Brexit: What You Need to Know for Drug Development

Episode 16

Ed Narke
Welcome, everyone, to CMC.Live! Today we have a special guest. Joining us here, again, as always, Meranda and Brian. Today we have Amber Sheriff on the podcast! Amber is a Regulatory Affairs and Quality Assurance Expert. She recently joined our group here at DSI, supporting that. She's joining us this morning from Chicago. She's worked at Baxter Healthcare, Acorn, Marathon Pharma, etc. Today we're going to be talking about a few things- regulatory pathways in the European Union is the overarching subject, some experiences around centralized and decentralized filings for our listeners. Also, Amber will be talking a bit about Brexit and some of the filing issues and concerns there. So Amber, let's get into this episode, starting with some of your background, how you got started in regulatory, and get your thoughts on some of these things. Welcome.

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Amber Sheriff
Thank you, Ed. Thank you, Brian. Thank you for inviting me to this podcast. I appreciate it. If you want to hear about my experience, my experience has been pretty long and intense. I have worked in the pharma industry for 25+ years, starting with drug development and to regulatory and quality all the way. Now, I am a subject matter expert in regulatory strategies, filings, and submissions processes. You name it- I've done it.

Ed Narke
Okay, so tell us some of the experiences that you've had. We had a somewhat recent experience with some of these things in Europe. Can you talk to us a little bit about the mutual recognition process versus decentralization, centralization procedures, national procedures- some of those things, maybe highlight some of the areas around CMC to be thoughtful of?

Amber Sheriff
In principle, there are three procedures for obtaining market authorization in the EU. One is the mutual recognition procedure. The second one is decentralized. Then the third one is the centralized procedure. The difference between these three procedures is the mutual recognition of basically submitting to the country, and you have your reference member state submitted over there. Once you get approval through there, you go to the other states, and you get separate approvals. So once you get the mutual recognition, you can take that, apply to the other states and the member reference states, and get approval over there.

Brian Lihou
So Amber, just for my benefit, once you make that application in that mutual recognition, can you then take that same filing content and submit it to the different states? The different member countries?

Amber Sheriff
Yes, you can. In a way, you can repeat that, and it is called repeat procedure. So you can take that and go to separate states, and you can ask them for that. It takes time, but that is the main way because they are mutually recognized. So you get one, and they agree on that. And you can go through the other one you submitted separately and get the approval of that. So you target the countries that you want.

Brian Lihou
Oh, I see. Are there separate fees for each as well?

Amber Sheriff
Yes, I think there are slightly separate fees for each of them. It can also be done simultaneously where you have the reference, you finished off this, and you have already aligned that my reference number state was Germany. Then you go to France and Spain if you've already targeted these five countries that I want to get approval on. So you choose one recognition country as a recognition procedure to follow that.

Brian Lihou
And that becomes the template effectively for filing in other countries. Okay, understood.

Amber Sheriff
The centralized procedure is somewhat different. If you go to the centralized procedure, you get approval in all 27 EU countries and the other three- Norway, Iceland, and another country that also agreed to it. So you can get approval in all of those countries together. That's the main difference between centralized and decentralized procedures. However, the decentralized procedure has some products that can be approved and some that are not. You have to fall into that category for it to be included in that procedure. So there are again, some differences like age medications, and all of those things, vaccines- they can fall into that, or you already have an approval for that product in there. You need to follow the same pathway; then, you can fall into that same decentralized procedure. So some products can be included and some that can be not be included.

Ed Narke
That's a great point. I always had questions about that. So the centralized procedure is mandatory for certain types of products, correct?

Amber Sheriff
Yeah.

Ed Narke
Okay. Then what type of products would those be? I think you mentioned a few with the biotechnology processes. You mentioned immunodeficient syndrome products, cancer, neurodegenerative disorders. So I guess a follow-up question- besides the definition for mutual versus decentralized and centralized, there's a pretty good description of those on the European agency's website and some of the protocol and process, some of the effects on the CMC development/drug development in that area, is there anything that you can speak to in regards to that? Can certain things be delayed or discussed differently? Could some of the information that you use in discussions with the US FDA be used?

Amber Sheriff
So with the EU, we have to keep in mind that the more we go and engage them upfront with the scientific advice meetings or any of those meetings, it's more helpful than keeping it until the last minute. Have a scientific advice meeting with them the minute you think of a project, product, or whatever. Tell them what you have, initially, and ask them the questions. That becomes the process. You also have to go ahead in that process and tell them your timeline- when you will be submitting it. Become engaged upfront.

Ed Narke
I have some general questions—the difference between regulations. When you're talking drug development, FDA versus Europe, I've always looked at it as there's a different mentality. There's sort of a top-down versus a bottom-up review and discussion. Can you talk to maybe some of that, maybe things to be aware of if you're simultaneously looking to file in Europe and the US?

"If you get an approval in Europe, there are testings that you have to do for EU."

Amber Sheriff
If you get approval in Europe, there are tests that you need to do for the EU. So if you are developing a product and want to target both US and EU, set the testing standards so that you test the product for the EU and US. So those products, the components, the API should all be compliant for the EU and US. That's the main difference that people forget. Then they want to add up there and then come back and say that you haven't tested it for EP requirements. So as long as that's done, it becomes easier because the same NDA you submitted in the US can be submitted for MAA. There are very slight differences in the CMC sections, mainly that you have to write in the format they want. Other than that, you can take this and submit it over there as long as the testing and all the requirements are met up front.

Ed Narke
Okay, any specific differences or requirements?

Amber Sheriff
These are the same testing standards that you meet, the standards of EU, ISO standards, all those things, so nothing major in there.

Ed Narke
How about any additional need for stability or additional specifications?

Amber Sheriff
If you meet the FDA requirement for stability, then you are fine with the EU. The one major difference I've seen is redoing the PPQ after getting the approval, and we're ready to market. In my products that we have submitted to the EU, they want the PPQ done before. So they do want that and, that's one of the things that we have submitted along with that.

Ed Narke
Sure. Yeah. So I know Brian has a lot of questions about the centralized procedure. Brian, did you want to bring in any more of those that we chew on sometimes?

Brian Lihou
Well, yeah. When you're submitting the MAA, is it a multinational panel that reviews it? Are there certain countries that handle certain aspects of the filing?

Amber Sheriff
You choose the reference member state. It could be Germany, France, etc. Once you use that reference member state, they are also from the other countries that can be chosen too. They are in the centralized procedure, repertoire, and co-repertoire. The co-repertoire are the other countries, one of the other countries participating in the review. Once they review it and give you your assessment, you respond to that, which is what is approved. The reference member state is the main one.

Brian Lihou
Got it. Okay, so, for me, a lot of our clients come with defined budgets and timelines, and, as you can imagine, they want to get the most economical path to filing they can find. So, our job is to help them get to that point. Now, listening to you describe the various types of filings, it seems that there are clear advantages over a centralized filing in terms of approvals, time to market, everything like that. So, is there a criterion that has to be satisfied to apply and perform a centralized filing?

Amber Sheriff
If it meets the requirement of what the centralized procedure is for, then definitely you can file it, but there are some certain requirements that you must go ahead and follow for that. Right now, from my experience, I have gone through both centralized and decentralized procedures. For the centralized procedure, it is easier to go ahead and get approval. One of the criteria is that you engage them and send a letter of intent. As long as they say, "yes, you are fine with this," you go with that. You do have to send a letter of intent and engage them ahead of time. So from the time that you are ready to submit, you have to engage them seven months before. The European Union does not meet like the FDA. We can understand them and say, "okay, we are submitting it." They have certain timeframes when they meet. Once a month, everybody gets together, and they look at what applications are coming in; they need time upfront. So if I'm thinking of submitting something in seven months, I will have to engage them, tell them what my plans are, and they will give you a slot to say, "Okay, that's the timeframe that you can submit." If you are not going to meet that timeline, then basically you have to inform them that, "I am not going to be able to meet the timeline, I'm going to be slipping. Can I go ahead and go to the next month" or whatever timeframe you need. In most cases, they agree, but if they're booked full and have given that time to somebody else, they will tell you, "No, not now. Maybe the month later" or something like that.

That's the other thing. Although there are 12 months, they don't meet all 12 months. There are times when they take off during the time of Christmas or something. There are 11 times that they will meet in a year. Two of the months, I think it's the August to July timeframe, they go on vacation. You will not be able to get anything from them. So you have to be working with them. This is the other criteria with the European Union- that they have specific timeframes and, it's all set up. Procedures are much easier, not like with FDA, where we do not know when we are going to get approval. They have timeframes which they meet. If they say they will give you this preliminary assessment response in 80 days, they will. Then you get it in 120, your assessment over there. Then it's 180 days. So all those times are set and, you know that you will get approval as long as you have satisfied the requirements. Now, if you need more time in between to respond to them, you can request and say, "I will not be able to go ahead and submit it in three months, but can I go ahead and submit it in six months or something," and they will be fine with that. You need to be in direct contact with them.

Brian Lihou
So in that regard, it is a lot different from the FDA, but it comes down to effective planning, looking at your calendar.

Amber Sheriff
Effective planning is key because you know when you will get the approval and when you will be able to market. So that is the main difference that I see in there. With the European Union setting their headquarters in

Amsterdam, there are some slight delays there, not by much, but by a week, which was never expected in most cases. So I do see that some of the things are delayed by a week or around a week.

> "Effective planning is the key. Because then basically you know when you're going to get approval and you'll know when you will be able to market."

Brian Lihou
Now, looking at the climate of things, my experience has been with the MHRA and a driver in our filings, now you've got Brexit and the impact of Brexit on the EU. So just when I was about to understand the EU and how everything works, Brexit comes along. So would you mind just providing some insight on the impact of Brexit and what that means for people that are still filing in the UK? How is it done? What's changed?

Amber Sheriff
So what is happening now is people who have filed in the UK can no longer sell their products in the EU because the UK walked away from the European Union. So now they're setting up their procedures. They are going through that. By the end of this year, they will be fully separated from European Union. Their approval is separate from what you will get from the EMA. When you get the approval from the EU, you can sell it in all 27 countries, or you can follow the procedure from mutual recognition and go to the other countries and keep on adding over there- they will be recognized over there. Not so much in the UK; they're separate now. If you had approval in the EU, you might have to go back and submit it. That is what I'm hearing. Nothing is clear now because guidance is still coming out. From what I heard earlier this September (2020), they are coming out with some guidances that are talking about them following somewhat of the EU procedure, but then again, some standalone procedures for the UK only. So the guidances are going to be defined pretty soon.

Brian Lihou
Now you've got additional fees. You've got additional timelines to consider. So it's a bit more complicated. Some of us remember the days before the EU. So it's going to be a little bit like it was, but good to know.

Amber Sheriff
So whatever you were following in MHRA, it will apply to the EU right now. You can still follow the same path, but it will be set up separately for the UK. Since a lot of the scientific people were in the UK, they were the major part of it since the EMA was based in the UK in London. So that's one of the reasons they lost a lot of the people who were subject matter experts when they moved to the Netherlands. You can still submit scientific advice that you took from them to the EU. But I think it's going to be a third party, a consultant or something like that. You still have to go to the EU for scientific advice to get their approval.

Ed Narke
I started back in the day doing some light stuff for Europe, etc., but that was long ago. Many changes happened. So the way I look at it now, before Brexit, the centralized procedure seemed to make the most sense. What are the benefits? Everyone gets authorization at the same time. There's a collective safety monitoring, so all the information is coming in one thing. Everything was in standard language, etc. So what would be the advantage to do decentralized or mutual recognition, which may have changed with the Brexit situation, but what are some of the advantages, if you're even eligible? What would be the advantages of doing a mutual recognition? I'm just not familiar with it. Is it just a little bit easier, a little bit more fluid?

Amber Sheriff
A little bit easier, and you're focusing on one country, so if you want to market in one country, you want to go with the mutual recognition and then take your time going through the other countries getting approval over

there. So instead of marketing in all the European countries, just market in one country first and see how it goes. Then start adding those because the fees are not that high, and they are mutually recognized, so you have already gotten approval. So it's easier that way. A lot of people go that way also.

Ed Narke
Is there a chance you can answer through mutual recognition for a country with a little bit less requirements for CMC?

Amber Sheriff
I think people have their ideas on which countries are easier and which are not. I find that it all depends on the reviewer naturally. Some countries are open to it, and some ask you questions. So I would not be able to say that one country is easier than another. It depends on the reviewers; it depends on the people reviewing and how much experience they have.

Ed Narke
Are there any regional requirements that you notice that are pretty transparent depending on the country? So, for example, maybe somebody's looking for more stability, or somebody's looking for something specific around compliance. Are there any examples that you've come across in the last few years where you've seen certain countries focusing on certain areas of drug development?

Amber Sheriff
Not so much. All the countries are following the same standards, the ISO standards. There are not many differences as long as you meet those.

Brian Lihou
You know, it used to be different. In the early stages of the EU, you started to see some of the nuances with the member nations. For example, there were always cleaning protocols, cross-contamination, and things like that on the CMC side in the EU. We always expected questions about that. I know with our experience early on with the French, it was stability questions and challenges. This is years ago, so I would imagine that the EU has finally become a bit of a more standardized state over time.

Amber Sheriff
Especially the stability part of it. They have come out with a lot of those stability protocols and all of those things. If you follow their guidelines and do all of those, they are fine with it. Most of the questions, if you're following it, you will be able to clarify and answer them. It's not that difficult. We have to follow the guidances that they have put in there: the q1, q2, q3, q4, all of them. As long as you follow the quality and the stability guidelines, you're okay. There are also specific products that go the same way as the FDA goes ahead and says, “This is the guideline for this product. This is the guideline for that product.” I can’t think of the names of the products, but there are specific products. If you are falling into that category, you have to follow that to the nail. They will ask you questions. In those cases, where you have some of those kinds of products that have particular guidance, it is very beneficial to have a scientific advice meeting with them and ask your questions. Give them a little bit about your product, provide the briefing package, and ask the questions. They will give you detailed answers as to what they are expecting.

Ed Narke
So Amber, just curious, any thoughts on where things are going? If we all fell asleep for five to eight years, and we woke up, where do you see the whole process going with Europe, post-Brexit- some of the procedural stuff? Any thoughts? Where do you see the process and the way drugs are regulated going? Is there anything that you see as a trend that could take precedence and become the new normal for the future process?

Amber Sheriff
The new norm between both the mutual recognition that is basically between FDA and EU, I see that as more and more becoming a norm. Now you see, between the FDA and the EU, there is mutual recognition. For CMC purposes, I'll give you an example. If you have a plant that FDA has gone and looked at and they find that in compliance, the EU is taking that and saying, "okay, fine." So those are the things I think we will be merging and begin to rely on each other a lot more than before. If the EU has looked at the plans and then the FDA says, "okay, fine. We will go ahead and give our approval based on that." So I think there will be a mixture between both the EU and the FDA working together to bring the product to the market earlier and not stopping at things. I think COVID is another example that has brought this to everybody's attention because a lot of the traveling cannot be done. So if you rely on everybody to be going there, I think either they're going to be doing virtual, or they're going to be going ahead and relying on each other's expertise and agreeing to that.

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Meranda Parascandola
So do you see any trends in drug development in the EU given the current situation? Do you see, over time, anything evolving other than the collaboration between the EU and the FDA?

Amber Sheriff
Nothing comes to my mind that I can see a trend, but I would say that they are keeping their timelines. People are going to Europe more and more because it's becoming much easier to get approval when you have a time set and say that you will get approval in 210 days, given that you've done everything. Where do you think you would go? First Europe and then after that the next people go to. Once you have the European approval, it becomes easier to go to Canada because Canada accepts the EMA approval. So people are also trying to go ahead and do that- get the EMA approval first, then go to Canada, and then lastly, the US. So I've seen that trend a lot recently. If you look globally, you will see that a lot more countries from outside are coming to Europe and bringing the applications over there first and getting the approval over there. The US is second after that. So people from countries like India and Asia will see their products being approved in the EU first. So I've seen that trend also.

Meranda Parascandola
So a lot of our clients are on a shoestring budget. So going to the EU, would they benefit from a centralized procedure or decentralized? I know that there are fees for each.

Amber Sheriff
Once you get the approval, you get it in all 27 countries, including Norway, Iceland, Lithuania, or something like that. So three other countries come along with it.

Meranda Parascandola
So the filing fees aren't extravagantly different. So if they wanted to try the EU, it wouldn't be a stretch, budget-wise, to go centralized.

> “The mutual recognition that is between the FDA and EU, I see that as becoming more and more the norm.”

Brian Lihou
The difference is you've got the burden now to market and launch in those countries because you've gotten approval. The timing for those activities, I guess weighs into that decision.

Ed Narke
Anything you want to talk to us about that people should know about, Amber. Any great stories about working in regulatory or any things you can share that might resonate with anyone growing into the regulatory space.

Amber Sheriff
Basically with EU, like I said, if you are planning on a submission, just be aware that they are not there for the summer. So if you're thinking that you're going to get the approval in September or August, you better think twice. You probably will not get it if there are any questions and delays or any of those things. So you have to work around that. That has happened with us where we thought, “Okay, well, if we miss June, it doesn’t matter. We'll go in July. We'll ask them if it can be submitted in July.” Well, it does not happen that way. So you have to keep those timings for Europe because they are very standard. It's not like FDA, where we think we can go ahead and slip a month and submit it, and they will take it. So it's not the same case as that.

Brian Lihou
That was hard for me. My first encounter was working with a German company, and August was essentially just not on the table. It’s fascinating.

Amber Sheriff
A little bit of December too, but what they do is they try to have two meetings in November to kind of offset that for December, which is good, but August is off the table. Not only that- if you have people working over there, things are closed. So if you have a manufacturing site over there, if you have an API manufacturer over there, or you're trying to get some documents, you have to be mindful of the fact that Europe closes down in July and August. It even impacts your application. It impacts your timeline because you cannot get the information from them even if you're filing a US application. So we have to be very aware of that and keep that in mind. In the US, we tend to forget that because we have been working here all 12 months. So basically, that's one of the things that I find. I've had numerous examples of that where we had to kind of go ahead and tell them upfront, “By the way, I need this information over here. I know you are going to go on vacation. Will you have a substitute for you somewhere?” This is with the manufacturing sites or with the API manufacturer- having that conversation with them upfront and making sure that I have somebody over there because if my timing is such that I am getting an assessment and I need responses from them, I need somebody there to be able to respond to them; otherwise I won't meet my timeline.

Brian Lihou
I think that August slow down even predated the EU, though, because that was the trend in Western European countries. I know Italy honors the same thing. They're on holiday. You have to respect it. Absolutely.

Amber Sheriff
That's not something that we think about when we are in the US. You take your vacation when you take it. It's not a whole countryside shut down like that.

Ed Narke
Okay, so in principle, there are three defined procedures to obtain approval for products in Europe. We discussed an overview of a few of these procedures on the podcast today- decisions based on dependent nature, active substance, a couple of other things, target indications, even history of the product and marketing strategy. So, Amber, thank you again for joining the podcast. We'll see you soon. Thanks, Brian. Thanks, Meranda.

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