

Outsourcing in China: How far Can it go?

Episode 15



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Dave Blasingame
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Ed Narke

Hey guys, it's Ed Narke. Welcome to CMC.Live. I'm here to play another round of 'what are your thoughts' with my co-hosts, Meranda and Brian, as always. We're going to get right into it. Let's see what's going on this week. We talked about this in a prior episode for the drug product. Trust is important in the relationship of picking CMOs, particularly offshoring. Outsourcing has become important these days. It always has been. Effectively managing and taking care of this is an important topic. So today, we have Dave Blasingame on the show. Dave's a process chemist by training and has worked at the likes of Gilead, BioMarin by Moran and many emerging biotechs on the west coast and all over. Dave, let's get into this episode, starting by going into some of your background, how you got started, and get some of your thoughts on contract manufacturing in Asia.

“One of the key activities for any manufacturing oversight at any CMO are the person-in-plant activities.”

David Blasingame

I got my start at Gilead Sciences as a process chemist. I think that was a fantastic place to be trained as to how to be a process chemist. I did that for a few years and moved into the chemical outsourcing group for API for their commercial drugs. That was a very interesting window into manufacturing large quantities and lots of different organizations. Then from there, I've been focused on outsource manufacturing ever since. It's been all over the place, from the US to Europe to Asia. I spent almost a couple of years and quite a bit of time in Asia.

Brian Lihou

Dave, we talked in an earlier podcast about what it's like to be the person-in-plant and support a contract manufacturer. However, you have the unique opportunity to spend large amounts of time in various China locations and work closely with their technical teams to manufacture a product. I imagine there are some subtle differences between Western Europe and US manufacturers and working in Asia, aside from obvious cultural differences and language barriers. Can you maybe talk a little bit about the allure and what drives people to manufacture at sites in China?

David Blasingame

Sure. I think it's a natural go-to for early projects to make GLP material, maybe some early phase one material, for all the obvious reasons. I think China is known for being very quick at producing that kind of material, also significantly cheaper most of the time, compared to US or European counterparts. So I think it's a natural go-to for the first stages of any clinical program. That's certainly one of the reasons we were there, originally. We had projects that progressed a little bit further from there, and that doesn't always happen. So that's kind of unique to every project. But, again, the allure is time and money for early phase programs where you maybe don't need to

invest a lot of time and development right off the bat because you need to get tox studies underway. You need to get some understanding if you've got a program or not.

Brian Lihou

So when you compare apples to apples and look at quotes, there are some significant cost advantages to manufacturing in China. One of the things you could expand on is that it's a little more than just the quote you're presented. Other challenges and costs associated with manufacturing in China may not be very apparent when you see that initial quote. Can you maybe elaborate a little bit?

David Blasingame

Sure. One thing that's never captured in the quote is one of the key activities for any manufacturing oversight at any CMO are the person-in-plant activities. In China, that's not going to be captured in a quote by any means or in a contract. It's going to be a fairly significant amount because of the travel to get there, the amount of time that it takes and how long you are likely to stay, you're not flying there and back on the same day, it's going to take you a day to get there. So the travel can add up to be quite a bit on top of what's in the contract. It might be surprising just how much you would spend on a flight alone just to get there, especially with any kind of routine frequency.

Brian Lihou

For the larger manufacturers, those in the West envision a certain environment when working in China. Still, these larger manufacturers are built to handle outside clients and cater to outside clients. What's the experience like? You've touched down. You've gone to this site- you've been to many sites throughout the world. Clearly, there are some differences in China. What has been your take on it? You've spent much time there and have formed relationships with individuals there. What are the big differences?

David Blasingame

I think you need to see a wide variety of plants, both in size and condition. There are lots of plants that are repurposed, lots of plants that change hands quite often. Like many CMOs, they're trying to extract every dollar out of that investment and make the most of it. So you'll see a pretty wide range of nice, shiny new equipment that was just dropped in the week prior to you being on-site, to equipment that's been around for 20/30 years and has been repurposed through multiple organizations. I think that was probably the most striking because they could be right next to each other or be in different cities as you're traveling around China. You never quite knew when you showed up what exactly you were going to see. It could either be a piece of equipment that was just installed that day or something that they got somewhere else that had been used pretty heavily. It's pretty noticeable right off the bat. You can spot it pretty quickly. It reiterated or reinforced that it's good to be on-site and see these plants for all the usual reasons. You need to make those connections and those relationships. More importantly, you need to know what you're working with. I did have some occasions where there was a plant, we had an address, we'd even seen the facility and made material only to go back to it maybe a week or two later, and it was no longer there. So it is certainly something to be aware of and stay on top of.

Brian Lihou

We had a podcast a while back where we had someone speak to the merits of being on-site for the CMO on behalf of the client. I've done it. You've done it. In China, however, do you find there are particular advantages/disadvantages to being on-site? Do they see you as an outsider, or are you integrated into what's happening and exposed? It varies from place to place, even in the US and Western Europe, but largely in part, being a value-added on-site presence seems to help the process. It seems to garner the attention that it needs. What's it like in China?

David Blasingame

I think that's a common thread, probably with multiple CMOs, but maybe more important with the agency that you might work with. So we were told very specifically with our project teams that being on site as person in plant gave them the leverage they needed to go within their organization and ask for resources, whether that was time in plant or maybe extra equipment or extra people be on the project. They couldn't do that unless you showed up physically on site. So being on-site not only forced them and their upper management to be with you in the boardrooms or on the plant floor, but it meant that the project was important to you enough to be there and spend the time and money to be there. So the project teams asked us a lot to be there for that specific purpose. The other reason I thought it was important to be on-site, what I learned was, 'yes' doesn't always mean yes. We would ask for something during conference calls or even boardroom meetings where we were all together, even face-to-face. The answer would be 'yes.' But what we found out later was either there was a miscommunication or misunderstanding because of the language barrier, or it was an appeasement tactic, meaning they never had any intention of actually following through with the request. Still, they said yes, so that we could move on to the next topic. So you would know that, or you wouldn't be able to follow up unless you're on site. So person-in-plant was very, very important.

Meranda Parascandola

Yeah. I've had a similar experience to that 'yes' response. I found out they meant that they would look into it and not mean, 'Yes, I will do that.' It's like, 'Yes, I understand' and kind of move on from there. So I get it.

Brian Lihou

We talked about the challenges, but what about some of the advantages beyond price, because companies make real investments in China, and it's not just drug substance. There are drug product facilities or testing labs. There's a vested interest in seeing manufacturing in China. What are some of the really obvious things?

David Blasingame

Well, with the dollars that we can invest there on top of the dollars that their government also hands out to companies that guarantee jobs for their citizens- you have a blank slate to pretty much do whatever you want. You can build the facility how you would like to. You can run the facility how you would like to. So there are lots of big-name companies who own floors at each of these organizations because they've either put in the money or guaranteed the projects that would allow them to build it the way they want to build it and run them, operationally, how they would like to run them. So, in essence, they truly become an extension of your organization without having to make the larger investments anywhere else that would be required to get to the same degree of quality.

Ed Narke

I wanted to go back to the person-in-plant. We talked about this with Dan Torok, just in general, the person-in-plant, the white coat effect. He mentioned that if there's someone outside, the white coat effect makes a difference in US facilities and European facilities. Still, I could see it having the same effect in China, manufacturing-wise. Any thoughts on that? Is there something else to the effect?

David Blasingame

There was definitely a white coat effect. I would say it was also a little bit interesting, maybe a little funny. There'd be one or two of us from the sponsor side teams, yet there would be maybe eight to 10 of them. So there'd

“You better make sure you have an easy to manage process. You better make sure it's well-identified, easily transferable, and you have to budget to have a presence on that floor”

be 12 of us in white coats in a little hallway overwatching one or two operators right in their kilo lab or in the plant, operating their equipment. Not that we were talking or communicating about the project, but because, again, us being there forced them to reciprocate with oversight alongside us. So it was sometimes interesting. We can at least read the batch record- we may not be communicating in English, but we can at least see what they were doing and learned from that.

Brian Lihou

One of the things when we talk to contract sites, Western Europe and the US specifically, we talk about the operators, the level of training of the operators, if we are going to have a team dedicated to our process that will understand our process or if it is going to be first come first serve. So a lot of that gives you that comfort level that you're starting to develop some process knowledge within the CMOs so that they can handle things. Is it the same in China? Typically, you have a lead, either a process engineer or a lead operator, that becomes your confidant and kind of ushers you through the process on that site. Is it like that as well?

David Blasingame

Yes and no. I found it to be maybe a little bit different in the European organizations particularly. What we found, at least in our projects, was a high turnover rate. These guys are graduating hundreds of thousands of chemists each week, but there's no shortage. So these guys were rotating through their organizations, maybe every year, year, and a half. For the projects we had, we probably ran through four different project managers in a couple of years. So it wasn't easy, I would say, to maintain that kind of consistency. You also weren't quite sure the level of experience or expertise you would get with these replacements. A lot of them tended to be new. There's a hierarchy there that I think they're pretty open about. So if you're from a big-name company, you're going to get the best that they have to offer. The rest of it is a little bit less clear about their experience or their expertise. So you may not be getting the 18 unless you were from Big Pharma name, which meant that you were probably going to give them large amounts of dollars. So we found turnover to be pretty difficult, to be honest, for a couple of reasons. One, you kind of lose that familiarity with your project. Two, as a side effect of them trying to maintain the security of the information, the other thing we found is that with the change in turnover to your project team, access to the information wasn't always granted to everybody. So it was hard for everyone to get up to date with where we were with the project and what we needed to get done. I think some of that was intentional, and some of it was a byproduct of that security concern that they were trying to relay to the Westerners that they were managing our IP and managing the security of our data. So the security concerns, as I said, sometimes led to a coordination issue.

I did also have a project that spanned raw materials through API and drug product. While we were told that we were sold on the basis that they would manage all of that for us because they were one organization, what we found was that's not true. You end up having to work your way in to coordinate for them across their sites because they just did not do that for one reason or another. Either they didn't have access because they were new to the team, or because they were disincentivized, frankly, maybe to do that kind of coordination. They were incentivized to do their job, but maybe not much more than that. What we found was that because there was a severe consequence to making a decision that was above your pay grade, the other thing that made coordinating projects a little difficult was everything had to be rung up to higher management, usually VPs and above if you needed a decision to be made because the team was waiting for someone to tell them what to do. And they were very, very hesitant to make any decisions independently without running up the ladder. So yeah, managing projects was very difficult both on the plant floor and outside.

Brian Lihou

We started by saying there are cost advantages to manufacturing in China. We have a lot of clients, a lot of people out there that consider that the way to go, independent of the current climate with COVID and everything else. If

you think about it, you better make sure you have an easy to manage process. You better make sure it's well-identified, easily transferable, and you have to budget to have a presence on that floor. All these things have to be factored into your decision to move to China rather than just that quote.

David Blasingame

It is cheaper in black and white on a contract. The resources it would take from the sponsor side to ensure that that project is successful, as we know, it's never usually factored in, but it's significant. It's not a small part because they're not an operation where you can just hand over a piece of paper with your synthetic scheme and call it a day. That's just not how it's going to work over there. You're absolutely right about what you just touched on. Another issue that we had when we were there was, we thought we had a commercial process, but we found out very quickly that we did not. Because we had quoted it with them and their commercial team, we found ourselves very quickly misaligned with the skill set that we needed to work through the development side and make it a commercial process. I think that's the other thing that maybe I would speak on. If you're looking for a commercial process that you might be able to take anywhere, I'm not necessarily sure that's the place that you would go, and certainly, maybe not your first place. I think you're going to get material that can be brunt forced, if you will, chemistry-wise, to get your material at the end of the day. It's not necessarily going to be scalable or commercially robust for a process. Again, their emphasis is on speed and cost. They are okay with making multiple batches to get you the amount of material you need rather than making the most efficient process. Their focus is not on efficiency. It's on speed and cost.

“If you’re looking for a commercial process that you might be able to take anywhere, I’m not necessarily sure that [China] is the place that you would go.”

Ed Narke

So there's no way around it. It's the political question here, and I think you touched on it, though- China Rx. Since I've been in the business, I've heard this—the risks of our dependence, America's dependence on medicines from China. We heard about it last year, tariffs and things like that. So being on that front, can you give us two facts that are true and then two myths that aren't true to segment those two. You could give us more to help the audience understand. We've all heard a few things. What are some facts, and what are some myths?

David Blasingame

What are some facts that we've heard or submit? First, we hear that not all APIs come from China in the pharmaceutical industry. I would say that's a myth because that's glossing over is the fact that almost all starting materials do. So while it's maybe true that not all APIs do, most

source back into China. The one interesting fact that I learned with my operations was that that is their preference, but when they can't do it, for one reason or another, they will outsource it to somebody like India to meet their needs. The second fact is that they do put China's interest above all else. So if they can manufacture it or show that they can build the plant to make it happen, they will do so because it's in their best interest to do that. They are very reluctant to have to rely on anybody externally themselves. They'll make sure that they can find a solution to be solely reliant internally for those kinds of pharmaceutical projects. The second myth, I don't know.

Ed Narke

Okay, does Brian have any myths that he's heard?

Brian Lihou

The stuff that we're covering is insightful because, again, you think of China, and it's growing in leaps and bounds, but what quality is behind it? I don't think that's a fair assessment to make. There are good reputable

GMP firms in China, they do good work, but there are obvious cultural challenges. I think your decision to go to China has to consider the process you're trying to send over there, because I think there has to be a fit for manufacturing in China. It's not just, "I have a process go there." It has to be something that is solid to transfer, that's well characterized. You have to try to answer those questions before you transfer it. You want to try to get in front of that. I would imagine, Dave, when you do have an issue, there's a lot of back and forth and translation that has to happen to work through that resolution. Let's say you're doing GMP material. So you run into a GMP issue, an investigation, or an OOS - how is that conducted? I know sites, from my experience, some sites in the US or Western Europe are notorious for writing the bare minimum in the investigation in hopes that you're going to add your piece to it. Then for some metamorphosis, you'd come away with a good solid investigation. How is it with China, because that I don't have experience with?

David Blasingame

Well, honestly, not that much different. I think they are very much looking for the sponsor to provide input on how the investigation should be run and how it should be written. They're, for the most part, I think amenable to that input. They will gladly take it and incorporate it. What you can't do as a sponsor is sit back and hope that they're going to figure out the root cause, or even the Kappa, necessarily to a potential investigation. We ran into that multiple times. To your point about communication, that translation became so demanding on our side that we hired a Chinese speaking person to help us, with not just our face-to-face conversations, but in the documentation side as well, because there were differences between the English translations we were given, or being verbally told, versus what we were hearing when they were speaking amongst themselves or written on paper. So we found it paid for itself, having somebody on staff who could speak the language because the communication style was very different from when we didn't have one. It was much harder for us to just rely on a translation service, which you can do at its own cost, but more importantly, it's on a timeline. That's a much slower way of going about business, especially when you're on the floor in a manufacturing campaign, and you come across a deviation. The last thing you want to do is wait for a translation service to understand what's going on.

Brian Lihou

Now, when you're going about selecting that site, did you ask to see examples of GMP records, or was there prior experience with the firm you were with in that particular Chinese site or were you involved in the vetting of the site?

David Blasingame

Yeah. There was no previous experience with them. They were selected because, quite frankly, they were the largest CMO in China at the time and still are to this day. So that gave folks some confidence that all the people we can work with in China would probably be the best because they would have the most services. They could provide the most solutions to any of the problems or project needs that we had. So for that basis alone, they were selected.

Brian Lihou

Okay. Understood.

David Blasingame

I think there have been heavy influences from the US and from Europe in particular to their regulations. The Chinese FDA has tried to take the playbook from the FDA and the EMA and install similar guidelines and practices within China. That's a big deviation just the last five years compared to, say, 10/15 years ago, where it was more of the Wild West kind of frontier-style of manufacturing to get projects into the country. Now, they're much more focused on making high-quality APIs, not just for early phase. They really want commercial drugs as well. They want to be able to control them internally for their citizens. So there's been a large push by the

government, in just the last five years, I'd say, to significantly ramp up their requirements to be much more like the US. I think in that regard, that's a step in the right direction before certainly later stage drugs.

Meranda Parascandola

Dave, you spoke a lot about drug substance manufacturing. At what point would you consider transferring out or the benefits of staying within the same company from drug substance to drug products within China? You mentioned that you've been to multiple sites in China, whether it be drug substance or drug product, and I wondered if there's a benefit to staying at the same manufacturer from your drug substance to your drug product?

David Blasingame

We were hoping to realize that with a couple of projects that we have there because we thought sticking with the one organization, you're given a project team, a project coordinator, and all the SMEs from the various functions. So we thought they'd help us integrate and coordinate the manufacturing schedules, the shipments of raw materials, or API for the drug product manufacturing, and the like. What we found was kind of the opposite. Each unique function and unique building within each city was just an independent organization. That was, I think, a reflection of how the CMO we were working with came to be as large and as well-known as they were because they acquired multiple organizations. They gave them the same title, the same company name. They were different organizations that only shared the parent company's name and still operated in independent silos. To your point, we were hoping to rely on them a whole lot more for integration and coordination among the different sites that we were using. What we found was the opposite- we had to do that for them. Again, it falls back on the resources at the sponsor site. When you're a smaller organization and rely on your external partners, that is a consideration to make because you don't have enough resources internally sometimes to compensate for what you may not be getting from these vendors.

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Brian Lihou

I think it's important that we understand some of the challenges, but just as importantly, some positives to going there. As you laid it out, there are benefits and challenges to these scenarios. To me, knowing what you know, having been at the sites that you've been in for as long as you've been in, would you say that not necessarily every program is a fit for China? If so, what are some of the real basics in your program that you want to make sure are on a solid foundation before transferring your process to Asia?

David Blasingame

Yeah, good questions. I think for early phase programs; clearly, they are the go-to place for very quick material that maybe doesn't need to be as high quality as you might need in a later stage project. For a later stage project, I would feel much more comfortable if we had a well-worked out process that we had maybe developed elsewhere, but known of the impurity profiles, know the NORs and PARs, and aren't relying on these firms to do anything other than repeat what was done, given the procedures that they're given. As long as that is clear upfront, you're going to be more successful on the back end. Learning from our mistakes, we thought we had a turnkey process but quickly found out we did not. That's when we were significantly out of pocket with the firm that we had contracted with. They just were not geared up for the development work that we needed on a 17-step process that was very technically challenging every step of the way on a highly potent compound, which made it even more challenging. But, if you could have a process that maybe is worked out and handed over to them, I

think they could be very successful with that. One of the reasons you would want to be there is access to the Chinese market. It's much easier to do that if you're manufacturing internally in the country than externally. So that's something else to keep in mind with the projects, depending on where you want to market from.

Brian Lihou

Yeah, those are really good points. I hadn't thought about that. It seems that we always say that an ounce of prevention is worth a pound of cure. It's a commitment financially beyond that original proposal. If you make that commitment, you really should have a good, realistic handle on your program.

David Blasingame

Yes, and plan to be fully involved the entire time. I think it's maybe a little easier in some other CMOs and other countries in the US and Europe not to be as hands-on because maybe they're more mature with their commercial processes and procedures. I think if you're planning on doing manufacturing in China, plan on being hands-on.

Brian Lihou

Yeah, and that's a note for some of these smaller companies where they may not have a CMC group. This is just another product in their portfolio. We've seen it time and time again, right, Dave, where clients have wholly invested support and trusting in the CMO. But to a CMO, in all fairness, you are one of the projects in their portfolio. Understandably so, that's the CMO model. So this is a situation where it does require a presence. You can't balk at the price of an airline ticket because if you weigh that against the price of not getting your product available when you need it...

David Blasingame

That's right and particularly important for a smaller organization because there is a hierarchy there. They look at Big Pharma names versus other names they're not familiar with, and they will react and treat the project accordingly. So to help yourself, you're going to need to invest some time to be on-site to help your project succeed.

Ed Narke

Okay, this is good. Anything else you want to share with us, tell us, confide with us?

David Blasingame

How about the one practice that they have that I'm jealous of. I wish we had it here in the States. I don't know if I've told either of you this, but I told you that they graduate a lot of Ph.D. chemists and others across all their universities, and these are top-notch schools and top-notch candidates. They have a very heavy recruiting process where they would shut our project down for a week while they go send their top VPs and project managers to the universities before they graduate those students to say, "Here are the jobs we have for you. We would like you to come to our firm." What was described to me was just how aggressive that recruiting was because there were so many CMOs vying for the same pool of candidates that they had to be creative with how they enticed them to join the organization. I remember being jealous because that was not the situation we have in the States, where we have lots of PhDs and not all of them have the job they are looking for or wanting. I just remember how different that was over there for them. As I said, they would shut down for a week. It was almost like Chinese New Year, where they shut down, and it goes quiet for a period. Same thing for the recruiting cycle. It was a full week.

Brian Lihou

Talk about commitment to getting the best people. Wow.

David Blasingame

That's right. That's because the government has funded that many companies that need that many people to be employed. So it's a win for them. They are graduating a ton of PhDs and masters and everything else, yet they have jobs for them all lined up. It's fantastic. We haven't had that in 20 years maybe in the States, maybe more.

“I think if you’re planning on doing manufacturing in China, plan on being hands-on.”

Brian Lihou

Wow. Yeah, no kidding. It seems at times like a different world, but again, in the same way, similar. Over time, like you said, the last five years have been heavily influenced by the West and independent of the political landscape- business is business. So there's an incentive for Asian sites to become marketable and appealing to Western companies because they're always looking for that cost of goods advantage. China can offer it, and China will always be a value-added proposition for somebody's program.

Ed Narke

Okay, Dave, thanks again! It was great. In short, when dealing with Chinese CMOs, the person in plant approach is pretty important. Establishing and maintaining partnership relationships relies on understanding. It's the first step to trust, of course. So if you're doing business in Asia, plan to be hands-on, as you mentioned. There's also an old Chinese proverb, I didn't plan this actually, but 'if you want to find out about the road ahead, then ask about from those coming back.' I think you have a lot of experience doing that.

In our next episode, we'll be talking with Ed Narke, myself, as well as Brian and Meranda. It's a guide to CMC regulatory drug development pathway. We have a lot of resources on our website, blogs, etc. It's really about the importance of strategy and implementing things like that- how can you make your product get to market quicker and efficiently as possible? A good regulatory strategy. I just don't see a lot of it out there sometimes. So with that, thanks again, everyone, and join us on our next podcast. See you then.

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.