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Gene Therapy Analytics: Making Proper CMC Investments to Reduce Risk and Maximize ROI

Mike Kelly, Senior Vice President, Atsena Therapeutics

ABOUT

Mike Kelly is senior vice president at Atsena Therapeutics. In this interview, Kelly discusses how companies can make proper CMC investments to reduce risk and maximize ROI, including the make or buy decision; ensuring CMC investments provide regulators what they need; scalability considerations; identifying technologies and assays to support your strategy; controlling COGS; and building a commercially feasible program profile.

Mike Kelly,
Senior Vice President,
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Ben Locwin,
Vice President of Project Solutions,
Black Diamond Networks

Ben Locwin, Black Diamond Networks: Hello, Mike and welcome. Will you share a brief bio of yourself?

Mike Kelly: I work at Atsena Therapeutics currently, it is seen as a startup company focusing on AAV gene therapy for inherited retinal disease, ophthalmology. Prior to that, I had number of roles in smaller and larger companies in lenti-virus and AAV gene therapies, and cell therapy work as well. I have been doing this since the mid 90s and I've been in research, development, and CMC throughout that time.

BL: Can you explain how you'd recommend going about developing a strategy for make versus buy decisions and why hope is not a viable strategy?

MK: It's important when we transition into the CMC realm, that we understand how to do it, that we understand the technology and how to apply technology, and directly meet expectations that hopefully will give us an approved therapeutic. In general, make versus buy is not unique to CMC. Everybody depends on service providers in some way, shape, or form. Therefore, every company as a core competency must have the tools to do outsourcing, as well as insourcing operations. It's important that they know how to identify, how to evaluate, and select vendors that are well matched with their technical and operational needs. There's a number of very small companies using outsourced services, and it's important that both parties come together to enable the rapid and efficient transition into the clinic and eventually out of the clinic.

BL: Do you have a quick mental rubric that you might use where you're thinking about identifying, evaluating, selecting vendors, and at what points you go from one column to the other for make versus buy?

MK: Most small companies don't have the option of building internal capability upfront. It's a significant investment both in of dollars and time. So leveraging the existing infrastructure is important. Selecting those vendors is just as important. We've come through several years where the demand for ISO services is huge. Uncertainty has outstripped the capability of that infrastructure. In choosing who to work with, you need to know how their experience matches your needs. It's also important that you clearly understand your needs. Because if you don't, it's going be difficult to make a good selection. There are many factors to consider. You need to understand the fit between the sponsor and the service provider in terms of technical capability, operational capability, experience, management experience, and how you work through problems. You can't just hand it over to a CMO. One of the hard things when you're giving a program to a CMO is you're giving them essentially all of the control, but you still carry 100% of the accountability. Obviously, that needs to be matched with operational capability. That is where companies that are very stretched in terms of demand, don't always have the ability to meet the promises around time and technical capability, nor should we expect them to. As a sponsor, we own the process, and we own the accountability, and we need to leverage them for their skills, but we can't depend on them to give us the answer. It's complicated. Understand what they can do for you, understand the risks associated with it, understand where you can have misalignments and miscommunications. Also, understand that there are forums, and environments where you can have good conversations and good escalation processes to make sure everyone is working in the same direction.

BL: Let's think about right sizing. Frequently, CMC investments can be overkill. How would you go about ensuring that your investments deliver what they need to deliver? No more, no less, so that they do exactly what regulators want to see?

MK: Investing in CMC is a risk-based, proactive activity, right? We have to do it early in order to be ready to meet program needs on time. One of the things that scares me is this idea that you're trying to get it just right, because it's not always easy to predict what the expectations are going to be two or three years down the road. This idea of getting it just right and not over investing is a risky proposition. Because if you get it wrong, you certainly don't want to end up on the wrong side of the line. It's important to understand the technical and regulatory expectations—there are forums to get there. Scientific advice meetings allow you to propose your strategy, get feedback from regulators, and understand what those expectations are. In the last couple years, we've had significant improvements in technology. We've also had a number of large pharmas come to the table to help push CMC capability forward. But in parallel to that, the bar was being raised. We're seeing new guidance all the time and I think the FDA, and the rating agencies in general are holding sponsors to a higher level—this idea of continuous improvement. It's important we don't come up short and if you're going to make a mistake, you're probably better to be a little over than a little under. Overall, the onus is on the sponsor to know what the needs are, and make sure that you're ready to meet those expectations.

BL: Can you recommend best practices for scalability considerations to transition operations from R&D to clinical?

MK: This is a pretty big area for discussion. Recognize that if CMC are coming into the R&D process late in the lifecycle, it's too late. It's important that CMC are engaged as a partner in the R&D process and can inform and educate in terms of what transitions are going to look like, and that the platforms and the analytics used are not a mystery. In an ideal scenario, you're not going to have different product quality and different analytical methods to support those decisions. In an ideal scenario, R&D would be using the platform methods, both for production and testing, that CMC will eventually be putting in place. That's not always easy to do, because CMC is an evolving capability. But you don't want to have comparability challenges, to make sure you're not getting different results. Product comparability is important, all the way through the lifecycle. You should also understand the impact of making changes on a technical capability downstream—even something as simple as the formulation that the research folks use. If it's different, you may get a different result. I would say get the CMC process in place as early as possible.

BL: Are there, in your estimation, best ways to improve technology platforms and assay designs to better support operational strategy?

MK: Absolutely. The starting point is to know what the platform needs to deliver and what improvements and what benefit you're trying to achieve. It's very easy to apply new technologies, but you need to know what you're trying to achieve, whether that's removing animal derived components, or improved purity, or improved yield, or improved accuracy and precision. One of the things is, it's never good enough and sometimes you have to decide on the timing of when you're ready to make a commitment. But it is really based on an understanding of what the process needs to deliver, and what the product quality attributes are—understanding the CQAs of the process, understanding the CPPs and KTPs of your process that drive those performances. And then this idea of design for manufacturability, knowing what eventually you need to have in place in order to ensure robust operations. Technology for technology's sake is probably a risk. But understanding the rationale for why you're making changes and have ways and means to measure the effectiveness of those improvements in the platform will go a long way. One final point is eventually your tools have to be validated, whether that's a process validation, or legal validation. So, recognize that you're building capability that will fit validation need.

BL: Now to get to all of these points in the process as things mature, COGS—cost of goods sold—are an ever-present reality. Any thoughts on best ways of controlling COGS?

MK: When a lot of people in CMC talk about COGS, they talk about the cost of goods manufactured, and that's certainly a big component. But COGS also includes storage and distribution, and more importantly, licensing. Companies, when they license programs or license technologies, usually make royalty commitments as part of that. That's all going to be considered cost of goods sold. It's also important to understand why reimbursement strategies and reimbursement capabilities exist. One of the challenges we're struggling with today is, particularly with those high demand programs where we've got weight-based dosing, and some patients require E15 or E16 particles, that's an expensive proposition. We need to know that we can meet those costs, which I don't think we can today. But to be commercially viable, we've got to get there. There are some easy things you can look at, but they'll only get you so far. Ultimately, you have to look orthogonally at all the components that determine and drive cost, product yield, cycle time, and manufacturing suites.

Another point is products in cell and gene therapy are administered one time, there is a one-time sale. When we think about supply dynamics, we think a lot about the prevalence population and the incidence population. If you've got a situation where you're meeting patient demand, there's no repeat supply. We can model what we think it will take for an approved therapeutic to successfully catch up on patients that are in the prevalence population, but eventually the demand for those materials is going to go down. Understanding how you're going to transition to discontinuation of supply and the impact that has on overhead is important as well. It's not typically the kind of thing that we talk about in early development, but when we think about transitioning to commercialization, a lot of the principles that are established based on biologics are based on a continuous supply of drug to patients, typically for their lifetime. The dynamics we have in one-time administration is changing that and we need to be cognizant of that in our approach.

BL: Can you share any parting thoughts on building a commercially feasible program profile?

MK: Working with payers and understanding what reimbursement models exist, is an important component. It is also important to understand the label that you get with drugs and how you design clinical studies to get a maximal label. You don't want a label that only allows you to treat a subset of those patients. You also have to try to bring these to all territories, making sure you've got a global view. There are other financial components to think about like reimbursement. Everyone talks about the million dollar, or now the $3 million and $4 million gene therapy product. But there may be a scenario where we don't get those drugs paid for in a single payment. There may be annuity models where we are paid over a certain number of years based on maintaining the therapeutic benefit in patients. There's a number of things we need to work on with payers to understand how we can get there. Ultimately, commercialization is going to look a lot like the biologics world, with the with the big difference that you're selling this product one time in the life of a patient—at least that's what we hope.

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This case study was presented at Evaluating Biopharma's virtual networking and educational event *Gene Therapy Analytics: Implementing Better CMC Strategies*, which included two additional presentations and two interactive networking sessions.

Details of future events can be found here.

You can watch Mike's presentation in full and on-demand here.

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