CELL & GENE THERAPY INSIGHTS

SUPPLY CHAIN FOCUS:
BIOLOGISTICS STRATEGY
FOR SCALE-UP

CHANNEL CONTENT

INTERVIEW

Mitigating raw materials risk during preclinical-clinical transitioning

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Q The transition from preclinical through to commercial manufacture presents a number of challenges for cell and gene therapy companies. What do you view as the critical pain points pertaining to raw materials in this transition?

AH: One of the key challenges, as I see it, is that through the early development stages of your product you become very dependent on raw materials from specific manufacturers or suppliers, and that often leaves you in a position where you have a single source for a critical raw material, which as with any supply chain, is a situation that presents several disadvantages.

For example, due to the relatively low purchasing volume you have as an earlier stage developer, you don't have a great deal of leverage with the single source suppliers. That can lead to a misalignment or imbalance in the relationship between the supplier and the cell and gene therapy manufacturer.

GM: Regarding this concept of purchaser leverage, in addition to impacting supply continuity this can also affect your ability to gain access to audit the quality management systems of your suppliers to make sure we have the right partner with the right supply quality.

Q What approaches can you take to mitigate these risks and challenges?

AH: To build on Gerry's point, you can view this from two different perspectives. One is more the strategic or business perspective and the other is the quality perspective; in some ways it's much easier to work with smaller companies that may be more open to collaborating.

Relationships with raw material suppliers are critical, and where you can develop a truly collaborative partnership, they can prove to be a big asset as you're moving through development phases. This isn't something that's always achievable when working with larger companies. Whether or not it seems achievable, you still need to make every effort to build that relationship, like we have been doing here. Part of our company's strategic plan is to identify key relationships and continue to nurture them through our path to commercialization.

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For example, we currently use Roche CustomBiotech's Liberase™ MNP-S GMP Grade upstream in manufacturing to digest tissue samples from the study participant biopsies for further processing in our autologous therapeutic clinical programs. We consider this enzyme blend a critical raw material for manufacturing. In working with Roche and developing a strong relationship, we were able to conduct an audit of their manufacturing facility in Penzburg Germany site and that was a great example of a positive experience with a key supplier.

Being able to visit sites of critical suppliers and provide documentation to the regulators to show we have performed site visits and audits is essential. It demonstrates that we've assessed their supplier relationships, to show that not only they're providing us with consistent quality product but also they're providing a level of sustainability for the critical material so we wouldn't run into any supply issues for the general population. I think all of that is important from the agency standpoint, so obviously it is just as important from our standpoint.

GM: We completely appreciate that it's a real challenge to host a large number of audits each year, over multiple days, and deploying your staff to support that need. But I think with the understanding that the agency requirements have that quality centric mind-set of making sure that the supply chain is robust from end to end, we have to do that with all our critical suppliers to make sure our risks are managed.

We've also found that by forming partnerships in this sector, we have been able to find access points into those companies where we haven't previously been able to gain audits or even technical visits. This can certainly be an approach to improve your leverage when you are a start-up or earlier stage company.

For example, there's a consortium we're exploring called Rx-360 where you can work with other companies to gain audit access to suppliers. This is a win-win, in that the supplier does not have to schedule multiple audits, but through one audit they can share that audit report through the broader network.

And the hope is always that as we grow we can form these partnerships with our suppliers and grow with them, and help them understand that while we may be small now we hope to be much larger in scale and supporting the quality of life improvements with our cell therapy product.

AH: When looking at this from the quality perspective, whether dealing with a large or small supplier, you have to develop your own vendor qualification because those processes are central to ensuring you have good insight into your supply chain. To this end, we have created a cross functional team – our material review board – to help prioritize the management of all our material risks and vendor relationships.

The safety of our study participants is always at the center of our risk assessments and risk management tool, and that enables our material review board to assess the impact of material changes in terms of product critical quality attributes (CQAs) for example.

By taking this approach, you start with that raw material and understand how it can potentially impact your product, which then translates into how that can impact the study participant. This enables you to understand which of the supplier relationships are truly critical, and those that may be less so.

As in the example with the Roche CustomBiotech Liberase™ enzyme blend, over our clinical development we followed and adapted to the progression of an enzyme blend that years ago initially caused some concern from a TSE/BSE risk perspective to one that is now GMP-compliant and mammalian- and avian-tissue free. As the need for high-quality, well-defined, GMP materials in our field continued to evolve, Roche CustomBiotech took the approach of taking the needs of cell and gene companies and generating an improved Liberase™ enzyme blend that gave us the ability to continue to keep the safety of our study participants at the center of our risk assessments.

Q As a therapeutic developer at what point did you have to start thinking about the longer term commercial manufacturability?

AH: When I joined the company there were about ten of us here, in the middle of a Phase 1/early Phase 2 study, with about 15 or 20 study participants in Canada. Already at that point we were thinking about scalability.

Of course, this is a big challenge – for us we have a very manual process, as a lot of cell culture processes are, and therefore the biggest question is around how can we ensure consistency in the training of our production staff, in the materials that we're using, in the manufacturing process, and in the facilities and equipment we're utilizing to ensuring appropriate capacity growth.

Over the 12 years we've launched dozens of initiatives that were aimed at trying to secure a more sustainable and consistent input into our processes. And we continue to do that today, I'm sure we'll continue to do that even through commercialization.

GM: I joined the company a year and a half ago and commercial manufacturability is one of those things that has kept me up because I've come from that background of having a wealth of suppliers to pull from, whether it's by availability or price, having a consistent set of quality standards.

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But every day I see us making inroads towards being more proactive in understanding our risks better so we can get ahead of these supply chain challenges.

Q What tools and techniques are currently being used to establish consistency between different batches, and does this QC toolkit meet your needs at present?

GM: Our current demand may be small but we still need to make sure there's consistency over an extended period of time. Therefore, in our bulk purchases of critical raw materials, we may look to supply that inventory from a single source, and have the variability of lot-to-lot testing minimized because we have a single lot. That does carry with it some costs and capacity issues that we have to manage through storage and inventory management.

We have confidence in the quality of our suppliers, but we also reassure ourselves with secondary testing of critical attributes on each one of the product C of A's.

I would like to see us do more to refine our specifications as we evolve. Because there's things we don't know that aren't tested on C of A's, to ensure a robust incoming quality control management program. I know over time there's going to be things that are required such as better characterization of our raw material supply chain, whether that's through on-going multiple lot testing, certification processes for suppliers, more trace material testing of things we don't know are there or how they affect our process or product.

It's just a constant evolution as we understand our products better but until then, we'll continue to use our material risk system to determine where a C of A confirmation is sufficient or where we'll need to do an onsite audit (or anything in between).

AH: It is more difficult to characterize a living cell product in the same way as you would a pharmaceutical product or otherwise. That challenge in characterizing our product also leads to challenges in characterizing our material, and so we've very much relied on the consistency and quality of our suppliers to leverage their release specifications for qualification of the individual material. Historically we have been able to obtain documents from Roche CustomBiotech that have helped answer critical questions we've had throughout product development.

> "...a very big challenge throughout the industry, is intrinsic particle management."

In some instances, we've been able to work with our suppliers to gain a little bit more of their testing data for release of their batches where we felt like we needed to characterize the raw material further than just the results presented in their statistical analysis.

This is something we will continue to do: work with our suppliers to ensure that ultimately the specification needs for our raw material, process and product, all align with either their off the shelf or customer order option.

> "...we have to be willing to open up our supply chain in a smart fashion so we can make sure our continuity is there but we don't risk quality..."

The last thing I would add as a very big challenge throughout the industry, is intrinsic particle management. Many of the consumables we're using as part of our manufacturing process are single use plastics that have an inherent potential to introduce particles into our process and that has resulted in the need to have a very robust particle identification and risk management program.

The hope is that we will always work with our suppliers to continuously reduce the potential for particle introduction, but at this point in time it is almost impossible to expect there will be no particles being presented from the plastic consumables we use in our process. Therefore, developing robust particle removal and visual inspection processes is key.

Q Supply shortages of critical raw materials is a major current bottleneck and barrier to commercialization for the field. What is the answer in your view?

AH: In the short term, strong quality supply agreements, which we've had in place with Roche for example, are probably the most efficient approach. We recognize that as a manufacturer we have constant fluctuating demand which we are presenting to the supplier, and that we're purchasing relatively modest volumes. Therefore, as we touched upon earlier, we somehow have to tip the scale to make the relationship a higher priority to the supplier. I think those supply and quality agreements give the supplier an opportunity to provide us input or tell us what they think it will take for us to realize that priority relationship, which we understand is critical to our on-going success.

GM: Communication is really central to this – between suppliers, planners and buyers. If you can communicate early and often regarding your forecast needs to your suppliers, buyers and planners, then they can have early information about demand peaks, lulls, and can work together to keep that continuity of supply.

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Managing our supply chain team here, I'm continually asking them to look at opening up our global supply chain opportunities and to find secondary suppliers. I think we have to be willing to open up our supply chain in a smart fashion so we can make sure our continuity is there but we don't risk quality at the same time.

AH: As well as the emergence of auditing consortia, we're starting to see similar supplier consortiums or shared purchasing agents utilizing this approach to help gain the leverage that these small companies are seeking and also try to smooth out the demand put on suppliers.

Obviously the challenge with that is companies are often pretty reluctant to work too closely together. But eventually I think economic forces will be strong enough it will overcome that seclusion mind-set.

Q The pace at which CGTx developers are moving through development is quite intense – how can suppliers build in flexibility to allow scale-up of manufacturing capability and raw material supply within these short timeframes?

AH: Our relationship with Roche is a great example to speak to the necessary flexibility in the supplier-manufacturer relationship. We were purchasing enzyme in, what I would consider to be bulk form from Roche that was not really in an efficient packaging for our production process. We were looking for something that was more single use.

In working with Roche CustomBiotech, they were able to identify other customers with similar requests, and thus were able to initiate a project to accommodate our needs. Roche covered the project costs to launch this new packaging form to create a new catalogue item. As a result, we've seen increases in the efficiency of our process and we've run into a far fewer issues with trying to manage the stability of the reconstituted enzyme.

That individual example is a great example of how the manufacturer and the supplier can work together and even identify solutions with other customers that can really fulfil industry needs, especially in the cell and gene manufacturing industry. A small customer request coming from an emerging market or company like us, could often turn into your next catalogue offering for broader industry support in future.

GM: I don't know if it's an option for suppliers, it maybe is in both a short term and long term play, but if the market continues to grow at the pace of development to commercialization, there may be segments of their business that they dedicate to rapid

manufacturing or prototyping for early clinical stage research-only raw materials like Roche CustomBiotech's approach to support customization, including lower pack sizes. Where the turnaround can meet expectations in smaller batch manufacturing.

If there's that ability to dedicate those smaller niche areas of development or small satellite manufacturing for rapid turnaround, it could dramatically help reduce cycle times in scale up.

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