Expedited Drug Development

Episode 1

Ed Narke
Hello everyone, welcome to CMC live. My name is Ed Narke, host of CMC live. In this episode, we speak with Dr. James Mencel, who looks after API process consulting and analytical here at the DSI.

Keep in mind this is not authorized advice; please check with your regulatory group or have an official conversation with the agency before acting. Jim, hello.

> "When you are in a program that gets expedited, the attention is for the program to move quickly. And there are several ways in which it can move quickly. But almost all of them lead to a very shortened timeframe for CMC. So, what it gets you is the FDA's aware that there is stress on CMC."

James Mencel
Hi Ed, thanks for the introduction. It is a pleasure to be here today. I will be speaking today and hope to engage those who are listening about everything associated with CMC and Phase Three in the context of an expedited drug development program. There has been a lot of expedited activity recently, especially in the smaller emerging biopharma space. It presents some unique challenges for the CMC group on the verge of two and a phase three programs.

The components of the discussion today are going to be, first, Phase Three terms and definitions. There is a lot of jargon, but I will define some of those terms that will come up in this discussion so that you have an idea of what these refer to. The next point will be a listing of the key Phase three events that impact CMC. There is a handful of those that we need to anticipate and plan for. A third point I will cover is what I call a 'lock point'. A lock point is where your process itself must be locked, whether it is a drug product or drug substance, your physical properties for your drug product, good drug substance, drug product, dosage form, or formulation. I will discuss where those are and why that is the case.

We will move on to expedited programs and the regulatory expectations that they placed upon CMC. From there, we will talk about the Phase Three experience in the context of an expedited program. I will also discuss the critical areas for CMC planning and activity.

The first definition for Phase Three that I think is particularly important is **the regulatory starting material**. People have various concepts of what this means, and I am surprised by the number of people that do not have a clear picture of what this is. The regulatory starting material is a structure in the process, where after that point, all processing must be GMP. Now there could be several regulatory starting materials entering the process at different points, but there is a particular one where everything starts at the very beginning of the process. The regulatory starting materials must be proposed to the

agencies. This is important because, before the regulatory starting material, the agency does not see what goes on in the process. So, the agency needs to accept that you have control of everything up to that point. The proposals must satisfy ICH guidances.

The critical thing to note here; authorities may not agree with the FDA, the EU, the KFDA, or the TGA. I have seen cases where all four agencies have different views or different feedback to different clients. The regulatory starting materials are made non-GMP. As I have said previously, this information is not provided in registration filings, and the agencies are blind to this aspect of the process. The manufacturer must be indicated in the filings and must be fully available to the agency for inspection. Sponsors must manage the regulatory starting material, and there are stringent controls over sourcing and manufacturing. These are provided in the registration filing. The sponsor makes some commitments; even if the FDA does not see the detail behind the regulatory starting material, there is an understanding of what the sponsor must do. So, this is the first definition.

Ed Narke
Jim that is great to know. As you know, we talk about strategies and CMC issues on CMC.Live, if I can push ahead a little bit to breakthrough expedited programs, what does breakthrough designation or an expedited term get you for CMC? Can you share any experiences that you may have seen?

James Mencel
Well, what it will get you is a lot more interaction with the FDA. For example, the FDA is aware when you are in a program that gets expedited. The intention is for the program to move quickly, and there are several ways you can move quickly. However, all expedited programs lead to a significantly shortened timeframe for CMC.

What an expedited program gets you is the FDA is aware that there is stress on CMC. They are also mindful that they are not going to give way to their quality requirements. The FDA will meet with a sponsor more frequently than usual to help the sponsor navigate what is required to ensure that the drug substance and drug product can be made to suitable quality. This is to ensure that the FDA is happy with the direction the manufacturing is going. So, what it gets for CMC is help, but it also brings stress. You must remember the filing must occur, and the FDA must approve.

Ed Narke
A few things that you are offered for the breakthrough or expedited program status. Frequent communications with FDA seem to be in play and then less waiting if you are engaged with them to get answers to the critical questions that might come up. What are some of the breakthrough designation items associated with that, that you do not get? Are there any freedoms to do different things and normal?

James Mencel
Well, it is all negotiated. So, for example, I tell this to people all the time, there are certain aspects of regulations where they are almost like rules, but there are a lot of aspects to the ICH guidance's that are guidances. It suggests what will come out of a scientific approach to developing a drug, a process, a drug product.

For example. What you can sometimes get that is different is a stability commitment. There is a specific amount of stability data that is required for standard filing. There are circumstances where you may be able to get an agreement from the FDA for a shortened amount of stability. You must have a good base of data from earlier development, preferably from the same chemical process at the same site, but there are mechanisms by which you might make a deal with them to have less stability than you would normally be required to have.
There are times when you must change elements of the process, or even the site of location, because suddenly the demand is different, or a new impurity has shown up. Normally, you may have more time to address this, but

with an expedited filing, you are staring down the barrel at launch. If you approach the FDA with a proposal to say, 'we've manufactured the site. However, Site A is not big enough to handle what we project now to be the amount we need. We're going to have to move to Site B'. Now, we cannot move to Site B until we start our process validation.

The FDA would have to hear your argument for how you will justify changing the site between where your pivotal clinical trial batches from a registration batch were made to where you will do your process validation. You must have a plan that says how you will show that the material produced at both sites is equivalent. That is something that the FDA will give you that is different than you normally would get. They do this because they understand you do not have a three or four-year window in Phase Three. You might have a one-year window. You must do all the things that normally occur in that one-year window, that generally, you can do in three years. This is kind of what you can expect that is different. You can cite a reasonable position to enable you to get this important drug to market and back it up with sound science and say, 'This is what we need to do. Here is why we think this will work,' and get their opinion. The FDA will typically listen, they may say no, but they will at least listen.

"If you know you've got a biomarker receptor site – a validated model – some sponsors know from the outset they're going to approach the FDA even before they go into Phase One because they have a receptor site model. And if they get a model that hits then they're going to request some sort of expedited status."

Meranda Parascandola
I have a question for you, Jim. We get this quite a bit. When should a sponsor consider going for expedited drug development? And what should they do before they even ask for that? Is there a certain phase or certain triggers that they would realize, 'Oh, maybe I should be asking for expedited drug development or a certain phase of development?'

James Mencel
Meranda that is such a multifaceted question. So, there is a business aspect, and there is a scientific aspect, right? Let us look at it from the standpoint of anti-cancer agents. Often an anti-cancer agent program is based upon a model that is essentially invalidated. If you follow a receptor site, for example, which is a biomarker, in essence, you will impact this cancer. Then the question is, does the drug hit the receptor site? Well, suppose you know you have got a receptor site, a validated model. In that case, some sponsors understand from the outset. They will approach the FDA even before they go into Phase One because they have a receptor site model. If they get a molecule that hits it, they will request some sort of expedited status. Especially if it is cancer that is not treated, for example, pancreatic cancer, we would all love to see something for pancreatic cancer. The other thing that can occur during your clinical development, you start seeing good data.

We have a client at DSI in this position right now. They are at the end of Phase Two. They had spectacular data that showed a cure for people that have an incurable disease. Well, between them and the FDA, to be truly clear, this should have been an expedited program because there was no drug available, and the medicine cured the subjects. In this instance, the sponsor would decide, based upon data, that they have something unique; it meets the categories and various categories of consideration. Unmet need is better than anything out there. There is a variety of considerations for an orphan drug. If you are in a situation where you have something significant with data to back it up, there is no harm in going to the FDA and saying, 'here's what we've got. We'd like to get the expedited status." First, get advice on what you are asking for.

It is also important for the corporate entity to look across the board at whether everything they have is ready to go because it gets broadcast once they get that designation. There is an expectation for a certain level of motion of the program. If there is no necessary infrastructure in that company to support that motion, it does not look good for the funding agencies. It also does not look good for the FDA because if they put themselves out there as offering to expedite the status, they want to know that that drug will at least make it to the point of failure or make it to market. Hopefully, not stall somewhere because the client is not ready to take it forward, despite their approval of expedited status.

It is very multifaceted. There are business drivers. There are science drivers. Sometimes the sponsor approaches FDA. Sometimes the FDA sees the data and says, 'You need to expedite.' There are some diseases we are automatically expedited because you are there—for example, Nash. The FDA automatically expedites any program in Nash.

Ed Narke
Yes, Jim, that is a great point, and we have worked on several breakthrough designated programs together. In my historical dealings with breakthrough, I have seen several things. A lot of it goes back to Meranda's question, based on the therapeutic indication of the availability of other therapies out there that are available versus unmet needs. A lot of that discussion happens to be clinical. One of the things you are aware of, Jim, is that when it becomes a fast-track program, or the timing becomes different because it is a breakthrough, CMC is usually far behind the clinical program.

As you know, certain things take time, like process development or drug development. A lot of this cannot be condensed. Even with more money, it just takes time to happen.

> "The first question to ask yourself is, 'Can this process do the job?' Because, if this program goes expedited, this process that I'm running right now may be the commercial process whether I like it or not."

I wanted to go back to your role here at DSI. If you have a pilot-scale and need to get to the commercial scale in six months, it will be challenging. For example, finding the supply chain, etc. Have you dealt with any situational issues like this? Have you dealt with any discussions with the agency? Can you say anything about comparability data, leveraging earlier stage development data to make your case, or bridging some of the earlier stage stuff so you can try to bring the CMC program up to speed so that it is not on hold?

James Mencel
We see this a lot, Ed. There was a specific case where the sponsor did years and years of clinical work with a process that was a specific raw material, as it turns out, not even a starting material. They had not approached the agency about where the regulatory starting material would be. It had an exceptionally long synthesis. The upshot of the process is that this particular material they started with had a vinyl group. They would carry the vinyl group through the process, and, near the end, when they would do a general hydrogenation route protected groups, the vinyl group went away. The vinyl group went for the ride. As we all know, vinyl does not do very much to change the behavior of a molecule chemical.

What happened, though, they could not make enough of the vinyl compound to satisfy what they saw as being the clinical need. The company that manufactures the vinyl compound developed a compound with ethyl. The

ethyl turned out to be a crystalline material at that point in the process where the hydrogenation would typically have occurred. They went from an intermediate, late in the process that was an oil that was purified chromatography to an intermediate, that same crystallin stage, which was a complete shock.

They had a comparability program with the FDA because all their clinical data had been developed with the vinyl-based molecule. They showed that the API derived from the ethyl series was identical to the API derived from the vinyl series. They went far enough to propose to the FDA that the ethyl group converted to the vinyl would be the regulatory starting material. That was a noticeably big thing.

Also involved in that same circumstance was a site change. They were very constrained. To refer to what I said before about a company going from Site A to Site B because of capacity, this company was in the same situation. This company has to change the nature of the material they are carrying through the process, but they had to change the site of the manufacturer. They had two changes, and they had to use comparability protocols to handle both the site change and the change in intermediate. I assisted with both of those. The FDA, contingent accepted them upon certain things being fulfilled by the time of filing. So yes, we have dealt with that a lot at DSI, and I have certainly seen quite a bit of it. There is that one example I can cite that is almost extreme.

Ed Narke
Okay, that is interesting. Two questions came out: if I can ask you first, what's your dog's name (dog barking in the background)?

James Mencel
His name is Duke, and a nurse came over to care for a family member. So, the dog is protective of that family member.

Ed Narke
Hey, this is life working from home, which we are pretty used to for over 14 years now.

The second part, the serious part of the question, is having been in the trenches and dealing with agencies, companies that are considering they might have a potential candidate for breakthrough, is there anything to think about, for example, process-oriented, supply chain, or chemistry-oriented things that they can do early to get ahead of the curve? So, they are ready if they must move forward quickly.

James Mencel
Well, now that you have touched on it, Ed, I think that is where my involvement would be the most useful. My advice is to know the process. If you begin to hear rumblings that this will occur, you have an operative process. Let us call that the operative process. The first question to ask yourself is, can this process do the job? If this program goes expedited, this process I am running right now, maybe the commercial process, whether I like it or not. The question is, could it possibly do the job? What do I know about the process?

My advice to anybody in any small pharma is to really pay attention to the chemistry at every point along the way. Suppose there is any indication from the corporate leadership that they are looking at an expedited designation. In that case, it is even more important to get development personnel involved and to pay close attention to the chemical process of the drug product. The analytical methods because at some point, what you are working on maybe the actual commercial route with all its flaws.

What you need to understand is where the flaws are? Can you get the materials? Is there a showstopper in that process? Can it control quality? There are several things to look at; profile the process, understand how it

behaves, and you must pick your battles and say, 'Okay, so these steps work, we could live with this, this step I can't live with.' The thing to bear in mind there, Ed., that is important for people to understand is that two things cannot change after a certain point. One is that drug product for the salt, the polymorph, the particle size, they must anticipate that early so that they do not get stuck in a situation where they are in clinical development on the cusp of their pivotal trials or phase three trials with a physical form that does not work well.

The next thing they need to realize is a certain point in the chemical development and manufacturing that they simply cannot change the process. Close in changes, but there is a lot of work to make them. They need to begin looking at what they need to change about what they currently have to satisfy a longer-term picture. This requires knowing what you have, knowing what you need to have, and the gap between the two.

My advice to people is to make sure they get people involved, who know how to do this, who knows what to expect, get a team on this, and decide what battles to face, what things need to be done that are not compressible, what things are compressible, and what is the point of no return for certain types of activities that simply must be set in motion. There is a lot of thinking to be done. It is almost a fire drill upfront. Having been in a room with a client, I can tell you it was very much a fire drill type setting. The people were nearly holding their breaths, trying to deal with the fact that they had an expedited program, and were now frightened by what this meant. So, a company in San Francisco that we know was an interesting experience with those folks.

Ed Narke
Great information. Unfortunately, we are up against the time, so we will have to continue the conversation on Part Two.

Jim, I wanted to thank you so much. You are one of the first guests here on the CMC Live podcast. Obviously, one of the best guests so far and we look forward to speaking with you soon.

James Mencel
This was fun, guys.

Meranda Parascandola
Thank you, guys.

FDA CMC regulations and guidance are simplified through examination, real-life experiences, and risk-based advice. This podcast hopes to educate sponsors and individuals on agency-related regulatory CMC matters. We will focus on the critical CMC issues and build programs that enhance drug development. CMC topics will include Regulatory Starting Materials, API and Drug Product Process, Formulation Development, Supply Chains, Analytical Controls. Advocating and interpreting CMC Strategy, directing CMC Operations and Quality Assurance oversight in conjunction with developing CMC submission content that represents the best interests of emerging biotech. NOT INTENDED TO BE PRESCRIPTIVE ADVICE BUT RATHER AN INTERPRETATION THAT IS RIGHT FOR YOU. Since 2007 we have provided our partners with innovative strategies and exceptional advice to enhance program development, product approval, and marketing presence.