Trust the Process with a CMC Process Champion

Episode 8

Ed Narke
Welcome back to CMC Live! Surprises are good when it comes to birthday parties, winning the lottery, but not so much when it comes to developing and manufacturing critical active pharmaceutical ingredients, or APIs as we call them. On this podcast, we will be talking with Dave Adams about handling pesky surprises in API manufacturing. The fact of the matter is that even with the soundness of methods, processes, strategies, problems occur in manufacturing for the API that are beyond the control of the contract manufacturing organization. On this podcast, we hear from Dave and his experiences over the years. Live from the Poconos. So, Dave, welcome to the podcast.

> "Manufacturing of APIs was very much a technical job, not a scientific process."

Dave Adams
Thank you. Morning All.

Meranda Parascandola
Good morning. Thank you for joining us, Dave. I would just like to know; how did you get to DSI? What was your connection here? Or did we pick you up off the street?

Dave Adams
Well, my connection is that I was the one that trained our business manager, Ed Narke. Way back many years ago, he worked in a development laboratory with me.

Ed Narke
That's right, fond memories. A lot of stories, too.

Meranda Parascandola
It's good to see the connection of how we all have come together. Some of them I know, some of them I don't, so it's really good to just know that up front. We really appreciate you being here on the podcast, Dave. I'm looking forward to learning more about APIs. It's not one of my areas of expertise, but I know that we can support our clients there, so I look forward to it.

Ed Narke
Right, so the story is, I did work with Dave for a few years at Lonza – it's a small Swiss manufacturer. I did learn a lot of my background; my API processing, chemistry, tech transfer and scale up, etc. Dave worked in different areas. Dave, tell us a little about your experiences. I know you got into the API world, some time back. From what I remember, I just followed your career. Over the years, you did a lot of different things; a manufacturer or a CMO, they call them contract manufacturers. You worked at Lonza, and that is where I met you. Can you tell us a

little bit about how it was back then versus how it was more recently when you left? I know, the industry has changed a bit. Maybe touch on some of the topic areas or problems that you always came in contact with, that were never insurmountable things maybe with technologies and how that may have changed some of that offshoring. Some of the regulations and guidance's, if you had any thoughts on those things like that and the industry in general. Also, maybe you can give us some specific stories.

Dave Adams
I did start in this industry in the late 70's. I would say a big difference is that was before GMP. Manufacturing of APIs was very much a technical job, not a scientific process. In fact, I started with SmithKline Corporation, one of the predecessors to GSK. Their entire manufacturing operation was run by a bunch of people in a division called manufacturing. There was no quality assurance, no quality control, no environmental and no scientists. It was a bunch of on-the-job trained individuals who knew how to follow batch records but had very little knowledge about what they were performing. Troubleshooting any deviations or difficulties, was a physical process. Finding out what went wrong and fixing it. It was not an understanding of the chemistry or the engineering.

That had an interesting or positive effect on myself that a lot of the problems had to do with just things that were happening in the plant, things that affected the throughput, the cycle time, the operation of the equipment. That led to my realization that you have to have an understanding of the plant when you develop a process. If you understand how the equipment and the processes are going to work in a plant, up front, you can make much better progress putting something into production than you can by just taking a laboratory procedure and introducing it to a plant.

Brian Lihou
With that being said, how much input do you invite? I mean, you're down the floor, you're troubleshooting, you've got these operators that are there performing the process. How much input do you invite in that problem solving? Or is it kind of, 'I'm a fresh set of eyes, and I'm there to check what you do.' What's your mindset with that?

Dave Adams
Sounds like a leading question, you know, do I involve the operators? The answer is absolutely, yes. There are numerous occasions where operators have told me something. They point something out, and I look at it with more of an educated view. I say, 'Wow, that's really interesting. You know, I'm glad you told me that. Here's what it means.' One time I had an operator come to me because he was smart enough to recognize that the process he was distilling was up to temperature but not physically distilling. He said, 'something's wrong'. I said, 'You're right, something is wrong.' I looked at it and I said, 'Well, you probably don't have vacuum in the reactor.' He says, 'But the gauge says, I do'. I said, 'I don't believe it. The laws of physics say if you put the right solvent in here and you have this temperature, then you don't have this vacuum or it would be distilling.' So together we troubleshot the system and we found where the vacuum leak was and the fact that the pressure gauge was located at the pump, not the reactor is why it was reading vacuum, but the reactor itself had no vacuum. So, operators are there, they see what's happening and they have a lot of information.

Another example of using operators, back in the days before GMP, we had a process with a very difficult phase separation. Two very dark phases that could not be visually separated. This operator says, 'I'll show you how I fixed that.' He took a bucket of water and slowly poured it into the reactor from the top after it had been settled. We went downstairs to do the phase separation, and sure enough, when we got to the interface in the sight glass, that one gallon of clear water came through the sight glass between the two phases. The fresh water was dense enough to sink below the organic, and light enough to float above the saltwater layer. Because he poured it in gently with a laminar flow, it went right to the interface- it didn't mix and get dispersed. I stood there and said,

'That's amazing. I never thought of doing that.' It's also wrong. You can't throw things into a GMP process." So, as I said, this was many years before GMP practice, I learned something. I've incorporated that into other processes in years hence, one even in the past couple of months. We had a process, a very difficult phase separation. The plant didn't have conductivity sensors. There was no way to discern the face separation. So, you can learn things from them. In the last example, for many years we were operating a plant with a team, sort of organization, one member from each department: QC, purchasing, warehousing, etc. There were maybe eight people on a process team and this team would have full responsibility for running a batch, a campaign. We also included operators on the team and having one operator sit in on the team meetings was quite invaluable. One of the very first meetings we ever did that way an operator says, 'Well, you know, starting material comes in paper bags, it gets caked up, because it's not sealed. We have to slam it on the floor to break the up the cakes. Sometimes it's a mess, it's back breaking work. It takes a long time and it's a lot of bags, can we get them in drums? The purchasing agent said, 'Of course it comes in drums. It's cheaper that way. But I thought they were too big, too heavy to move.' The operator says, 'No, we can tip a drum over, it's no effort. Lifting the bags is an effort.' So, we made a change. It was cheaper. It was faster. It was more facile. It was definitely safer for the operators, and it was simply because we sat and talked with the operators. A bunch of engineers anticipating how to charge a reactor did not have the answer. So yes, I do involve operators all the time, and I think there's a lot to be learned from them.

Brian Lihou
I can appreciate that. So, there are a few things that you said that got me thinking, and it really kind of highlights the importance of development. You made a statement at the very beginning, which is understanding where that process is going to wind up. Can you talk to some of the mindset of when you go into an organization that has a process and they intend to scale it up, but you're not quite sure if it ticks all the boxes with development? How do you approach that? What do you look for in a comprehensive thought-out development program?

Dave Adams
Well, there's about three stages to having a product manufactured; you have to invent it, which is research, you have to prove that you have some sort of molecule that maybe invitro or animal study somewhere has an effective response, but once you have researched how to make the molecule, you then have to develop it. That's where you need the knowledge of the plant and plant operations and come up with a process that takes your research chemistry and adapts it to physical plant manufacturing. A third step of course, is getting it into a plant with pilot batches and scale up.

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So, in that middle step of process development, you need to involve someone who has plant experience, or a lot of development experience – who knows how chemistry fits in a plant. Yeah, there's a lot of things that individuals learn in school about doing little distillations or filtrations. A big thing, of course, is putting something in a separatory funnel, shaking it and separating the phases. Some of those operations are easy to do in a plant and some of them are quite difficult, especially a phase separation. What somebody can do in 10 minutes with a separatory funnel can take three or four hours in a plant.

In production, time is money. The longer it takes to run the process, the more it's going to cost your company or more that a CMO is going to charge you to manufacture your product. Cycle time is money. And the faster something is produced, the lower the cost. So, as soon as you see a distillation, an engineer can calculate how

many hours of work that's going to be and what that is going to do to cycle time. A phase separation is the same thing. Filtrations are fairly easy and fairly quickly in plants, but it takes an understanding of everything. If there's something in the lab where somebody says, 'Well, I look in to see if it's doing X, Y or Z,' in a production facility, you cannot look in the reactor, there has to be some way to monitor it with physical temperature parameters, etc. but you cannot do things the way you do them in the laboratory.

Brian Lihou
So that's a question, if I can interrupt. At what point is the interface with the process engineers that are engineering that eventual process and equipment train that goes in the plant? I mean, we talked about the development and to a large degree, some bench work, maybe small pilot scale, but how do you interact with the process engineers that are specking the flow meters, the sensors, sight glass, the tank dimensions? How do you work that in? When do you work that in?

Dave Adams
There are two answers, I guess. One, it helps to know specifically what facility you're going to put your process into. As I mentioned recently, I've been working with phase separation. We simply went to a plant, and they had no conductivity sensors on their reactors. If you knew that in advance, you could know that that's going to be trouble. I think generally when somebody is developing a process, they're scouting for manufacturers, and they may not know the capabilities of the different plants. So unfortunately, I don't think the engineers have much input. It's up to a development chemist, hopefully with plant experience to develop the most facile process that can be thrown into a plant. Make a process that does separate well and doesn't need conductivity sensors. Or make a process that filters well and has good crystallization, not one. If it's slow to filter and a Buechner funnel, it's going to be a disaster in a centrifuge. Another thing to consider is your choice of solvent. Different solvents have different boiling points and different densities. Picking a solvent that boils easily or has cheap cost or works well for your process means that the engineer who gets the process won't have too many difficulties putting it into his plant. If you give him a solvent, with a very low boiling point, he's going to have difficulty condensing that when he distills it. He's going to have difficulty controlling fugitive vaporization, but there's nothing much he can do if he's got the wrong solvent to begin with.

Ed Narke
Dave, that's great. These are things that can happen. I can tell that you worked in a CMO for 30 plus years there. I remember some of that stuff as well. I wanted to talk a little bit more about how to handle pesky surprises, things that you should be aware of that a lot of that operational stuff is going to happen. A couple topics- raw materials is a big question always. Where does GMP start? Where does it come worse? Where does source raw materials come from changing a supply, tech transfer purification strategies and yield problems and scale up and those type of things like that- analytical challenges. I think you have exposure to all of them. Meranda and I were speaking yesterday, and she's getting involved with some clients asking specific questions about raw materials. We got two questions yesterday, one of them involves QBD. I have something to say about this, but I want to hear your thoughts. Meranda, what was your question about raw materials?

Meranda Parascandola
Right, it was something about sourcing the highest quality raw materials and how critical is it for the process. I know you were just talking about the solvents and the boiling points, but when they source raw materials…. Ed, help me out.

Ed Narke
I think Meranda was wondering, she hasn't worked in manufacturing like we have, but when you order things from offshore you look at two different sources, right? Based on the quality of those sources that could affect your process and we get questions from the other side from the regulatory, where does your regulatory starting

material start? Where does GMP start? It could depend a little bit on the quality of that starting material. The chemistry is involved, and that makes a big difference on impurity profiles. You've done this over the years, I remember working at Lonza and seeing drums all over the place stacked six stories high. Were you involved and can you talk about maybe some of that? There are folks that were involved with operations to order those things. I know you have stories, Dave, come on. I remember he said he read the Bombay Express when you open the canister one day, and you knew what the news was yesterday. So, can you get into some of that stuff, how that might have evolved with some of the compliance things? What you mentioned in the beginning was back in the early 80s, it was manufacturing, there was no QA, there was no regulatory. I think that was Meranda's question. For me, I don't have the deep knowledge and experience that you had on the floor. Can you talk about raw materials, GMP, some of that QBD stuff that came in and how that works and where that's going?

Dave Adams
In the current state of things, we do have regulatory people, quality assurance people, and all of their concerns with the new process. So obviously, as you start defining a process and designating what will be raw materials and what will be intermediates, it is very necessary for a regulatory viewpoint to carefully define the specifications for the raw materials, the quality of the raw material, and so forth. This is because in your filings, you have to define what potential impurities might ensue from the starting materials, and what the fate of those impurities are, whether they're going to react and carry on, or whether they're going to be purged or washed out. In your documents you need to define limits of quality and so forth. That's from a regulatory perspective.

From a practical point of view, you really need to cover your butt. You need to define what you expect from the supplier so that you don't get surprises from the raw material. I have a customer right now who's using a common solvent that's used all over the world, and the manufacturer produces huge quantities of it. The manufacturer set a spec, that says it's 99.9% by GC, it's a solid. It's good. Well, working in production, we have discovered a slight contaminant that turns into another impurity into our product, and it's affecting our final API. We've gone back to the manufacturer and said, 'do you have a spec for this' and they said, 'We don't test for it.' They will admit that it can be a side product in their material, but they don't test for it. They never have. They're not about to start because they make large quantities for many people. They're not instituting a new spec. So, it is a major problem. We have a major impurity in our product coming from a solvent. You need to very carefully scout your suppliers and make good agreements with what it is they're going to be supplying to you very carefully.

"You need to very carefully scout your suppliers and make good agreements with what it is they're going to be supplying to you."

You mentioned past history. I have seen everything come in with raw materials. We had one drum come in from a supplier that had a two by four in it. We had another process that came in and unfortunately, we did not have tight enough specs. We ran (I suspect) GC or something for area percent, and it always looked good. The customer or the supplier did their analytical work and said it was good and it looked good. It made a good product for us. We ran the entire campaign of about 20 or 30 batches. We were happy until we opened the first reactor to do post campaign cleaning and found out that the glass lining of the reactor was gone. The material we purchased had been made in a third world country and they admitted to pumping river water into their reactors, including the sand. The sand went into the reactor, the sand went into the product, and we sandblasted our reactor. At the end of the campaign, we found out that we had been taking the glass off our reactor. It was an early intermediate step. It was filtered, *etcetera*, and so forth. This was a major issue because we didn't set specs tight enough. I've been with quality assurance people who have gone to do audits and found birds, rats, and things climbing through the plant. You know, it's very difficult if you have open drums being filled, and there's birds flying overhead. You do need to be very careful when you set the specs. Just because the supplier says, 'I

have 99% quality on this,' if you're worried about heavy metals, if you're worried about sand or two by fours, you need to spell that out. You need to be very careful and do an audit to ensure that they're not going to give you surprises.

Brian Lihou
I think our quality group would appreciate you saying that. I think a comprehensive site audit is important to get a feel for the types of people that you have in the facility they're working in. All of that is important.

Ed Narke
I think a lot of this is determined by price, right? So, what I inferred from that was price shouldn't be a leading factor. It's more about quality. That's kind of how some of these things work, expensive processes. You're looking at multiple raw materials. Some of them might be very rare or expensive. You have to be on top of your game, you have to make sure there are specs involved and stuff like that. Overall, from the regulatory side, you see what happens, right? Not only do you lose reactors by sandblasting them, you know you're also going to come up with majorly failed batches or worse. That's not going to be good for the prospective emerging biotech or pharma company sourcing. So, from the manufacturing side, that's important. Obviously, many small emerging biotech folks haven't been involved, like you have, in manufacturing.

Brian chime in here. There was just one thing I was curious about. I worked with Dave at Lonza. Let's just say it, right? There was a lot of failed batches, and it was frustrating. We did a lot of good process development in the lab and sometimes scaling it up or just putting it out in the floor you know , it's not just equipment, it's not just the materials, sometimes it's operation errors. Late at night – we won't get into that yet.

Purification strategies. I know that was one of the things I worked on when I was in process development because we had to fix a lot of things that went bad. How do you deal with that? How do you avoid that? Is that something you build into a process? Is that something that you build in early on? Is that something you would advise customers that you work with currently? A lot of this stuff goes into regulatory filings. Just talk to me about that.

Dave Adams
Well, I think a very important point is development again, to pay close attention to anything you see or anything that you discover. And to investigate it deeply. You mentioned a difficult process we had. One that comes to mind is when we entered it was running the lab successfully. A couple of pilot batches were run and maybe 50-liter reactors and they were cold successful, and the process was handed over to production. The first batch when the operator went to do a face separation, he called me because he opened the bottom valve and all he saw was emulsion. He went upstairs, opened the manway and all he saw was emulsion. The entire batch was foam. So we spent a couple of days trying, throwing in filter aid and running it through filters and reading deviation reports and trying to separate the two phases, so forth. And we struggled with this second batch, same issue and so forth. We changed the process. We instituted constant filtration and it was a problem. We struggled with it for years and it always emulsified. I finally went back to the development chemist and said, 'Did you ever see this problem with this emulsion?' He said, 'No because all of my lab things worked fine'. I said, 'Well, what about the pilot batch?' He said, 'Well, there was a little puddle of emulsion.' I said, 'What did you do with it?' He said, 'I threw it out.' So there was a slight change – a little thing he didn't even think to document it or talk about it and what it came down to, ultimately, a year or so later, we discovered that in the process, there was an intermediate step that was physically unstable in the reaction and scale up. You know, you need to scale when you're doing lab development work, you need to emulate everything in a plant, including time cycles. Running the batch in three hours in the lab, it's not a problem, running it over 24 hours in the plant was enough time for the material to degrade and cause an emulsifying agent. If we ran it really, really fast in the plant, we could get less emulsion and that was ultimately our solution. We just said, run the batch, heat it, cool it, as fast as you can, do the phase

separation as fast as you can, and throw out any emulsion or leave it behind and just keep going. The longer we took trying to filter it and mess with it, the more it messed up. So an observation that was seen but ignored in development.

Brian Lihou
So Dave, one of the things that I get a lot as we talk to prospective clients is everyone is budget conscious. When you mentioned development, they really want to narrow you down and we'll get it all the time. 'Well, how many hours will it take to troubleshoot and develop this process?' And our typical response is, 'You can't put a finite answer to that question.' So because the data is going to take you where the data takes you, so in your example, with the pilot scale and not being recorded, would that have been something because we talked about cost, if you want to try to rush this thing and transfer it without truly vetting it? At the pilot scale, you're going to be paying a lot more money in the long run. So in that, in that pilot scale example you gave, which in hindsight, would you have maybe stretched those parameters even further to try to push a batch to failure to understand or there's something you'd have done differently?

Dave Adams
Yes, it's that old expression pound foolish – penny wise or something. You have to put the time in to develop it. One very important thing I've asked every time I'm involved with some new project is, 'Did you try it on the plant time cycle? Did you hold it?' Now, I have one client working out and they intentionally held each step for 12 or 14 hours just to stress test it, they went purposely slow at each step, you know, a filtration step that could be done in half an hour. They just had stopped and held it for 12 hours, then filtered it, they have to prove that it's going to work. The very first process I ever worked on was with Smith Kline- it was a billion-dollar drug that was actually going into production. And the first word coming back was the batches had a new impurity in the chromatogram. It was a corporate panic, brand new billion-dollar product, and the batches were failing. So the first thing my supervisor did which is, 'I want you to run a reaction and cook it for 10 or 12 hours.' So for a number of weeks, I came in at five in the morning, started up the reaction in the lab and then sat for 12 hours till I could filter it at six that evening. And sure enough, we saw the impurity being formed. So it's a time-dependent side reaction. You can't go into production and shortcut things like seeing what happens with long hold times, long heat ups. I mean, there's so many cases I can see where people didn't do that same process. They had a lab development- heat it up, hold it for two hours, cool it down. When we got to 4000 gallons scale, it took three hours to heat it up. There was no point in a two-hour hold.

I had another process somebody gave to us to pilot. They said, 'I want you to heat it with a sodium hydroxide and water so it boils at 100. They said, 'Heat to reflux, hold one hour and take a sample.' I happened to be the chemist on shift at that night when the sample was ready, and I took it, and it showed the reaction and was already overcooked and made. It's degrading. It was an emergency decision to shut it down, cool it off. And so, on the second batch, we tried to follow again, and I asked him to take a sample before they heated it up. And surprise, it was already done. The reaction was that fast in the plant, they didn't need to heat and hold for an hour. And so by following their process, they were degrading it. So yes, you need to investigate every ramification of development. And some of them might lead to surprises. You see a new impurity, see a new emulsion, and so you're going to have more development. So, Brian, you are correct. You cannot anticipate how long the development is going to go. And you know, it's multiplicative. The more steps you have, the more chance something's going to lead you down another pathway, but to Ed's comment cost is not just materials. I mentioned working in a team organization for many years, we had a very good spreadsheet model that would cover the cost of manufacturing and it included everything from operator salaries, material costs, equipment time, environmental waste treatment, and quality control testing hours, etc. It was amazing to work with these spreadsheets and track our processes. Some things that started with a bunch of cheap chemicals and were very cost dependent on cycle time. The cost of being in the plant for five days was a significant factor. I've had other processes where, solvents – I had one process – the solvents were unbelievably expensive – two very rare ether

compounds that were just designated as solvents. So again, development- It is important. These were chosen by the drug company that wanted these solvents used. So we had to use them, even boiling and distilling and reusing the solvents, they still entailed 60% of the cost of making that product. So, a little more expensive starting material, another operator to help speed up cycle times, would not make much difference. Regardless of anything we could do in the plant. 60% of the cost was already defined by the expensive solvent we were buying.

Ed Narke
Okay, Dave, I just looked it up. I think it's penny wise and dollar stupid. I think pound stupid is a British thing. So I could tell that you worked somewhere with a British person, anyway.

Dave Adams
Well, I thought it was an expression from Ben Franklin, who was British.

Ed Narke
He was British. I think he was born in Britain. I'll look that up next. All right, Brian. Hey, you know, you're a drug product guy. I know you know about the nice stuff, but I know you have a ton of questions. Dave is like a wealth.

> "So yes, you need to investigate every ramification of development. And some of them might lead to surprises – you see in new impurities or new emulsion – and so you're going to have more development."

Brian Lihou
I just think it's a really important point, the things that Dave spoke to, there's two, in addition to further understanding and characterizing your process. It's wonderful. But also, as you go to develop your validation protocol and, in your submissions, identify your critical process parameters, having that information to stretch your process and extend those hold times and build in those safety factors are really important to developing a robust process that will get into a CMO. So Dave, I know the climate lately has been very difficult to get times at CMOs. I mean, really, with the model, moving everything, mostly to CMOS, getting production slots is key. How important is it when transferring the process to the CMO? How important is it to the CMO that you have a well characterized process? Will they bump you in priority or will you find yourself kind of waiting for your time if they feel as though the process isn't true/characterized enough?

Dave Adams
Well, I think it's important for the developer to have the expertise or insight into manufacturing, so they are informed when they go to a CMO. They know what they are asking for. They know I'm asking for four reactors over five days. You can make estimates of what that's going to cost, know what your materials are going to cost. You can have a very educated process estimate before you even start to talk with the customer. I am working with a client who has had no prior experience in production, and they went to a less experienced CMO and together the two made a production contract that is very bad for both companies. It simply says we will pay you X dollars for every batch you make. There's nothing in it about cycle time. How quickly they will produce, how quick or how much they will produce. And even if a batch is a failure and gets only a 20% yield, they still get paid. So the developer doesn't get their product, they're losing money. The CMO has no incentive to work faster or more efficiently because they get paid to work. It helps to have somebody on your side who understands production and knows when you're being taken advantage of and even up front when you're making your contracts.

Brian Lihou
That's a really important point to make. I think knowing your supplier and developing that good rapport with the supplier is important. How much involvement do you take? Let's say you're transferring your process. In fact, I

think I know one of the examples you're talking about, and you're transferring to that site. How important is it for the input of the client or, in your case, the consultant to be received at the new site? I mean, I've been in situations in the drug product side with, 'okay, if we know certain things adversely affect our process and we pay attention to those and we try to write those in whenever we can.' But in the tech transfer, you hand it off to a team and they just simply go through the protocol exit and put it in and put it on the line and they have problems. So how important is it to get those relationships established where you can actually be involved on behalf of the client with the actual work being done at the CMO?

Dave Adams
I think it's very important. I've been on both sides of that fence. I think it's very interesting to have the manufacturer know the people he's working with personally. I start with the CMO side when I worked in manufacturing. We always set up our teams and asked right up front who in the developing company is going to be involved, who's going to work with us. And we would cross connect people between quality control and the two companies' production engineering, so forth. It made it very facile, when the CMO is trying to plan and put the process into the plant, questions come up. It's very easy communication to have somebody in quality control call their counterpart in the other company and say, 'Oh, you do X, Y, and Z in this development method. Why do you do it... Okay, I understand now', or the engineer says, 'you suggest this type of agitator. Is it that important? I don't see it on the critical process parameters. Is there a reason you know...'? Back and forth communication is much easier and things go better than if the CMO is just blindly reading a document saying, 'well, we have this equipment, let's put it in here and see if it works.' If you're not on a one-to-one basis, you don't get that kind of cooperation. From the other side, now, I'm helping clients put things into plants. And having met the individuals in the plant, the engineers, having talked back and forth about the process, the chemistry, and discussed issues about cycle times and centrifuges, and phase separations, they know that we know the issues. So when they come up with a problem, you know, they can say, well, it's not centrifuging or filtering as well as we had hoped. But they know that we understand the difference between, you know, a Sparkler® filter, filter press, a centrifuge, and we can discuss how their equipment is working, whether it's equipment, whether it's the process and so forth. It's also encouraging because if these people are conversant with you, they're going to give you updates. They're going to tell you how things are going and give you current news about how production's going rather than you just sitting there for weeks or months on end saying I hope it's going well.

Brian Lihou
That's a really good point. I think it establishes that rapport that pays dividends in the long run. Yeah. I mean, you really become part of the problem-solving process, rather than just a CMO reporting to a client.

Ed Narke
Right. And I'm seeing this from the other side, like I keep looking at this from a regulatory filing approval inspection, you know, that the other side of things less from the development for my end again.

Meranda Parascandola
Dave, I did have a question about tech transfer. So how can a CMO ensure that they are receiving the highest quality raw materials that they can? The key is to properly know your suppliers through on-site visits, references and audits, while also having a backup supplier on hand. Additionally, once a CMO has a good trustworthy supplier, it's important to maintain a strong relationship and establish ongoing communication.

Dave Adams
Yeah, I think what is useful, again, it's sort of like it's two ends. The CMO in the middle is trying to buy raw materials, they're also trying to produce a product. And it's still the same issue that they need to establish the rapport. If, if it's possible, I think it's beneficial to buy material directly from a manufacturer as opposed to buying it from a vendor who's buying it from secondary suppliers so you can actually talk to the people who are making it. As I mentioned, recently, this issue I had with a company that's getting a solvent with a trace amount of impurity, there's been a lot of back-and-forth communication with the actual manufacturer of the solvent. How do they manufacture it? Because there's a couple different ways. Do they test for the materials and so forth. Working with a supplier of a raw material, assures them two things, one that you're concerned about the product and how they're doing business and of course that you are intending to remain involved with them- that you're not just buying from them this month and you're going to buy from somebody else next month, you're talking to them, working with them. It gives them the assurance that you're serious about their business.

> "It helps to have somebody on your side who understands production and knows when you're being taken advantage of and even upfront when you're making your contracts."

Ed Narke
Dave, that was our Jeopardy question. Meranda gave you an answer and we were just looking for the question. So what is tech transfer and CMO raw materials?—for a hundred dollars. Dave, I had a follow-on question to Brian's point there. I look at things from the regulatory side, the submission, the data generation, the inspections and stuff, the later end. I assume everything's done well, and processes are in place and stuff like that, from where I used to sit in a chair -to reduce the risk of late phase surprises, those type of things. When bringing a molecule, any molecule, into a GMP suite, or would it be called a train these days or just a facility, the process could take much longer, it could be complicated, it may be a resource thing- we talked about timing and stuff like that. So given the need for this greater supervision for certain types of processes, certain facilities might have this-sign offs, quality control. We talked to somebody a few weeks ago about getting started with a product development program, Judy Magruder, on a prior podcast. We talked to her about, some of the steps, some of the things you would give. So, just talking about governance, supervision, integrating tech spec folks, analytical folks, management folks, sign offs, quality assurance, quality control, the labs downstairs. When you're kicking off a tech transfer, to kind of play off Meranda's thing here- what are kind of some of the steps? Is there a process? Does it change each and every time, or is there a sort of a recipe, you know, you bring a process into the facility, we've done this right. What would you recommend? What kind of oversight would you recommend?

Dave Adams
Well, there's a couple of things that affect the direction it's going. The very first thing of course, is a chemist, coming up with a process series of synthetic steps. Even then he needs to be aware of as much as he can of physical issues in the plant, cost of materials, and so forth. If he picks an expensive catalyst, that's going to be a problem all the way through, regardless of what sort of engineering you come up with – with the plant. If he picks an expensive solvent, you're going to be stuck with that. So some smart decision up front, but after that, how the different chemical steps are developed is going to define what kind of critical process parameters need to be investigated, what kind of analytical testing needs to be implemented. And what kind of regulatory issues are going to be involved- waste stream handling so forth.

Ed Narke
Let me ask the question a different way. Let's assume you have a process. It was developed somewhere in the mountains in Switzerland, okay, and it was running kilos scale, or maybe was running a large facility there.

There's a tech transfer and maybe you scale up even, you transfer to another facility in the US and you want to scale it up. You have a process, you have your catalysts picked out, right? How would you advise going through with management teams, sign off, supervision, QA? How would you transfer a process?

Dave Adams
I think, again, because it's the regulatory issues, you need to have a tech transfer procedure, SOPs at your company. Document between the two sides, whether they're in the company, or they're between two companies, such as CMO, to document between the two- what you want to transfer, who's going to be responsible for what, who's going to supply samples, references, test procedures, what's going to be developed at which site. What I find is very important is connecting the people on both sides. Going through management or regulatory things to pass information back and forth is very ineffective. It helps if you connect the analyst and both sides of the transfer, the engineers on both sides of the transfer, the chemists and so forth. They work together as teams; they still need to follow SOPs and document everything they're doing. They sign it every time a method is transferred or batch record goes back and forth for approvals and revisions until both sides agree that it's transferred correctly. All that needs to be documented, but I'm definitely not in favor of having this done through a management organization.

Ed Narke
Okay, you said something that triggered something when I used to work in manufacturing- there used to be something called a process champion, who was in charge of a lot of stuff. I don't know I think you were a process champion at one point. Can you tell us what a process champion is, and if they still exist, and perhaps the need now for toll manufacturers dealing with small emerging companies, if they don't have that, using consultants, could someone such as yourself be a process champion?

"It is very important to have one process owner – process champion – one person who represents the process."

Dave Adams
Over the years I've heard the term of process champion, process engineer, process chemist. It is to my understanding the process owner and also, technically the team leader. And as I said, I like the fact of having different members of the teams from both sites work directly with each other. The process champion is the one who coordinates the activities for the other people, sort of like a project manager. The difference, however, is that a process champion at a site could be a project manager, keeping track of batch, campaigns, startup, material ordering, supply, delivery, testing, and so forth. But at the same time the process champion is the one who owns the process. He basically understands the chemistry. He understands some degree of the engineering, the unit operations in the plant and the analytical testing in the lab. It's an overall subject expert. And such a person is the one you would go to when you have issues, not problems, but issues related to increasing production or moving to a different site or placing orders. He's the person who has an overall view of everything related to the process. He may not be able to go run an HPLC instrument in the lab, but he understands HPLC chromatograms. He understands the reason why you run chromatograms. He can talk to engineers, he can talk to the chemists, he can talk to the schedulers and the material purchasing agents. It is very important to have one process owner, process champion, one person who represents the process. Presently I'm working with a CMO who is producing a five-step process in three different plants around the world. And unfortunately, they have a project manager who is very overworked. We need to designate within that company, a process champion, someone who can just look at the production, look at the process, and not be worried about billing cycles and overhead and personnel management issues. Somebody who can deal with the issues of

scheduling different plants and ensuring that production at one site is ready in time for delivery to another site and if the overall plan is going to work together.

Ed Narke
Dave you know, it's a real pleasure actually to have you on this podcast. Process champion, all around awesome person. And thank you again, I'd like to thank the folks here, Meranda and Brian as well on the podcast. Next week, next podcast, we'll be speaking with someone that I know personally really well. His name's Ed Narke. Hey, that's me, right- served as a mentor and a person who started the company here. I used to be a regulatory person and I still have a lot of thoughts and information and experiences. So I think next week, I'm looking at discussing opportunities and I'm going to call it designing application. I'm going to focus on initial INDs. For this week's podcast again, thanks, everyone, and we'll talk to you soon.

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