CREATING A LOGISTICS STRATEGY FOR COMMERCIALIZATION

SPOTLIGHT

INTERVIEW

Opportunities and Challenges for Decentralizing Cell and Gene Therapy Manufacturing

STEVE GOODMAN

Steve Goodman is the head of drug product manufacturing at bluebird bio, where he oversees production of cellular therapies across their portfolio of products and is accountable for the long-term technology strategy to expand access of these treatments to serve global patient requirements. Before joining bluebird in January 2018, Steve was at GSK where he held a number of roles across research, development, manufacturing and supply chain. These included roles leading cross-functional teams in the design, development and transfer of clinical and commercial chemical manufacturing processes; designing and implementing supply chain strategies for ex vivo and in vivo gene-modified cell therapies as well as for small molecule medicines; and managing manufacturing operations to ensure the safe and efficient supply of important commercial respiratory products to global patients. Most recently he served as Director of Manufacturing and Strategy for the Cell and Gene Therapy unit where he was responsible for the external manufacturing of the entire value chain to support GSK's ex vivo cellular therapies, and for defining and executing the vector manufacturing strategy. Steve joined GSK in 2002 following a PhD and post-doctoral fellowship in organic synthetic chemistry at Harvard University.

Q How do we define the spectrum of options around decentralized manufacturing?

SG: Understanding it as a spectrum is the key starting point. It is widely recognised that the traditional pharma model for manufacturing is not necessarily applicable when dealing with highly personalized

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treatments. In the case of *ex vivo* autologous treatments, for instance, the product stems directly from the patient and therefore we need a paradigm shift in how we think about these novel treatments. When thinking about manufacturing models for ATMPs, I split these into two main categories with various 'flavours' in between.

At one extreme is the fully centralized model, where a single manufacturing facility can provide the medicines or treatments to a global patient population. This of course is often what happens in a commercial biologics or small molecule scenario which typically benefit from significant economies of scale. This is feasible in large measure because the supply chain logistics are not overly complicated.

Obviously, in a situation pertaining to patient material which must be transported back and forth, these different logistics requirements pose a varying set of issues. Thus, on the furthest extreme is the fully decentralized model or 'bedside' model, where the operations are not only in specific hospitals, but in time could ideally be performed in very close proximity to the patient, allowing the patient to be even more intimately involved with the manufacturing process. Here the process is not necessarily run in a cleanroom environment. This is perhaps both the greatest opportunity in the field and presently the furthest from reality.

Then there are the two models in between the fully centralized and the bedside models. Closest to centralized model is expanding more regionally, which you can subdivide according to whether you are looking at it on a continental or a national basis, for example.

And as you keep taking that model to smaller and smaller regions, you might be getting to the hospital setting but involving specific specialist treatment centres that already have their own GMP manufacturing environment. Importantly, from a cleanroom perspective, this means many of the control systems normally associated with centralized manufacturing are mostly still in place.

Within this spectrum of models exist different aspects of viability, both now and in the future, and obviously, many different associated benefits and challenges.

Q What do you see as the key benefits that could make decentralized manufacturing attractive to companies developing cell and gene therapies?

SG: The fundamental objectives around decentralized and centralized manufacture are the same: for instance, reducing variability; reducing the manual aspects of manufacturing as it currently stands; improving sterility controls (building that into the

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process itself to control sterility upstream). All of that is meant to improve quality, reduce the number of personnel associated with the process, reduce reliance on cleanroom environments and so forth. In turn these improvements will reduce costs and broaden access. So it is important firstly to recognise that the majority of improvements we need to see are the same regardless of where manufacturing is located.

The benefits that I believe are very specific to decentralized manufacturing are first and foremost around taking away geographic and temporal separation between the product and the patient—and this proximity to the patient really does drive certain specific improvements.

Chief among them is the potential improvement in viability of the product itself. The less you must manipulate the incoming material—apheresis, bone marrow, whatever it is—the better. For instance, refrigerating or cryopreserving that material and shipping it has a significant and generally detrimental impact on living cells. Likewise, on the backend, the same process of cryopreserving and then shipping it to another location for infusion or treatment—all these operations and manipulations to a patient's cells reduce their viability and potency.

Another benefit to decentralisation relates to the speed of treatment. Eliminating the requirement to ship the material to another location and then return the final product back to the point of care translates to days or possibly weeks of treatment time saved, which clearly carries the potential to positively impact patient outcomes.

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A third benefit is around overall risk. The closer you get to a centralized model, the greater the dependency and therefore the risk placed on a single facility in terms of operations. You can look at that risk through various lenses—overall dependency on cold chain logistics solutions, different issues associated with natural disasters, quality issues at an individual manufacturing facility, etc—whereas if you establish

decentralized local manufacturing while fostering a synergistic relationship between a network of partners, then you have the option of going to other regional or localised manufacturing if one facility has a bottleneck.

Another key benefit of decentralising is enhancing the connection between these personalized medicines with personalisation of the manufacturing component. The patient becomes more connected with the process used to make their cells viable for their treatment, so they form an even tighter connection to their own product.

Finally, in a socio-economic sense, there is the important consideration of localising jobs and opportunities, and of what decentralisation may means from reimbursement and patient access perspectives. It may help open pathways to different patient populations that would otherwise experience greater challenges when taken out of their locale, for example. I see this as a means of opening up specific opportunities and doors to the treatment paradigm.

Q How do companies determine and weigh up these different facets in terms of business and patient drivers to determine what their optimal approach could be?

SG: This is an extremely complicated question! There's an approach that looks at the traditional return on investment, or NPV analysis—putting this fully into facts and figures—but I think that will only take us so far. The question I would try to ask is 'how is the patient best served by the decision and strategy?' There may not be one clear answer which applies to every situation—you can make the argument on either side, from decentralisation to centralisation, of how it truly benefits the patient in the long run.

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One way that companies and innovators in the space should be trying to address this question is to model out different scenarios and see how they play out—building supply chain models around the various options and assessing the costs and benefits in terms of risk, redundancy and other measures. The most important tangible elements are broken out in terms of quality, time, speed, cost and effort.

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From my perspective, there is a lot more work in the near-term in getting these treatments to a fully decentralized model. It's certainly the one that requires the most time and effort in planning and in overcoming many of the challenges. But the pay-out at the end must be factored in, too. That's where those trade-offs come in.

Of course, on one level, it is about how much would a company wants to invest and when. As we get more evidence that these treatments are safe and efficacious, they become de-risked as a modality. And there will be more interest in making these investments up-front, knowing many of these fundamental concerns around making these products commercially viable have been reduced. Those investments will come earlier, as these treatments transition from traditional, in-hospital academic and physician-led activities to being thought of more as global products. The question then becomes, 'how does manufacturing of these treatments then get back in the hands of the physicians to enable a global treatment at a localised level?'

One key consideration which must be front and centre is assurance of quality: as you get more decentralized, there's a quality aspect that will improve around the product itself, as I said, but the quality management becomes much more complicated. You need to weigh that up against how each model improves access and reduces risk.

As long as companies are doing their analyses with these aspects and more in mind, they ultimately will arrive at the decisions that make the most sense for their patients.

Q Which of these do you see as the most critical—or again, is it a case of 'product-by-product' to determine which model you should adopt as a company?

SG: Fundamentally the underlying issue is that because these are personalized treatments, there's no scale up option—it's all about scaling out. And at a functional level, everything we produce must be done 'identically'—and that's not just around how the process is run, because we often emphasize the cell processing component and while critical, that's just one piece of the puzzle. There's also the testing, the release, the data, the logistics…. All of these have to show that what's manufactured

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at location 'A' is the exact same as at location 'B' (obviously with patient variability factored in).

When I look at these multiple areas, I think the one that is most challenging is going to be quality systems. Operating in a single manufacturing facility is something pharmaceutical manufacturers have decades of experience doing. While there are obviously quality challenges with this model, the process of implementing a quality system and functions, of looking at improvements and maintaining compliance, is something with which the industry has a lot of experience.

Although many companies have experience in harmonising global standards across a handful of sites, with broad decentralisation there is the need for global harmonisation and standardisation around a wide network of sites. As you multiply things out, that model may becomes less about standards and more about a certain level of automation. We talk about automation and integration from a development stand point—how do you automate a process, close it up, etc.—those are challenges I think the industry is really facing head on and trying to address directly. But I don't think we're holistically looking at what it really means where quality systems are controlled at a global level but implemented and maintained at a localised level. In other words, the quality system at location A is functionally the same as at location B; and whenever there's a quality event at location B, there's a quality improvement at location B—but how does this then get communicated and implemented at every location worldwide and the quality system improved as a whole?

I think this significant challenge is one where data plays a key role: automating the data flow out from the local setting so that we're not looking at what's going on at just one location in isolation, but from all locations percolating up to allow us to look at the network as a whole. Alongside that, we cannot just be looking at the outputs from a specific manufacturing outlet, but as importantly how we're maintaining global quality and compliance standards.

Another aspect that might get overlooked in terms of complexity is standardisation of training. It falls back onto the quality management systems, but the idea that personnel should all be trained to the same level and operating the same process in an identical way is really an immense challenge. Decentralisation creates a situation where the knowledge is incredibly profuse, instead of a knowledge base that traditionally is within, say, a handful of individuals. You now must have a certain level of expertise at every level as well as a system whereby the core centralized knowledge is easily obtained. So again, it gets back to information flow and knowledge flow that is critical for success.

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On the supply chain side, decentralising manufacturing certainly reduces the complexity of moving patient-derived material. But it conversely adds more complexity around all the other materials involved in the manufacturing process—media, consumables, reagents and so forth. This should be considered and likely controlled on the global level to ensure standardisation at a local level. In addition to globalised supply chains of consumables and reagents, it is critical to consider the appropriate level of redundancy and secondary sourcing, and at how robust your supply chain is for critical reagents and materials so they can be maintained at the globalised level to ensure harmonisation at each manufacturing location.

I must say, I think about Starbucks a lot when I think about decentralisation! They have 27,000 locations around the world, but when you go and order a latte from Starbucks, you expect it to be the same in London as it is in Boston—and generally, it is. That's because of what they've implemented. I expect they have their versions of 'SOPs' so the baristas all know how to make a latte, and the equipment to make a latte on one continent is about the same as on another. There are processes they run, training they implement… At a very basic level, that's the kind of mode of thinking we need to adopt for a cell and gene therapy product.

What's interesting from a commodity perspective is that there is no such thing as a 'hot' supply chain, right? Nobody would consider trying to make coffee in one location and ship it hot. But for various reasons we have decided to do things involving cold storage and transport and must therefore try to overcome the problems associated with such a supply chain.

Q You've mentioned issues of quality control, standardisation and training as key challenges. Do you see those as the biggest barriers to being able to achieve point of care decentralization for cell and gene therapies?

SG: Those are certainly enormous barriers. On the subject of quality control, one of the key challenges that the industry has to face is how we build a body of knowledge around our products to enable simplifying our release process. And that is certainly a challenge when we're dealing with products with very small patient populations. Building a body of evidence that transcends one individual product in terms of overall safety

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It is fairly well recognised that the testing and release process for cell and gene therapies represents the lion's share of the resource burden and is the most significant bottleneck. It's certainly true now and it will only become exacerbated over time as these products become more widely implemented. Manufacturers are looking at simplifying the release process with the ultimate goal of identifying the key testing requirements and reducing overall testing burden. But manufacturers will need to simplify not only the testing requirements themselves, but also look at how testing is actually conducted so that we become much more robust and automated—that will be critical.

One key thing that will also need to be addressed when we go to localised manufacturing, especially in Europe, is the release process specifically what will be the requirement around the QP? I think the idea of having a local QP at every bedside manufacturing site would pose a significant challenge! Are there other mechanisms—for instance, to have a regional QP that is releasing across multiple localised facilities? Or perhaps some automated release process is developed and accepted whereby QP involvement is on an exception basis.

The burden of proof obviously sits with innovators in the space, but it is an area where regulators are particularly keen to engage. As innovators build their body of evidence, we can share that and work with regulators on what the accepted requirements should be.

Q And so how is the field actively seeking to address some of these challenges? And have you got any examples of how we're making headway in doing so?

SG: Unfortunately, we don't have strong examples in cell and gene therapy yet. There's clear evidence that efforts to enable decentralized or point of care manufacturing are progressing—this is certainly true around automating, integrating, and closing systems from the cell processing perspective, as well as the QC testing process. But I've seen very few visible examples of innovators approaching the decentralisation challenge holistically.

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Many are going it alone, so to speak: not only in the sense of focussing on specific aspects of the problem versus the entirety of the issue, but also in the sense of doing it in specific collaborations or on specific projects. And while there's certainly a large amount of visibility throughout the industry on this problem, both in published literature and ongoing discussion in forums, we are not necessarily pulling together to come up with a comprehensive solution.

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It is important to recognize that as innovators work to develop bespoke approaches toward decentralising their own manufacturing programs, the more diffuse the collection of solutions becomes and ultimately the less viable truly decentralized manufacturing will be (i.e., at the patient's bedside). It will become extremely challenging to embed multiple approaches at the local level if each innovator tries to implement their own solution. Moving towards global standards on what components of decentralisation looks like will make it easier for localised manufacturers to produce different treatments and therapeutics that may be coming from difference sources without having their own warehouse of manufacturing equipment, and without having to manage myriad testing methods.

And all these equipment and systems must 'talk' to each other. It's not just one operator that has to carry a product from the washing device to the labelling and cell selection device—those systems themselves ust communicate with one another. Not only do they need to communicate, the data then needs to flow to the analytics and back again. It is a vision of a complete and connected manufacturing ecosystem: linking equipment and data and testing to seamlessly create an executed documentation source that automatically releases products. This entire ecosystem of documentation and process data all has to flow together, which is perhaps something best addressed by the industry as a whole.

There's a real opportunity to work on parts of this problem through industry consortia or research groups. I recognise some aspects of this may be seen as generating competitive advantage in terms of providing the best treatments for patients under certain regimes, but I think we should be looking at where a consolidated voice will help drive this strategy forward

for the industry as a whole. A potential starting point is around alignment with regulatory expectations: what are going to be compendial testing methods or testing expectations? What will be the principles of overall testing and release requirements? As I said, this will be driven by data, but there may be a way to look at this in a fresh way as we start to work through some of these problems. We won't necessarily have all the answers, but there's been a clear indication from health authorities that they're open to these discussions.

Those changes that will take the most time are the ones we need to start early—such as where regulations may need to change to open up those doors and enable decentralized manufacturing. There may not really be a competitive advantage for one company to have this access and others to not have it. It will benefit everyone.

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