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Oligonucleotides: Technology, Strategy, Collaboration
The Essential Fundamentals For Success
A Conversation With Chris Oswald

Chris Oswald, Founder, Coswald Consulting LLC

ABOUT

Chris Oswald is Founder, Coswald Consulting LLC, and Former Plant Manager, Agilent Technologies NASD, Boulder, CO. In this presentation, Chris recently sat down with Scott Merz, Asahi Kasei Bioprocess Sales Manager for the Americas, to discuss and provide insight on oligonucleotide production and manufacturing strategies to support scale-up and sustainability.

Chris Oswald, Founder, Coswald Consulting LLC

Scott Merz, Sales Manager, Asahi Kasei Bioprocess America, Inc.

Scott Merz: Chris is going to be talking to us a little bit about production manufacturing strategies to support scale-up. Chris, we'll go ahead and jump in, do you want to give yourself a quick little bio?

Chris Oswald: For those that don't know me, I've been doing GMP oligos for 25 years or so, since the late 90s. Danced around on the sponsor side, but mostly I've been on the CMO side. My claim to fame is that I was the plant manager at Agilent Technologies for several years, and I've been an independent consultant since 2015, helping folks do drug substance and drug products, CMC consultation.

SM: You're not just domestic, correct?

CO: That's right. I do have clients scattered all over. It's good but can be bad—for the calendar and for waking up and going to sleep kind of thing.

SM: Well, fortunately, yourself and other people in the industry are really helping and guiding, using your knowledge to shape the industry, especially the CMO world, to help transition these drugs from the academic society or the R&D industry out into truly being made. So your knowledge is truly important for us. How do you find the common ground and equipment to accelerate scale up?

CO: I think David touched really well on this point. You could have a great idea and you could have it in an academic setting and maybe for whatever reason, maybe you could develop it with whatever techniques and equipment you have at smaller academia scale. But then if you're going to take it out from that idea and really scale it up, whatever you have on the bench from an academic side may not be directly translatable to some of the CMOs that are involved. For instance, on the small scale bench, somebody might use a sintering funnel for filtration. Well, if you transferred that to one of the CMOs, if you just did a direct scale up, that sintering funnel would be the size of a room, and that just doesn't exist. So you have to be ready to compromise. You have to trust the CMOs on stuff like that. That's kind of a hyperbole example, but it's intended to just show that you have to be ready to give up some of the things that you might have developed in academia.

This is true especially when it comes to process; you might think you have a robust process, but the CMOs a lot of times will have access to data or they've been doing this for enough years that they might be able to selectively tweak your process preferentially to give you a better impurity profile. They might look at the four phases of the synthesis cycle, for instance, and they might say, “Hey, you've got X number of thiolation equivalents. That's probably too excessive. You know, if we back this down, we're going to get better chemistry”. They're going to give you some recommendations. You have to just be ready when you have an idea and a sequence that you're going to bring out, you have to be ready to have a little bit of a compromise when you put this thing in a CMO, because obviously even with the number of CMOs that have come online recently and all the established ones that have been doing it for years, they have limited equipment, and they're trying to use that equipment to hit as many processes as they possibly can. You have to understand, at some level, the sequence or your approach might have to have a little bit of “give”. You just have to have that conversation, understand what your CMO can provide, what they can offer, as you go through the RFP stage and getting proposals, understand what equipment they have, what limitations they have. That might drive some of your decision process, you might choose to go with one CMO because they have access to a certain platform or a certain size of equipment or whatever it is.

SM: Are your clients asking you directly to guide them to link them with a certain CMO? Are you doing the initial review of their process and then seeing what's available based off of your knowledge of the industry?

CO: Yeah. A lot of times. I'm familiar enough with the CMOs that I can give the CliffsNotes version to a client, like “here’s their strengths and weaknesses", because all of the CMOs are great, but they're all going to have their strengths; they're all going to have their weaknesses. That's just the fact of the matter. So if you have this type of molecule, this site might be better just because of their proven history or whatever. And then also, yes, I do look at the process. A lot of times I go through synthesis files, process descriptions, all the parameters and look it over and just say, hey, we might be doing something excessive here. We might be doing too much detritylation or whatever it is. How can we optimize the process? So, yeah, I do both of those things to help clients out.

SM: Okay, great. Implementing a CMC strategy, I know it's key. I know it's a huge topic, can you kind of condense it within our timeframe for the priority? How do you identify the priority or help guide your clients to identify what the priority should be?

CO: Well, it's very similar to that perfect triangle, right? You have speed, budget, and quality. And a lot of times you have to choose two and it's no different with this. When you're setting up a CMC strategy as a small company, you have to basically drive what is your priority. A lot of times if you need to stick to timelines to do that, you might have to pay a little bit additional just to make sure that the timeline gets scooted up, right? You have to pay a little extra to get into the CMO earlier than they might have prescribed. So, again, if the timing is important, the budget goes up. If your budget is important, sometimes you have to let things slip. You might have to get in line behind somebody if budget is your priority. Partners as well, I think that's noted here—are you developing a partnership for multiple platforms? Or if you develop a pipeline as a company, are you going to diversify your processes over multiple CMOs where you drive the process? You have to kind of consider what is your overall company strategy when it comes to the CMC. Sometimes maybe even geography drives the CMC strategy. The CMC strategy, like shipping material from here to there, depending on who you choose as your drug substance CMO versus your drug product CMO. There's a lot of import-export considerations that you might have to take into your decision tree as well. So ultimately, there's a lot of topics. You're right. You can really delve into this really deep and it can go on for a while. But ultimately, you know, companies and the core group, the tech group inside a company needs to decide what's their priority. First thing, timing. Second thing, budget? That's typically what I see. But, you know, some people, again, they might like to dance around amongst different CMOs. They might want to try to go do a mid-scale process at one CMO and they have an opportunity to do a larger scale process at another CMO. That can work, but a lot of times, it can be challenging as well because now you have a process that you developed at one site and you have to bring it over to the other, and that timeline for transfer can extend things as well. It's risky, but it can be done also.

SM: I'm going to circle back to the whole timing and some expectations. Let's just roll right into a pinch point that the industry has been having for a number of years. With the recent ramp-up of additional drug approvals, acetonitrile supply is a critical pinch point for the industry as a whole. Can you shed some light on what you're seeing and how can one manage production of this?

CO: Yeah. I mean, we all know how critical and central ACN is within the synthesis cycle. All the rinses and everything like that. When I look at the process, I'm trying to look at that and say, hey, can we have an opportunity to optimize this? Somebody might come in and say, I need five column volumes of ACN at this phase. And I'm like, hold up, maybe one is sufficient. Can we do some process development work to confirm that we have whatever chemistry rinsed from the column in one column volume so we just don't have to waste it? We've been lucky. I think Dave touched on this as well, that we don't have too many blockbuster oligo products. But if that delivery puzzle gets solved, as he was noting, pretty soon we might have some larger population blockbuster products, right? Leqvio is out there for cholesterol. So, that's the nearest one we have. But if we have several of those, the ACN demand and push is going to be even more critical.

Right now, we have a lot of orphan drug targets and things like that. It's kept the ACN demand more manageable, I would say. But every opportunity, when I'm looking at a process, I'm definitely looking at how can we minimize the ACN within the whole operation. There's been a lot of journal articles out there about PMIs around oligonucleotides, just trying to understand how can we minimize that. The focus is trying to develop these things where they're scalable but also green. David obviously touched on that as well. You have to know what your indication is. A lot of times, I talk with my clients, and the production volume is tied to what their indicator is. If they're going to be doing a high dosage indicator where they have to dose a patient, you know, once a month, every two months, that's a whole different consideration versus somebody that's dosing a patient every six months. And then, based on what their phase one, phase two, phase three population sizes are and what batch sizes we need, those are all considerations. It's all, as you can see, very variable. It's on a case-by-case basis. As an industry, we know that we have to take ACN consumption seriously and try to do what we can to minimize it because at some point, it's a relatively finite supply.

SM: So, just on, not only the synthesis portion of it, but also purification, do you suggest moving towards more of an ion exchange purification manifold or even using methanol or something other than acetonitrile?

CO: I've seen some folks, rather than methanol, use toluene. They might have, on their campus, access to toluene. They might use ACN up front and then complete the rinse with toluene just because they have access to it. I've seen that done. But it's a major challenge, and it's not going to go away. I see the ACN used more in reverse phase, obviously. A lot of times that's used for the longer guide RNAs. And so, their scale, what they need is smaller.

But again, that doesn't necessarily decrease the amount of ACN from a waste perspective that they're generating. Relative to the amount of product they're producing, it's actually kind of less green, you know, based on the grammage that they're pushing out. That has to be taken into consideration. But ion exchange, it's very, very hard for these longer chains to do ion exchange right now. The technology for resins just isn't there to be able to resolve these things. You're depending on charges…it's just not there yet. There's other techniques that are trying to come on there, like Frag CE and other techniques.

SM: I think this leads us into this next bullet point very nicely. When you're conversing with your clients and/or the CMOs, you're evaluating current availability or current scales, what's out there and what's upcoming? This leads into a little bit of talk about enzymatic. How are you doing this evaluation? Are you asking people to look at changing the process to maybe a greener technology as they move the scales?

CO: It's not necessarily an ask. It's definitely a discussion up front. I mean, it's definitely a weird dichotomy just because right now, obviously, solid phase synthesis is readily accessible. It's been done for, you know, 25 years. And so, it's been well optimized. That's the easiest access. Even for small companies, that approach can seem very costly. But when you get into discussions like stirred bed technology and you get into enzymatic and other liquid phase type technologies, those are a little harder. They're being researched, which is great. But they're still relatively unproven at a larger scale. It's similar to how solid phase, 25 years ago needed some seed money to come into that and get it really kicked off. I believe that's what it's going to take on some of these other things, big pharma or smaller companies that have a great idea and they have some great financing behind them, if they can come in and start these types of technologies early on. A lot of times what you do from a CMC perspective is you've developed a process on solid phase synthesis and you've developed it all the way up to commercial. It's going to be very challenging to now pivot that after you do a filing because there's potentially a different impurity profile. That's a major change. There's all these different reasons. You've pushed a solid phase all the way up because you had access to that. It's relatively cheap compared to what's out on the market today. But then maybe liquid phase, if you had a huge commercial metric tonnage product, that would make sense. But you have to have this post-filing change. And that's big from a CMC perspective.

There's just a lot of different variables. It's almost going to take some of these larger companies—maybe it's the Ionis and Alnylam since David mentioned them—maybe it's those folks that can jump in early, maybe Biogen. Maybe they could jump in very early and help with that stuff and maybe make these technologies more mature and come online quicker so people have more access to them. Because that's the thing, right now you have access to solid phase technology. You do have a little bit of stirred bed technology if you were to use a peptide manufacturer. But that's still relatively new, unproven. Stirred bed was done 30 years ago and it was switched over to solid phase. Maybe there's a reason for that. There's not a right or wrong answer. There's just a lot of considerations when it comes to developing these oligos.

SM: So, are you seeing a trend? Are you seeing the other companies, Ionis, Alnylam, Biogen, are you starting to see them move in that direction or do you see them resistive?

CO: I haven't seen or heard. They might be doing it, internally. But I don't think there's any resistance. Having good conversations with all the Alnylam and Ionis folks, they seem on board with the push for green chemistry. We all as an industry want people like that to succeed because if they have a blockbuster product, and they can have it more green and it gets more notoriety from that perspective, it benefits all of us, right? To show the industry is trying to make more pushes towards green chemistry. My guess is they're definitely considering that every day in everything they do. There's other technologies. There's Blockmer technology that's being researched. That would potentially be a big windfall for long guides just because you could reduce the number of couplings. If you're doing a three-mer or four-mer, you could make those like 94 to 98% pure and then couple those, you only have 30 couplings instead of 100 couplings. There's all these different things that you can do to increase scale and increase the green capabilities.

SM: Let's talk about reality. Can you shed some light onto the reality of what maybe a bench chemist is currently working on to how long it might actually take for that drug that he's working on or the molecule they're looking at to actually make it out to manufactured scale.

CO: I would say that range is going to be anywhere from probably 6-18 months. Six months, I'll give you an example. There's somebody I know very well. He and I are both obviously very knowledgeable about the oligo process, so we can put together a process very quickly. And even for us, it took us six months to get something kicked off the ground with a CMO. Contrast that with somebody else that maybe is less experienced and maybe has more of an academic focus. They're going to have some struggles, right? Maybe understanding the CMO management piece, whatever it is, understanding regulatory starting materials that they need to have on hand, lead times for resin, lead time for amidites, all the things that support it. There's all of those types of things. I think 6-18 months is probably a pretty fair range, depending on what the team's expertise is. I led Agilent, and this other person led another CMO organization, and we were both able to push the process together very quickly. And so six months was probably pretty good, I would say. That's just the reality of the matter. But the scale-up is not easy and it takes time. Even when you think you're an expert at this thing, scale-up can sometimes humble you just because something will slip through the cracks. So, you know, when you are a sponsor and you have a platform chemistry, then I would say scale-up is a lot easier just because you've been through it the first time. You kind of understand the strengths and weaknesses of your process. But if you're doing it the very first time, it definitely takes time to just make sure you're understanding what changes or approaches you're doing or what your chemistry is to make sure what those long-term impacts are.

SM: Let's bounce back to the ACN supply for a moment. We've had several conversations with a number of engineering firms and sponsors, trying to figure out and identify a way of ACN recycling or ACN recovery. Can you shed some light on pluses, minuses, advantages, disadvantages? Do you have any expertise or knowledge in that area?

CO: The only expertise I have is when I have conversations with people. When I'm helping design and build facilities, I try to have them set aside a footprint in case this can come online. But I think that's something where we're going to need some of the bigger companies out there that have better connections to the regulatory folks to bring this up, because there's obviously some regulatory concerns when you have potentially “dirty" or “contaminated" ACN that you're going to be bringing back into the process. You'd have to have a company that not only knows oligochemistry but is very strong on the analytical side that could use those analytical capabilities to prove, if you divert the first column volume to just a general waste, but the next column volume of ACN, collect it, and send it through a still and can show analytically that there's no impurity contaminants that are coming through in that ACN that's distilled, then potentially now you have some ACN recovered that could be used. Now all of a sudden you'll get that more green part. Then do you have some of these CMOs start putting in a closet with a continuous distillation cabinet to recover ACN for reuse? If you've shown it analytically, could that ACN then come back into the mainstream and be used? But there are some regulatory bullet points that basically state you can't do that right now. I think that's where we need additional focus and help to get over that hump and show why it is acceptable, because there's just this natural cringe right now, I think, by regulators to not do it. There just has to be scientific demonstration that it would be acceptable.

SM: I was not aware of the regulations of not being able to use recycled. I'm glad you actually brought that up, because it's definitely a concern and thought process of how do we get over that hump?

CO: I can't remember which document. There is a note where basically the ACN that you've collected can only be used on that particular cycle. And that's not very conducive, because if you've recovered ACN from the detrit phase, it's not like you're turning around and doing detrit again. You're recovering that ACN to potentially be used later in the molecule. To me, it is similar to the siRNA approach, in terms of two strands coming together to become the one therapeutic molecule. A lot of times those two strands can be run on the same equipment or in the same room and you don't have the cleaning concerns, because whatever the impurities are, they're already impurities of the same siRNA duplex, right? It's similar to this. If you use the ACN on the same synthesis cycle of the same molecule, is that a way you could do it? That's the first step. Then the second step would be that you could show that you don't have contaminants that cross contaminated on the strand. The biggest sensitivity is going to be guide RNA. Because of the gene editing capability with guide RNA, there's absolutely no tolerance for impurities. So I think that's going to be the sub-industry that's probably going to have the most hypersensitivity when it comes to ACN recycling.

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