4 Experts, 120+ Years Of Drug Substance Experience: Major Trends You Should Know

Episode 17

Ed Narke
Welcome to CMC.Live. Today, we have a special new format- lively and informative. Joining us here today, as always, are Meranda and Brian. Hi, guys. First off, the market for the manufacturer and supplier of APIs is changing rapidly, still, continuously. Many factors are influencing these changes. But, precisely what major trends you should know and be aware of and how you can use them to your advantage are what we'll be discussing. In this podcast, our industry API consulting gurus give their views and latest overviews. Being aware of these trends is important, but perhaps what's even more important is how you leverage the opportunities they bring and how to react to them. Of course, it depends on your current engagement in API outsourcing. Are you already fully engaged? Are you on the stage considering a change? Today, we have a group of our drug substance service experts with 150+ years of experience. I'd like to go around and introduce the. Most everyone here was on a previous podcast. Dan Torok, who previously joined us on the podcast called *The White Coat Effect is Real*. Hello, Dan.

> "We're certainly seeing a very rapid change in the API/CMO world. I think if you went out with an RFP maybe two years ago and you threw this RFP out to eight vendors, you'd have eight proposals back fairly rapidly."

Dan Torok
Good afternoon, everyone.

Ed Narke
I believe I heard Dave Adams, who joined us for a previous podcast called *Trust the Process with a CMC Process Champion*.

Dave Adams
Hi. Happy to be here. Hello, everyone.

Ed Narke
I see Jim Mencel, who joined us for the first two of our podcasts starting this series, *Establishing Regulatory Starting Materials & Understanding the ICH* and *Expedited Drug Development*. Hello, Jim.

James Mencel
Hey, everybody. I'm glad to be here.

Ed Narke
Last but not least, David Blasingame.

David Blasingame
Hi everyone. Good afternoon.

Ed Narke
So, folks, we covered a little bit about your backgrounds in some of the previous podcasts. Let's get a little bit deeper and discuss a range of recommendations and how best to use current trends and situations to the benefit. Perhaps let's start with the landscape of API manufacturing and available capacities.

James Mencel
An important thing that people need to think about is that many internet sites for these companies are good, domestic and foreign. You need to understand what they're offering, what equipment do they have. If your process has special needs, like high pressure or temperature, you must ensure that their equipment can do what you need it to do or specific configurations you need. If you know your process enough, you should find out if they can set up a training that will run your process because many people will try to sell you anything. These are often multi-use plants but were purposely built in the past for some specific drug. So your product might be a skewed fit. So it's really important to assess the places you're going to and whether they really can be a fit for what you want to do.

Ed Narke
Can you talk to us a little bit about the competitive marketplace out there- the API marketplace? Is it competitive? There are many small producers who specialize in making niche APIs in some cases, which leads to intense competition. The market is growing. Can you talk about the competition going on out there and how that's evolving?

Brian Lihou
Dan, you've done a lot of work with us in this type of discussion with clients. Do you have any thoughts on that?

Daniel Torok
I think we're certainly seeing a very rapid change in the API CMO world. I think if you went out with an RFP, maybe two years ago, and you threw this RFP out to eight vendors. You'd have eight proposals back fairly rapidly. I was part of one of these, and we threw out the RFP to about seven or eight people, and two immediately just said no. It wasn't that they took a week to look at the chemistry. They just said, “No, we don't have capacities.” A couple of others looked at the capacity and said, “We're sorry, we can't fit. We'd love to work on this project; it looks like a great fit. We don't see volumes opening up for another two years.” Some of the other guys can comment. But I've been doing CMOs manufacturing for most of my career in one form or another, and I've never seen this in the small molecule world before. I've been bumped out of some of the more premier sites and am told they didn't even want to look at it. Now, to have this large number who seem to be filling up, there's certainly some large dynamic change within the industry.

Brian Lihou
Dave Blasingame, you're working with a client who will get into this. You have to get that message across that the landscape has changed. You're now looking around. Are you seeing the same thing, in particular with the US sites?

David Blasingame
Yeah, definitely. Especially with a couple of projects that have been more barter-related. The ongoing trend is to onshore all of those programs as well. That's a lot of programs taking up a lot of capacity, potentially. First of all, we're getting proposal turnarounds much slower, that's if they're interested. I think that's because they have a large number of requests from a lot of folks, big and small. Everyone is trying to figure out whether or not it's got real potential with government funding and whether or not they can tie up resources for those projects. That's

been the other challenge, convincing them that it's a real project and that they should set aside some resources for it.

Brian Lihou
I was thinking about that. I sit in on quite a few BD calls, and a surprising amount of small, virtual companies have these projects. They're all passionate. They all believe in them. They're all taking up space, which, Dave, is what you just mentioned. Meranda, are you seeing a trend in the types of requests we get? You can see how that directly filters into what these guys are talking about.

Meranda Parascandola
Yeah, for sure. We've been getting a lot of requests for CMO searches. The small companies probably tried to find a place and couldn't find a place. That might be why they're coming to us to see if we have a better 'in' or different companies to look at.

> "I don't know how many of you guys have been involved in plant build-outs and plant qualifications. It is not a slam dunk, especially when you're trying to retrofit an existing site."

Dan Torok
I think one of the interesting requests we had a month or two ago, Brian, Meranda, I'm not sure if I drug substance guys even got to hear about this one- A prospective client called us. They had something in the barter realm and their drug substance, as the guy put it, is a generic. He wanted to find a generic drug substance made in the US. I don't mean to be mean, but it's hard not to laugh at that one because, for those of us who've been in the industry, I think we could probably put our heads together and maybe name a few generic manufacturers in Europe.

Brian Lihou
It's something you kind of take for granted. Jim had mentioned in a previous conversation how the trend into investing back in the infrastructure of these stateside sites is not there at the level, at least, that we see in sites abroad. I know that's a broad paintbrush to make that kind of statement. I'm from the drug product realm. So I have a little different perspective, but it's very similar in a sense. I see the same thing in drug product. Dave Adams, you're on the call. I know you're working on a particular situation where you're transferring a product to the US. Do you find that the site to which you're transferring this process has resource constraints? You represent a project that we now are transferring within the United States to another site. Do you see some of the same problems in terms of capacities?

Dave Adams
They're definitely tight. They've told us this. They're booked out day by day for the next year. We can't slip a week. If we don't get our product into the schedule, they've told us it would be a year and a half until we can get it in. They're definitely packed. Even with our product, the other processes that a company has to succeed at, all the paperwork, the quality control, they have to have all of that capacity along with the equipment. Even that's putting constraints on their corporate business possibilities. You can tell that the entire corporation is very busy.

Brian Lihou
You can't afford any missteps, or it could potentially set a project back six months to a year. So it puts you on alert to make sure that that process and those deliverables are ready as they're needed. I know the same thing happens on the drug product side.

Meranda Parascandola
I have a question. It might be a silly question for the drug substance side, but does it matter if the company has Fast Track designation to the CMOs to get their product in and made first?

James Mencel
It's a good question, Meranda. Honestly, many CMOs don't even know what that means yet. It's something where it's more awareness of the sponsor's part. I don't know that the CMOs are as savvy on that whole area, at least not the ones I've seen in the US. So it seems like that's something that the awareness and the activity is driven more by the sponsor or by their consultants.

Dan Torok
I think you have a very good point with certainly the American manufacturers. I'm not sure they fully wrap their head around it. I see a small handful of European manufacturers whose business development team seems to get it. They understand that if they get a piece of this action, they're going to be locked in for longer than other things, most likely, because they're going to be moving at 100 miles an hour to get there. So there won't be time for a secondary supplier to come in. They also realize they're closer to that commercialization point, where every drug substance CMO wants to be. You want to have your plant filled with commercial products because they're stable. A few get it, but for the most part, I don't think there are. You might go to find a couple you could manage to sweet talk your way into with the special background, but there is going to be few and far between, I think.

James Mencel
I agree, Dan. The EU has a mission statement to become the top API manufacturing location in the world. That's a mission statement in the EU. I see the investment following that mission statement. So I agree about their awareness. The funny thing is, fast track is an American concept. Yet, Europeans have latched on to it as a business opportunity more so than the US has, at least on the supply side, not necessarily on the sponsor side, but on the CMO side, CMOs have been very slow to latch on to that.

Brian Lihou
Speaking for the drug product side, one of the things that we notice is that when you've been doing it long enough, you're used to the same names, used to the same comfort zone, you know competency, and you drive your clients over to a site that you know the project will be well in hand. Still, new sites, smaller sites are opening all the time. They're making commitments to do work, and now once you get in the door, you're finding that they may not have the in-house expertise. They may have the equipment; you can buy equipment, you can IQ OQ PQ, they'll even sell you the protocols to do it. However, the depth and experience that you can trust them with your process, your timelines, especially in those expedited projects, is something we're always cautious of. There's a new name in town. Okay, well, who's there? What exactly do they know? What exactly do they do? So, Dave, you had an interesting experience about a month ago.

David Blasingame
You are right on the money. They sold that they could do everything and anything. It turns out the client would end up funding the buildout of that plan and hiring people who could then do what they said that they could, what in fact that they could not at that moment in time. In his mind, it was going to be possible in the future. They just needed a client to get them there. That's why we keep coming back to the same names for exactly that reason.

Brian Lihou
Right. The good ones are busy. I don't know how many of you guys have been involved in plant buildouts and plant qualifications. It is not a slam dunk. Especially when you're trying to retrofit an existing site, existing utility

loops, all that stuff. It is not as advertised. So if you're betting your project's success on buildout space that's not quite realized at a site, that's another thing you have to look at. You have to take it seriously, the risk.

> "The number of people in the U.S. who have manufacturing backgrounds in small molecules is just small and diminishing rapidly because all the jobs have been offshored."

Dan Torok
Brian, what you're saying ties in well to what Dave and Jim said earlier. I think Jim was the one that said the US sites need some infrastructure built into them still. They need some updating. They need to be modernized in containment or utilities, and someone can do that with money. There's no doubt about it. That's one of those great parts of the world where if you have enough money, you can buy stuff. We saw from a client recently that the problem is that even if you build it out, you have to hire that person to grow it. There's just not a lot of people in the US with the expertise of sitting on this panel right now today. We landed one of our more recent clients because they did a job search for six months and could not find anyone who had the resumes of the four of us sitting on the panel that they could just pull in who wanted to work for them. The number of people with a manufacturing background in the US with small molecules is just small and diminishing rapidly because all the jobs have been offshored.

James Mencel
I agree, Dan. It's a vanishing breed. It's painful to me as an American to see that happen, but the schools are not jam-packed with chemistry majors either. I can give you an analogy. We had a place up in Connecticut, a cabin in the mountains, and the guy that took care of the cabin was an old boilermaker. He was in his 90s. Companies in Connecticut hired him back to teach kids how to re-rivet boilers that they were reactivating, coal for natural gas. So he went in and taught these kids in his 90s how to do rivets inside and outside of the boiler. I feel like, at our age, some of us are 50+; I think that we're going to be the ones that are going to have to train a younger generation for how to do this stuff because there are not a lot of veterans that know how to do it. A lot of my friends have retired.

Dan Torok
The reality of it is, it's not something you're going to teach somebody to do. I had a client who asked me, "Dan, I want you to teach me to review batch records as fast as you do." I said, "Fine. The first part is you have to write 100 of them." Look at somebody like Dave Adams on here. I learned writing batch records from Dave Adams in a previous life, a lot of it. If there's any way Dave knows the number of batch records he's written at this point, it'd be amazing. I've done enough of them wrong. I didn't mean to do them wrong, but I still made mistakes, and you learn from them. Without doing it, it's a much slower process to learn.

Brian Lihou
So now I've kind of put two and two together, and I've come up with three. At the top of this call, we talked about how there's been a lot of investment in infrastructure and manufacturing abroad. That's been the trend for years. This is not a few-year anomaly. I mean, that has been the trend. Asia, enough said. Blasingame just did a whole podcast on that. The industry has grown accustomed to APIs manufactured elsewhere. So now you can understand that you've starved the US API manufacturing capacity because you've moved it over for a better break, a better cost. It comes down to unit cost. But then you think about it, all those jobs go away because there's no great demand for them here in the US. I don't know of many people that have gone and said, "I can't wait to go work in that province over there in that Asian company because I can do that work." No, of course not. They're rethinking what they want to do, and as a result, there is a gap.

I think about the trades. There's a big push to get more people into the trades. Kind of to Jim's riveting point, right? The last guys that put the last rivet in the Titanic have since gone, and that skill set has gone with them. There's a gap between real tradesmen, true electricians, carpenters, and plumbers. Who's to say that that doesn't happen in pharmaceutical manufacturing? Good operators are worth their weight in gold. I don't know about you guys, but when you're looking at a batch being manufactured, and you're told it's being run on a Sunday afternoon, your experienced people are home because they've earned the right not to work on a Sunday afternoon. So you have to babysit that process more. The reality is that there's a gap. That was my point earlier about these new places that will pop up. One of the things that we're seeing that I thought was interesting is these VC groups trying to get into speculative buying and trying to see how much they can squeeze out of a site if it's a viable candidate for manufacture. That's got a whole host of other problems.

James Mencel
The question comes down to what can we bring to people to deal with this? So one thing for sure is the experience. As Dan said, each of us has different types of experience with this. You can't just impart that experience to somebody else; you can mentor. I think what we can bring to clients is that we sort of know what to look for. We can sort of sniff out when something is real and when it's not, at least begin to wonder if we need to do a little bit of sniffing around. The point about places that advertise they can do things that can't do them - the world is rife with places like that. I think the API industry in the US is kind of getting there. So I think we can at least sound out the places and understand what's real among the places that will talk to clients and sign a project. Who's real? Who's got staff? If they don't have all the capability, can we, with the sponsor, fill those gaps so that it's a successful enterprise for them?

Brian Lihou
Right, because it can't necessarily be a dead issue or moving on, because those options to move on become more and more limited. All of you, and I've watched it happen, have mentored either directly or indirectly the client or the CMO, and they're learning from it. And one of the reasons that we stay as long as we do with our clients is because it's not an adversary relationship; it's a mentoring relationship. Several of you are involved in interviewing on behalf of our clients to try to help them build that experience. However, even when they hire, you know immediately if you're still going to be there, you're still going to be imparting that experience and knowledge. Nobody here has less than 20 years of experience in this group. That's a low number. So it's that ability and that willingness to impart that experience. I think that's a real big message. I look at Dave Adams, who's doing that transfer in the US. Dave, I know that there isn't as in-depth in-house expertise for the process that you're transferring. So you are, by default, in a mentoring capacity, right?

Dave Adams
Correct. It's been an observation of mine for many, many years. I've watched many people come into the industry from academia- bright, smart people, and in their first two or three years make some pretty big goofs because universities don't teach physical operations; how to pop a batch from one place to another, how to do a physical filtration on a large scale. As we're talking expertise, the learning curve to understand the chemical engineering in a plant, it's sort of a cross between chemists that understand chemistry and engineers that understand heat transfer and mechanical properties of fluids. Somewhere in the middle is the person that can make it come together. It takes a while for that to be accrued. I'm seeing it now in various plants. I've mentioned things to people, and they've never heard of that technique, never thought of that, or didn't know that kind of equipment existed. People say, "Can you give us some training? Can you give us some learning?" It would take months and months to explain everything that's been happening over the past 30 or so years. If you lose the practice, you lose the people, and then you end up with a bunch of plants with equipment.

Ed Narke
Right. Let's talk about what you think the industry looks like in years from now. I saw stats that 50% of APIs for drug product in the US come from Asia; it seems like it's growing faster than the overall market growth. Dan talked about the talent and the training that happen that aren't there anymore. You're talking about Asia's talent pool of engineers; they have their scientists. The cost structure is lower, and labor and materials are lower. There's also a discussion about buying APIs produced in Asia and the pitfalls. We all know what those are. So do you expect to see more Eastern migration? Is there some sort of balance? How do you think the industry and supply chain look moving forward ten years from now?

David Blasingame
I think the trends got momentum swinging the other way out of Shanghai and out of China and maybe back into the states or at least ex-China, whether it's Europe or America. I'm not sure yet. Peter Navarro, since 2012, has had a real big push to move things out of China to secure our own supply chain, and he's not just talking about APIs; he's also talking about raw materials. All raw materials are essentially now coming from China. That's the real problem. You can say APIs may not be, but the truth is starting materials are. So if your starting materials are coming from China, essentially, your API is also no matter where you're making the API. It's like with iPhones, where they're manufactured versus where they're put together. It's not always the same thing. Ten years from now, I hope that that trend continues. It would be nice if we could secure our own supply chain.

> "Good operators are worth their weight in gold."

Ed Narke
Right. As far as the facilities, Dan and Jim mentioned the need for upgrades the talent there. How does that work? We have these grand plans to bring the supply chain back to control it and control the quality. What's the plan on the other side, though?

Dan Torok
I'm going to step out on a limb and put something out there that may make me sound like a heretic. I'm wondering if this investment that needs to be done is going to be done by Europeans and perhaps even Asian manufacturers. I don't know if this is the case, but I never thought I'd see a day when a Nissan was made in the US or Mercedes. You may start to see that happen certainly in the raw material areas and some of the simpler APIs. I hesitate to say they're simple to make because Brian will never let me live it down. You could rapidly bring something in, set it up, and get it going, certainly for raw materials. There are some old facilities that you could revamp, but it's going to take someone who knows how to do it to do it. The whole recent episode with, was it an Eastman facility or an old Kodak facility that was going to be put over? That's a pretty good example of probably how not to do. But if you could find somebody who wants to stay in the industry and has the capital to put in, they can then support that bill. I fought in my career with the buildout of the wholly-owned facility in New Jersey. You may like them; you may hate them. That's a whole other thing. But when they built that facility, people moved from around the world to help start it up so that the company's knowledge base was already there, and you didn't have to restart from zero. So maybe it's a way to go. I don't know.

James Mencel
I think what has to happen, Dan, is that the industry has to know the demand is there. Let's look at raw materials. Dan Blasingame made a really good point. In one of our projects, our two starting materials come from Asia. You guys may know, we've had some very serious issues with provenance, fake COAs, and everything.

It's just been a nightmare for that program. We've looked at setting up Western manufacturers. They are very skittish to get involved because they need to see the demand. They know that if they get involved, they're in a marketplace where not only is the playing field uneven, but other countries subsidize the industry. In the United States, other than bailing out GM or some other massive employer, the United States does not subsidize the CMO; they don't subsidize the fine chemical makers. You either make it or break it on your own here. So they've got to see a business proposition that makes sense to invest in a facility and make a piece. So for us, this one thing we want to make, we're getting people interested, but we're paying for all the research. I don't know if the facilities will be big enough to make enough of it, and the places that can make it, Kodak, for example, want a metric ton order to start with. I think that a lot of it is that they need to know that they would get the business instead of somebody overseas if they make the investment. I think that's what's hard, is how you prime that well, for companies to feel comfortable that they can invest and know they'll get a return on the investment.

Brian Lihou
Yeah, that's well put, because the trend has been that way for so long. It comes down to the cost of goods. We covered a lot. I had envisioned going through a whole variety of topics in my head. I didn't realize that there were so many aspects of just this one topic and the impact, more importantly, on the US industry. So I think for me, I learned quite a bit from this.

Ed Narke
Yeah, same thing. My last question, I always like to throw in a regulatory question: the volume of this production increases over time, right? We're going to have to make more drugs over time. The population is increasing, but unfortunately, so are the number of issues in quality compliance, which also leads to increases in regulatory demands, expectations, and guidances. Is there anything anyone has to share? Maybe some of the trends there based on some of the supply chain, any of the regulatory trends that might be relevant per the discussion.

James Mencel
I'll share something, and it comes out of the guidance that came out recently for nitrosamines. Nitrosamines aside, the guidance is very interesting at what it leads to. So it's one of the documents I've seen from the FDA, one of the few recently when they talk about the sponsor going back to the source of material they used to make their starting materials. They're making it clear that even though they don't have visibility beyond the starting material, they expect the sponsor to be tracing the sources of everything that's being used to make their starting material because they're speaking about the water used in plants, the nitrosamines, and materials that are used as Row Still, the expectation is that people will go further into an almost opaque supply chain to figure out where things are coming from and that the supply chain is stable. So going back to Dave's comment about Asia, you could have a material that's made in Asia, but then you got to find out where its materials are coming from. So how far back can you and do you go? It's clear from that guidance the FDA put out that their thinking is that you go back as far as you can to dirt. That's pretty tough when you're in the US or Western Europe trying to figure out where you are in Asia. So I do see that as a trend that the FDA, in particular, is asking more and more for sponsors about what they can't see and making sure you are looking at it.

Meranda Parascandola
I just have one serious question. How many batch records, Dave Adams, did you actually write?

Dave Adams
Well, I did check it once, and I had just processes. I've put through over 175 different processes. That's in a 12-year period. Then, of course, they go through revisions and so forth. So, about 70 different products in over 175 different processes.

> “I think what has to happen [in the future of API manufacturing in the U.S.] is that the industry has to know that the demand is there.”

Brian Lihou
My dad is 79 now, and he's still swinging a hammer as a carpenter all over the island where he's been since 1959. In every job, he has either nicked a thumb or something. He's convinced that his DNA is everywhere in that town, and if there's ever a crime in some sort of advanced crime lab, my dad is going to be implicated by default. So it's kind of like that; your hand is in everything.

Ed Narke
I want to thank you guys again, Brian and Meranda. Brian is turning into a polished podcaster here. Dave Blasingame, Dan, David Adams too; Thanks for the happy hour. Also, Jim, thanks again.

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.