# The Parenteral Drug Association & Evolution Of Drug Development

Episode 25


**Ed Narke**
Hi guys, its Ed Narke. Welcome to CMC live again. I'm here to play another round of what are your thoughts and tell us about drug development with my co hosts, Meranda and Brian. Hello, folks, how are you?

**Brian Lihou**
Hello.

> "The PDA was kind of the bridge. It's the Parenteral Drug Association – its focus is sterile injectable product. But it's into all kinds of different things."

**Ed Narke**
Very good. Thank you. So today, we have a special guest, Mike Carroll, who joins us. Mike is an accredited microbiologist according to our website. I'd would love to hear more about that. And over 35 years of product development, quality control, GMP manufacturing experiences in the drug product, microbiology side as well. So, today happens to be the start of the PDA Conference 2021 Style live from New Orleans digitally, virtually. And it's also a great town to visit, unfortunately, probably not this time, but down the road. So, interested to learn more about what microbiology in the pharma industry means and how it applies in any other, you know, true stories from Mike. So at this point, why don't we get started? And Mike, maybe tell us a little bit how you got into this role? And maybe some of the experiences and certainly I think we all have a lot of questions for you.

**Michael Carroll**
Oh, well, thanks. I actually have been very lucky. In my career, I have gone with companies that used to try and get into new areas and new types of product lines, which let me learn an awful lot about an awful lot of things. Radioimmunoassay, different types of blood dripping and typing Syrah and eventually in the parenteral drugs. My first company made RhoGam, which was the first Rh immune hemolytic disease of a newborn treatment. And then into OKT3, which was an essentially an immunotherapy. It reduced rejection of organ transplants. It was a monoclonal antibody. And that's where I met Brian first in reduction of that drug.

**Brian Lihou**
Yeah, no, yeah, that was a long time ago.

**Michael Carroll**
A great little serendipitous experience in different companies and different types of products. And I've been hands on involved in developing and validating and registering and getting approval for all kinds of different

parenteral drugs and other products, which makes it kind of an interesting career. And it also gives me a certain kind of versatility. Now I've had a hand in a lot of different and kind of cutting edge stuff, isolators, all sorts of different new technologies and sterilization and so forth. So it's, it's been a lucky run, and it's actually 44 years total, although we aren't counting.

**Brian Lihou**
Well you know Ed, to Mike's point, I did meet Mike at that OKT3 facility, kidney transplants right, was the indication they were going after, and my first foray into the industry. And the appreciation and respect for aseptic processing actually came out of Mike's teachings. I was Darrell Field Operator a while ago. And I really didn't know much about it. I had actually been promoted from operating a forklift, and which is a little bit different than aseptic processing. So, I was lucky that I was surrounded with people that Mike had trained that had the same equal respect for aseptic processing. And then I took those lessons throughout my career, just passing those teachings on and I actually borrowed quite a bit from what I learned from Mike, pawned it off as my own, but it was really helpful. And then I was lucky enough to I was lucky enough to go to another company where Mike was, and we just we carried that on and kept pushing the message. But one of the things I want to talk about Mike, was your experience with the PDA, the Parenteral Drug Association. Back when we first met and I first got started, you know that the PDA really was the industry standard for the way the industry relates to a regulations and their position on regulations. But, perhaps you could maybe just talk a little bit about, well, how long you've been in the PDA, and then some of the early days and what the influence the PDA had in the early days on industry.

**Michael Carroll**
Yeah. I probably been, I got to be senior enough, I think to belong in probably 1980 or 81. And at that time, the basic thing was that FDA would come out with regulations and then occasionally they would put out points to consider documents or guidelines and things like that. And the industry would get these things, and in a lot of cases, they will look at them and say, is this written in Serbo Croatian? What does this mean? How do I deal with this, and PDA was kind of the bridge. You know, it's Parenteral Drug Association, its focus is sterile injectable products. But it's in the all kinds of different things. And the earliest things that I remember were these joint conferences, and the best and most wonderful were the ones where they got industry represented by John Lee, from I think Altana, out on Long Island, and Hammerin Hank Avalon from the FDA, was their heaviest Inspector, particularly if you had sterile facilities or water for injection production. And those two would put on what amounted to a floor show. I mean, they really had tremendous respect for each other and they worked very well together but it was like a comedy team. And you came out of it with your sides hurting but you learned an awful lot about what does FDA really expect you to do? And how do they really expect you to comply with these things without giving you any direct instructions? You know, because the GMP 's are super broad brush. You know, how do you actually physically comply with those without causing yourself into the stratosphere?

**Brian Lihou**
Because the regulations don't come in two directions, he just had to figure it out.

**Michael Carroll**
Yeah, right. And PDA was starting to put out these technical reports and documents that would really hands on guide you through it. And if you were trying to validate an autoclave or a sterilizer, or a lyophilizer, or something like that, those documents were invaluable, because that would actually give you the How to, and then if you complied with that, you knew the FDA was going to walk in and look at what you had and say, okay, you're cool.

**Brian Lihou**
There's a couple that stood out. I mean, filter validation was one, but also the guidance for media simulations, right? So

**Michael Carroll**
That is still a massive one, yeah.

**Brian Lihou**
Yeah. Still today. In fact, I mean, people that don't know how to set up their programs, that is the blueprint for how to do it.

**Michael Carroll**
Yeah. And we could give you a few blueprints on how not to do it, as I recall.

**Brian Lihou**
Yes, we can.

**Ed Narke**
Oh, Mike, I have two questions for you. Sorry, I have to get the second one. But first question is, can you give us like two talking points, maybe two things that you learned out of those conferences with those gentleman, just that you feel kind of hear in your brain every time like some two things that really stood with you over time? And then the second one is, can you tell us more about the PDA technical reports, because I learned a little bit about them. I actually use them a lot when I was kind of doing just trench work back in the day, you still are they still relevant? Have they held up the test of time? Can you pull them out and still, you know, kind of be up to speed with what the expectations are? So those two questions

**Michael Carroll**
Well, to the second one first, yes, they are still being updated regularly. And new ones are being published all the time. They pull, really experts from the industry, you know, they don't fool around, they get the guys who work with life analyzers to work on the technical report for life analyzers. And the same with autoclaves and ovens and you know, deep origination and endotoxin testing and all of that stuff, ditto for environmental monitoring, things like that. So they're still absolutely relevant and, more importantly, the FDA, and now the EMA, and the Japan pharmacopeia, and all of those agencies are also cooperating and looking at those documents, as you know, the guidelines. They're still absolutely relevant and they still carry a lot of weight, as well, they should. Yeah, the other question was, what again?

> "The biggest things that are most frequently used in my case are the media fill, as Brian mentioned, and environmental monitoring."

**Ed Narke**
Well,  to the point of the technical reports, you had excellent resource and valuable folks that aren't aware of them, you know, certainly they're modified a bit over time, but some of the core stuff it's, you know, accessible for anyone interpretation and implementation different, right, but we can get into that later. So the first one was the original PDA conferences that you attended with some of the individuals that were some of the industry, you know, king pins and you listen to them, obviously have a lot of respect for them. A couple things I was wondering, you know, two or three things or one or two things that you learned that were instilled inside of you, you know, that you can still hear and you practice everyday that you can share with the any audience of this podcast.

**Michael Carroll**
Yeah, well, the biggest things that are most frequently used in my case, are the media fill, as Brian mentioned, and environmental monitoring. You know, FDA, not FDA, PDA has a guideline on setting up an environmental monitoring program to support a sterile operation. And it's extremely good. And more importantly, it makes it clear that there are certain guidelines that you have to meet initially just to be able to get approval, but that is all moving targets, they want continuous improvement. So you are supposed to be looking at them routinely and seeing if there are any trends and seeing if there are things you can improve and reduce those limits further. You know, the goal is absolutely sterile, which is virtually impossible with aseptic processing with humans involved. But you want to go for that goal.

**Brian Lihou**
Yeah, I mean , one of the things, Mike, that I remember, I learned from you early on was, you know, if you're running a program where you constantly pick up nothing, well, then perhaps you ought to look at what you're actually monitoring. Because it's there. Yeah.

**Michael Carroll**
And why are you picking up? Right, exactly.

**Brian Lihou**
Yeah, exactly. And I took that forward, because right after we work together, I went to a company out of the West Coast and they were quite proud of the fact that they had no recoveries. And then I looked at the sampling plan, I looked at what they were doing, and it made perfect sense why they were no recoveries, and

> "When you cite regulations from Europe, it used to be you would pull the British because they were gonna be the standard. If you could pass Brit, you could worry about anybody else at all; you were fine."

**Michael Carroll**
Nothing happened.

**Brian Lihou**
Exactly. I pulled out that technical report. And I said, Let's start with this. And we went through the whole thing. And we redid our interventions and what they represented and all of it and lo and behold, we got actual discernible data, we could make decisions properly. So yeah, yeah.

**Michael Carroll**
Yeah. Yeah, we are actually physically useful. You can print those things out and hand them to somebody and use them. Yeah. And that is, in most cases, not possible with a section of the GMP or an FDA guideline, you know, they're talking in the ionosphere up there. And if you have six doctorates, I guess you can make head or tails of that. But I look at that, and what PDA boils down to, okay, look at it this way. That, oh, okay, now I get now

**Brian Lihou**
Down to sample size and everything that you need to go into your SLPs. In fact, you know, we still use the technical report, as a reference with our clients. Because when we go and inspect a sterile facility, we're going to make sure at a minimum, then the first thing you go to is their media program. That's the easy one. And by the way, that's the first thing an investigator goes to as well, because they're familiar with it. So, you know, I learned that as well. And, you know, you mentioned the beginning with the whole floor show reference and, and I always remember that the that one particular investigator, Mr. Avalon, we prepped for those inspections with a healthy degree of fear, and to make

sure that we prepared and then some because, you know, you really did get scrutinized. And it really was that region, because I worked several places throughout the country and it was a different standard that it was in those early days coming out of out of the New York office. It really was.

**Michael Carroll**
Oh, yeah. Now one of the best things I remember, this was the same company, we validated an isolator to do sterility testing it. We were one of the first to get approval to test sterility in an isolator for that OKT3 product. And we heard that there was going to be an inspection I think of like Delfen Contraceptive Foam wine or something like that. I said, Okay, no problem. We're fine. I'm up here and micro working on the isolator. That's fine. So I'm over there looking through some data, and I look up and there's Hank Avalon, smiling at me as I go. And he just came by because he was part of the team and he wanted to see the isolator. So I ended up getting grilled for two hours by Hank Avalon on this freshly approved isolator. And believe me, I had to be on point, that guy knew exactly what he was talking about and exactly what to ask. And that's healthy. You know, he wasn't trying to bust anybody. He was trying to make sure that you had something reliable. It wasn't out of ordinary or anything. It was just compliance.

**Brian Lihou**
And I think that's why the PDA was always so appealing to me because it was an environment where you could challenge each other in industry, and then invite input from the regulatory agencies, like, yeah,

**Michael Carroll**
And they do that physically. They have specific conferences to bring microbiologists who run environmental programs and investigators from FDA and EMA, who investigate those facilities and approve them and put them together in one conference. Yeah, that's invaluable.

**Brian Lihou**
To consider the impact of the EMA, when it comes to sterols and the standard that they have, you know, it's good to have that insight in those technical reports, because, you know, you're kind of tunnel focused on, you know, the US and the FDA. But you ain't seen nothing yet till those guys walk in. You think you're covered? Perhaps not?

**Michael Carroll**
Well, their hiring mechanisms are somewhat different. The FDA can take an investigator or could take an investigator of Plumbing Supplies, and turn them into an investigator of pharmaceuticals. Now, the EMA would take somebody that had 15 years of experience in industry, some of it in management of sterile products, and then they would be able to be an investigator for the EMA on sterile products. So you were looking at it a slightly different level. Yeah. You know, not everyone in FDA who was doing field investigations had Hank Avalon background or knowledge. Now, it's quite different. Yeah, they are much, much more technically capable all across the board. Because EMA went that way, a long time ago.

**Brian Lihou**
And the EMA, before Brexit, the EMA really was that on site team, that was that the technical arm of the EU, you know, when they were part of it. And I think they're scrambling still a bit to this day to make up for what's been lost. We had a regulatory person on one of the earlier podcasts that was mentioning the impact of Brexit, and how inspections are conducted. And now that technical arm that used to come from the UK isn't there now. And they're trying to compensate for that and build that up because they brought a perspective that in the US, we hadn't really considered and we had to consider it.

**Michael Carroll**
Yeah. You know, when you cite regulations from Europe, it used to be you would pull the British. Because they were going to be the standard. Anybody else? If you could pass Brit, you can worry about anybody else at all. Fine, because that was the standard it was they were closest to FDA, and well beyond FDA, and in a lot of things. So.

**Brian Lihou**
And actually in how it's written as well, there's a little more descriptor, and yeah, you know, there and so you had the tech report, you had their guidance, and then you had the FDA guidance. And if you can't figure it out from those resources, well, then, yeah, perhaps you should be making bike tires. But yeah, yeah. I remember. So okay, so now we fast forward today. I mean, before things were virtual as they are now. And it was roundtable discussions, those conferences were key must have events. Now, it's changed a bit. How would you describe the PDA influence today? You mentioned already how the FDA makeup has changed and evolved. And industry and FDA seem to be a little more in sync, at least on paper. But how would you describe the role of the PDA today?

**Michael Carroll**
I think they're gonna be far more important than they have been, especially with everything being virtual. Even in dealing with clients. I mean, they're operating in a little bit of a vacuum now, because, you know, they don't have the exposure to these conferences in these, you know, roundtables and things in the local districts and areas that we had, you know, that PDA and other groups were having those little get togethers all over Pennsylvania, New Jersey, New York, all the time. And it was the same down here in the south as well, you know, the Atlanta region that has kind of fallen by the wayside, and the virtuals just don't have the same face to face. You know, that, you know, you could go to the cocktail hour and talk to these FDA and the EMA guys, personally, yeah, and find out exactly how they would look at something, you know, something specific that you can discuss with them. Yeah, that's missing now. And they're trying very hard to bring it back, no audits on the virtual symposia and things but they got a lot of catching up to do.

> "It's an entire system that you're trying to get where every little thing that fits into the process has been qualified and can be depended on. From the raw materials coming in the door to the viles, to the stoppers, to the machinery, the environment, the filters, the air quality and differentials – all of that stuff fitting together."

**Brian Lihou**
Yeah, I mean, I think about it. One of the things that resonated for me that you told me way back, when was if you're not willing to put your arm down to the table and take the medicine you just produced, then are you really in the right line of work? You don't have that passion for it? You will. And I tell you over the years, I have removed people from those roles, because they don't have that passion for it. And yeah, talk about CMOS. Yeah, when you talk about capacity issues and constraints and the rate at which you're turning out high volumes, you know, there's another component of this that can't be overlooked and, and the PDA is really still critical than I guess, and making sure that standard is understood.

**Michael Carroll**
Yeah, they've always been critical to that, I think and it's gonna get more so. Yeah, we need

**Ed Narke**
That's a great point. I think we heard that throughout the course of the year, right around having access to folks, you know, up front and in person in the middle stuff you lose. So I think for this weekend with the PDA, I hope to be listening in to some of it, but you know, we'll hopefully see some evolution and things will go back to where, you know, we're most successful. So one other question, it's kind of high level one, Mike, and just, you know, fascinated by my stuff, I don't know, sometimes, mainly, because I don't know it. But you know, people trained in pharmaceutical microbiology, like yourself, and it's like, certified or credited, you know, I get sometimes the impression that it's a quality control, quality assurance type of situation, you know, where your role is to make sure that, you know, raw materials are not anything coming with them, it's not affecting anything in the outcome, you know, monitoring any microbio quality of the environment and anything like that, for anyone that hasn't sat in your chair, you know, doing your job, can you explain, you know, what a daily experience is like, and you know, some of the things that you like about it, and some of the things that are, you know, just kind of only you can bring to the table, I think that's important. I think a lot of our folks that we work with here are very unique in the fact that, you know, they may be a handful of people in the world that can do what they do based on what they've done and learned. So I think it's pretty important. And I like to capture some of it here, too, for posterity sake. Because, you know, we can go back and listen to things like this and learn from them. So sorry, for a long question.

**Michael Carroll**
Well, it does start with the QC and the things, you know, the raw material testing, the environmental testing, and so forth. But it's an entire system that you're trying to get, where every little thing that fits into the process has been qualified and can be depended on, from the raw materials coming in the door, to the vials, to the stoppers, to the machinery, the environment, the filters, you know, the happens of all that, the air quality, and differentials, all of that stuff fitting together. And when anything pops up that is out of the ordinary. You know, it's kind of an all hands on deck, it's, you know, a murder mystery, you've got something contaminating the system, how did it get there? What are we going to do about it? You know, it's kind of a neat thing to be involved in, you know, and it can make you tear your hand out, the hair out by the double handfuls upon occasions, because you know, it's really tough to track this stuff down. But it's also indubitably fun. It's a nice thing to do. And you have to think all kinds of different ways and look at it from all kinds of different viewpoints. And as I said, I've been unbelievably lucky in my career, to have gotten into so many different kinds of products and different kinds of systems, and been able to work mostly hands on with them all. It's a lot of fun when you get into it from that angle and trying to manage something like that. You know, it's you know, you're what was the analogy, Brian, what was the analogy, herding cats?

**Brian Lihou**
Yeah, herding cats. Yeah, that's right.

**Michael Carroll**
It's kind of like herding cats. Yeah. Like this year.

**Brian Lihou**
Well, you know, and the thing is, it's ever evolving, too. So it's not it's not boring. What we knew in the 80s, and 90s, is not what you know, today. The one thing I will say that if you haven't been in a cleanroom, it's hard to appreciate the pressure you're under. When you're running that process. When you know, you hear on the news, turning out, you know, tens of thousands of millions of units for vaccine, but the pressure you're under in that room is really unlike any job that I've had before.

**Michael Carroll**
You're not depending on a what you're not having a life depend on you. You're having tens of thousands of lives depend on you.

**Brian Lihou**
Exactly. I was lucky enough in my career to meet two people that actually received medicines that I actually worked on, like I knew for a fact, if they got it, I had my hand on it. And it's a real sobering experience when you see the impact. I used to love in the old days with J&J, they come and read the patient letters, remember. And if that didn't make you sit up and pay attention, that was brilliant. It was brilliant to have that connection with the end user.

**Michael Carroll**
My last position was with a cancer immunotherapy company, which was a literally personalized product. The product was a unit of concentrated white cells from the patient that you gave an antigen to and then infused back into the patient to trigger an immune response. So it was literally personalized medicine and we had patients all the time coming in to tell their story. You know, this is prostate cancer. And this is a therapy where you are getting essentially your own white blood cells back so no hair and teeth falling out and no feeling like crap. This is something that's stimulating your own body to reject the cancer. And it's an unbelievable technology, but having that direct involvement with the actual patients who are still walking around, 8-10 years after getting the treatment, happy and healthy. That's something you know, that really resonates. That's worth one.

**Brian Lihou**
I remember you worked on a technology. Didn't you work on a, it was a fabric, it was for you were doing some crazy stuff with it was a mesh or a membrane. I thought it was harvested and manufactured in a sterile environment. It was a patch that would for fractured bone. And I know we talked about it. This is years ago.

> "With drug development, you're not having a life depend on you. You're having tens of thousands of lives depend on you."

**Michael Carroll**
Yeah, it might have been a bone repair gel that I Yeah, yes. Yeah. Yeah, it was. human bone. Yes.

**Brian Lihou**
Yes, that's it, That's it. Yeah. So you do it long enough. The technologies that you get exposed to I mean, it really is fascinating. It's a prime example where, you know, what are the regulations? Well, there really aren't any, this is the guidance we have to stick to, but there are no specific regulations for that, so.

**Michael Carroll**
Well, like, for example, what they have now wound sealants, which actually nothing but Krazy Glue. Okay, how are you going to filter Krazy glue? Tell me. Go ahead. Put it on a filter. And that's the end.

**Michael Carroll**
You do it.

**Brian Lihou**
Just jack the pressure up? Yeah. Yeah, so I guess in a nutshell, I mean, you know, to kind of bring it back, it's, this is exactly what I was hoping for Ed, Meranda, was a chance to kind of talk about PDA, the micro side of it,

and just the evolution and some of the stories. And, you know, when I look back on my career, I certainly appreciated the time, I was able to work with Mike and happy that I'm able to work with him again today. You know, just the real personal connection and the ethical component to what we do. I think it really resonates. And I hope that people listening to this podcast understand that it's more than just the number of units produced,

**Michael Carroll**
It's much more thing. It is, it is,

**Michael Carroll**
You know, you're doing something worthwhile. You know, you know, exactly, it's going into a sterile vial with no pyrogen and the stopper, sterile and it's processed clean. That's a good feeling.

**Michael Carroll**
That's the assurance part of it.

**Brian Lihou**
Right? That I think that's Do you have any more questions or Meranda?

**Ed Narke**
So yeah, thanks for the thing. I think Brian, this is good for like someone like myself, because not, you know, ever having witness or being in a facility doing what Mike did or does. You know, guys see the visual when I kind of apply it to, you know, what I think it feels like it looks like, but I'm helpful. I mean, we can go pretty far deep in technical questions and stuff. And, you know, I guess that could last forever here in this podcast, but we want to keep it short. And if anyone ever has any questions or issues or wants to talk with Mike, you know, certainly you can reach out to us and we can put you in touch with them . Mike, any personal stories that you'd like to share with us? I mean, I don't want to get too deep or too, you know,

**Michael Carroll**
What I like to tell people is that when I started, it was in the diagnostics industry, which are sterile products, but they're for diagnostic use. And when I started, it was routine to walk into a lab, testing human blood all over the place tubes and tubes and tubes of it with a cup of coffee and a cigarette hanging out of your mouth. And sit at the bench with a lab coat with a cigarette hanging out of your mouth playing with human blood mouth. pipetting. Okay, right now, that would be looked at as Paleolithic. Okay. And it was, but that's how far it's come in just my time in the industry. And right now we're talking nanoparticles, and actual use of them in it. It's incredible. It is really huge. It doesn't stop being fun and entertaining and informing.

**Brian Lihou**
Yeah, agreed.

**Michael Carroll**
Doesn't stop.

**Ed Narke**
Yeah. Okay. Well, thanks, Mike. We don't want to keep you too long. We know you're busy. Pella, I wanted to thank you personally, for being our final guest here on CMC Live in season one. We certainly have ideas and dreams and more ideas for season two coming up at some point. And I also wanted to thank personally, Brian, and Meranda who were here for most, every one of the 24 participated. I know, we had some great stuff since our last recap just started this year, we had some discussion with Paul on the complexity of project management and

drug development. We talked to myself a couple of times to filler, I usually want to talk about what I used to do since I don't do it so much anymore, but regulatory strategy and putting certain things, missions and when and how, and I think all of our discussions and competence technical folks that generate this data, including yourself, Mike, so I know a lot of us are familiar with that all the way you know we actually revisit it with Jim Mencel. I strongly suggest anyone goes back and listen to any of his Yeah, for he has the record for most podcasts with us, which is great stuff. We did some things on quality assurance recently with our panel of, you know, industry experts that have just lived it. So, I wanted to thank Brian and Meranda for going through this with us. You know, stay tuned for more. And let us know if you, anyone out there thinks of any topics or have any questions. You know, we'd love to bring you into this in the future. We always love your feedback. Very important. Yeah, subscribe to our channels anywhere. So you know, spread it to your friends, Big Pharma, large pharma. You know, I love that we got these little groups like PDA and wraps and APS. And, you know, I know things have changed over the last year. That's life, you know, if you don't change, you go out of business. And I'm sure that with some of the younger folks out there, learning from us, you know, mainly everyone, you know, hopefully we can carry that on and train and teach our, you know, our followers after that, and so they can continue to make medicine safe and effective. With that, thanks everyone again, and we look forward to talking to you in the future. Thank you.

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