Why now is the most important time for selecting a CMO

Episode 14

> "A lot of CMOs are now going to a one-stop-shop type model. Basically, they'll say, "We can take you from gram quantities right through commercial. We can do your API and your drug substance". But there are still a lot of smaller shops out there that are med chem shops. They can do the small-scale, preclinical work"

Ed Narke
Welcome to CMC live! Today, we have an incredibly special guest, and we'll be talking about some especially important things. I guess the common theme is making a commercial process out of a medicinal chemistry (aka 'med chem') process - the manufacturing search selection, working with a CMO, transferring, and optimizing your process and then developing a timeline and the implementation challenges. We'll be discussing some of our experiences. So today, we have Dr. Rick Offerman on the podcast. Rick's a process chemist by training and has worked here with the group at DSI for a number of years. He's joining us from outside of Richmond, Virginia. He's a Senior Project Management Consultant here with us. He's worked at DSM, Cambrex, BI (Boehringer Ingelheim), Eastman Kodak... I got a lot of stories from Dan about your interactions down in Tennessee. So, Rick, let's get this episode started by going into some of your background - how you got started and to get your thoughts on some of the topics that we discussed. I'm looking forward to it.

Rick Offerman
Okay, yeah. I'd be glad to Ed. I started out earning a Ph.D. in chemistry and worked for a number of years as a process and manufacturing chemist at Eastman Kodak and Eastman Chemical. I left there and went on to earn an MBA at Duke University. Since then, I've been doing a number of different jobs in pharma. As you said, I've worked at DSM as a project manager, I worked at Boehringer Ingelheim in business development, and for a number of years at Cambrex doing market research and business intelligence. I've been a consultant for about five years, doing account management and a lot of other jobs. I feel like I'm a jack of all trades and being able to bridge both the technical world with the business world. When I'm talking to the business guys, I can say I'm a Duke MBA and when I'm talking to the process chemistry guys, I can say I'm a Ph.D. chemist. I earn a little bit of credit on both sides on that.

Ed Narke
Okay, so you said something before we started here as we talked about making a commercial process out of a med chemistry process. Many of the folks we work with may not have an optimized process, maybe even later in development. So things happen- transfers, you find a new supply chain or improvements in the process. Maybe you can talk to some of that. I think Brian has some follow-up questions on specific things.

Rick Offerman
Yeah, certainly. With most drugs, you want to be quick and dirty. You want to kill drugs that are going nowhere so you don't spend a lot of time upfront when you're getting those first few grams or a few kilograms to optimize a process. You're looking for what we call a med chem process, which can be generated in the lab or a pilot plant on a few kilos. You don't worry too much about process yields or the types of reagents, solvents, that sort of thing because you're working on such a small scale. But if you're fortunate, your drug does well and goes into the clinic, does well in the clinic, and then suddenly, you're not dealing with a process where you need tens of grams, hundreds of grams or a couple of kilos. Now you're dealing with a process where you might need to make metric tons or more so the chemistry, the manufacturing process and safety work you have to engage in to understand how to make that safely are quite different.

Brian Lihou
Let me ask you a question. Is it one of those things where you're at a point where your existing vendor just can't make that transition for you? Do you usually find a CMO that can do both, or is it typically one or the other?

Rick Offerman
That's a good question. A lot of CMOs are now going to a one-stop-shop type model. Basically, they'll say, “We can take you from gram quantities right through commercial. We can do your API and your drug substance”. But there are still a lot of smaller shops out there that are med chem shops. They can do the small-scale, preclinical work, make you a few grams of API, and maybe they can scale up the drug you want or the API you want to a kilo, but really they're working in a small shop; that's their business model. They'll take you up to maybe a phase one, maybe they'll do some tox work, and then they say, “We're done. We're not going to change our entire business model to make commercial or late phase materials”. As a small biotech, you're in a situation where you have to find another vendor. If you're a small company, maybe you have less than 15-20 people; you probably don't have a lot of experience out there in the world trying to find a vendor who can scale up a process. So you start asking your friends or colleagues in the industry something like that to say, “Hey, do you know anybody who can do this?” You don't know the business models of the major CMOs. You may not get much attention from a big CMO simply because you only want phase II material or something like that. So you're in the situation of trying to find somebody who can help you go on to that next phase of making either phase I material, phase II material or going on to phase III and commercial.

Brian Lihou
Okay, terrific. Based on what you just explained- you've had your selection criteria, you've gone through your search, you've now selected your new CMO, you're taking your med chem process, and you're looking to transfer that. How much leeway do you have in looking at the process, the robustness, scalability, and the timing for change? How do you typically assess things like that?

Rick Offerman
Yeah, that's a good question. I think the important thing is if you have the initial discussions with a CMO. You ask them, “What is your process for doing this?” You try to get a good sense from them. “Have you taken a fair number of phase I processes and converted them into commercial manufacturing?” Then you let them talk because if you talk, they'll sit there and nod their heads and say, “Yeah, we can do that.” So let them talk, and then you interview two or three different CMOs. Then you find out, it's like, “Okay, is everybody telling me about the same story?” And you will say, “Look at my process, and tell me where the pitfalls are.” Maybe I've got solvents that I would never scale up to commercial scale. Maybe it's a methylene chloride-based process, or I've got a bunch of chromatography in there somewhere. You're never going to go to commercial with chromatography in your process. It's going to be very difficult. It's hard to scale. So you have to turn it loose with your CMOs and let them talk and say, “Explain to me how you would take my process from this methylene chloride-based process that's five steps with six chromatographies to a process where I could make five metric

tons or a metric ton," something like that, and let them tell you about it. You've done your background homework, so you've talked with some smart people who will tell you, "These are the types of questions you should be asking the CMO." Whether they're in the room with you, or you've done your background work, you let them talk, and then you assess what they're telling you.

Brian Lihou
Okay, so knowing that I'm a drug product person, and coming at it from a different perspective, you'd mentioned solvents a few times here. Are there solvents that are just not transferable? What are some of the things that go into selecting that solvent because it comes up time and time again from small to large scale?

Rick Offerman
Yeah. Is it an expensive solvent? If you're a med chem guy, you will grab whatever works, and if it's very expensive, you don't care because you're only making a few grams or a kilo. Waste disposal isn't a big factor. But as you're going on to commercial, phase II, phase III and commercial manufacturing, then the question could be, "I've got some solvents that are hard to dispose of, or I may have environmental limits on the amount of solvent I can use in my facility." So if it's something like methylene chloride, the state you're in may tell you that you're limited to the amount of methylene chloride you can use. And of course, with something like methylene chloride, how are you going to be able to bring the material in? You use it, and then what do you do with it at the end? Do you dispose of it? Do you try to recycle it? Those sorts of issues are big ones. Now when you go to a competent CMO, they'll start screening a lot of solvents. They'll start looking and saying, "Instead of using methylene chloride, let's do some simple screening experiments, look at the yields that we get, look at the impurity profile, all those types of things." Cost is always a factor, but it's not the major one. You have some discussions ahead of time, but you will ask the CMO, "What would you do to eliminate something like methylene chloride in my process" things of that sort. When you get into manufacturing, you want to go with a minimum number of solvents that you can, the readily available ones, the things you can bring in by a tanker and dispose of if it's burning or something like that. That's the way you typically go about it. But a lot of it is making sure that you get a solvent that you can use that isn't going to change your product profile - a lot of different impurities or new impurities, and, ideally, you'd swap something in that wouldn't change the product profile, and wouldn't affect the yield, and would just be easier to purchase and dispose of.

"Cost is always a factor, but it's not the major one."

Brian Lihou
I want to loop this back to Ed, to the regulatory component, in a minute. You've gone through that process. You're now moving to the new site with the process and that understanding. There are a few things that you have to do to orchestrate this whole thing. Some considerations have to be made for change control. So how do you manage that? Let's say, for example, you are moving to a different solvent. It wasn't a good fit. The new vendors became comfortable and capable of handling the solvent that we're going forward with. How do you do that? You talked about the product profile and altering the product profile. There's a big change control component of that. Can you talk a little bit about those steps and those considerations - what you do and don't do?

Rick Offerman
Yes. This is a discussion that you have with the CMO and ask them, "How will you go about doing this?" There will have to be some comparability protocols or something that will have to be done to show that you're getting the same impurities. If you're getting different impurities, then there's going to be work that will have to be done to identify what effect they might have on the drug, or what effect they will have in the body, those types of things. It's a big regulatory exercise to demonstrate that the new process is producing a comparable product to the old process.

Ed Narke
A long, long time ago, on a planet far, far, far away, I used just to know anything and everything about the API side of things before I got into regulatory, but I think I picked up on what Rick was talking about here. It's a collaboration; it's an integrated approach. Just to speak to the collaboration part of it, anytime you're transferring something, or scaling something up, or changing a process, you need to collaborate. There are people involved at the facility, CMOs, the DPI planters, the process chemists, the analytical. Still, you almost have to have a little presence from formulation folks, too, because some of these changes might affect the active- certainly, as you mentioned, Q.A., and regulatory. When I worked in manufacturing, some of the materials were already approved in certain markets for certain drugs, so you can't just haphazardly change things without effectively updating that filing, wherever that might be the U.S, if it's in new drug, if it's an active that goes into an already approved drug, or if it's just something that you have a few INDs open for. Any major changes or even minor changes need to be updated, and they have potential safety consequences.

So knowing what you know, Rick, there's never normally regulatory folks sitting in CMOs, so it's really important to actively manage that if you're a sponsor. So knowing what you know and some of the changes that can occur, how do you feel about that as far as handling not just the transfer, the scale-up, but your relationship with the agencies to make sure that you're fully compliant?

Rick Offerman
Yeah, that's a good question. Like you say, sometimes, when you're dealing with CMOs, you're dealing with a manufacturing facility. They don't have many regulatory people, so you might have to go outside and bring someone in on your behalf if you don't have that expertise. You're a small biotech company. You have half a dozen or fewer people. You probably don't have a regular regulatory person, so you might have to go outside and bring someone in to provide that kind of expertise. You made a very good point about having the formulation people involved because switching over solvents, you can get into situations, for example, where you get a different polymorph or different crystal form, so you say, "Well, the API looks the same. We analyzed it; everything's good." But suddenly, you realize we've made a different crystal form or maybe several different crystal forms. When we try to put that into a tablet or something like that, suddenly we're having problems with this solution. So you will have to have an integrated approach through the system to understand the API you're producing, the impurity profile, the crystal morphology or the polymorphs. Be able to justify those things through the regulatory chain, to say, "Okay, well, we are getting a different polymorph, for example, but we find that the dissolution profile or things of that sort didn't change." If you're lucky.

Ed Narke
Can you talk to us about selecting or using a CMO partner that understands the whole process from preclinical where you're developing a little material for tox studies, safety information through commercial manufacturing? As we all know, it's quite expensive to move facilities anytime yet alone at the end. So a full-service facility, can you talk to us maybe about that, but then explain some of the limitations of having a large CMO?

Rick Offerman
Yeah, so there are CMOs that will be able to take you from the few grams of preclinical through phase one, all the way through commercial manufacturing. Sometimes, they're an accumulation of companies. Many CMOs got into the one-stop-shop, but really, you're probably dealing with a different site for the phase I materials. I'm always curious to know how many processes have you taken from your site in this city or at this facility? How many have you transferred into your major manufacturing site that can do phase II and phase III material to commercial? Give me your experience on that, because everybody will tell you they can do it, but the question is, have they done it? You go to a one-stop-shop because you want to avoid some of those hurdles you have to jump over as you're transferring from one site to another in the learning curve. Suppose you're dealing with a big CMO. In that case, whether the facility is on the same site or not, they can always pop in and watch the process,

understand it better, talk to the people who are doing the early phase work- and then you go on. They have their internal documents, so you should have some seamlessness in going from phase one to phase II and then on to commercial. You can run into the problem when you get to a big CMO because they might have hundreds of projects going on. How do you get their attention?

Some of the larger European CMOs used to talk in some detail in their investor calls about having 200 or 300 projects going on. Well, you're a little biotech company; maybe you've have ten people, you've got a drug. How do you get their attention and get a deal with them to manufacture all the way through? What are you giving up to do that? As I said, some of the companies were very good API manufacturers. They bought formulation companies. The formulation companies may not be someone you would prefer to use, but now you're sort of locked into their system. Or maybe you've got a formulator that you like, but now you've got to change that formulator to fit into the one-stop shop of a CMO. Most of the CMOs have gone that route. They'll do the early phase stuff, preclinical, phase I, try to transfer to phase II/III and commercial, and then do your commercial manufacturing. Then they've got a partner that will do the drug formulation part. The question is, how seamlessly does all that work? Because that's what you want. You want efficiency in that process, and if you're not getting efficiency from it, then frankly, why am I going to a one-stop-shop?

Ed Narke
You gave us a few nice examples of questions that you should be asking one year, after route scouting, when you're playing the scale-up, for example, raw materials if you can even get them on a larger scale. For example, if you're using solvents, are they acceptable to be using in your process, with your equipment, or for safety reasons? Are they affordable? Can you give us a few other examples of questions that you should be asking at the beginning of this process?

Rick Offerman
Going in any place, you look at their experience. For example, if it is going to be a solvent, are they handling a solvent? Can they handle a bulk solvent? Instead of people dealing with a lot of 55-gallon drums of solvent, they're like, “Yeah, we got a tank farm outback here, and we bring in a tanker of this solvent once a week.” Things like that that make your life a lot easier. Anything else - you have to get a sense of how many processes have taken commercially because that's why you're going to a CMO. You're not going there just so they can manufacture something, but you're going to try to get a lot of other useful things done by them dealing with the agency. You don't want to be in that situation where they're learning along with you. I'm paying for expertise when I go to a CMO, and that expertise includes manufacturing, engineering, troubleshooting. I'm not going to be able to be there all the time, so they got to be able to make a process. When it runs into a problem, they have to troubleshoot it. They have the chemists and the engineering people on site, who can come out in the middle of the night and solve problems, and then deal with the agencies as well.

One of the first things I'll look at is the FDA or the regulatory record of any particular site. So you're sitting down with somebody, and one of the first questions I will ask is, “What was your last inspection? Who was it? What was the outcome of that? Did you get any warning letters or 483, things of those sorts?” All that stuff is readily available. I had a colleague who used to say, that's your driver's license. What can you do if you're a cab driver and lose your driver's license? You can't do much. So if you're a CMO and in trouble with the regulatory agencies, you could be shut down. So you have to have people that are very competent in the regulatory aspect of it. That's what you pay for. You pay for them to smooth over these things so when I sit down, it's like, “Okay, you've got chemists.” Everybody has a presentation where they show you the aerial view of the site, show you the buildings, show you reactors, and show you some guys in coveralls standing in front of the reactors. Well, everybody has that. So what's the expertise that goes along with that, to make sure that the guys in the coveralls are doing the right kind of things, the guys standing in front of the HPLC's in the lab are analyzing things properly, quality assurance is doing their part to see that things are released properly. Then you've got a regulatory pathway to get

your drug to the marketplace? They need to walk you through all those things. If they give you the “Well, we haven't done that, but we think we could,” then I'll find somebody who's already done it because I want that experience of professionals who've done it before and who can do it again.

Ed Narke
Right. That's interesting, Brian, because I think we talked with Dave Adams and Dan Torok in previous podcasts about what goes on, really, how the sausage is made. You get facilities, and usually, it's the business development team that walks you around and shows you the pluses and pros of everything. Very often, that's not the case. Things happen in the middle of the night, let's just say, or, based on the management style and what they've done, or how they operate. Molehills turn into mountains. There are problems scaling up chemistry. So kind of leads me to another question, Rick. The name of the game is to manufacture your drug simple and cheap. Right? With that lies problems, right? If the production is not cost-effective, it may never reach the market or make sense, especially for companies early on. Can you talk to us about some relatively simple, cost-effective points to consider as you either select or you’re getting to the process of building scale-up, commercial process?

Rick Offerman
Yeah, the cost of APIs is always kind of interesting because although CMOs get beat up on the cost of APIs, you're not going to pay ten times as much to go to one CMO as another. Realistically, when you look at the cost of an API as a percentage of drug product or the final prescription price, it's usually fairly low. Sometimes it's as low as less than 1%. It’s a purchasing person's job to beat up a CMO and get the best price possible. Overall, it doesn't affect the drug price that much. So there are always three things you will look at. You're going to look at quality and regulatory history, and you'll look at cost. If they have a poor regulatory history, if you've entered a site that’s ever had a consent decree or a warning letter, you realize how much that diverts their attention. You want to make sure that, above all, you get quality and regulatory expertise. I'll pay more for that. I really will because I can go to the cheapest CMO, whether in the U.S. or India, or China, or Europe- I can go to the cheap one, but if they have a major regulatory problem, I may never get my product out of that facility. Recently, we have seen many things in the news about nitrosamine problems, nitrosamine contamination in a lot of drugs. Those were situations where, from what I read, it appears that there were process changes that were being carried out by certain CMOs that were never documented. They decided it was cheaper to go with another solvent, but they didn't look into the ramifications. Now, what do you do? Now you're a big drug company or even a small biotech company, and you've got a drug that's contaminated with a nitrosamine or something like that. You have to pull your product off the market. It's a bad situation to be in cost-wise. That usually would be my third consideration. Do you have the capabilities to do what I want? Do you have the regulatory expertise? Which is pretty easy to look at when you sit down and say, “Tell me about your regulatory record? When was your last inspection? Are you inspected by the following agencies: the FDA, the EMEA, Japanese authorities? What other routine inspections are carried out? Talk to me about your 483s.” If you see minor 483, okay, we've all seen those, but if you see recurring 483s that are worrisome- something like, contamination problem in a drug product facility or mold or something like that. That, to me, sets off the warning sirens completely. You've been beaten up on this 483.

Ed Narke
Rick, that's an interesting point. The more you talk, the more thoughts I have. When you speak about the regulatory importance, there are two ways to look at it, like you mentioned, the compliance pieces, the inspection issues, those things like that that could trip you up very close to the end with inspections and launching. You were saying that there are minor changes that could come back and haunt you. When you have an open IND, you have very limited information in there. You're not necessarily required to have justification of your GMPs. You're not supposed to have your final specifications. But you don't look at the data and where you're generating it, what you'll have at the end- normally at the end, to go back to Brian's point, why it’s variable and so hard to

predict what to write and how long it takes to write an NDA- going back and not having this information, not having justification and conformance information on why you chose certain, not just starting materials, but any materials, your solvent, your catalysts, anything that goes into the process. You mentioned something about nitrosamines.

You make these minor changes. These aren't necessarily updates that you make in your information amendments, but when you start to look at the information that you have when you're putting your marketing application together, and you're trying to bridge that back to the safety information, materials that were used early in the clinical studies. If there are variables there that can cause safety concerns, these are questions raised during the review, and you don't have the luxury to go back and justify them. So looking at it from that angle, the compliance and 483s and inspection records and history and how many folks have commercial products launched and going out the door. Very important from my side, I can vouch for this. Thinking about the information you're going to need in your NDA, every time you change anything, how does that affect what that information would look like? What of that information will you need at the very end? It's very important.

Again, back to the integrated approach. Most CMOs have fairly technical, very efficient folks, but, again, they're making something to a spec for that phase of development to put into a drum or bag into a drum and strip out the door for payment. They're not necessarily looking at if that's approvable, if it conforms with the safety information, tox information that's filed in the IND. So, again, just from my perspective, these things could be very costly in the end to come and fix. So looking at it from a regulatory eye, it's kind of important. So, Brian, I know you have a million questions. I think I saw you your brain is thinking or question marks above your head there as we talked.

Brian Lihou
No, listening to you both, the one thing I would say is that kind of a little bit further back to Rick's point about that CMO that you select. One of the things that I will say, and we have certainly seen in recent years, is that the cheapest choice may not be the cheapest choice in the long run. We talk about things like the cost of inspecting, of sending an audit team over, the cost of getting them into a compliance state where you can actually release material. All of those things are considerations. We have many clients who come in and say, "Look, we are on a finite budget," and we understand that. Some things, however, do cost. I think, Rick, that's to your point about 'pay me now pay me later.' It's making sure that for yourselves, whether it's with DSI or another consulting group, you're trying to chart out the most effective course possible through the whole process. So, Rick, I want to ask you one question about the importance of the project timeline. Who are the stakeholders that feed into this? How often does it stay current? As you said, I think those kinds of things are really important to make sure all those boxes are checked. Do you use timelines often? Or is it an outdated tool? Or what are your thoughts on it?

> "Realistically, when you look at the cost of an API as a percentage of drug product or the final prescription price, it's usually fairly low."

Rick Offerman
Oh, no, I think you'll see with every CMO, there will be some sort of a timeline, typically in the form of a Gantt chart. We'll say, "We have to get this material. What's the critical path to get us to where we want to go? For a transfer of a process, for example, how quickly can we get the methods? How quickly can we get batch records? How quickly can we get API and reference standards and things of that sort? As those things tend to lag, the chemists in the lab can't do anything until they get raw materials to work with. Somebody's got to have an overall Gantt chart. Typically, the project manager will have something that's extensive that says, "If we're not getting, the reference standards or something like that or the analytical methods, for example." If we're not getting the analytical methods, the analytical people can't put the methods in place. If the analytical people aren't up and

ready to go, then when the chemists start running stuff in the hoods, how do they analyze it? Well, we don't have methods, so they're kind of going on a wing and a prayer.

Brian Lihou
Are you basing decisions off of that data too?

Rick Offerman
Hopefully, hopefully not. But yeah, some people will try that. So you've got to have somebody who's a project manager over the top and reviewing that project management, the Gantt chart, or whatever it is, hopefully, on a weekly basis, in a combined team. You don't want to get into this situation where you simply throw things over the wall and say, “Well, the CMO will take care of it.” You’ve got to be on top of it, make sure things aren't slipping, both on the CMO side- and for example, with the clients I work with, because often with DSI, we're doing things on behalf of a client We’re gathering information from other CMOs and sending it on to the new CMO. All those things have to be hitting the mark, or suddenly your timelines start to slip. So it's got to be a weekly, maybe bi-weekly at the latest, but you got to be on the timeline all the time, or things will slip.

Brian Lihou
You know, it's funny, I've had discussions with clients, and if a CMO doesn't come with that Gantt and that overall project understanding and transparency, you question it right off the bat. You question it, but there are situations where we'll have to provide that, and it's fine. But I've had discussions with clients, and they'll say, “Well, why do I pay for a Gantt? What does it do for me?” It's not so much about the individual, but it's the team. You're right. I mean, there are predecessors, things that have to be linked, and they're critical path items. Just like with a regulatory filing, you're tracking those critical path items. In the long run, it saves you money because you have that transparency. I can recall so many conversations, “Why do I need it?” Well, the fact that you're asking for it is a different problem, because you've got a team of people. You may not even know everyone that's in it. You may not know that bench analyst who will be doing the method transfer, but they're there. They're looking for that information and the time at which they start. To make the most effective use of your resources, you want to line them up so when they're sitting down, scheduled to work, they have everything they need to do the work.

Rick Offerman
Yes, exactly. The lab chemists can’t start doing anything in a round bottom flask in the hood until they get raw materials, till they have a batch record to deduce what's going on and get familiarized with the process. I've always been a big proponent of when you can put the SMEs, the lab chemists, sitting down with other lab chemists talking about the process because chemists always come up with the same ideas. They say, “What if we did this?” They can waste a lot of time. They’re Ph.D. chemists, and they like to chase ideas. “What if we did this?” “Well, we already tried that, and here's what we saw.” “Okay, well, so much for that idea.” Then you move on. You say, “Well, did you try this?” “No, we didn't try that. That's an interesting idea. Maybe that would work.” You get the people, and sometimes this isn't in a formal meeting; sometimes you've got people hanging around in a break room or just chatting about the process. “Did you ever look at this as a catalyst for this process?” “Yeah, we screened a bunch of them. We have that information. We didn't provide it. But yeah, we screened 25 catalysts, and this is the one that worked the best.” “Oh, did you try these?” “Yeah, we did.”

It makes everything more efficient, but getting the SMEs together, whether it's the chemistry SMEs, the analytical, and getting them to talk to each other - for me, that has solved more problems and getting chemists working side by side. You bring in chemists from a biotech or something, and they work with the chemists at a CMO side by side in the lab. “Now, here's what we did here. Here's how this worked. Sometimes we tended to see an emulsion.” “What did you do about the emulsion?” “Well, we threw it away and started over.” “Okay, that's going to be worrisome, because at a point you're going to be out there in the middle of the night with 1000-gallon

reactor, and there's going to be an emulsion, and it's probably not going to be an option to open the bottom valve and drain it away. Probably not, so why is there an emulsion forming? Can we understand that a little better?" You will always run into problems in manufacturing when you scale up. The heat histories are different. The time things are in a reactor is different for APIs. Those things often are the problems you run into in the middle of the night that need to be solved.

Brian Lihou
You're setting those initial parameters with the best guess based on your experience, and then you have to dial them in. The one thing I will say, after all of that and discussing the importance of a timeline, one more lovely facet to this whole process is that lately, as you can attest to, CMOs are getting busy, and they are getting booked well out into the future. If your processes aren't ready at the time your slot is available, you're not only going to be paying for the delays and the rework; you're going to miss opportunities that are critical to your company's success. So I think all of the things that Rick covered are helpful because the biggest underlying point is that when that milestone for production is missed, all of the ramifications result from that. Doing that homework upfront, all of those details, everything that we discussed here, really comes back to that. It's the end result. Are you on time with your program?

Rick Offerman
Yeah, if you're dealing with another vendor who's supplying the raw materials and the raw materials don't show up and can't be released, you missed your manufacturing slot. Now you go to the end of the line, which might be several months out. So you want to be there. When the other person misses their slot, you want to have your process ready to go and say, "Hey, can we slot our process in maybe two months early because we're ready to go. We got raw materials. We got expertise. We're ready to go, and they're not. We'll take their slot." You got to make your luck in a lot of cases. You do that by having a process that's well worked out, and you're ready to go. You let the other people make their bad luck by not being ready.

Brian Lihou
I think that's the experience part. There's the difference. That's rubber meets the road right there. It's having been there done that. There's a lot to be said for that.

Rick Offerman
Some of the lab chemists at a CMO have manufacturing experience, but they're always interfacing with the guys who are literally out on the manufacturing floor. It gets to a point where the guys from the manufacturing floor are coming in and watching the process being run, and they're making, based on their experience, a judgment that says this process is ready to go to manufacturing and to do it on a 50-gallon scale or a 500-gallon scale. They use their expertise and looking at a one-liter round bottom flask in the lab to say, "You know what? This is going to be a problem. We can't contain the heat. We don't have enough cooling. What is this emulsion?" "Well, I leave it to sit overnight; it typically goes away." No, that's a process that's not ready. That's the level of expertise you want- people who've done it before can do it again and recognize where this is a problem. This will be a problem in manufacturing, so you need to figure out a way in the lab to get around this so that we don't have this issue cropping up in the middle of the night on a holiday weekend.

Brian Lihou
Which is typically when it happens. Well put.

Ed Narke
Okay, so I think Meranda had got a call, but she did have a question for me to ask. I would try to do a dial-in from her and do a voice impression, but I'll leave it on this one. So Meranda was asking me, can you name some of the influencers on you in your career in less than a minute? How you came to these formulations, people that you

worked with. I've often heard from folks that worked with you what they learned from you. I think Dan Torok mentioned a lot of stuff on what he learned in API process chemistry and manufacturing and transfers. I learned a lot of my stuff from Dan. So, in essence, I may be your grandson. Can you tell us about maybe two or three people who influenced you throughout your career that you practice the right ideology, you got the sense of who you are from them, just to recognize them?

Rick Offerman
Coming out of graduate school, you don't really know anything about manufacturing. You come in with many small-scale, round-bottom flask-type experiences, but when you go into a manufacturing area, it's the experienced process chemists who work around you. You see those people who can work with the manufacturing folk. When I was a young chemist working in the lab, the manufacturing areas were on the other side of a plant that employed 15,000 people. It was a building I drove by every day but didn't know anything about. It was the kind of people you would run into who had worked in manufacturing, had a lot of expertise and who could tell you 'This is a problem'. I worked for a couple of years in the lab, then I worked for three years on a manufacturing floor, and then I came back to the lab. When I came back to the lab, I viewed things differently regarding what I needed to do in the laboratory based on what I learned in manufacturing. A lot of what you can learn working on manufacturing is you learn it from the operations folks, the guys who put 20 years in a plant, running the equipment who can tell you, "It's nice that you can heat a flask in the lab in five minutes, but based on what we do out here, it's going to take you about this amount of time to take 1000 gallon vessel that's 80% full from, 25 degrees up to 100 degrees." So you learn a lot of things about that. How long will it take to transfer things? When you have those learnings from the people in manufacturing, you could do things in the lab that will help you understand our yield losses.

> "If the analytical people aren't up and ready to go, then when the chemists start running stuff in the hoods, how do they analyze it? Well, we don't have methods, so they're kind of going on a wing and a prayer."

Working with Dan on a particular process many, many years ago, we worked side by side in the lab, and we ran things as we would as a lab chemist where you can heat things in five minutes, cool them down in five minutes. When you drain something to do a decant in the water, you pick up the flask, you dump it over into a beaker of water, and you're done. Now, working side by side in the lab, we discovered that the heat history was killing us on a process. We lost 10% of the yield because it took so long to heat things, cool things down, transfer things around. That was a learning we had where the customer was complaining, "Well, in the lab, we can get an 80% yield, but you idiots out in manufacturing could only get a 65% yield." So, when we went into the lab and ran the process using what we call "plant times" to do the heat-ups, the cooldowns, and all that, we didn't get an 80% yield in the lab; we got a 65% yield, just like we did in manufacturing. That doesn't lead to a contentious situation. That leads you to a situation where you say to the customer, "Okay, well, if we were able to add this type of a chiller or do something on heating things more quickly, that would get the process through." So you start thinking about cycle times and things like that. We know that at this point, you got to heat it, cool it down, and get this thing quenched, or it's going to be a problem. You're going to be generating impurities. The people that I learned a lot from were those guys who'd been in manufacturing, whether they were wearing coveralls or a lab coat, who could tell you, "This is going to be a problem."

Brian Lihou
At the start of this podcast, we talked about all of your academic credentials and how impressive they are. But the first thing out of your mouth, when you talk about people that influence you, were those people. I got to tell you that's what sets you apart because you're right, people can hear a motor, and a pitch will change, and they can

understand what that means and jack up temperatures and all of that. So, you've taken all of your accolades academically, and then you've married it with listening to the people that are operating the valves and running the process. I think that's where when I listen to you with some of our clients in the time that we've worked together, it comes across in everything you say. So, to me, when you say you're influenced by those people, it's clear in everything you do, and it is really appreciated. We're lucky to have you.

Ed Narke
That's amazing, Brian because I thought the same thing. I didn't hear anybody's name specifically. I worked in manufacturing, and those are the thankless people, right? The faceless people that gave you all the experiences, and then you're transferring them to other people now.

Rick Offerman
Often, the guys that are out in the manufacturing areas that have the tattoos on the arms can tell you, "You're a nice young man, but we just can't heat this vessel in five minutes. It's going to take us an hour and a half. You tell us what we need to do, and we'll do it, and then we'll tell you what the equipment will do. Then you need to figure out if that's adequate or not." So they're not people you just walk by. Those are the people who will give you the real practical experience that you can take back to the lab and say, "Well, what does happen if I can only heat this at this rate, or I can only transfer quench" or something like that. Those are the things that you only get through being willing to listen to a lot of people and understand where they're coming from.

Ed Narke
I wanted to thank you again. Brian and I both appreciate this conversation. Thanks for joining us and sharing your thoughts. The conclusion- I made some mental notes. There are several challenges involved with the scale-up process. It's not easy; it's different every time. It's different with each vendor. So as such, evaluations and necessary steps should be carried out along the process from the beginning to manage these complexities, reduce the timelines, and prevent any issues. An integrated approach is also important. We talked a little bit about that. So once again, I want to thank you and talk to you soon, everyone.

Rick Offerman
Alright, thank you.

Ed Narke
So next week, we're going to be talking to Dave Blasingame on the podcast. Dave is a longtime process chemist who has traveled the world in search of the most efficient API CMOs. He will be joining us from the San Francisco Bay Area. That's it for this week on CMC. Live.

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