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Meeting Growth Challenges Roundtable Panel Part 2: Aligning Science, Talent & Expertise

Thought Leadership In Association with Freyeur & Trogue, Impactiv BioConsult, and rbb Communications

by Mike Ward

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Starting up life science companies has probably never been easier. Our understanding of disease biology continues to grow, the pool of experienced biotech executives with the battle scars of entrepreneurship has never been deeper, and the cash pile to bankroll their development continues to grow. The challenge these days is what do company executives have to do to ensure they can translate their ground breaking ideas into sustainable businesses that develop products that make a meaningful difference to patients.

Scrip spoke with Gil Van Bokkelen, chairman and CEO of Athersys, Inc., Daniel R. Orlando, chief operating officer of Vericel Corporation, Robert McNeil, general partner and managing director of Sanderling Ventures and CEO of Dalcor Therapeutics, Ali Fattaey president and CEO of Curis, Inc., Mei Mei Hu, co-founder and CEO of United Neuroscience, Inc., Gregory Hanson, CFO of MabVax Therapeutics Holdings, Inc., and Dennis Podlesak, partner at Domain Associates LLC, in a roundtable interview about the challenges company executives face as they try to build their

business. Sponsored by Freyeur & Trogue, Impactiv and rbb Communications, the roundtable took place during the J.P. Morgan Healthcare Conference in San Francisco.

Translating Ideas Into Real Products

Translating a promising discovery into a product that helps patients requires input from various stakeholders, many of whom are not part of the original research and more often than are actually outside the company. The challenge for investors and management teams is to ensure that the nascent business has access to the right expertise at the appropriate time.

“It is about marrying promising technology with great talent. One doesn’t do well long term without the other. Great technology without the right management team probably won’t get very far or funded or succeed. Conversely, great talent without really valuable technology tends not to go far either,” noted Domain’s Podlesak.

For entrepreneurs, CEO and companies, he added, it is about accessing the right experience. “In some cases it is the formation of the early management, in others its augmented by great key opinion leaders.”

Indeed, scientific founders may have great ideas and science but that is different from developing a drug. “That requires a much more comprehensive development plan – what are the studies you are going to have to do preclinically? What are your clinical plans? How many drugs fail because they don’t get the dose right? Because they didn’t have a great clinical plan to get the endpoint for approval?” questioned United Neuroscience’s Hu.

“There is the raw drive to get the idea, then there is the task of translating it into a drug and then there is the executive decision of assessing which programs to pursue based on unmet clinical need and/or good payer coverage. That takes different skills and why it is a team effort. I don’t know a single person who can do all of that,” she added.

Often that means having different people at the helm as the company evolves from research idea to discovery program, development plans and finally product delivery either to a pharma partner or to patients directly. That decision is often made by experienced executives in venture capital syndicated.

"Before Adennyx was created I met with the French founder in Paris and he had this idea about how we can prevent chronic pain and it was one of those big ideas that is hard to get your head around. We actually studied the company for almost two years before we invested. We took all that work that he had done and sent it to Stanford where we replicated all of the clinical work, including a lot of the preclinical work, to validate the model. And while we were figuring out whether it was something we wanted to invest in we started surrounding the company with key opinion leaders and experts in the area of pain – some of whom eventually became part of the management team," noted Podlesak.

The challenge is how investors convince the scientists with great ideas that they may not be the right people to advance a program. "Our job is to make sure that it is something worthwhile. We then have to put together a team that can grow cost effectively and develop the compound into something that you can submit an IND and take it into the clinic and do all the studies," added Sanderling's McNeil.

DalCor was created in such a way. In 2012 he had discussions with investigators at the Montreal Heart Institute led by Jean-Claude Tardif and Marie Pierre Dubé who had made an interesting observation about dalcetrapib, a CETP inhibitor that was being developed by Roche and Japan Tobacco. The companies had conducted a large, double blind cardiovascular study, dal-Outcomes, randomized over 15,000 patients already taking statins for cholesterol control but the study results were equivocal. While the drug was well tolerated, there was no significant reduction in CV events in the dalcetrapib group, and the dalcetrapib development program was terminated.

The Montreal team, however, found a significant association between the effects of dalcetrapib in altering CV events and the allelic polymorphism at the rs1967309 location in the adenylate cyclase type 9 (ADCY9) gene. When comparing dalcetrapib with placebo, patients with an AA polymorphism had a 39% decline in cardiovascular events, while GG had a 27% increase, and GA had a neutral effect, in the cohort of dal-Outcomes patients.

"They described what they had seen having conducted a GWAS on dalcetrapib. It was a compelling argument right there so I said OK here is $50M let's go. We put together a $150M round because we were going to go directly into a Phase III study. We know now we have retrospectively a gene – ADCY9 – and we know prospectively that it reduces atherosclerosis the same amount as statins. The scientist stayed in his lab and the rest of us went out and figured how to put together all you need to have: a board, an executive steering committee to run a 5,000

patient trial," he noted.

Dalcor in-licensed dalcetrapib from Roche in 2015 and raised $50M in a series round in the same year and $100M in a series B round in 2016. The company is conducting a double-blind, randomized, placebo-controlled, multicenter Phase III clinical trial that will enroll 5,000 patients recently hospitalized with ACS and who express the AA genotype at variant rs1967309 in the ADCY9 gene, determined by an investigational companion diagnostic test developed by Roche Molecular Systems (RMS). The primary endpoint of the study, which started in 2016, is the time to first occurrence of any component of the composite of cardiovascular death, myocardial infarction and stroke. The trial will be conducted at 880 sites in 33 countries.

Advice offered by both McNeil and Podlesak to biotech boards is find the right marriage of both science and talent. "One of the great things about our space is it is so rich in talent that you don't always have to have it residing inside the company. In fact, a lot of companies that grow up very nicely start out using the right external resource to help them navigate their path forwards," added Podlesak.

Aligning With Key External Stakeholders

One key group that biotechs need to engage with as they pursue the development path to market and even sustainability are the regulators. And the advice is to get in early as they are more receptive and helpful than some may think.

"It wasn't too long ago that we were talking about how tough it was to work with the FDA – and why isn't anything getting out? You are now seeing guidance and breakthrough designations and different approaches that make it easier to develop drugs that both the FDA and companies think have the potential to be really advantaged treatments," noted Domain's Podlesak.

Indeed, the metrics bear this out. In recent years there has been a significant increase in the number of new chemical entities being approved year on year by the FDA and other regulatory bodies. In 2017, the FDA approved 46 new molecular entities, while the European Medicines Agency gave the green light to 28 new products containing 29 new active substances.

Regulators are taking a more pragmatic view around approvals to get to help patients as quickly as possible and biotechs are being encouraged to open communication as early as possible.

"The first thing start-ups should do is develop a very firm understanding of the indication they are addressing and the status of existing treatments. Second, they have to meet with regulators to get their perspective on what they find acceptable in terms of different development approaches. I would argue that we have never been in a better time with respect to the transition and evolution of the way that the FDA and other regulators are actually viewing highly innovative therapies," added Athersys' Van Bokkelen.

During the J.P. Morgan meeting, the Alliance for Regenerative Medicine revealed in its state of the industry report some of the dramatic progress taking place. "These are all reflections of an evolution in thinking at the FDA, EMA, Japan's MHW and other regulatory bodies that has been occurring in the past four to five years. That has been underpinned by the efforts of a lot of stakeholders including advocacy groups such as ARM and BIO that have met with FDA leadership in Washington DC," noted Van Bokkelen. "I think the regulatory environment has changed dramatically. Under Dr Gottlieb's leadership it is going to continue to evolve in very important and effective ways."

Companies should see the regulators as potential allies and not antagonists. "We have got to stop punishing the FDA every time something bad happens, making the FDA the scapegoat when the unexpected happens. It is not productive – it may be good political theatre but it does not help new medicines get developed," he added.

The interaction with should be both as early as possible and open-minded. "You know the one thing the FDA and other regulators hate most? It is coming to them with the mentality that you want to cut as many corners as possible, spend less, and take less time to do what needs to be done. They hate that," he cautioned.

"If you approach them with a rational intelligent model then the FDA will work with you in a very productive way. I think more and more companies are learning that there is a right way to do it and a wrong way to do it – come at them with a pitchfork or an adversarial mindset – that you want to cut as many corners as fast as you can -- then they are going to resist," he warned.

Interestingly, there was a consensus among the panelists that biotechs might find it easier to work pragmatically with the regulators than the multinationals. Progress with CAR-T has been achieved without the need for enormous studies being conducted. Regulators have been willing to draw on a lot of relevant data from real clinical experience.

Tapping Real World Data & Evidence

One of the ways in which the FDA has demonstrated its willingness to being open-minded is the conversations it is having around how companies might utilize real world data and evidence. The challenge, however, is that real world data can mean different things to different people.

"The FDA expects you to be very clear about the type if real world data you are going to utilize. How did you obtain it? How are you prospectively going to use it and gather trial data in the context of enabling them to make an objective decision about whether your therapy is safe and effective. Unfortunately, a lot of people talk about real world data and they don't know what that are talking about because they have never had to make the case and present it to regulators and explain to them how they are going to use it," argued Van Bokkelen.

While it sounds like a relatively simple thing -- accessing the data in electronic medical records or health records from clinics around the world -- the reality is that data are not collected or created in a way that is universally acknowledged. But there are ways that companies can use real world evidence, benchmarked against standard of care, that can move the needle and speed things up.

Real world data and evidence, however, is mostly collated to inform pricing and reimbursement discussions. – I have a commercial background and have for more than a decade used real world outcomes sourced through the many payers to leverage for better contracts. That is the traditional use – use in clinical studies has not really changed. When you go to the FDA now they still want the placebo-controlled demonstration and clear differentiation and safety and efficacy.

That is a view that Vericel's Orlando concurs with. "If you ask me where I really want to see RWE is for getting expanded use and expanded indications. Why would we not all pursue the real clinical data to support the payers – its expensive for payers, physicians and everybody loses. Instead of us pursuing that next clinical study, if we were allowed to use real world data we would be able to expand that authorization of products appropriately and reduce costs in general," he noted.

With his commercial background Orlando has been using real world outcomes to leverage for better contracts with payers and while acknowledging that the FDA has been very helpful to Vericel with its pediatric indication for Epicel, Orlando believes that the FDA's appetite to allow real world data to expand labels is still not in place.

"Use in clinical studies has not really changed. When you go to the FDA now they still want the placebo-controlled demonstration and clear differentiation and safety and efficacy. They want you to go back and make huge investment and do placebo-controlled trials. Some of the markets are a bit smaller so it is not realistic for small companies to do that," he added.

The FDA still has a very strong orientation towards wanting data from double blind randomized placebo-controlled studies. Companies can augment that with real world clinical experience and patient testimonials but the regulators are still reluctant to make arbitrary decisions about only one treatment group, that by definition is open label, and compare that to ad hoc datasets that companies may have constructed without giving them full transparency about where the data came from or the limitations associated with it. A position that the roundtable participants recognized is perfectly rational.

Recognizing The Value Proposition

Where real world data and evidence is gaining traction is in the pricing and reimbursement arena, so companies, irrespective of their maturity or the development stage of their programs need to lay the foundations for payer discussions. That is something venture capitalists consider

when evaluating potential investments.

"I think that it has to be both early and through the entire process – although the way through to post-approval-- that the ability to validate these around empirical data becomes critically important because it helps fine tune and refine the decision making. If a drug can get approved in Europe but it can't be sold at a price where it has to compete favorably with generic drugs – even if it is better -- it will probably never end up being a drug there," warned Domain's Podlesak.

To be investable, companies need to understand the therapeutic area, its market dynamics and the competitive environment. Not only today but what will it look like at the time of approval for the decade plus post-approval. Consequently, managements need to understand how payers will perceive value throughout the entire drug development, approval and post-marketing process.

"It has now become more a part of the investment thesis. So when we see things that are really well presented – it is not about providing $10M to run a clinical study but is $20M needed to show how it would be attractive to pharma and payers in the therapeutic area," he added.

This is the second installment of a multi-part coverage of the Meeting Growth Challenges Roundtable, sponsored by Freyeur & Trogue, Impactiv and rbb Communications, conducted during the J.P. Morgan Healthcare Conference in San Francisco.

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