Recipes to Build Towards Your NDA/BLA

Episode 9

Ed Narke
Welcome everyone to CMC Live! Today, we have a special guest, actually three special guests. One of them is Ed Narke, me. As always, we have Brian Lihou and Meranda Parascandola. In today's podcast, we will have a Q & A to get everything out of my brain. Hey guys, how are you doing?

Meranda Parascandola
Good. How are you?

Brian Lihou
Good. Good. Real Good.

> "Filing an IND is important to get a trial started. Folks start clinical trials for a variety of reasons."

Ed Narke
Good. So, I was telling Brian or somebody the other day- and for those new to our podcasts, we have done- I think this is about the 10th episode now. There was a ton of things that if the podcasts were available several years ago when I was much younger and had a lot of the information still in my brain that I could have shared, that would have helped. I was telling people my experiences over the years. I stopped doing it, I guess, when I started moving more in the business development side with Meranda here, but I think they're worth talking about. I think talking with you guys with some of your frontline hands-on experiences with some of our clients and customers and authoring their marketing applications could help draw out some of those memories and useful information that I learned over that time. So, I provided some ideas for you folks. You guys have a lot of questions.

Meranda Parascandola
So, as a high level, coming in from the regulatory operations side of things, I know what most of this means, but I don't know the origin of how it came about. So, I get the pretty package at the end that goes scrambled to get together. Common Technical Document- what is its role in drug development? What did it originate from, and what are its purposes?

Ed Narke
That's sort of where I began my work, where I was born into regulatory. I think it was circa 2000 or 2005. It was somewhere between those five years. I worked at a large, vertically integrated company involved with many other large vertically integrated companies to create a new standard out there. Prior to that, there was a different format for marketing applications, as well as INDs that didn't have a rhyme or reason. It wasn't consistent across

global regions. Europe had something that was looking different. So, anytime you had to file something, and I'm mainly talking about the CMC, the Chemistry, Manufacturing, and Control section, you would have to cut things out of one thing and put it somewhere else. Sometimes, there were no sections equivalent. So the International Council for Harmonization, the ICH, pretty much got together and developed this thing called the Common Technical Document, which is internationally accepted in any of these markets: Japan, anywhere in Europe, in the U.S., and a lot of other countries. It's, in other words, a way to harmonize the look and feel of the application where information is nested, so reviewers in any market can have access to any of their development and compliance information, whether they're looking for it or not. In some instances, they rely on other countries, other markets that need certain things in certain areas to vet that. A lot of times, there's reciprocation and approvals- I won't get into that.

Anyway, the CTD module 3, mainly, and the Module 2 Quality Overall Summary- they're the basis for the chemistry section, which is the story and evolution around the materials that go in to, not just to the clinical trials during the clinical studies, but also what goes out to commercial approval. So, INDs…I talked to folks a little bit prior to this call. It's just my firm belief that any company that submits an IND should essentially use that as their blueprint and carry that as their blueprint moving forward throughout their program, whether it's a fast-track program that happens over six months or whether it takes ten years to do. I mentioned to Brian that I was involved with many programs, and so are you, Brian and Meranda. You know where we get involved with a program, and they want us to help them author an NDA or a BLA, and they think they have everything together. Still, we find out that- these are drug sponsors- they'll have an initial IND. They'll have a slew or a giant number of PDFs containing CMC information amendments, which has changed control in development over the course of development, and a lot of times, it's not uniform. A lot of people lump these together. A lot of five changes at one time. They'll submit it. Sometimes they'll do it in the annual report; sometimes, they'll forget to submit changes. So, whatever they have in their documentation, their Module 3, may not be reflective of what the current process is, what the specs are.

During development, there's a little looser criteria and compliance. As long as you're dosing patients with material that's been formally or informally accepted throughout dating the IND, it's not a big deal compared to when you're actually on the market. You're selling this to maybe hundreds or thousands of people. I think it becomes much more of a compliant issue at that point. Essentially, that's the role of the CTD- to harmonize the different pieces and the different information for a drug product, so it's all in one place, and for each market, you can find it in the same area.

Brian Lihou
With that understanding, can you maybe talk a little bit about the evolution of the CTD from an IND to an NDA? I know they're markedly different, but how are they different?

Ed Narke
Right, let me expand on it. When you submit an IND required to run a clinical study to dose a patient- that's part of the requirements- you have to file an IND. I won't speak to the clinical or non-clinical or the safety issues like that. We are not experts. I'm not an expert, although I do know a lot about it. Filing an IND is important to get a trial started, and folks start clinical trials for a variety of reasons. Sometimes, it's to get on the market and sell something that they could sell a lot of and make a business out of it. More along the lines, in other cases, there's an unmet need out there. There's a therapeutic need that's not met by a current product out there, or there's a product that's not necessarily the safest, but it's the best standard of care, or there's nothing out there, and there is no standard of care. So, it's really important to get an IND open. That's also a value chain for any biotech company. As you know, for any company that has an open IND, there's more value than if it has nothing or a concept or something in the early drug development research stage with potential.

As I was going forward before, it's really important to identify if you're submitting an IND; if you have a small team, start by generating what type of information you're going to require. There's going to be a process for your active; it's the ingredient you get to put into something that makes the efficacy. You're going to have control of that. You're going to be able to make it somehow. You're going to control it. It is going to include your acceptance criteria, which are your specifications which are going to be somewhat uniform, hopefully between batch to batch, so you're going to hit these milestones whether it's a certain level or keep certain impurities under a certain level, and these are tied mainly to the safety studies that you'll have to do preclinically. Every batch that you make from that point on will have to meet the same requirement, or you're going to have to re-run testing, tox studies, which happens on occasion. Sometimes you scale up, and you can't make the same material. Sometimes it's dirty, or unless you can bridge that ensure that there are no safety issues, you may have to run costly tox studies. The truth is, you want to define where your specifications are based on your manufacturing capability early on.

Next thing, you're going to look at container closure. Those are storage units; whether it's a vial, a bag, anything- usually with an API, it's a drum with a plastic bag inside. I can talk to the drug product, I bet, but that goes on to stability- that's something that's very lightly required early on because you're not going to have a lot of stability data. You're not going to wait two years to put something and get full stability data without knowing that it has any potential in the clinic. On the drug product side, you're going to have a compostition which not only talks about the act of but any excipients in the drug dosage form. It also depends on the dosage form that you're dealing with. I won't get into the minutiae there. It depends. There are many things involved with the excipients, which are a big discussion point. If you have novel excipients, it means that they've never been used in humans, food products, or cosmetics. In that case, you may have to do additional work, or you actually may have to document that process, how to make that excipient- because just like your process to make the API, any changes prior to a certain point could affect the impurity profile, which could affect the safety profile. So, if you have a common excipient using other products, whether it's an emulsifier or any excipient you use, you wouldn't have to put so much information on the process side.

It's the same thing with the API side- you're going to have your process for drug product, and you can make that in a number of ways depending on if it's a sterile-filled product, a solid oral, or if it's some combination product. These are just recipes on how to make them consistently. Somebody should be able to read this as a reviewer and say, "Okay, I get it." They should understand it's very common to make a solid oral capsule. In the IND stage, you're going to have acceptance criteria to meet and match what you've done before. You'll have your specifications. Early on has very loose specs, not many. There are core ones that are well developed in the guidances and well laid out in the guidances. You also have a chance, usually in a pre-IND meeting, to discuss these types of things with the FDA, especially if you don't want to set very stringent and stern specs if you don't have a lot of manufacturing experience. Also, on the instability side, it's the same thing- any dosage form, formulation-developed type of thing, any information that you can gather from that work, you should be able to use that for your stability for the IND.

I think the message I'm trying to get to here, and I'll slow down in a little bit, is there's a lot of information that you can get over the course of that plan, and I think that's what I mentioned in the beginning. If you write this down on a piece of paper, what you're expecting in each of the areas, when you're going to get the data, how much you're going to get, and what you don't need. Put that in the parking lot. That becomes your next plan, which you can turn into your regulatory strategy document, which, eventually, if you tie that to this and update things as you go along, you have your NDA. I won't get into the different phases of development. Sometimes they're clouded. A lot of folks think they're later than they are. Some folks get breakthrough and are later than they are. It's really about having to look at when you think you can get your final patient and get that pivotal study done, get that data, and that could be anywhere from a year to 10 years.

Meranda Parascandola
I do have a question, and it's not related to the new drug development side of things. Coming from a generic background, a DMF is a Drug Master File, and it could be an API, or it could be a component within your full ANDA. For the IND, since all the clinical trials have to happen, does that get a reference from the NDA, or does it transition from an IND to an NDA and is not really referenced as much? Do you use a lot of that information?

Ed Narke
Excellent question! I think these are questions that came up in the past that I used to be able to nail but let me think about that one. A Drug Master File is not associated with an IND, an NDA, or anything, actually- its own entity. So there are different types of Drug Master Files. The one I think you're referring to is more type two.

Meranda Parascandola
Yes, for API. Correct.

Ed Narke
For the API, that's the most common. In general, Drug Master Files are filed for a variety of reasons. If I can recall, one of them is if you're making an active that's going in multiple different products, maybe different sponsors, different companies are using an active. One may be formulating this way and using it there, and others may be doing it this way and doing it there. Usually, a manufacturer will file a Drug Master File for that reason so they can maintain and update that with the changes. They can control it essentially. That's a good thing for any sponsor because they don't need to worry about compliance. They might have to generate another analytical section, especially if they take material and further processes that are tested to a different set of specifications- that's a different topic. Usually, the manufacturer wants to control what type of information goes in there. Usually, that's a good thing because when making changes, they can update that fairly easily. I think that's where I started regulatory and stopped at Drug Master Files because I worked for an API CMO, which held many of them.

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The second part of it is a business decision. Most CMOs want to hold the Drug Master File for a couple of reasons. They have you locked in there. You don't really know the process. They might have an open section that they share with you that you would need. Then there's also a closed section, maybe a proprietary process, that they certainly wouldn't want their competitors or anybody else to learn any information on. So, Drug Master Files can be referenced via an IND. Basically, you need a Drug Master File letter, DMF letter, that you can get from your vendor- it just certifies that everything is up to date. It's routinely referenced in NDA submissions, thus allowing you not to have to rewrite the drug substance section. Unless, again, as I said, there was an analytical piece or some additional information that you're required to provide because you do some extra processing on your product.

Meranda Parascandola
Thank you for clarifying. I always envisioned that you have the drug substance, a DMF, and then bring it into your NDA. I thought the IND was something to that effect. Eventually, once exclusivity ends, typically, the sponsor would probably have a closed DMF.

Ed Narke
Yeah, I have to admit that, for the last 19 years, I've worked in drug development pre-approval. So, I don't want to say much more because I haven't really felt how things change. But, I could certainly tell you a little bit more about other Drug Master File types. There are four types on the FDA website if anyone's interested.

Brian Lihou
To step back a little bit, we talked about the IND and the contents. Specifically in terms of the NDA, sometimes we wrestle with clients in getting to understand that level of detail and completeness. When they say, "Well, it takes X number of hours to put together an IND. Why indeed, does it take that much more to do an NDA?". You're still writing in the CTD, but it's the depth of information. Could you describe why the NDA takes the time it does to write, at least at a summary level? I mean, I know that it's different than an IND, but how? Some of these sections are very involved, very lengthy, and a lot of strategies. Could you maybe cover a little bit of that?

Ed Narke
That's a common question. For anyone who's developed a drug and had a hand in CMC departments, whether it's authoring or strategy decisions and those things, usually that's not the part of the program that's emphasized unless it becomes a problem. I think that's the start of it. It's not the priority, let's say. I think the clinical studies and safety issues are the company's focus, and not many companies have folks to tend to the CMC. So I think the general answer is to define two different types of companies. One of them is a vertically integrated, large company, large pharma, that has resources. One that generates their marketing application, their Module 3, from the beginning. They file a very well-defined IND with just enough information to have an idea open with the compliance issues. Still, they're sitting on a large amount of research and development data that they're either going to use later on, or they're never going to use because they're going to change things, but they have a ton of it. So they purposely don't file an IND, and this is why most folks shouldn't file too much, especially things that are going to change because you're mandated and obligated to update that information anytime it changes- cause, concerns, if somebody looks at it, or if a reviewer looks at it and finds something else. So you obviously want to make it streamline.

For the most part, it's the folks from small emerging biotechs. You know who you are- you've inherited an IND that was filed many years before, and that therapeutic area has transformed. Out of academia, we see a lot of this very light and dirty information, very little information filed into an IND. Then very little information is generated up to the point where you get to phase 2 or 3, where you see efficacy data. Suddenly you have to file an NDA because you have clinical efficacy and power to show that there's some improvement. So you'll see that you have an NDA. You plan to file an NDA, and what you start with is an IND that has maybe 5% of what's required in the NDA- all the conformance information, all of the stories from the beginning, how you got this process, why the process is under control, how the process was scaled, if it needs to be scaled, how's it scaled, how it's controlled, how changes to anything in the process affect the control of the product, how the methods were selected, why they qualified, were they qualified, how were they validated, justifying the specifications. You can't just pull out random numbers and say plus 90%. There has to be a rhyme or reason early on manufacturability. You don't want to set your specs too tight because you'll fail every batch, and you're not required to set them too tight. But, again, you're supposed to relate it to the toxicology work, and as long as you do that, you shouldn't have a problem, and you shouldn't have to run studies each and every time. To go back just generally to answer your question, typically, the idea is not developed properly to get to the NDA. So thus, you're going to have a lot of work to put an NDA together.

I'm trying to come up with an analogy here. It's almost like if you want to build a massive great seven-room beach house. As an investment property, you want to sell it. Well, when you submit your plans, you buy the property, you submit your plans, and they require you to put a fence around it, so no one falls in the hole in the

middle, and that's all you do. Well, when you want to sell it, when you're looking to unload it after you're done building it and getting that value back… that's all you really have. You have a fenced-in yard with a hole in the middle. That was fine for that time, but if you want to get your money back out of it, or if you want (talking about patient population) folks to be able to use it properly and get the most out of it where it's on the market- at some point, you got to put efforts into building the house. That takes one floor at a time, using different materials, depending on what you want it to look like, what colors you want. Those are things I think you can equate to drug development. You can put as much into it, make it as great as you want it to be, or you don't have to.

Brian Lihou
To build a little bit on what you said…You talk about a plan, referencing the fence. A lot of times when we talk to a client, we'll ask them, "Are you filing just in the U.S.?" and the answer is, "Absolutely," or, "We're pretty sure," or, "We don't really know." We like to tell people that when we write these NDAs, we write them considering that they may be filed in other parts of the world. What does it mean to have rest of world awareness as you're authoring and developing your NDA?

Ed Narke
Great question, Brain. When I started in regulatory Big Pharma, there was the U.S., and there was Europe. They each had different divisions, and there was ROW. Guess where they plopped the young Ed Narke? In the ROW space, so it was a lot easier. We didn't do a lot of decisions. We weren't very strategic with the FDA. I never went to meetings early in my career. I would get everything that was already written, and I would go and apply for a certificate. It is called the Certificate of Pharmaceutical Performance, or CPP. When a region in Europe would get approval, I would request that. I would put together a dossier redacted that would send it to AC Markets in Asia or NEMA markets, North Africa, the Middle East- rest of world awareness. I think bringing that conversation to currently how we operate 20 years later; there's a lot of value in each of these regions for companies developing a product they want to license out. They want to take into consideration if they want to submit something in the U.S. and get approval. They might want to take that to Europe. There's a patient population there for what they're doing, or they may find a partner that they license out rights to Europe or other regions. Those folks might have more experience getting approvals in those areas as regions. So, what you want to do is this, the CTD is intended to serve as a common global structure for drug development; as I mentioned, for the documentation, there are regional differences that exist in requirements. So, for example, U.S is a new drug application. A lot of us know what that looks like. We can find the guidance.

> "It's hard to become an expert. There's no real training. I think a lot of it is just experience. It's going into meetings with FDA when you don't have all the data."

I touched on it earlier. In Europe, there's something called the Clinical Trial Application, CTA, and in that, there's a lot of clinical stuff. The portion of that is the CMC portion is called the IMPD, The Investigational Medicinal Product Dossier. It's very similar to the IND Module 3. It's the same, except there are regional differences that exist in requirements. So if you are planning to take your product either simultaneously or ultimately through a partnership, you need to know some of the regional differences. There are certainly stability requirement differences and even specification differences. Then if you get into biologics, there's quite a number of significant differences.

Suppose you're planning to do even the rest of the world. In that case, you'll want to take your regulatory strategy document out and make sure you're aware of what those requirements are because it wouldn't be great if you can develop a perfect product to submit and get approval in the U.S., and then you're missing 10% of it. It takes you another two years to get approval and in other markets. It's partially a business decision. A couple of things come into play with pediatrics: IP, exclusivity, and

reimbursement. There's a lot of business decisions involved. So again, from the regulatory perspective, you'll want to think about, not just on what you put in it, but what are the ramifications for the business in general, and is it building value there?

Brian Lihou
Okay, that leads to another question. You talk about a storyboard. You talk about long-term strategy, but the submission itself has to convey everything that a reviewer is going to want to know about the product. It's going to have to tell a cohesive, complete science-based story. You reference the use of storyboards. What are they? And when's a good time to use those in the process of authoring?

Ed Narke
Okay, so storyboards bring me back to 20 years ago to that big pharma where I got some of my initial training. Storyboards are kind of what they are. If anyone's a movie buff here or watches how movies are created, there's a storyboard involved. In our purpose, and Brian, let's talk about some of our processes because I think we've translated how we do things virtually across channels, such as email, and literally over the phone where we're not in the same room. When I was growing up in Big Pharma, we would have a representative from each team. We would have a regulatory rep, we would have a technical person who was either a process person, maybe an analytical, maybe a QA, someone from business development, someone from marketing, and not everyone would be involved with the writing of each of the documents, but if there was a tablet, for example, we decided it has to be embossed, or there has to be some ink put on it to make it the brand or whatever…This would be fed into a story, I guess, in a sense. Someone would be standing in front of the room with a white flip chart writing all this down, almost like a flow, and that would be translated into sort of a process, which would be translated into a deliverable.

I think a lot of it from my end as a regulatory person who needs to put this together and file it; we just wanted to make sure the alignment of the messaging was upfront- what needs to be carried out and done and put into the CTD was transparent, so everyone was on the same page, data that needed to be generated and when it was obvious, have all the important issues been addressed versus just generating data haphazardly and then at the end, just saying, "Let's pull it all together," and then does the data align across all the sources. I'm not going to get into too much of the details, but if you're doing something here, how does it affect you over there, and the same thing, vice versa. Then it's messaging. I mentioned earlier, one of the things that you could do for any marketing application, or your IND or investable application, is transform this storyboard. This is the basis or foundation of your Quality Overall Summary. Talk about why you're not going to follow a certain guidance, so you have that message that answers that story when you get that question, or maybe you don't get the question because you've addressed it. That's the foundation of data tables and those types of things. Those things come from source information, raw information. They start to flow and become the messaging, and that's the art of writing a submission.

Meranda Parascandola
That kind of goes back to some of the podcasts we had recently with our team here. Make sure that you tell a story from the outside because they haven't been there in the process. In those storyboards, you also take into the regulatory agency perspective. How do you think of them on the outside? If you have a large team, do you go to another team and say, "Hey, does this make sense to you," or do you look for outside help? What's your recommendation there? It just depends on the dynamics, I assume.

Ed Narke
Yeah, that is a phenomenal question. I don't know how you thought of that one, Meranda, but that is a great question. That's one of the things with our regulatory colleagues- it's hard to become an expert. There's no real training. There are courses and certifications in regulatory, but I think a lot is just experience. It's going into meetings with the FDA when you don't have all the data, when you have to address issue gaps in development where nothing was done, where you need to get a product on the market because it is efficacious. Whether it's Europe or U.S., the reviewer on the other side has two different review techniques. One is top-down, and the other is bottom-up. This goes back to the submission, the piece, the IND, the maintenance of it. So anytime you're doing any of this, if you own a product or you're looking after a product throughout the lifecycle, it's important to keep in mind the agency or reviewer perspective- they do not have a daily conversation with you. Sometimes you never talk to them for a couple of years. They just don't know your product.

> "Make sure it looks good, because it does reflect on the actual data and content in there, just like anything in life."

When I was early on in regulatory, and I first got into the U.S regulatory, this was 20 years ago, I think, they allowed you to call your PM at FDA or even sometimes the reviewer asks a simple question like, "Hey, we're finalizing this." That stops suddenly when they became overburdened, underfunded, and they all started working from home. That does not happen now. There's a process. It's very formal, and it's kind of convoluted, and no one knows if they're going to get the right answers. Usually, if they do, it's the day before something pivotal, or maybe they don't before they have to make a decision. I always say the agency reviewers are part of your team, whether they're there every day or not.

So ask yourself three questions. Many reviewers have told me this too. Where does the sponsor want me to go? You have to lead them. They're reviewing something, and you have to lead them. The reviewer said this to me once, "Where does the science tell me to go?" You have to make sure those two things are aligned, and if you do that, usually, you'll have a lot of questions. I think what the reviewer, and also the sponsor, should ask each individually, it should align, "What does common sense tell me?" This is where I mentioned earlier that no one has to do everything. I did work for a large Swiss manufacturer who generated tons of data because that's the culture there, very, very great stories to tell if anything happened, batches failed, you can go back. Common sense tells me that if I have a certain product that's fairly simple to make and control, that I'm going to be doing what I need to do to get that thing on the market so the patient population could benefit from that. You can also come back later and improve the process, increase your yields, scale it up where you can make it quicker, faster, whatever, but you want to make sure that you're aligned. What does the sponsor want? What does science want, and what does it tell you? Then the common sense part is a key thing to think about from the perspective of either side.

Brian Lihou
With all that being understood, we get into the space of authorship and Q.C. of sections. You've described the company mindset, the company process to get to this point. Where we come in is a bit… We're outsiders- we don't have all the institutional knowledge that the client would have. Not each client has the capabilities in-house to write their NDA. They all want to be a part of it. They want to go through that learning curve, but they don't have the experience. One thing you'd said several times, especially as it relates to common senses, is that's where experience kicks in. That's where everyone seems to think they know what the FDA will do because they read it somewhere. But if you think about it, it comes down to how many times you have done it. When you're talking to people, you know when people have done it before. It doesn't take long to sniff it out. So when you talk about authorship and Q.C., how do you describe that process?

Ed Narke
That's right, Brian. I'm going to ask you to say something about how we currently operate afterward because I think we've developed a nice hybrid model. I think I mentioned earlier that when you have a large building and many conference rooms and a lot of experienced people, it's sometimes a little easier. Now that I say that, it wasn't that easy. There's a cross-functional team aspect of it. No regulatory person has done everything in drug development. They highly rely on technical experts, subject matter experts, who can read the data, interpret and expound. The generation of a cross-functional team, whether it's two people, if you only have two, you only have two. Still, if you have a few more (that's how we operate here- we have a lot of technical folks that come in), your plan is to generate high-quality documents. They need to be improved over time, as I mentioned, through a series of reviews or discussions. That's not always the case. The luxury is that you have all your information. You could write it up, discuss it, prove it, get more information. A lot of times, this rule is loose. Having a team is a luxury and having many reviews is a luxury. I'll leave it at that, but common sense, that's kind of how you want to operate, whether you're a one-person company or you have a large company.

Some of the other things, I think, just in my dealings back in the day- I haven't done a lot of authoring, and maybe you can talk to this- a lot of it is document quality control, authoring, and Q.C. That's the way I look at it. We've dealt with some issues over the years where we were told that we have data and this and that. It starts with getting the available source information, which is the GMP documentation, which is the batch records, which is development reports, which is specs, methods, etc. Those are things that I would say that anywhere early on, no matter what you're doing, if you're starting an authoring project, you want to take an inventory of what you have versus starting right away, just jumping in, because some things may kind of interrupt how you write things, or they may be the greatest order to write things. You may want to sort of take things in spurts to tie them all together. You want to have a content review. You can probably talk about how we do that. You want to get a group consensus too. As you said, there are different personalities. You want to get a consensus on how that material and information will be put together and cross-reference because what a lot of folks do is write things up from information. When there are questions during review, they don't know where the information came from. It's kind of an organizational exercise. You'll want to do some data accuracy checks, especially for questionable source information. Ultimately, you're going to want to format it. I won't get into that. That's just making it look smooth and pretty.

Meranda Parascandola
That's the fun part.

Ed Narke
Yeah, that's the part I used to love the most because I knew whatever I finished that day, it was done. I finished it, and it was done. I hated it when I wrote something, you would always have one or two, I wouldn't say stupid questions, but you know, just questions that kind of annoyed you. You're like, "Okay, it's a style thing." Then the formatting at the end, you want to make it look good. One reviewer said that every submission that they get from x company looks the same, feels the same, tables are the same…and it was Merck, a large company, that had the luxury to do this. They have a team of reg ops people that do this at the end. Any company that's trying to do it has a one-off. You don't have to put standards or recipes in place. Make sure it looks good because it does reflect the actual data and content in there, just like anything in life.

Meranda Parascandola
Brian tells an excellent story of either his past company or a client here or there where they had everything. They had everything ready for us. They had everything ready for you. You walked into the office, and there are about 16 filing cabinets, and they said, "Here you go."

> "As the author goes through the process with the client, there's still another piece. that's the publishing group."

Brian Lihou
Yeah, they all say that. You're right. Every prospective client starts out by saying, "We have everything we need." They all do. Our approach is a little different in that, as I mentioned earlier, we're coming in from the outside. What we offer is that team that you had mentioned. When you have the smaller departments internally, they don't have the resources to truly check and fact check and make sure the science supports the statements being made. It's critical. We run the project, the structure, everything based on the CTD format. Over the years, we've been doing this a long time, and we do quite a few per year; we realized that a lot of inefficiencies are built at the beginning of a project.

When you go into a client's e-room, and they say, "Here's all our files, good luck." One of the problems is something as simple as a file name. You look up, and you'll see *Report xy002*. You have no idea what that means. You have to open it. You have to read the title. Then you have to determine where it goes. It may seem simple, but if you factor that in just the sheer number of documents required to support an NDA, you're losing valuable time. What we've come up with is a model that's broken down from CTD. We will start with a pre-determined checklist of documents broken down by section. The client, who knows their documents very well, will put them in a file transfer site based on where it needs to go. That cuts down a lot of the back and forth and a lot of the, I hate to say, wasted time, but it is, it's wasted time. Now you've got all of your sources of information broken down by the sections that they need to be broken down in. You ask for all agency correspondences, anything that paints the flavor of the document that you're going to write, any past commitments that were made, any future commitments that are going to be made. You want to have all of that, and it builds into, Ed, your point about the storyboards. We're not there with that group of people that are flipping that chart in that conference room. Sometimes this is just as good though. When you have all of that source information, you have the regulatory expectations on top of it, and you have a flavor for how this will be written. What we do is we'll start with a regulatory author, who will start to pen those sections as a draft. Then we'll have our technical person QC those sections against the relevant source information. I can't stress this enough. It's not just, do the numbers match what goes in the table, but are the assertions made in the technical documents, particularly around development, method development? Are they relevant to what's being written? Do they tell the story? You want to get credit for the work you've done, and sometimes, getting that out of that source and document is not easy to do.

Then after that, there are comments. There's back and forth, and then you have that regulatory strategy check on top of that to make sure you're telling that cohesive story. Then, we send it off to the client, and that's where they do their review, where we would all be in a room. We don't have that. They review that document. Versioning control is essential. You make sure that you control what goes over, and you control what comes back. Then your project manager works intimately with their project manager. Then you can track the ebb and flow of the sections. Some sections are lumped together; you need to have them to do an effective review. Some things are staged. Some information is not available. Where you can, you make that placeholder, and we talked about this, I think early on in the conversation, the importance of a placeholder. You write enough of the section where you still can do some work on it and then drop information. Typically, in batch analysis tables or stability sections where you've got data coming, you have a placeholder for it. That's how you write that.

We also advise that we don't touch the Quality Overall Summary, the Module 2 section, until Module 3 is understood and agreed to because otherwise, you're now tracking two different changes at the same time. It's difficult to make sure that that QOS truly represents the Module 3 section. We're able to come in and provide an extension of what the client wants to do with the NDA. I think it's really important to know that it's a collaborative effort. It's not us taking their information and dictating, "This is how it's going to be." It's a learning curve for both parties to a degree, but it is a joint effort. That's really how we've managed to do that kind of virtual model where we can almost as though we're in the room with them.

Ed Narke
Right. I was going to ask you a question about a quarter way into that, but I think you answered it, and that was the contributions of each functional area. I was trained by some of the finest regulatory submission content authors ever. They were a combination of European folks that did this for 20 years in the old format, and we transitioned when pharma changed to the CTD, Common Technical Document. I went to every meeting to discuss each section and why and how, so it's very clear. Two of the things I just wanted to highlight: subject matter experts, authors, reviewers. This is how we work internally now, and I see how you operate and how our team operates.

Folks need to stay in their swim lanes. That's a common cliché these days- I heard that 25 years ago. Each sub-team person has to understand the responsibilities. This is why we talk about efficiencies. This is what our group does well. I could say that with a lot of pride. People have responsibilities, and they leave others to theirs. Then the document review part, we mentioned how we operate with those things. Every reviewer cannot review every aspect of a document. There are certain individuals involved. Folks with the most project familiarity, they're the ones on the project. Reviewers who are naive to the project also play a role in some cases because they see things that certain people don't see. So that's a good point you made, Brian.

Meranda Parascandola
Brian, if I gave you all my documents today. Can you turn it around in two days? Realistically what's the timeline of submissions? Do you wait until you have everything? Or do you start drafting what you can?

Brian Lihou
That's a great question. It's one we're asked all the time. If you think about it, as the author goes through the process with the client, there's still another piece, and that's the Publishing Group. A lot of decisions and a lot of milestones are based on when an application is submitted. You have to work backward from that. Publishers routinely will give you "we need four weeks or better, to hit your target date, everything has to be in by then." Realistically, to dump it all in at once… doesn't work. It never works. There are sections in CTD that we consider to be low-hanging fruit. We encourage you to start writing right away. Bigger sections take longer. That's where, as mentioned before, the placeholders are essential. You want to keep the momentum of the writing going. If you stop and pick up again six months later, there are continuity issues. You have to make sure that terminology hasn't changed. Those long-drawn-out processes are difficult to manage. The sooner you can start to get that low-hanging fruit done, the better when it comes to timelines. The really important thing for us is to have transparency for each section as it's being written. And then to make sure if you have a critical path item, you're tracking it, that you know, to the week you expect to get that information, then from that the week you expect the draft to be generated. That way, all parties, both within our organization or the sponsor's organization, know what's coming and they can fast track it to make sure we hit the timeline and not stress the folks at publishing.

Ed Narke
That's right. One other thing, Brian, as you remember and you recall every day, working out differences in interpretations before anything's finalized in documentation. You never want to come back and change stuff because you're not on the same page. So, before you finalize, there are discussions. Then you also have to remember that this is a very stressful time. We know this. We haven't had a disagreement or anything like that ever. You have to be flexible and supportive of your team members. When you're working with external party sponsors out there, it's very easy for them to get frustrated or upset because of missing data, or this delays something. It's part of the process.

Meranda Parascandola
Brian, you brought me back to my publishing days where it's just waiting for P.A. to be done and waiting and waiting. Then you could just submit, as soon as you've gotten all that in there, and did all your hyperlinking. I hear you there. I'm so happy you gave me four weeks to do it. As far as timelines go and the quality, can you tell me more about that? Typically, a lot of things are driven off of, "we need to submit on this date." If I was to come to you and give you two weeks to do something, what would you say?

> "One way to alleviate that [stress] is to be able to give an update on any given subject or any given section at any given time."

Brian Lihou
It's a good point. If you think about it, you have timelines versus the quality of the submission you're putting in. At what point do you draw the line? You can do it quickly. You can do it well. The bottom line is, at what point do you make concessions timeline versus quality? At what point do you say we're not ready? This needs to push. Can you kind of expand on where I think that line moves all the time? It's very project-dependent. How do you approach that subject because so much is at stake on that filing date?

Ed Narke
I'll sort of lead into maybe tracking progress, where I think you have many experiences with different dynamics and circumstances. We can get into those as well. Timelines and quality, that's the main thing. Could we have this by the end of the year? Could we have this in two months? How fast can we get it? I guess the question is, "how long does it take?" I think I got that question every time I talked to somebody, whether it was the early days of Big Pharma, another group that wanted to file it, or small biotechs that want to serve their board and make announcements. I think that meets the fit for purpose. When will it be ready to file where it's approvable? I'll go back trying to touch on it again. It really should be being built over time. That'll help alleviate a lot of these issues, last-minute decisions, discussions, bottlenecks, etc. The right answer, "how long does it take?" The answer is it depends on how much time is left. If you only have three months to file it, and that's the goal, you got to get it in for three months. It's not the ideal thing.

The reality, though, is quality must be part of the process. You have resource constraints, conflicting priorities, maybe missing data. Things move up fast, sometimes without any reason. You have a partner. Quality control checks need to be built into the timelines. Then the question always is, "when is the actual document done?" We talked about this a little bit. If you're missing a little piece, what do you do? Most assume it's when it's approved is when it's done. You'll never know until somebody reviews it. Meranda, you can come back here. You know regulatory publishing and a submissions prep. That's a big part of the ending of it. Be mindful that that does take a little bit of time. It's an important part of the interlinking process for a reviewer.

Brian Lihou
I think it's important that you mentioned that three-month scenario. That's where a cross-functional team is really important to have checks and balances throughout the process to ensure that if you are moving at a good clip, and you are trying to get four months' worth of work done in three months, having those internal checks and balances in your system and your authoring workflow is essential and how efficiently you remediate comments and questions. Do you wait until there's an end-of-week meeting, which we advise you don't. You have targeted focused meetings, and you get something done, and you move on. You can affect the quality if you're working in a condensed timeline using checks and balances from different disciplines to look at the submission. I think it does help.

Ed Narke
So, Brian, tracking progress…you are, not so much anymore, but you have seen this, right? Microsoft projects are sometimes involved, right? Project tracking tools…you have to follow documents. You have to manage resources, authors, reviewers, QCers, approvers, publishers, timelines, and dependencies, right? Can you give us a little bit of a preview of your daily operations when you're working with a submission project?

Brian Lihou
Yeah. You mentioned how stress levels and anxiety slowly ratchets up at this time, especially as you near that endpoint. One way to alleviate that, or at least minimize that, is to be able to give an update on any given subject or any given section at any given time. Once you do that, it does two things. One is you'll get your answer, and two is it just instills a sense of confidence in the whole team that things are being tracked. What we do on our side is that we put together a project tracker. I know everyone's got a project tracker. Ours is specific to the CTD. If we have a critical point, we will highlight that. We will update the sponsor weekly on the status of that critical path item that impacts that section. If we have to move things around, Meranda, as you mentioned, as P.A. comes trickling in at the end, we make sure that that is truly the last thing you have to do. It is important to track every aspect of a section as it goes through the workflow, from authoring to Q.C. review, remediation, client review, and formatting. It's important, and what people don't seem to understand is that it doesn't just stop at formatting because if there is a review to make that section final, if someone so much as makes an edit, that could impact all of your linkages, your tables…everything could change. It could generate another six hours' worth of work that people don't see. Having that transparency per section throughout the CTD helps everyone overall. Sometimes it is a bit cumbersome and labor-intensive. But, in the long run, it pays off, especially when you're working in a relatively condensed timeline.

Ed Narke
We're getting close to the time here. There's one last thing I'd like to bring up-it's not a question, it's just a sort of an observation, and we've all seen it following the NDA submission. It isn't over yet. There are things you need to do. Think about this. We talked about the beginning of an IND, generating enough information, building a story, building chapters out…etc. Preparation…when you submit this, there are going to be questions. So, prepping for agency questions can be done all along the way. Normally, once you have your filing, you're going to want to do another gap analysis if you haven't done it. You're going to want to address anything that hasn't been put in there because it's going to come out. You may be able to justify certain things in the Quality Overall Summary. But, as you said, Brian, in the end, prepare for responses, prepare the anticipated questions so when you have questions come up, you're not spending weeks and months, or maybe you can never find an answer. You have a game plan.

That's the end of this podcast. I think we did a fun job together. I think that if any folks have any comments or concerns about this or if you have any questions and would like to speak with us, feel free to reach out or hit subscribe below to capture or listen to future podcasts. We'll be back shortly in the next couple of weeks with other podcasts on this topic, going into more depth and detail about submission content, some of the pitfalls, and

some of the areas that are hot topics before and also now. On our next podcast, we are joined by Dr. Daniel Torok, a seasoned synthetic organic chemist. Dan has served the industry for over 30 years in many aspects of development, ranging from synthetic to process development chemistry. He's hands-on. He's results-oriented, and he's focused on process development, CGMP scale-up and transfer, and CGMP commercial production. Dan will be talking about person-in-plant. Dan will also share many of his travel experiences over the years, both for business and pleasure. Dan was a mentor of mine when I was younger. I'm very much looking forward to this conversation. So check it out.

FDA CMC regulations and guidance 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 INTERPRETATION THAT IS RIGHT FOR YOU. Since 2007 we have provided our partners with innovative strategies and exceptional advice intended to enhance program development, product approval, and marketing presence.