

MEETING THE UNPRECEDENTED SUPPLY CHAIN CHALLENGES OF CELL & GENE THERAPY: DELIBERATIONS OF INDUSTRY EXECUTIVES AT BSMA CONFERENCE

Calabasas, September 7, 2021. Executives of Life Sciences addressed the unprecedented supply chain challenges of Cell and Gene Therapy at the BSMA Conference on August 5, 2021. Deliberations focused on delivering personalized medicine with a production batch size of one, where matters of chain of custody and temperature-control are paramount in the marketplace of limited suppliers. The pipeline of Cell and Gene Therapies has been growing rapidly since the first one, Kymriah of Novartis, was approved in 2019. Research suggests that by 2030, up to 60 new Cell and Gene therapies could be launched, treating upwards of 350,000 patients. Today's drug development environment is largely designed around small molecules and biologics, such as proteins and monoclonal antibodies, a constrained system that has not significantly changed in 50 years. The executive panel highlighted how to incorporate technology, processes and insights to ensure clinical trials as well as commercial production of Cell and Gene therapy.

PANELISTS

				
<p>Aileen Baquiran Vice President, Supply Chain, Orchard Therapeutics</p>	<p>Chris Bogart Vice President, Supply Chain, Bayer</p>	<p>Kevin Cast Partner, Archbow Consulting (Omnicom Health Group)</p>	<p>Matt Yedwabnic Vice President, Supply Chain, Atara Bio</p>	<p>Moderator: Devendra Mishra Executive Director, BSMA</p>

HIGHLIGHTS OF DELIBERATIONS

Devendra Mishra: *How would you describe your current engagement in the evolving supply chain of Cell and Gene Therapy?*

Aileen Baquiran: Orchard Therapeutics, with headquarters in London, is engaged in the hematopoietic stem cells (HSCs) innovations. We have launched an ex vivo, autologous therapy for eligible patients with early-onset MLD Libmeldy in Europe. I am responsible for planning, site qualification and global distribution for clinical and commercial supply. I think our discipline and supply chain has never really been front and center until now with this therapy.

Chris Bogart: We're building out a clinical development and drug launch capability for cell and gene therapy at the Berkeley site which is our biotech manufacturing hub. We must build the

business processes to support our growing pipeline, which the company has been investing heavily, mostly through, external innovation.

Kevin Cast: We spend about half of our time in Patient Support Services, helping cell gene therapy manufacturing companies build a patient support service platform. The other half is downstream supply chain which is demand driven. In cell gene therapy, conforming to the downstream supply chain, consisting of the institutions and the mechanisms for patient delivery of product, is of extreme importance. How to get the product into the patient with all the various models out there? Many services should be offered to these patients and families in need. We must also address the payers who face a \$1 million plus security per therapy. They're now developing unique mechanisms to pay for these products.

Matt Yedwabnick: Atara is focused on allogeneic T-Cell therapies. I've led our clinical supply for the last 4 1/2 years, from phase two into readiness for commercial manufacturing and supply. Our second program is an exciting opportunity for multiple sclerosis, which represents a much larger population than our lead program in lymphoma. Our company must bring our process to large-scale manufacturing of allogeneic T cells and build a supply chain to handle the downstream.

Devendra Mishra: *How does the patient care facility look like, whether it be at a medical center or at a hospital?*

Aileen Baquiran: Qualified treatment centers for us are centers of excellence in the neuro-metabolic disease space. We have established centers and approved them all over Europe in the last year and a half. There are four main pillars of our site location process. The first is an introduction phase where we have a kickoff meeting and site assessment, followed by an audit phase where we do a GMP audit of shipments, which is mock shipment training and the mock shipment itself. The knowledge and experience are shared for the product manual and training for shipping and logistics. That's what it takes to be a qualified treatment center. The hospital sites are very busy. Our key to success has been three things. The first is a clearly laid-out process, timelines and expectations. Number two, make it easy for them. So we move to Zoom for remote places wherever possible, including our audit. And three, we have forged partnerships to help with the qualification process, such as with Be The Match.

Kevin Cast: They look different today than they did when CAR-T therapies were first launched when the institutions had good experience in the clinical trial world while the commercial world was totally different. We were battling with the PBMS as to who was going to pay for the product. So we researched the institutional marketplace and the global orbit. When Kite Pharma launched the original CAR-T Cell therapy, minus 180 freezer was not common. And now that hospitals have SOPs, they have cell gene therapy teams, they can get their arms around better administration of set products. The future of cell gene therapy isn't always going to be in the hospital administration. It could be outpatient administration, it could be community medical oncology, where the biggest care is new or most of cancer care is given today in the States, different of course than in Europe. We must work together and help standardize the SOP processes in and amongst the institutions.

Matt Yedwabnick: Just like Atara's second program, we expect to be expanding much beyond that area of expertise to smaller outpatient clinics that will not have the same capabilities. From a development standpoint, the task is to simplify the life of the patient at site of care, such as standardizing dosing and its ancillaries, cold storage and cold chain requirements. Ensuring chain of custody, chain of integrity, and all the documentation is going to be critical.

Devendra Mishra: *How does one conduct S&OP in a situation where you are patient dependent and the flow of patients is unpredictable?*

Aileen Baquiran: Compared to traditional S&OP, the emphasis on the demand planning arm of S&OP becomes really critical in CGT. For partnering with our field-based colleagues, we've

instituted, a strong demand planning process where we can gain insight on patient leads, understand the lead time between patient enrollments, all the way through reimbursement, and through when they're actually scheduled and treated. This allows us visibility to oncoming demand.

Matt Yedwabnick: If you have the ability to store inventory and put it on the shelf, you have a manageable planning process. From an upstream manufacturing standpoint, in case of allogeneic, it's made to inventory. But from a downstream standpoint, we effectively have a personalized medicine environment where we are identifying based on the patient's HLA typing and the appropriate products to send to them, which is an individualized shipment. It requires coordinated distribution planning with the sites, your logistics team and vendor depots.

Devendra Mishra: *I freeze or shudder at the thought of packaging that product and shipping to the manufacturing facility! What does that look like?*

Matt Yedwabnick: For our products, we're leveraging cryogenic, liquid nitrogen storage, from manufacturing to the patient. Not every site of care or 3rd party logistics provider may have liquid nitrogen freezers. Managing a complex cold chain is part of what we must do. Liquid nitrogen enables amazing shelf life. For allogeneic cell therapies, using liquid nitrogen from the standpoint of storage is key. We saw the COVID vaccines leveraged with a similar kind of approach with liquid nitrogen and bulk storage. Temperature studies were used to qualify lesser requirements, like dry ice or frozen or even refrigerated facilities, to enable the vaccines to travel much farther throughout the world and treat patient. We like the advantages of liquid nitrogen at bulk level, but we want to plan to adapt to the better temperature conditions down down the supply chain.

Devendra Mishra: *Considering how knee-deep you already are into packaging with temperature controlled distribution, are there any guidelines for the startup companies?*

Matt Yedwabnick: For cryogenic, you realize that labeling becomes almost a permanent aspect. You label the product and you send it into the freezer and it's not going to change. So designing your primary label, versus what information you can maintain on a secondary package or secondary carton, is certainly something you should take advantage of where possible, designing as much flexibility at the bulk primary containers. In labeling and packaging operations, postponing as much as possible for the secondary package is desirable. We have seen that the regulators are willing to work and understand those challenges. Cryogenic gives you the kind of flexibility needed. The other piece is the analysis of what's available in the industry and make decisions about investing yourself versus finding a third party in terms of storage and distribution. It is a significant portion of the cost and complexity for cell therapies that can't be underestimated.

Chris Bogart: I recommend, a supply chain design that we have done which essentially simulates various different supply chains with thoughtful assumptions. Interestingly, we have come to a very similar make to stock and make to order approach. We can hold inventory, frozen inventory, but it's expensive. The analysis showed that the skew setup to personalize the therapy was basically based on body weight. The total cost of the product in the supply with the whole supply chain model was higher than with these additional SKUs that the development team had put in place.

Kevin Cast: There are two different issues, one for clinical trial, which is simpler, but labeling has to conform to the dictates of the Board of Pharmacy. And that's why you have all these companies, like Express Scripts, Credo, CVS, Optum Frontier Therapeutics and Eversana. They've developed flash title models for the commercial delivery product, which should be vetted.

Devendra Mishra: *From a systems point of view, of achieving this mandatory requirement of tracking, traceability and accountability, how do you begin?*

Aileen Baquiran: We are a startup with a small patient population. Our business processes are manual, but you fasten a belt around it, and you're comfortable. Today, we're in the process of evaluating our digital capabilities and how do we grow. The main thing is the voice of the customer. How do we make it easy for our hospitals that may have multiple multiple tools at their disposal, and which one do we use for which therapy?

Chris Bogart: We don't have a process in place and are still in an evaluation mode. We must have the traceability as well as the integration. By the time we get to commercial stage, we will have a system and process in place.

Matt Yedwabnick: We plan to have a validated system from inventory to patient. But when it comes to the upstream supply chain of allogeneic process, we thought it was not appropriate to extend the system as a manual process can work effectively with documentation and validation. I have looked at technologies that really enables barcode likes for tracking in cryogenic storage, which oftentimes gets interfered, give ice covering a barcode can become a challenge.

Devendra Mishra: *I would like to move to something that was alluded to briefly, the enormous cost of a treatment and the landscape of the payer, the payee and other stakeholders in our in our industry? What are the challenges and opportunities?*

Kevin Cast: In the States, the entities that control prescription are the PBMS who force prescriptions to go through their specialty pharmacies and specialty distributors. I worked for Script Express for 14 years, so I know the market. The problem is here comes cell gene therapy that is curative, they're not chronic. CAR-T's need to be administered in the hospital. Hospitals want to get reimbursed and compensated for said products. But then you have the payers not wanting to maybe enact that mechanism. We have seen develop over the last couple of months with different payment mechanisms and schemes. There are companies like Optum getting into different types of mechanisms to pay for these ultra-super expensive products. It might be a PMPM, price per member per month model, or might be an initiation fee. So plan sponsor members are covered for emergency use type of products. In cell gene therapy, they all seem to have a different twist, that they all end up being longer, like pay overtime mechanism. But the biggest problem is insurance companies where planned sponsors are thinking long term for 1, 2, 3, or 4 years. Well, how do you amortize a two plus million dollar drug over a couple of years for a 58-yea- old patient? The system still needs to advance, evolve and adapt itself to follow the patient.

~~Devendra Mishra: How are you dealing with the chronic problem of being single sourced or lacking supplier sourcing reliability?~~

Devendra Mishra: *How are you dealing with the chronic problem of being single sourced or lacking supplier sourcing reliability?*

Matt Yedwabnick: In our industry, there's lots of single-sourced materials. And oftentimes, some of those suppliers don't have the maturity because of the revolutionary nature of our innovation. What has worked well for us is identifying the most critical supplies and leveraging the relationships on that front, and then planning accordingly. Be The Match Biotherapies is our most critical supplier for the apheresis starting material, and we have a very close relationship with Bayer. Be The Match helps us identify the right donors, secure them, and deliver them to our facility with the appropriate control and quality. We also mitigated risk with inventory across the supply chain. In case of the pandemic, we were all a bit uncertain about the impact on our therapies. We decided proactively with Be the Match to halt our collections until we could implement additional safety test for COVID for the donors. Stored inventory helped us mitigate some interruptions.

Chris Bogart: I am reminded of the Wild West, for there is considerable risk with many vendors. We were uncertain if many of them could be commercialized. It's an area where the supplier landscape must grow with the industry. Where we have had some successes in partnering in the disposable space where we have been active for 30 years. Our procurement team spent years

working with some of these smaller suppliers and helping them develop their business to be more robust. Partnership is probably the way to go. In the COVID-19 world, we're ordering way ahead of time, through 2022. We've got a development project where they want to order stuff for development runs 15 months ahead of time, which is kind of unheard of in the past.

Aileen Baquiran: We are now planning lead times that are longer than what they were originally quoted to us, and in our S&OP process have taken to approving such long lead time buyers.

Devendra Mishra: *What is one single message you'd like to give the supplier community that could help advance and accelerate the evolution of this very revolutionary therapy called cell and gene therapy?*

Aileen Baquiran: Successful operations in our environment requires a seamless transition in this ecosystem of suppliers, manufacturing, quality logistics provider, and then ultimately, patient and physicians. We will see a lot more of the sharing and sharing across this ecosystem. We have not achieved transparency. How much inventory everybody has? We need more transparency and sharing.

Devendra Mishra: *How would you prioritize information technology deployment in track and trace or logistics or interfaces with the CRO or CMO?*

Aileen Baquiran: I think it's going to have to be all of them. If I look at it from a customer lens, the most vital one would be material to the customer, right material to the patient, that we would prioritize, the distribution and logistics point first. From the manufacturing standpoint, I'd like to address what's downstream as well and finally, the supply base and the transparency and visibility.

Chris Bogart: The suppliers in this exponentially growing industry must ensure GMP capability in clinical and commercial operations. They must grow with the industry and not play catch up.

Matt Yedwabnick: There's a tremendous amount of therapies in cell and gene that are coming quickly from development, from an academic setting, to clinical trials with commercial dreams. Many suppliers are hesitant to make the kind of investments to achieve a commercial ready product and want to protect themselves by classifying things as research use only and put the liability back on the innovative company. If a few small startups are using your materials and have long term intentions, share some of that cost to get to commercialization and you will transform your business. Communication and partnership from the suppliers are welcome.

Chris Bogart: Here is a relevant example with one of our new products in the pipeline where one of the exotic suppliers is looking for a 10-year volume commitment. The time horizon for the partnership may be too long but they want to be assured of revenue to be able to invest in themselves.

Devendra Mishra: *I want to thank our eminent panelists for helping us understand supply chain challenges, and also provide some direction on how we go forward as an industry. Thank you!*
