finally, she has also developed expertise in topics including, QMS development, implementation, certification, and remediation.

Michael Husband, M.Sc – Director, Medical Devices
Michael is a proven expert in the areas of FDA marketing applications for highly innovative Medtech and Digital HealthTech products. He has more than 20 years of experience in the United States Federal Government including FDA, BARDA, and DoD encompassing advanced clinical decision support software, connected devices and digital monitoring systems. Based on his technical and FDA background, Michael successfully bridges the gap between scientists, Medtech engineers, and US MD regulators.

Welcome to the Ask the Experts session. My name is Christophe Amiel, and I will be the moderator for today's event on unveiling the regulatory drivers of the SaMD Market in the US and the EU.

Question: What other key regulatory differences for software's medical device product between the EU and the US?

Answer: OK, so what are the key differences and let me start with some similarities first, because it is important to always consider that there are similarities while there are, of course, some differences in these two jurisdictions. Both US and the EU follow a risk-based approach in terms of classification and therefore applicable requirements for devices. A device associated with higher risk to health means a higher classification and more stringent requirements whereas lower risk goes the other way around.

A difference in terms of classification is related to, of course, the fact that, in the US, there is one classification system applicable to an in vitro diagnostic SaMD, versus general medical devices that are software.

In the EU however, there are two different classification systems, depending on whether a device is actually an in vitro diagnostic software, or a general software medical device and it still follows a risk-based approach.

Another thing to think about in terms of similarities is of course the fact that conformity is a link to some of the same key recognized standards. For example, for software, we are looking at IE 62034 as a key standard for software development lifecycle activities.

Since the question is really focusing on the differences, though, I wanted to highlight the basis of assessment and evidence that needs to be assembled. In the EU, the CE marking is focusing on safety and performance so really the general safety and performance requirements listed in the regulation, whereas FDA approvals are primarily relying on safety & effectiveness. Usually in the software space, in the US we are looking at devices that are mostly in moderate risk (class II). I would say, on average, this would be related to 510K, primarily based on predicate devices; with De Novo the assessment would be focusing more on risk/ benefit as no predicate device would be available.

In terms of helpful resources for the US, especially, the FDA has a good list of frequently asked questions to actually guide you through the different steps that you need to follow to find out how to classify the software device, and of course, to identify a predicate device. Several guidance documents specific to software have also been developed and are available by the FDA.

In the US classification gets into defining what that the regulatory control for that risk actually means.

- Class I devices and software would be the lowest risk, and those regulatory controls would be general controls that would be applicable to all medical devices, and that is important to note that the controls kind of build upon each other.
- Class II is the most common, and where most medical devices and software falls, usually a 510K comparison to a predicate device. Those are special controls, mainly because FDA would consider special controls as specific standards or specific guidance documents that outlines the performance data that you would need to provide for that particular device.
- Then just to touch on the highest level, Class III, that is usually reserved for clinical validation, very high-risk devices usually used to sustain or support life, usually implants. Those are not as common for pure software devices, but for sake of completeness, as I said, those are often done with some sort of clinical validation.

Question: What are the typical challenges for, innovative, software-based device to access the US Market, who take the 510K route?

Answer: The most common challenge with an innovative or disruptive software that wants to follow 510K route is going to be making sure that you meet the definition of a 510K, you have the same intended use and same fundamental technology as the predicate device.

Now intended use is really what the device does, so that can be fairly broad and what is a subset of the intended use, the indications for use, which is the reason you use the device. That is where it gets a little complicated, because you must have the same intended use, however, indications for use can differ. The whole basis of your 510K is to demonstrate

through existing performance data or existing special controls that your device, with the different indications is just as safe and effective as the predicate device.

So, you are basically saying that the innovative features, while they are different and while they are different indications, you have shown through your justification and through your regulatory controls that they are safe and effective and fall within the overall intended use of the of the predicate device.

The second point is fundamental technology, I mean, we are talking about software and so, fundamental technologies are going to usually be a little bit of an easier argument and to make. However, it is just as important because you do need to make sure that any sort of AI or, algorithms that are making decisions, or influencing the output of your software, that that that would be considered a new type of technology, depending on the area that you are targeting. So, it is important to look at this for that aspect as a difference, and whether or not that difference, again, raises new questions of safety and effectiveness, or that you cannot answer without existing controls. In other words, you are looking to do a specific clinical validation, or even specific performance testing, to demonstrate safety and performance.

Because we are talking about disruptive devices, one thing to consider, is, how will you demonstrate the valid clinical association of the software output. So, based on the inputs and the algorithms selected, you have to be able to demonstrate how this is associated with that targeted physiological state or clinical condition.

So, to do that, depending on what is out there in terms of information, and you may be able to demonstrate this through literature or professional guidelines, and very often it can be proof of concept studies, or your own clinical investigations and performance studies. So there is not just one way of showing this, of course, but this is a particularly important point to think about when we are talking about disruptive devices, because maybe the disruptive element is in the technology or the actual association with the condition, and so that is an important thing to keep in mind.

Question: Are there any MedTech Health innovation programs proposed by the authorities that can be utilized to facilitate market entry in the US and in Europe?

Answer: When we talk about early interactions and how we can facilitate getting a particular product on the market, the most utilized and most popular, and something that is definitely recommended is the Q Submission Program. There are several different types of Q submissions that the FDA has put out in guidance. The most applicable, is usually a pre submission used to de-risk any future marketing application. So, to facilitate market entry, you would want to utilize the pre submission, to get the FDA's early feedback on your proposed regulatory pathway, what you are doing from a development standpoint and get some answers on what you are doing to demonstrate safety and effectiveness. You can use those for 510ks, and it is especially recommended you use them for DeNovos. You can even use them for Class I devices, although those are less common.
In addition, under the Q submission program, you also have the Breakthrough Devices program. Those are for devices that are innovative and targeting a particular disease or condition that is serious and life-threatening. These devices have a significant impact on patient care and there really is not anything on the market or it is a significant and innovative improvement of what is on the market. It is truly unique to what is already the standard of care and in of itself is its own Q submission. Really what you are asking is whether or not you qualify for the Breakthrough Devices program and what you would get from a successful submission would be priority from the FDA.

It Is not a guarantee that it is going to accelerate market entry, but it is something that will be at the top of their queue and something that will get their attention. A step down from that is the Safer Technologies Program, it is the same basic process, however, if it is for devices and software that really does not meet the qualification for breakthrough devices or have the very specific qualifications to be in that program. Safer Technologies Program is similar, but the qualifications are a little less stringent than for Breakthrough.

In addition to the Q submission program, there are also some other ways you can interact with FDA if you have specific questions in the following areas. The first is, if you are unsure of the classification of your software, you could look at a 513G request.

And, if you potentially have a combination product, if your software is coupled with a therapeutic or therapy, there is also a request for designation, which would let you, work with the FDA to determine the lead center of review. So, in other words, would it be CDRH, or would this be managed under CDER, or even CBER; that covers it for the US.

In the EU right now with the new medical device regulations, there has been a lot of effort put into actually implementing them, and there have been a number of delays. The focus is on making sure that there is time for all the relevant parties to go through the Conformity Assessment routes that are existing in the regulations. There has not been a lot of movement at an EU wide level, I would say, with regards to innovation programs available but there are still some local initiatives that you can find. For example, in France there is Guichet Innovation, a program really offered by ANSM as a support service for the development of innovative health products, and it really allows people to actually make a request for scientific, technical, legal and/or regulatory support from ANSM teams. Of course, we expect that we will be seeing more of these programs, at least on a regional level, however there is no known initiative specifically covering the whole of EU. Right now, despite focusing specifically on EU in this case, I would add that in the UK, specifically, and while not falling per se under the current EU medical device regulation, there is a lot of movement in that space. So I would want to mention the innovative devices access pathway (IDAP) being launched by the MHRA.

There is actually a pilot running, or at least initiated at this stage; submissions are now closed, as far as I am aware, but depending on how this goes, there are high expectations on supporting innovative devices, including software devices, through this pathway. And definitely keep your eyes peeled for what is happening in the UK in general because, there is a lot of movement and desire to support businesses that are innovative and are trying to benefit the public. One more thing to add here is not a pathway to consider, but, again, talking about the UK, one of the initiatives that UK has taken is to actually expedite access to the market through submissions that come from other regions. There are already discussions with other key markets in accepting under conditions, for example, approved devices from other key markets.

So, again, it is important to keep in mind, because if you put the effort into entering the US and utilizing for example this market authorization, this could help entering the UK market a lot easier and in the future.

Question: Can SaMD validation data, recognized by European regulators also be used to support a US submission?

Answer: That is, indeed, quite a typical question, especially for those who manufacture that have already either made some steps in the EU already, or are approved in the EU, and are looking into going into the US.

Let us start with what first often comes to mind, which is usability and human factors testing. So, you have done that already, and you want to know if this would be sufficient for the FDA.

The answer is, I would say quite straightforward, in a way, because the key thing to think about for this question is, what are the differences in terms of clinical practice, and patient population, that we are trying to address in these two regions? And so, if, for example, there is a difference in clinical practice for the application that you are looking at, you have to be able to demonstrate to the FDA that the data you already have would be applicable to the US.

And if not, you would have to do an additional study, a bridging element there, to demonstrate that the product will be applicable as is to the US market. The other thing that I talk about is patient population. Again, there are considerations there, in terms of any specific population characteristics you may have to think about.

For example, and let us say literacy level for the areas you want to target is different in one market to the other Are you focusing, for example, on a particular part of the US, where the literacy levels may be different to what is considered average in the EU, and is there any difference in terms of, for example, skin color or other characteristics like that that would impact your device? You then have to be able to demonstrate through your data that these are considered.

So, if that is already covered in your data, and that is great, you can support your submission with this data To be honest, more often than not, FDA would expect a percentage of, any studies conducted to be including US population and, of course, intended users; for example, if the intended user is a health care professional, FDA would expect to be able to see that you have included US clinical practice considerations.

They would expect to be able to see how the affected population and intended users will be represented in the data and going beyond usability, again, clinical evidence, in general. So, if any studies were conducted and focusing on EU population only, you have to be able to demonstrate how the differences to the US have been considered. Going back to one of the previous questions answered just before, this is why the pre-submission process is of great benefit here; it is actually the best way to de-risk your future application to the FDA. And you do not want to be in the place where the FDA comes back to you with a question around your data that would require another study to be conducted in the middle of the submission.

Ideally, you want to know that in advance, that you have the blessing from the FDA to use your existing data or the plan you have shown to them on the bridging elements to US patient population and clinical practice. And then go on and either, do that additional supportive study or submit what you have, if that is what is going to be accepted by the FDA per their pre-sub responses.

The FDA is looking to make sure that any data you provide is applicable to the US in terms of clinical practice and the patient population that you are targeting.

In addition to that, the FDA is always looking at harmonization, especially with the recognition of standards. The standards databases are constantly being evaluated and updated as international standards are published. There are guidance documents that talk through how some standards are applicable, and what parts.

And, as an example, the quality system regulation that FDA has is becoming closer and closer to ISO 13485. We are there, but there are still some differences. If you are following 13485, you are you are in particularly good shape to make sure that you are in line with FDAs quality system regulation as well.

So, yes, you would definitely need to make sure your data is applicable, but, you know, there is a particularly good degree of harmonization across geographical regions.

Question: A company submitted a 510K application, which they had to withdraw because of lack of effectiveness proven for the device. How do you overcome the situation of the potential withdrawal of your application based on the methodology and the type of data that will come support the demonstration of your successful equivalence?

Answer: Without really knowing specifics, when you look at demonstrating effectiveness, in the case of a 510K, you really are looking at supporting the claims, specifically, the intended use, and that is a global, intended use. It is important to realize that the intended use is a global intended use, it encompasses everything you say about your software or your device. It has to do with any promotional material, anything on your website, the labeling. All of those claims can be interpreted by the FDA, as claims that you are making and FDA does take a very, even subjective look at that, on how some phrases could even be interpreted, especially in terms of advertising. So, each one of those you are going to have to support and sometimes it could be just the language you are using that you may not meet for a given claim of effectiveness. What they would think a standard for effectiveness is may be different for a particular device and sometimes you may need to consider softening that language.

For example, if you say, you are going to diagnose a particular condition, then, they are going to expect that it is accurate, very close to 100% of the time; diagnostic accuracy needs to be very high. But if you said that you were an aid to diagnosis or you assist the clinician in making a diagnosis, those are a little bit of a lower bar to reach; as long as you are very clear that the clinician isn't to solely rely upon your software to make a particular decision, you can have a less burdensome approach to that. But again, you do need to be, at least in the case of a 510K as good as the predicate.

Sometimes you can only match a subset of an intended use of a predicate device and still qualify for 510K. There are other times where, being a subset, the FDA may look at that as being less effective. It is viewed on a case-by-case basis.

Where we can help is taking a look at what you have claimed and what you have proposed to support those claims, and then help you either adjust those claims, if you can, or design some studies or performance testing, to better support those claims. It is a case where you could have avoided the painful situation of withdrawing your application if you had engaged with the FDA in the pre submission meeting process.

There are many cases where it is viewed as a least burdensome approach for reaching the US Market as compared to a CE marking under the MDR, which can be the case in many situations. But the price to pay for 510K is actually a bare minimum to be able to pick the right predicate device which, might be jeopardized not only based on the similarity of intended use, but also in the fact that, technologically speaking, your device might be too far away from the fundamental technology used by the competitor.

And unless you can, based on adaptive data, justify for the fact that this different technology is not going to be the object of any new questions around safety and effectiveness, it might be a situation, indeed where if you are not convincing the FDA with the right data to evidence that equivalence, you are going to be stuck and actually asked to either withdraw your 510K or moving towards the novel application, which is, of course, more cognizant than just for traditional 510k, especially regarding the requirement for clinical data.

From experience the main gaps we have observed when companies approach the FDA with a CE Mark already in place and one of the FDA will typically react on in terms of either reinforced or different expectation requirements regarding the derogatory evidence that presented to them in the frame of 510k or the DeNovo application.

There is one point I want mention here because, it is very frequent for SaMD and very often, from my experience forgotten or minimized by companies, which is actually the situation, for example, of your cybersecurity and controls you have in place, by design, in this area.

And the reason you can be, fooled is the fact that, you know, in our opinion, at least the FDA is really running far ahead from notified bodies in that domain apart from major ones, which would be equally comfortable with cybersecurity. We have been in a situation where CE marking may have been granted, initially, without necessarily going deep enough, in terms of risk analysis, for cyber security, giving the impression that everything was under control. The FDA then picked up a lot of threats and fragilities from their perspective in that cyber security approach on that given SaMD, which actually broke out some 510k success on the ground. So, there are areas, of course, where there is a common understanding regarding requirements, but not necessarily the same expectation regarding how much in-depth you need to go into the topics in order to fully be per FDA expectations.

When you look to make that transition, one of the things that I see is usually a gap is the harmonization of standards. When you look at compliance with standards, the FDA is a little bit more particular in how you make that declaration, especially if the standard does not call out specific methodologies, the FDA is really going to want to know how you applied the standard; if there are any deviations or if a particular test setup was not specifically defined. And that gets into what we mentioned earlier with cybersecurity.

The first thing I would definitely take a look at is what we do as far as trying to help technologies transfer their CE marking to a more successful 510K is really take a look at what are the applicable guidance and standards that the FDA recognized and recommends as part of their 510K and really making sure that not only is it addressed, because in most cases it usually is, but also that you have adequately described and shown how it is addressed.

The real key is that the FDA does want to see how you applied a standard, how you justified a particular test or study; it is usually not going to be enough just to say that you are complying, they usually want to see a little more than that. I would definitely take a look at your documentation and make sure that you are you were really walking through the FDA on how you are demonstrating safety and effectiveness.

In other words, you can present results, but they really want you to describe, and make an assessment that you have to the best of your ability, demonstrated safety and effectiveness, and how that particular test does, especially in the case of a 510K and even a DeNovo where you are developing your own special controls for a particular product.

One thing I would definitely want to highlight, and I am sure people here will be familiar with this, is there is a lot of good guidance available from the FDA. I know that we talked a lot about the standards that are common in terms of applicability within the two jurisdictions, but I would say if, especially if you are transitioning from EU to US, is to pay particular attention to the guidance documents already released and freely available by the FDA.

And, in addition to that, there is actually a lot of recorded webinars on the CDRH website with a lot more information on specifics for these guidance documents, that you can look up and try to align what you have already done in the EU. There is not a gap per se but a way of articulating the information that FDA is more particular with, that is actually explained through the guidance system and can be easily implemented by you in practice.

So thank you very much for joining us today and looking forward to our next expert session.