2020: A Year in Review

CMC LIVE
CHEMISTRY - MANUFACTURING - CONTROLS

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Episode 18

2020 Recap

A DS Inpharmatics Production

Episode 18

Ed Narke
Welcome to the CMC.Live introduction. Here we have Brian Lihou and Meranda. It's been a wonderful, happy year. We're ending the year here on a high note with the Best Stuff show, we'll have a lot of new stuff in the future, and we'll talk about that the end. We started off this year with this podcast, CMC.Live, simplifying and examining everything out there that involves CMC and regulatory and quality assurance. We're hoping that it's not intended to be prescriptive advice, that's maybe why you might call us and engage. It's a bit of an interpretation of what's right for you. Every program is different, every budget is different, resources are different. Every program needs a specific plan. However, a lot of the underlying issues and concerns out there - and questions that have been around for 20 years - are the same.

> "One of the things that resonated with me on that particular podcast was how Dave [Adams] took a step back and said, 'You really can't underestimate the importance of the skilled technicians that actually run the process."

We took a little bit of everyone's combination of experiences and combined them and documented them so you can see some of our activities, and maybe learn from that, or find that it resonates with you or validates some of the things that you've been involved with. In the beginning, sort of mid-year, we had Dr. Jim Mencel in the podcasts. He brings a lot of experiences with our API world. Jim talked about expedited drug development. It's been a hot topic for a number of years. It involves breakthrough designation, orphan products, any kind of accelerated approval pathways. There're a lot of misconceptions about what you can get away with, what wouldn't be required based on that. We gave some insight on some of the experiences that we have with the agencies, discussing certain topics with Episode number 1, Jim Mencel.

James Mencel
When you are in a program that gets expedited, the intention 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. What it gets you is that the FDA is aware that there is stress on CMC.

Ed Narke
Brian, was there anything that you learned from that episode, as far as expedited drug development, having some exposure yourself with some of the programs?

Brian Lihou
Yes, I think it was one, getting Jim's perspective on that, in terms of how DSI does a lot of work with expedited drug development programs. It seemed to match some of the things that were said on the regulatory side, where there are certain assumptions that sometimes companies will make that it's going to be accepted by the FDA, because it's under the guise of expedited drug development. But to Jim's point, there are certain steps you simply can't overlook, - impurities, drug development - all those things that go into a typical filing still need to be gone through, they still need to tell that story. And a lot of times, at least what Jim was trying to say there, is that there is an understanding that CMC is under a great deal of pressure, because now you're skipping large portions of time where a lot of that development and a lot of that characterization would have taken place. So, you still need to tell that story with data. I thought that was really insightful. And it was nice to see that his drug substance experience agrees with my drug product, and certainly the regulatory team saying the same thing. I thought that was very helpful.

Ed Narke
Yes, that was really well played. And Meranda, you agree, I think two things I remember vividly from Episode 1 and Episode number 2, where we talked a bit about starting materials and ICH requirements. One of them was the reference that Jim made to the playbook: if you have a playbook, you really have a script. We talked about football and the analogy there and how that works. So, discussing things and having that playbook, that plan, in place is a lot better going into any type of accelerator program than just winging it based on what you know the outcome or what the decision needs to be that day. The other thing I remember about that was that his dog Duke joined us which was a very special treat there.

Brian Lihou
And it was the first Yogi Berra quote that we had had. I think that's what he ended with that.

I see this as like being an advance scout watching another team play ball. You know, if you could stand at the field, and watch how they approach the way they do things, you're prepared when you face that team yourself. And I think that if you can approach the FDA and say, Look, here's what we have based upon the guidance, what do you think? I think you're better off than waiting until you face them down when you have to do it better, because you've run out of time, and you really aren't prepared.

Ed Narke
We also had Dave Adams on podcast Episode number 8 later in the season. I had a pleasure to work with Dave over the years at a CMO, learned a bit of process chemistry. But you know, Dave has been a lifer in the manufacturing realm. We call Episode number 8 "Trust the Process." Here's a sample.

Dave Adams
If you understand how the equipment and the processes are going to work in a plant upfront, you can make much better progress putting something into production than you can by just taking a laboratory procedure and introducing it to a plant.

Ed Narke
Okay, that was a high-level snippet. We don't want to get too far; you must listen to Episode 8. But Brian, thoughts?

Brian Lihou
Absolutely. One of the things that resonated with me on that particular podcast was how Dave took a step back. And he said, "You really can't underestimate the importance of the skilled technicians that actually run the

process." And oftentimes a disconnect exists between the scientists that develop the process and the technicians that have to actually implement it on the shop floor; having their input and expertise infused at an early phase really ensures success. On the back end, I thought it was important that Dave brought a real practical approach to scale-up of a process and getting it to the manufacturing floor. I think that was important for me.

Ed Narke
I agree. In this episode we were building on the process here now, besides trusting it, but we also had a discussion with Dan Torok, who's a longtime API/drug substance slash everything to everyone. Same thing: Dan worked with Dave, and we talked about the white coat effect and how it's real. We talked about process champions, we talked about oversight responsibilities and accountability.

One of the things I remember well is, we had large pharma customers when we worked at CMOs, and they had their team come in look after the process - they basically rented our facilities, we had the inherent equipment knowledge and some of those understandings. But they actually were responsible for some of the decisions based on somewhere they wanted to be with their business model. So, we help folks every day that aren't used to dealing with the CMO. The CMO is not used to dealing with a business model, an exit strategy; they're making something to a Certificate of Analysis and trying to get it out the door. They're doing as much work as they're getting paid for literally, to find out the ins and outs of the process. And that varies based on budget. Let's go to Dan now and visit where we were at.

> "The reality is they still need that person-in-plant. So, I think what Dan [Torok] brings to the table is what a lot of clients look for. Some clients don't have that infrastructure and they blindly trust the CMO – and sometimes not always to the right result."

Daniel Torok
Probably the most touching experience was when I spent a lot of time on an API facility on the East Coast. And on the last day, when I was finally walking out, their process chemist said, "You know, I want to thank you. You're the first person in plant who's ever actually helped me."

Ed Narke
Okay. That sort of sums up Dan's personality. I remember a long time ago, I asked what he liked about process chemistry; he said, he always likes to fix things. He was an avid biker, and he used to put bikes together. So, I think the same applies, but that's sort of the background, Brian. A lot of what we do is act on behalf of - basically become representatives of - small companies, to make sure that their outlook there is good, there are no bottlenecks, no surprises.

Brian Lihou
Yes, I think Dan personifies that person-in-plant, and one of the things that he said in that podcast was, and you heard it in that snippet, where they actually thanked him for his presence. You know, it's that personality, it's that disarming nature that really makes you part of the team making the batch, whether you're the person-in-plant observer, or your technicians are actually making the batch itself, and having that trust and that understanding. Once you establish that, I think what Dan was saying, that communication line is always open. And you're just looked at as another member of the team, you're willing to be there at the door at 3am when the process starts. People see that, and they identify with it. It really makes for the most effective use of your time when you're in the plant overseeing a process. That was a good podcast. I enjoyed that one.

Ed Narke
Yes, one of the things that I still remember with Dan, like with Jim's playbook, was about the respect that he gives to CMOs. You're not in there to show them how it works or show them how they should do it; you're a partner with them. You're the interface between the customer and what they do that's their profession. That's their business model. I think Dan has a good persona; I think all of our API folks do, but he, in Episode Number 10, really nailed it. And if you listen to a couple of the clips on how he operates, how he puts the CMO management team at ease. I think it really is a good bridge, and things are easily productive when that happens.

Brian Lihou
Actually, if you think about it, though, Meranda, we do have people that ask about person-in-plant. And you know, they do say now it's unfortunate with COVID because we've had people insist on it. We've had to say no, but the reality is that they still need that person-in-plant. I think what Dan brings to the table is something that a lot of clients look for because I think, as you know, some of these clients don't have that infrastructure. And they just blindly trust the CMO and sometimes not always to the right result.

Ed Narke
Yes, Dan was a great guest this season. We also had Rick Offerman on Episode 14. And we talked about why now is the most important time for selecting a CMO that has many meanings. Clip:

Rick Offerman
A lot of CMOs are now going to a one-stop shop type models. So basically, they'll say, yeah, we can take you all the way from gram quantities right through commercial, we can do your API and your drug substance. But there's still a lot of smaller shops out there that are med chem shops; they can do the small scale preclinical work, they can make you a few grams of everything, maybe they can scale up the drug that you want, or the API that you want to a kilo, but really, they're working in a small shop that's their business model, and they'll take you up to maybe a Phase 1, maybe they'll do some tox work. And then they say we're done, we were not going to change our entire business model to make commercial or late phase material.

Ed Narke
Another really good podcast. I had three different things I thought about after hearing that last clip versus the original when I heard it. One of the things that jumped out, as you know, when you make a decision on your supply chain, you've got to think about where you want to be. As we understood and find out moving from facility to facility, especially an external facility, new facility, quite expensive, it's kind of a headache. Part of what I got out of that was kind of thinking about the big picture plan - what exit strategy you want, if you're going to divest your program or sell your product, lots of decision making. Then if you're going to take it through and commercialize it, you may want to find another supplier.

Brian Lihou
I think one of the biggest things for me, and I've seen on the drug product side, and I know Rick speaks for drug substance and drug product, is the importance of knowing the CMO that you actually partner with. When they say that they can handle everything from early phase on through late-stage phase and ultimately commercial, it would be really important to have that vendor cite some successful examples of that, because those small shops that Rick references, there is absolutely a place for that. It all depends, like you said, on knowing your own program. And what is important, if that program is going to stay with your company, all the way through your commercial filing, then fine, maybe it does make sense to partner with one group. But if that's not the case, you might want to try to find a place that's more suited to your need at that time. I think that whole podcast with Rick was really relevant for me.

> “I think people are now realizing that they do need to take a lot of different factors into consideration when selecting their CMO and they might need that assistance from experts like us.”

Ed Narke
Jumping ahead a little bit, we had Les Mintzmyer on the podcast as well. Episode 7 ties some of this together. But I think I find it interesting - did speak about CMO selection as well, mainly on the drug product side. He also gave us a couple of examples and gave us his thoughts on vendor selection process, how many CMOs to pursue and what to look for, and then maybe a little bit on how to make a decision based on that. We could play a clip from Les.

Les Mintzmyer
Tell you what - the money they'll spend on consultants early on is a drop in the bucket compared to change orders and change of scope and misunderstandings that occurred later on.

Ed Narke
Yeah, and Les also talked a little bit on using consultants there. That's kind of the game that we're in here, obviously to make a business out of it. Most everyone here at DSI is still doing what they've been doing, more or less; we've been virtual for 10 years plus two. So even though a lot of stuff changed last year, not a lot has changed, obviously things of all technology and some of the ways we interact. So that was an interesting discussion with Les.

I do remember a few things about the vendor selection process. And I think you, Brian, had some nice thoughts; everyone has a little bit different opinion on it. But you know, with multiple proposals, you have look at a lot of stuff internally as well how you can manage that. The biggest/best may not be the best for everyone, right? The smallest may be cheaper, it might be a little bit easier to work with/manage, but you might come into a later stage or phase development area where that vendor may not be appropriate for you. And we just mentioned that to leave a facility and find something else, if it's a scale thing or just dealing with a CMO thing, it's costly and something you don't want to get involved with later if you don't have to.

Meranda Parascandola
I think companies are actually realizing that earlier on. We've had a lot more requests come in about CMO selections, or at least reviewing the RFP and comparing apples to apples since they're all different. I think people are now realizing that they do need to take a lot of different factors into consideration when selecting their CMO, and they might need that assistance from experts like us.

Brian Lihou
Yeah, and it's frustrating. I think if you listen to that snippet from Les, it's kind of where he makes that statement about the money you're spending on consultants today pales in comparison to the potential mistakes you can make if you make the wrong choice. I think, to add to your point, having that experience coming on board as part of your selection process is essential. I know when Meranda and I are talking to potential clients, we highlight the fact that we've done this before, it's not something that we're just going to look at that lowest cost or that quickest lead time, all these factors have to be considered when you make this choice. I think Les did a really nice job of explaining some of the potential pitfalls if you don't do that proper due diligence up front.

Ed Narke
And - unfortunately, the audience wouldn't be able to won't be able to see the background there – but Les had the best artwork of anybody in the background. Best studio, apparently,

Meranda Parascandola
I don't know, I get a lot of compliments about my aquarium, okay? Now I have a tree to complement it.

Ed Narke
I do see some seasonal decoration that's actually very nice. So, we can go back to the last piece of the drug substance, I think it's kind of fitting when we talked about selecting the right vendor for the active costs that are involved with the management, where they're located. We did talk amongst all these last folks, and there are snippets in there about some of the cultural differences dealing with offshore, seasonality, sometimes there are seasons that folks may not be manufacturing as much, etc. I'll leave it at that. But to time it out, Dave Blasingame joined us in Episode 15, one of our more recent ones, and Dave's on the West Coast. Dave has just a ton of experience with outsourcing to Asia, and has been there and basically knows the climate and has seen a lot of the transition in the last 15 years - first to outsource there, and now maybe to outsource back. "So how far can it go?" was the title; there're things that we learned, there're things that we have basically accepted. And there're things that are changing based on, you know, just 2020.

Dave Blasingame
I think it's a natural go-to for early projects to make GLP material, maybe some early Phase 1 material. For all the obvious reasons, I think China, in particular, is known for being very quick at being able to produce that kind of material, and also significantly cheaper most of the time compared to maybe US counterparts, or European counterparts. So, I think it's kind of a natural go-to for the first step for stages of any clinical program.

Brian Lihou
I found that podcast very interesting, because there's the cliché that's associated with manufacturing in China and all the pitfalls, but Dave went the other route, and he offered some of the advantages. And not just in terms of cost; there's so much more than just cost. He talked about the evolution of manufacturing in China. I think the one thing that really stood out for me at that podcast is when he talked about their recruiting practice, and when they're graduating thousands of PhDs each year, and how literally industry just stops and opens its doors to recruit the best talent into their companies heavily and aggressively. I think he provided a very interesting perspective, having spent so much time in China himself. And it was firsthand experience, even down to the food. I really found that that podcast to be enjoyable.

Ed Narke
Yes, Dave did bring up a good thing. I think that resonated. Dan and I talked about this; we grew up in US manufacturing, when there were 10 or 15 CMOs making APIs in the US, and now we're down to five. And you know, there's not a lot of training going on; folks that come out of the school work in a facility - a lot of it's virtual, essentially, you're just managing an offshore, you don't get the sense and feel. It could be interesting that the folks that support API process in 15 years, as Dave Blasingame mentioned, could relate to the Chinese proverb, "Tell me, I forget; show me, I remember; involve me, I understand." It's part of that experience and being able to translate that to decision-making for the biotech community. We also had an Episode number 17, where we had a panel of our drug substance experts touching on all the topics that we just talked about, plus more. Brian, you can give a little bit of a preview on some of those topics.

Brian Lihou
Yes, it's funny, that panel discussion was really interesting. One of the things that came from that is when all these individuals with all of their years of experience and diverse experience, started to talk, they all came to the same conclusion: that while domestic manufacturing is trying to catch up in terms of competing with what's being done in Asia, and certainly in Western Europe, there is a gap. There's an experience gap that's been left in the wake of moving all this work out there. So, it's s matter of getting that next generation of qualified scientists and technicians to work at the sites that are being started up, and it's not just as simple as flipping a switch. I hear them all talk about that, and with great admiration some of the sites abroad that they've gone and visited, and how they all seem to share the same opinion that it's more than just the turning of a switch and saying manufacturing moves home at this point; there's a lot of infrastructure that needs to be created and cultivated.

> "If you know that you have properly identified and characterized the development history of your product, and its pitfalls, and its areas of concern – and you've explored those – it really makes for a much more robust filing that stands up to scrutiny."

Ed Narke
I thought that was important. This group that we have - James Mencel, and Dave Adams, Dan Torok, Rick and Dave - these are some of the greatest, they're a dream team, if you're relating it to history. They are a Dream Team for API with their collective actual manufacturing on site experience, with their travels, having complete control and understanding of the landscape of the API world, and how that's developed and how that evolves. I encourage anyone to check out that panel, Episode Number 17, but also go back to the individual discussions with Dave, and James, and Dan; there's a lot of just personal introspective.

We also had Kyriakos Michailaros. We had a slight technical problem on this one, so we had to go back and revisit it. I think the second one was better than the first. We talked about living development reports, we talked about the strategy and getting a blueprint in place, and being able to find out where you want to go on the drug product side. I learned a little bit more about that area versus the API stuff, because I've heard Dave and Jim, and you grew up in the drug product world, Brian, and I think he asked a good question. Let's listen to a clip from Kyriakos.

Kyriakos Michailaros
A good reviewer would do that. Yes. I mean, some reviewers, it seems, are primarily just box checking, and have less of a holistic, risk-based approach, which has been the trend for some time. Now, I try to focus on what is actually important for this particular product, and if that has been explored appropriately.

Ed Narke
I know a few of our customers and partners that we've worked with, reminded me of QBD (quality by design) - do we do that, versus quality by chance. I think that was a good podcast to talk about - why quality by chance, QBC, is not a good option. We advise everyone based on approvability and the sniff test, essentially, if you can get an approval, and there are always ways to generate more information if you want to do different things. But I think Q summarized that and talked about the importance of having a partner at the FDA, having them sit at the table with you, and how you document some of those things in the development part. Brian, any additional thoughts on that?

Brian Lihou
Yes, what he said is that we've worked with many clients over the years, and many different opinions on relevant sections as we support filings and things like that. But he said something in that clip that was really important. A lot of times, our clients will come back and say, “Well, this is what we expect the FDA to look for. This is what a typical review is.” But it's not quite so simple. When Kyriakos mentioned he looks at the development history as, are we representing the process? Is there a particular area of concern? Had we explored it enough? And is it captured in our summary? Is it captured with supporting data? Not so much, we're trying to anticipate what they're going to look at, because that's what they always look at, which sometimes that does happen.

If you know that you have now properly identified and characterized the development history of your product and its pitfalls, its areas of concern, and you've explored those, it really makes for a much more robust filing that stands up to scrutiny. I thought when he said that it was really important. Don't look at it as though you have to capture “just because”, but does it make sense to your product to capture this? Or should you do more? I thought that was that was insightful.

Ed Narke
And guess what: this one was brought to you by the year 2020. In podcast Episode Number 4, we spoke with Bettina Kaplan, who is one of our highly trained and experienced QA folks here at DSI. Bettina talks about quality assurance, obviously, that's her game. Auditing in the time of COVID, and virtual touring, virtual auditing. It's something that I'm sure a lot of folks are starting to hear about. We've actually had some experiences with it now. So maybe we can get a bit of a clip and then of recap some of what Bettina talked about.

Bettina Kaplan
You have to cover manufacturing, analytical, and all the quality systems in one day. To do a thorough audit, there's no way you could do just one person.

Ed Narke
Brian, you've lived a little bit of the virtual and so you and Meranda, maybe you guys want to talk amongst yourselves here a little bit, some of your feelings and how you tell things have gone.

Brian Lihou
Sure, you know, Meranda, we have gone back and forth with prospective clients on exactly how many people does it take to do this for how many days, and I think each case is different. I don't think it's necessarily a rubber stamp, it requires this for this; we had one group that's looking at us to do qualification audits and to do them virtually. We had to develop an internal virtual audit model based on client feedback, based on compliance requirements, all those things, and put that together. Then you have to look at it in terms of what team is best suited for that audit. As Bettina mentioned, if it's an analytical, let's say you're doing the release testing and the processing, you're going to want scrutiny on the labs, as you look at the quality systems as you look at the production floor. That's why we typically recommend a team. I know, it seems some people look at it just as the sheer number of hours. But if you are qualifying that vendor, and you're about to make a sizable investment in time and resources into that vendor, you're going to want to make sure that that audit really gets you the best bang for your buck. We've had these conversations before, don't you think?

Meranda Parascandola
We’ve been going back and forth with a few different prospects and clients about that, but I think they’ve been really accepting of the process and probably hadn't thought about it in that manner. So it's been really good, walk

them through it, talk them through it, so they understand how we do things. It's not just one-sided; it has expert advice, along with the QA.

> "We had a special external guest, Hedley Rees, who talked a bit about supply chain and how to create a value chain."

Brian Lihou
Yes, and I think the thing that makes that podcast good for me was a virtual audit is not the same as a paper audit. It's not the same as just it has to be, more because oftentimes, paper audits just aren't applicable to what you're trying to do. They're not if you're qualifying a vendor, a paper audit is not sufficient. You're trying to replace that experience of being on the floor, looking at the finishes, looking at how logbooks are stored, looking at the condition of the gowning suites and the airlocks and all of that. You can look at that from drawings. But when you have video access, and actually can see the rooms, most of the rooms, you may not get all of them, but I think that's really what sets it apart from say a paper audit.

I think Bettina speaks loads of experience in the audit world. She was instrumental in developing our protocol that we use within DSI. And just hearing her speak to the different challenges with audits and how she's overcome them I thought was really helpful.

Ed Narke
Great recap, Brian. So go back and check out podcast number 4. We talked about GMP audit alternatives during the pandemic, requesting, preparing, responding to anything, alternatives. We talked about paper audits, where things are going, how this has helped industry in the quality aspects.

On podcast number 6, we had Colman Byrne joining us, talking about analytical method development. And again, he's one of the Mount Rushmore fellows out there, as far as analytical concerns are. Colman has a really unique perspective, he taught us how he actually got involved with analytical to start, which I always wanted to ask him but never did until he joined us on the podcast. Let's hear a little bit from Colman.

Colman Byrne
It is typically less expensive to develop a solid test method than it is to develop a drug substance manufacturing process or to go through and manufacture bunches, or batches of drug products.

Ed Narke
So, Colman, just brought so much great insight. He's been doing this with us for 15 years, and prior to that for about 20 in the industry. He really has honed down in the game and analytical. He talked to us about the importance, when developing the qualifying method, of how to bridge the gap between the substance and the product, how to tie that to monitoring the impurity profile, and some of that profiling that you do; how building some of the methods that you can be used alternatively across any other areas, if there's different work that has to be done characterization work. Brian, any thoughts based on your frequent work with Colman, did you pick up anything from that discussion?

Brian Lihou
I really did. Thanks. A lot of times, people will ask, do you have testing labs? And the answer is no, we don't have testing labs. But well, how can your consultant help us if you don't have testing labs? And I think when you hear Colman's podcast, you'll hear him say things like he understands and has been there, when he talks about all that the challenges that testing lab is going through, and he can help them find creative solutions to move forward - and oftentimes, more than the client can because they may not have the same experiences or breadth of experiences that he has. And when you listen to his podcast, you'll hear him talk about the fact that again, much

like you've heard in the past in this podcast, it really comes down to trust; and once that lab understands that the person on the other end of that phone has been there and done that and seen those challenges, then they're more accepting and willing to share when mistakes are made or areas to improve, and then you've got the relationship to take it forward.

I think the thing that also resonates in that podcast from Colman is the fact that compromise has to be part of the vernacular, you have to find a means to reach an agreement with your testing lab and still meet the compliance requirement, and be somewhat bending at times in order to find that path forward. And I think that comes through in Colman's podcast.

Ed Narke
Yes, and Colman has been doing this, so he obviously has some experiences with other areas - regulatory and quality - so he's able to pull it together. I mean, he has great technical ability. Putting that in conjunction with his knowledge of analytical, what goes into submissions, he supports not only just initial filings. Everyone should have someone like this, that can come in and become a technical defense of the submission, some of that information around methods, why certain things are done. It's not clear sometimes it is a method, right? Colman's definitely was a podcast worth re-listening to; this is one you shouldn't miss, podcast Episode number 6, I believe.

Before we get into the regulatory, we had a special external guest, Hedley Rees, who talked a bit about supply chain. I think we were going to have this on the back end of this wrap up, tying it together with the supply chain, and how to create a value chain. It's a very also critical piece to your drug development profile, at least in my experiences, maybe yourself, Brian, as well. And Meranda, we talked about analytical and regulatory submissions and quality assurance audits since we've been doing this; this has been year of supply chain, a whole different element out there that I think has had an increased focus based on the conditions and travel restrictions and things like that. So, let's listen to a bit of the intro Episode number 12, Hedley Rees from the UK, someone I've known for a long time.

Hedley Rees
I talk to excipient suppliers sometimes and they say, you know, the guys were developing that product, they really didn't consult us, they didn't really try and understand what's going to work, what isn't going to work. And the main point between the strategic supply chain management is you actually engaged with the end user of your product, the same way as Apple would, or you know, any company who really builds value into their product.

Ed Narke
That was a nice external podcast discussion, there was a bit of discussion on how Big Pharma does things a bit differently. And you know, that's certainly a thing you have to consider working with small biotechs, that maybe are acquired by Big Pharma, there's an integration process. We hope that in 2021 we have a few more of our supply chain experts on who are pretty great. I guess, in the meantime, Brian, do you want to do a summary of our supply chain 2020?

Brian Lihou
I think what we've come to realize, and Meranda and I have been on the phone a couple times with prospective clients and current clients, is that supply chain was just another part of their main job. It's important for these early phase clinicals, where you're enrolling studies left and right, and you're dealing with label packaging centers and distribution centers, and how to accommodate them, how to relate to drug supply, and even something as simple as putting together a dashboard that management can understand. We've come to realize in this last year that a lot of it is really a bit of an afterthought, until it reaches critical mass. From that we decided internally here to really develop a supply chain resource for clients.

It started off as a supply chain resource for our current clients. But then we realized early on that it's very appealing to any client at that point. So, we're probably halfway into developing and refining that service, but of the folks that we have internally, we've got some commercial supply chain, and we've got the majority of clinical supply chain experience, where we have that knack and that knowledge of some of the main sites and some of the nuances, that got handed down by clinical operations people and their challenges. I think that's what Hedley spoke of where he said, it's having an understanding of the entire supply chain, that this all has to logistically work. Just because it's in the protocol, it still has to work, and having that understanding has really been the catalyst for why we wanted to develop a supply chain service.

Ed Narke
So go back and check out Hedley's podcast. Also, a shameless plug: he has a pretty interesting book called *Taming the Big Pharma Monster by Speaking Truth to Power*. I think for anyone that worked at Big Pharma and also small pharma, this will resonate.

> "Our job as regulatory reviewers, strategists, authors, CMC experts, is to decipher what the data is saying."

So, we talked a lot about the drug substance side, and had some guests this year talk a bit about the drug product areas; we did cover quality assurance, and a lot of these topics we'll be revisiting again next season. One of the things I wanted to tie it together at the end is our experiences with regulatory. Again, we have a pretty good group of folks there that have collectively experienced biologics and small molecules and very hairy situations. We talked with them about submissions. Not just writing the submissions, but decisions on how to generate the data that goes into submissions, when they generate that data. There are a variety of different things you can do, talking about strategy and submissions.

As I said in the beginning, every program is kind of unique. So as I mentioned in the podcast, if I recall, we're the industry version of the investigative reporter, the regulatory folks on the side. We go out there, and we're talking to the agencies, we're talking to our data people, we're talking to our technical functional people here who understand the science part and also to the people who make the materials, on-floor technical as well.

I mentioned there, and this has always been my training from marketing application, whether it's an IND, or an NDA, or BLA, or anything drug master file, it's a way of us telling the agency something. The data is trying to tell a story, it's always trying to tell a story. Anyone who is into literature reading and stuff, you know a good book from a bad book, right? Some of us like the books on tape, but that's not an option yet for the marketing application. So, our jobs as regulatory reviewer strategists, authors, CMC experts, all our technical people now are merged into that. Whatever we want our job to be, we have to decipher what that data is saying.

To become a good author, you really have to be able to streamline messaging, you have to be able to tie some of the holes/gaps together. Marketing applications speak the language; there's a language that's required per the regulations, and the Common Technical Document. We do here, and I think we'll get to some of these episodes here. I can highlight some, you know; we were able to interpret that language and what the data is saying. Sometimes, it could be standoffish, we don't have all the data. So, we have to create a legitimate story, and sometimes that involves getting down to the FDA or over to Europe, whether it's on the phone, in person, however it happens in the future, and discuss and also share, bringing the FDA the AMA, any other body to the table, to help them help develop this drug, help them understand and get to know and be feel comfortable with that.

We wanted to maybe start at this season, January, we deal with a lot of early stage companies. We've in the past attended JP Morgan Healthcare and Biotech Conference on the West Coast. And it's a really interesting dynamic out there. Like I mentioned to Brian, and you before, Meranda, it reminds me of Boston maybe 10 years ago, a few large companies very established, very successful companies, that laid a model out. And subsequently, my experience is seven years going there that time of year. You're seeing a lot newer companies, one product in development, again, same issues that we saw on the East Coast, not having a lot of experience, what do you do? How much do you spend? Where do you put your efforts in? In Episode number 3, we had Judy Magruder on the podcast, and I really enjoyed Judy. I've met her out there seven years straight now. She talked a bit about effective strategies for early-stage drug development. Let's have a listen.

Judy Magruder
The horses are great. The horses are terrific. And I tell people, it's like the cheapest therapist you'll ever have. Because when you get on that horse, everything else goes out of your head. You know, when people talk about focus, and about living in the moment, you better live in the moment, or it's not very safe.

Ed Narke
And Judy also has horses. So that's why that conversation. There's a backstory to that. I'll just say a little bit about it. Judy has a little bit of experience with CMC. But unlike a lot of our folks, she's not a deep technical person, enough to know and make decisions. Her background, I think, is really just facilitating the right discussions with early-stage companies to let them know what's important, certain things that you just can't miss. And I think that she does a really good job with that effectively; you may not need a consultant necessarily 40 hours a week when you're just heading into a Phase 1, especially on CMC, but you'll need somebody to kind of lay out a pathway.

I think as you start getting involved with selecting vendors, and maybe having a quick FDA meeting for an pre-IND, you're going to have experiences where you're going to want to ask the right questions. I thought that was a good one. I think everyone needs to be designated with a consulting expert just to get started, someone that's legitimate and has practical experiences. Obviously, no one's going to spend a ton of money or resources early on in development, you know; they want to get started, they want to have a proof of concept they want to get somewhere where ultimately, their asset has a value. So, they're either going to get more funding, or they're going to get some partnership, etc. Either license the product out. So I think Judy did a really nice job with that. Did you guys recall anything from Judy on that?

Meranda Parascandola
Yes, I did recall her "think big picture first" way of thinking as she supports companies and thinking about the big picture rather than just the timeframe or the mind that they're in right now. Because they want to get to a point. Right?

Brian Lihou
Well, it was really good point. Because she said it was really understanding the end goal, which was whether that that goal is to move on with an investor relationship and take the product so far, or it's ultimately a filing. A lot of this is in the preclinical space, obviously, but what we found in meeting with potential clients is they're really just looking for a sounding board for their strategy. Judy's experience, Ed, as you'd mentioned, is extensive. They really need that affirmation that the path they're on is the most expeditious way to get to where they want to be. I think that's the experience that Judy brought to bear, that holistic approach to a client's program.

Judy Magruder

Think big picture first, and then all the minutiae in the smaller, what I call the "microplans" does the product need to look like when it hits the market - all the plans underneath become that much more valuable and realistic.

Ed Narke
That was Judy McGruder podcast Episode number 3, very good for early-stage companies. Moving back into the regulatory realm - one of our long-term consultants here, Catherine Bernard, has many, many, many years of experience. We talked to Catherine in podcast Episode number 5. I remember this one - Catherine spoke about pharmaceutical regulations and CMC. That sounds very broad. However, I think she got down into some of the really specific minutiae, too. So, let's hear a clip from Catherine, Episode number 5.

Catherine Bernard
And that's where the interaction with the FDA is critical. So, the sooner the better. You need to be up front when you go to those meetings with the FDA. However, you don't ask questions for which you don't want to hear the answers.

Ed Narke
This goes a little bit back into being the investigative reporter. You have to get the facts and put them together. With all the questions you should ask, there should be an outcome expected. Not to do additional work, but to maybe make a decision. If you feel that you're going to have pushback based on that you're not doing what's expected, you'd better have a good story for that, or at least a negotiation tactic, because the FDA will call you out on it. So, any additional things with Catherine, we can talk in many directions…

Brian Lihou
To me it was her practical experience; that that little clip alone speaks to her practical hands-on experience, it's make sure you're transparent. Make sure that you're asking questions that you want to know the answer to. And I think one of the things that we always say is that that the consultant that works on that filing, really is there for the entire lifecycle of that submission, whether it's information requests that come or it's the meeting request, the briefing book, really having that same consistent person who is hearing your story, and then can also provide you seasoned experience to give you the best chance of approval with the FDA. I think in that podcast, you can really hear that in what she says, it comes from experience, not reading it simply out of the regulations.

Ed Narke
Right. And Catherine has tremendous experience with interactions with the agency. So again, it's become like second hand to her. Now we'll get to the closing up the summary of 2020 here. I always wanted my own regulatory show. Obviously, I got started back in February of this year, with a goal to do a podcast, and not knowing exactly what that meant, or who was going to help – I want to give a warm plug here, and thank you to you guys; you've made it such an interesting experience. Before we get into the final submission discussion here, you can't just dive into this stuff. I think you guys brought a lot to the table here.

We also had a couple of internal discussions on podcast Episode number 9, "Recipes to Build towards your NDA/BLA", with Ed Narke, Brian Lihou and Meranda Parascandola. I remember preparing for that, getting all my checklists out and all my stick/jump-drives and going back and seeing stuff. Doing this for 14 years, I remember collectively organizing all my help, my blueprints etc., and realizing what a wonderful collection of support that I have on my computers, and sharing that over the years with some of our individuals. I had some flashbacks, I got excited a little bit, too.

So, Episode number 9. I think it was me rambling about just everything that happens, and I think it was just a brain dump. Let's listen to that. That was a good one, if you're interested in that.

“It's hard to become an expert. There's no real training; there are courses and certifications in regulatory, but I think a lot of it is just experience, it's going into meetings with FDA when you don't have all the data.”

Yeah, I haven't said that before. Like I need a new a new pitch or whatever.

Brian, I remember when I met you originally - very hardcore drug product person, heard your stories about being on the dock and loading things. I sort of had memories of manufacturing, but as you know, I left manufacturing around 1999 and just had an office job, and virtual for about 80% of that since then. I'm proud of how much you've picked up on the regulatory space and how you've also developed your own feelings and thinking. Sometimes I don't agree with them. I think with the regulatory thing, there's a range, right? Some are either extreme this way or that way. I think you have a great balance; I think you're right in the middle. You pull things because you've seen things, and I do give the same that kind of testament to Meranda. I think these are my two most proud episodes just because it's the most I knew about, maybe felt most comfortable talking about, Episode number 13.

“I think that’s the experience that Judy brought to bear, that holistic approach to a client’s program.”

Brian Lihou
One of the areas that's really essential when you're putting together your authoring team, is to have somebody at the client that truly understands where the skeletons are, that truly understands and is forthright and saying, for example in development, listen, we don't have the following items, they are planned, but we don't have them. Okay, we will look at that, we will rate that risk. If the risk is great, then we may advise you to wait until that data comes in. However, if it may not be as long as you demonstrate the plan you have in place, and you can speak to it, whether it's referencing the protocol or content of a protocol, you may be able to work around that with the understanding, you may get questions. But for us, it really is someone who understands their Document Library. Exactly.

Ed Narke
So, you see how sensational that sounded, Meranda? I mean, I don't get me wrong. Brian was a bright guy back in 2008. But now he is like, polished. So again, Brian, in those episodes, I think collectively we just talked about some experiences, strategy decisions. We talked about the submission authoring, there are different styles, there's different procedural stuff, pat myself on the back, and everyone here, you know, we've been involved with over 200 companies and had a lot of success with marketing applications, worked on products that are actually out there, you know, in industry to patients.

I think at the end of the day, I remember my kids asked me what I did when I was younger (they still do sometimes ask me explain this), and I just said, You know, I help people make medicines, to help them and stuff like that. I guess that always resonates. I heard my son one time say that, you know, my dad helps makes medicines and stuff like that. So whether it's regulatory or quality, or CMC, you know, we're all just normal people here, obviously. But you know, we're kind of passionate about that. Anything else? Brian, you can share things that you learn, Meranda, same thing. We try to do it online, internal EDU, of course Ed University, by the way, that’s what it stands for. I have to make myself useful, right?

Brian Lihou
Yeah, it's funny - when I first started with DSI, like you said, Ed, I came from a production background. And filings were always a big source of anxiety. And when you're in the production side, you only see it as there's only

one way to do it. And that happens to be who's in charge dictating that that's the way it has to be done. And when I learned from you early on, a lot, believe me a lot, was that that finally can be written based on a person's style, because they're people. And when I first started talking to you about a range, you would look at a section, you would say, Whoa, wait a minute, that's a lot of words, but they're not telling you anything. And that could have been written in a fraction of the time. I had to learn that I had to see that. And when you pointed out the fact that no one submission is written the same way every time.

So now we've kind of rolled that into what we tell clients; obviously, it's heavily influenced by the client, with the injected experience that we bring to the table in writing successful submissions. And I've learned so much in the years with DSI that goes into those filings, that I think we've now built efficiencies into how we do things to make it more effective. But it all goes back to that very beginning where tell the story, does it tell the story? What I learned from you early on, whether it's an early phase IND, does it meet the objective? Or are we talking about an NDA? Well, then these sections are more refined, there's a lot of effort put into it. And it was really helpful for me, because our consultants that weren't in regulatory had to have that explained to them because they were contributing to that. And I think, overall, you've given us that across the board that culture of it's a work in progress, make sure it tells the story, make sure scientifically it's sound, from that very small start with a handful of consultants to where we are today. We try to keep that culture moving and keep that going forward. I've learned a lot and I've enjoyed it. And we've got quite a few projects that we could laugh about for sure.

Ed Narke
Yeah, that's certainly the case. Did you have any thoughts on your experience of regulatory submissions in the last two years Meranda?

Meranda Parascandola
There was something I wanted to have a podcast with you, Ed, on, and potentially Brian - is companies that are generic companies. It's my background, I came from generic companies with filings and submissions in that way. You know the different types of submissions - I think that would be a great podcast that we could do together, to talk about all the different types of submissions.

Ed Narke
On that note, that's talking about the 2021 and beyond. We'll be back at some point in season two. Last thing I want to touch on a new member of our group here, Amber Sheriff, gave us a little insight and podcast Episode number 16, about Brexit and about different types of submission mechanisms, whether it's a centralized, decentralized, national process, mutual recognition, etc. Let's listen to a little bit from Amber from Episode 16.

Amber Sheriff
So, what is happening now, people who have filed in UK can no longer sell their products in EU because UK walked away from the European Union. So now they're setting up their own procedures, and they're going through that which still, you know, by the end of this year, they will be fully separated from European Union.

Ed Narke
Oh, no worries. But you know, like I said, we're up against it here. I think Amber is going to have another episode with us in the next coming year. And we'll have a lot of different regulatory topics, especially hot topics as they come up. So, change is in the wind. It's always happening and it's a requirement to move forward. You know, the greatest measure of intelligence is the ability to change, according to Albert Einstein. We look forward to season number two for CMC.Live podcast. Please go back to listen to most, if not all, of our episodes; each one has a unique flavor and also how you know it's a culmination of years of experience. With that said, anything else guys?

Brian Lihou
No, I really appreciated the recap of the year and it really kind of reminds you of how broad people's experiences are and how they complement each other.

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.