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Oligonucleotides: Technology, Strategy, Collaboration
The Essential Fundamentals For Success
A Conversation With Mike Webb

Mike Webb, CEO and Principal, Mike Webb Pharma

ABOUT

Mike Webb is CEO and Principal, Mike Webb Pharma, and Former Vice President, API Chemistry and Analysis, GSK. In this presentation, Mike recently sat down with Scott Merz, Asahi Kasei Bioprocess Sales Manager for the Americas, to share his expertise on creating proper collaboration strategies to ensure long-term success.

Mike Webb, CEO and Principal, Mike Webb Pharma, Former Vice President, API Chemistry and Analysis, GSK

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

Scott Merz: Mike, do you want to give a quick little brief bio about yourself and sell yourself up a little bit?

Mike Webb: I spent the bulk of my career in GSK. I finished up heading up chemistry and analysis in the UK, but I did do a deep dive into oligos. David made a good point about picking these things up and dropping them too quickly, but we did get involved in setting up oligo CMC and collaborations within the company. And like Chris, I've been consulting since about 2016, worked on double-stranded, single-stranded oligonucleotides, and I've now worked with most of the CMOs, some big pharma like Chris, some biotechs with different flavors.

SM: Great. Thanks, Mike. Can you shed some light and guide us on how to select the right partner to properly connect science and funding?

MW: Yeah. You know, that's a big subject and we could do “motherhood and apple pie” because the right partnerships, that’s important for any drugs, right? I think it's very important before we dive into rare diseases and genetic diseases, we're moving into large things like dyslipidemia, hep C, and that's going to require people to think with the CMOs about large-volume pharma supply chains at the commercial end. That's going to be a whole big partnership area that we're starting to think about now. But for now, let's think about where we are with small biotechs who are now pretty much modality-agnostic, who are getting interested in oligonucleotides and maybe are experts in a therapeutic area, but now, like Chris was talking about, are getting involved in oligonucleotides for the first time. Now, obviously partnerships are important, but there's a few things that I think are important to recognize as special about oligonucleotides.

As Chris said, oligonucleotides are real expensive to make and really expensive to develop. And the platforms are expensive. For rare diseases, of course, they're less capitally intensive in terms of the clinic, in terms of the fact there are fewer clinical centers, patient recruitment is easier, and patient numbers are smaller. The CMC costs are quite high compared to the clinical costs compared to say a conventional small molecule. For a conventional small molecule, you're going fast to fail either in the preclinical studies or in phase one. With oligonucleotides, you already have big attention from your funders about the partner make. So you need a CMO that you're going to work with. You need a CMO that understands your supply chain, and you need people like Chris and people like me. You need a drug product CMO that knows a little bit about oligos and you need a drug substance CMO that may have to help you with the analysis of the drug product. People recognize outside of the DMF, the sponsor is responsible. Anything that you put into the patient, you as sponsor are responsible for, so your partnerships are incredibly important to your funders, and they're incredibly important to you. We have a rapidly expanding CMO market. We have a lot of people out there, all over the world. We're shipping oligos in cold chain all over the world. Setting up your partnership strategies is really, really important. The most important thing is your CMC is going to get the attention of your funders. The cheapest thing in the world would be to do your tox batch and your first time in human clinical batch in one go. That's probably the most cost effective, but that’s money up front, and that's going to get the attention of your investors. So you may want a batch for your preclinical and that has technical advantages because you can take a wider cut in purification, and you can have high levels of impurities qualified. When you get into this, you need to understand the strategy, and you need to justify that strategy and costs. And you're really plotting that strategy with the end product in mind because this isn't a med-chem route that you're going to scale up to a few kilos to go into phase one. This is building the same basic process for the future. So those partners, those early partnerships, that CMO selection process that Chris just talked is really, really important. And the connection between doing the right science at the right time and justifying this to the people who are funding you.

If you're in big pharma, especially if you're in biotech, it requires a lot of thought. And that period between selecting your lead to go into your preclinical studies at the point where you may be doing maximum repeated dose or maximum tolerated dose before you go into GLP, that period is a really important period to understand what you need to do in your strategy and get the funding to take you through first time in human.

SM: Building on what you said, you're not only selecting the partnership that you're going to have with the CMOs, you also have to look at who's going to get a grip on developing, who's going to do that approach. You mentioned here it's about front loading and who does the heavy lifting. Can you share decision ideas on that? Who does the decision making on that?

MW: Yeah, are you going to put that heavy lifting into the hands of your CMO or are you going to have an oversight with someone like Chris or someone like me that's going to help you with this? I think it's important to reiterate the fact that with oligonucleotides, they're expensive to make. We typically make a more limited number of batches, particularly in rare diseases. As Chris alluded, the solid state chemistry is basically the same. There are some differences. But you are quite front loading your process, and you actually need that batch history. It's really important to do the right amount of process development upfront so that you can start to build your knowledge base about your batches and your impurities from the get-go.

Generally most consultants will say that you need to front load your process. The truth is, if you're a big pharma that's doing a collaboration, you may only have one big batch, and then you're moving to a CMO quite late in the development cycle and you may have to do quite a lot of work later on. And again, Chris mentioned the move between CMOs, and with new technologies and solution-state chemistry, we may even be moving the process. So there is a decision to be made about where you're going to go with this process, what your doses are like, what your volumes like, what your market is like. And you really need to be thinking to having a target product profile at the beginning and deciding what you're going to do when. But in a lot of cases, particularly rare diseases, the best thing you can do is front load your process and build up a batch history because you'll have a limited number of batches.

SM: Which also then brings us into just manufacturing analysis challenges. Can you shed some light on what you're currently seeing?

MW: You know, I've been in this business a long time. One of the early drugs that went on the market is amoxicillin. Amoxicillin is hygroscopic. It basically establishes water depending on the environment that it sits in. Oligonucleotides do the same. What I don't work out is how much difficulty we have analyzing these materials when we've had them in our portfolio for 60 or 70 years. But we do. With assaying oligonucleotides, the other problem is we don't have 99.9% pure synthesis, and we have separations that would make a small molecule chemist's eyes bleed.

We have a lot of problems in assaying oligos. The key question, particularly for double stranded oligos, there's a lot of literature out there and I talk a lot about it at conferences in great detail, but correctly determining purity and correctly quantifying your impurities and then correctly identifying your impurities and making sure that they're quantified when you go into tox— particularly for double stranded oligonucleotides and oligonucleotides with a lot of diversity of chemistry, you're going to get families of impurities, you're going to get a lot of peaks in your chromatogram, and particularly if you're using ion pairing methods, which most people do, and also ion exchange methods, you're going to have impurities that do not separate: depurination, oxidation. It is very likely that you're going to be doing some work with quantitative mass spec. Therefore your QC methods, your analysis methods, and your ability to identify individual impurities is really difficult. Really, really difficult.

I feel a bit sad to outline the problems without necessarily having enough time to talk about what the potential solutions are. But then, you know, that's how I get paid. The other thing that's kind of come across is if you take gapmer ASOs, 20mers that are fully phosphorothioates, and we do not control that introduction of the chiral center that thiolation produces, your oligonucleotide is potentially a mixture of half a million compounds. There's been some literature suggesting that any variation in that diastereomeric ratio could affect the potency of your compound, and the regulators are starting to ask questions about reproducibility. If you can get an analytical method to separate and quantify half a million compounds, I'd be really impressed. We're having to look at that problem, semi-quantitative problems, or look at that problem during process optimization, process development, and process understanding.

Those are the challenges, I think. Identifying the impurities, quantifying the impurities, determining purity correctly so that you're meeting the standards of the guidances or the spirit of the guidances for synthetic small molecules, which at least, if not in detail, in spirit, are applied to oligonucleotides. Chris and his colleagues have done a phenomenal job in providing understanding for the synthesis. Analytically, we still have a lot of problems in giving you a really, really good, reliable number and a method that will work. So you're going to have a method that's got tiny shoulders and separation to quantify, and that method's got to work for the life cycle of the product. So that's where I see a lot of the challenges.

SM: Wow, it's more challenges than I'm aware of.

MW: You know, hats off to the instrument and column manufacturers. If we'd tried to do this with the columns we had 20, 25 years ago, we would have failed. We can do it now because these columns are so beautifully controlled.

SM: Let's touch a little bit on some of the supply side materials. We talked a little bit about the short supply of acetonitrile globally and how to deal with it. What are you seeing and how do you guide your clients on how to forecast whether to support the clinical trials?

MW: Yeah, forecasting is difficult early on. You're still determining dose. But it's really important that you are able to forecast what your batch sizes are and your CMO is able to forecast to establish what is a reasonable yield and therefore a reasonable cost. Because in my former small molecule world, the drug substance was not a huge part of the cost of therapy. For oligonucleotides, it's absolutely vital to the cost of therapy. The second thing is these batch sizes are quite significant in terms of supply and supplying defensive stocks. If you hold high defensive stocks, you have high working capital. On the other hand, if it's for a rare disease for a medically critical compound, you need massive inventory. Figuring out that supply side… if you're a small biotech and you want to go all the way to being a commercial supplier, you need to really understand that because a stock-out or a recall is the end. It's kind of the end. It may be the end of life for patients with rare diseases, so it's really important.

The other thing which I find a lot of my time talking about is it is OK to rely on your CMO to control your amidite supply and have quality agreements around amidite supply. But you are the sponsor. You are responsible. And so I think the whole of the pharma industry, and I hope big pharma colleagues will agree with me, haven't done a particularly good job in terms of change control upstream of their starting materials. Amidites are highly functionalized molecules, and we need to have supply agreements such that we know and we can evaluate any changes. Because as you know, if you're adding a G 10 times, a 0.1% impurity with the same coupling efficiency will give you a one percent impurity in your oligonucleotide. So a very small change in the impurity profile of your amidite has a very profound effect on your oligonucleotide. You can rely on your CDMO to do that, but you sure as hell need to know that they understand the implications and they have good change control agreements with their suppliers. And that's really important because those tiny changes could have a profound effect on quality, and that could lead to having a batch failure, which leads to a supply interruption. This is a complex business. And you know, this keeps guys like me and Chris in a job. The platform experience sits with the CMOs and sits with us. When you get into this for the first time, you know, Ionis have a platform, as Chris said, and so have Alnylam. They've done a phenomenal job. But when you're getting into it new, these are the major issues, in my opinion.

SM: That's great. Let's talk the growing role of CDMOs globally and choosing the partners to support bulk manufacturing. Big pharma, small biotech, choosing the right partners to support this. Can you shed some light on or your thoughts on this topic?

MW: Yeah, it seemed a couple of years ago, CDMOs were very capacity limited. Most of the big CDMOs have increased capacity hugely. And also, we're seeing a lot of peptide manufacturers getting into oligos. I get a call maybe once a couple of times a month saying, do you know any good oligo chemists? And I say, well, unless we clone Chris Oz, you may have to start with a synthetic chemist to learn this.

So you really need to know that the people you're dealing with have the experience and the platform experience. One quick problem that we have is that that platform experience is their know-how. That's their advantage. They work with a number of CMOs; their platform experience they own. But it's difficult for them to share because they're under CDAs with their clients. So actually, guys like you and your organization, Scott, and Cytiva are really useful, because you have some knowledge that is very useful. Obviously, guys like me and Chris especially can pick up that knowledge because we've done it many times. It's really important for a biotech to make sure they've got access to the knowledge that's going to do that early development that Chris talked about. The other thing is with the advent of Inclisiran, which David talked about, and hepatitis compounds, now the oligos spill over in large volumes. We're seeing guide strands for CRISPR. These guys are seeing really big dollars coming through and having large volumes. And if you're still looking at oligos, even for oncology, which is very diverse, but also for rare diseases, you know, you've got to make sure that you're going to get the attention of the really good guys in the CDMO who are going to be able to work on your lower volume, lower value compound. There is a need for more people, more consultants to be able to help with that because the amount of good process and analytical expertise is getting kind of diluted out. And there's some big manufacturing buck. So for a biotech, their first oligo, there's little bits of minefields around these collaborations that have got to be steered through so they don't end up going in the wrong direction. There are a lot of potential pitfalls. It's not like small molecules. It has its own characteristics, but it is applied to the synthetic and analytical standards that exist in the regulatory world in the spirit of synthetic molecules. And there's still a lot we have to sort out in that direction.

SM: Great. Mike, thanks for the insight there. I know as a company, we've been supporting this industry for well over 20 years. And we're seeing dramatic growth over the last 5-10 years. All the CMOs that are rapidly expanding, the number of CMOs that are coming online. To us, what's even more exciting is to see the big pharma companies actually take on the manufacturing themselves and bring that back in house. While they don't necessarily have the technology or the insight to do that, they're quickly learning. I'm hoping that the industry itself is growing the knowledge and growing internally how they're going to be able to actually keep this manufacturing going.

MW: Yeah, and I would just add, I agree in my world, what David said is incredibly important that big pharma being in it for the long haul, whether they work with CMOs or like Biogen, doing their own makes, that is going to help enormously, but it'll only help enormously if we move this forward together pretty competitively.

SM: Yes, I completely agree. We need people to stick around the industry and keep pushing the industry further along as we can. I thank you very much.

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