EXPERT ROUNDTABLE

Evolving autologous and allogeneic cell therapy manufacturing models in the commercial setting

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Roche

Q What is your organization's current manufacturing model, and how might it change as you get closer to commercialization?

GR: Century Therapeutics is focused on allogeneic therapies, and our model is to begin with induced pluripotent stem cell (iPSC) lines derived from peripheral blood mononuclear cells, or other sources.

These iPSCS can be modified using extensive genetic modifications. We can choose single-cell clones from these modified cell lines, and from there create master banks and whichever immune effector cells we require, such as T cells or NK cells. This allows us to make large amounts of cells per batch, thereby reducing the cost of goods, increasing the capacity per batch, and allowing us to make an off-the-shelf cell therapy that can be cryopreserved and shipped as needed.

EG: At Celyad Oncology we currently have a centralized model to manufacture allogenic and autologous CAR Ts. In fact, we have had our own manufacturing capability based in Belgium for more than 10 years, which has already supported us up to a Phase 3 trial where we were developing a cell therapy for cardio applications. I'm personally convinced that this brought a lot of knowledge to the organization and allowed us to quickly adapt in response to our clinical results.

Of course, the choice of the manufacturing model towards commercialization will largely depend on the type of therapy, and would be quite different for autologous or allogeneic therapies. A decentralized model could make sense for autologous, but probably less so for allogeneic therapies.

Nevertheless, multiplying manufacturing sites is key to moving towards commercialization, at least for increasing the production capacity. Having production on different continents can also ease scheduling and aid in delivering the product around the world.

The current pandemic shows how quickly we can be affected by what is happening on other continents. For example, apheresis supplies have been impacted by the COVID-19 pandemic, which demonstrates how regional measures on the US side have resulted in global repercussions. We have had great support from our own partners in securing supply and mitigating impact, but this situation demonstrates that having multiple collection sites for healthy donor apheresis in the context of allogeneic therapies, perhaps more locally for some markets, may be important in order to resist such crises in the future.

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DA: At bluebird bio we are focusing on autologous *ex vivo* cell therapies that are based off of lentiviral vector technology. Our manufacturing model is focused on centralized manufacturing in different regions. Therefore we are investing in a lot of contract partners to be able to manufacture these products in these different locations. We are also investing in internal vector

manufacturing, and we've been doing that for the last couple of years.

The biggest thing about going into commercialization, which is something we are on the threshold of, is that the regional and centralized manufacturing model requires a very robust control over the supply chain. The proverbial needle-to-needle time matters a lot. The manufacturing process, which as we all know is not hugely mature at these stages, is actually part of the patient experience. With the integration of the manufacturing model and the supply chain team, communication is really important to also integrate it with the commercial teams. This is fairly unique in the biotechnology field, and it's a really exciting part of what we're trying to do at Bluebird.

JL: Adaptimmune also has three autologous products in the clinic. We have a mix of internal and external manufacturing, both for vector and T-cell products.

Manufacturing is primarily internal for T-cells. We've learned that in the autologous space, as Derek mentioned, the vein-to-vein, which he referred to as needle-to-needle, time and turnaround time are important, as is flexibility. Having our own capability to manage all the aspects of needle-to-needle time has been valuable.

Additionally, as Emilie mentioned, the learnings you take at this early stage of the process internally are important. We're focused on an internal network, and this is the same for vector production. While we outsourced most of our vector supply initially, given the constraints in the market at the time. In addition, new vector production is a process that takes many months. As of now, though, we have been able to build our own in-house vector production.

As we move towards commercialization there is the obvious expansion of capacity, which we do intend to continue to do with internal resources. There's also the question of supply redundancy, in particular with autologous therapies. We are for all intents and purposes sole-sourced on one manufacturing site, and something that COVID can teach you is if you have something go through your facility, you can shut down trials and shut down commercial immediately. The idea of having redundancy in manufacturing for autologous cell production, which serves somewhat the same purpose as finished inventory in the allogeneic world, is something we're thinking about as we go towards commercialization.

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This can be prohibitively expensive when you're in early phase trials, but it quickly becomes something to consider.

Q With regards to centralized versus distributed manufacturing models for cellular immunotherapies, what do you see as the chief barriers to commercial manufacturing success currently confronting each model?

DA: We all wrestle with this all the time. Cellular immunotherapies encompass a broad range of manufacturing technologies, modalities and distribution models. It's a broad term.

If we look at the area bluebird bio is focused on, the centralized manufacturing of autologous therapies, we have a really big supply chain challenge in moving either cryopreserved cells or fresh cells with tight time limits, in a one batch at a time or one patient at a time mode. In addition to being very complex, it is also very expensive to do.

Centralized manufacturing allows you to have a measure of control over your manufacturing process, and to have a centralized area for all of the traditional biotechnology and pharmaceutical quality systems and manufacturing approaches that you can use. But the shipping and logistics of moving cells around, and making sure you can line up the scheduling with the patient experience, is a unique challenge with centralized manufacturing of autologous cells.

To me, decentralized manufacturing starts to blur the line between being an actual biopharmaceutical manufacturer or a provider of a device or technique in support of a clinical practice. It starts to become a little bit confusing, at least to my very traditional biomanufacturing eyes. How does decentralizing the manufacturing and having many different manufacturing sites look in terms of control of the manufacturing process? Is it even a manufacturing process?

You may be able to reduce the complexity of the shipping of cells, and certainly be much more responsive to patient needs for scheduling. This is really important because all of this is surrounding the needs of the patient, and speed is crucial, therefore the decentralized model has a lot of compelling features. For any Star Trek fans, my vision is to ultimately have a Star Trek-style replicator in the lab so that you can just dial in the cells you want, they appear immediately, and you can give them to a patient right there on the bedside. That would be wonderful. But in the meantime, we have other limitations we have to work around that present some interesting challenges.

GR: I'd like to expand on the challenges Derek mentioned around the decentralized model, and particularly the question of whether it's manufacturing,

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device, or technique. In my opinion as long as it's a manufacturing process, I don't see how the decentralized model can work.

It's a big challenge to transfer these processes which are fairly complex, and also subject to patient-to-patient variability from starting material. That challenge is hard enough when you have a site in each region, but in cases where you have hundreds of sites I don't know how you can do that and have a robust process and the right quality controls in place. Even though the centralized model is a batch-by-batch, expensive proposition, you have some economies of scale. All of the ordering, quality control and quality assurance is done in one place. You lose all of that economy of scale in the decentralized model.

Some may say that decentralized manufacturing is cheaper, and Derek is right that it can be cheaper because of the lack of shipping need, but it's so much more expensive in other ways, and much more risky from a quality standpoint.

If you think about autologous CAR T as it is today, cells are isolated, activated, transduced, grown – there are so many steps there that make it a manufacturing process. It's not simple. Until it changes and becomes much simpler, it has to be done in a centralized model, otherwise you really risk both the quality of the product and the safety of patients.

JL: One element to highlight is cryopreservation. Most autologous companies have cryopreservation on the apheresis side for the starting material, as well as the final product. Doing that regionally or at the clinical site, depending on the complexity, takes away at least some of the time pressure – particularly for the manufacturing side.

It doesn't alleviate the vein-to-vein time which is still very important, particularly in where we are with solid tumors. Turnaround time remains important, but these are operational issues that over time we will solve. We will figure out how to make that happen within a two to three week window for solid tumors and achieve that vein-to-vein time.

At Adaptimmune we ship fresh apheresis centrally to our sites, and we have a cryopreservation CDMO in Europe for European sites. I can see us ultimately moving that towards the clinic. But the rest of the manufacturing process is too complex. The economies of scale are such that the cost to decentralize at this stage will be much, much greater than being centralized.

EF: I would add that one advantage of decentralized manufacture is due to the fact that there's a lot of market dynamics going on right now in the cell therapy space. You know with a centralized model that you have a higher cost of operation, a large flagship, and very specialized personnel that aren't able to adapt very easily. This makes them less flexible to addressing market changes.

It takes years to duplicate a large facility, so it becomes a multiyear project to expand. Decentralizing and having multiple sites with different specializations can allow you to identify an increase in market demand and add a contract, or a new area that's attractive, and add a different expertise. These advantages support a small degree of decentralization.

EG: From my perspective, the key would be the development of allogenic therapies. This would allow the field to get rid of many of the logistic constraints without putting additional pressure on the hospitals. Off-the-shelf allogeneic products utilizing

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cryopreservation would have a much closer manufacturing scenario to that of classical drugs and could be accessible to many more patients.

Q In your view, where on the centralized/decentralized spectrum is the 'sweet spot' for commercial scale production of patient specific advanced therapies?

JL: As discussed above, the move to decentralized cryopreservation with centralized manufacturing is, in my opinion, the next evolution.

Getting out of the centers of excellence and into the community is another element of the decentralized model. It can make sense to be in these centers of excellence, which are huge sites that have the capabilities to manage these kind of therapies. To Evonne's point, in order to get out into the community without having access to those centers, you're going to need some sort of support for them and potentially do the cryopreservation closer to the treatment center, or the apheresis for that matter. This is the mix we're beginning to see, at least for the near-term for commercial applications.

DA: Right now, centralized manufacturing is certainly the default for patient-specific therapies, essentially due to inertia. This is viewed as simply how we do things in manufacturing biotherapeutics at the moment, and we have a way of thinking and an organizational design already in place.

I think the point that Greg made is that the quality control and quality assurance aspects, i.e. having one place to assure we can make a quality product, are a huge need right now. Especially because we're finding that regulatory authorities are trying to figure this out just like the rest of us – how do you look at quality control, how do you look at process control, and how do you determine what is a good product? They're trying to catch up just as we are, and they're looking at it through the lens of somewhat more traditional manufacturing processes for drugs. They're applying many of the same guidances and many of the same principles. This makes it a little bit harder if you're thinking about decentralized manufacturing, even for patient-specific products.

The other challenge for patient-specific therapies in a more decentralized sense, or even in the centralized sense, is in how these therapies have been developed. They've been developed in collaboration with some very motivated and brilliant clinical physicians, at some great hospitals around the world. This includes the folks who believe that they have a big stake in what this product really means for their patients.

As you get towards commercialization, there's this interesting dynamic of how to communicate with the treating physicians, and what is a good product. When you're using centralized manufacturing to produce your product and delivering it very much like a traditional therapy, there's a barrier to overcome in how much information the

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physicians actually want to know about the product. This is very different than if they simply had a bottle of bills in a pharmacy that they offered.

Right now are just scratching the surface of how we're all going to communicate on this, because it's really important that the treating physicians understand what's best for their patients. It's very patient specific, and the manufacturing process is part of all that. I'm fascinated about the interactions we're having.

GR: For decentralized manufacturing to have a place in the current autologous world, there's going to have to be two major changes. One is that there needs to be an incredible simplification of the manufacturing process. I know there are companies looking at building systems that in some ways would simplify that; you press a button or two and have a product at the end.

I think you need more than that, as the processes are still too complex. One approach is to try to find the right cells up front, and isolate them early, so you don't have to have as much *ex vivo* expansion. This would provide a more efficacious product with lower doses, thereby shortening and also simplifying the process. If that can be done, with a device that is foolproof so that that every time you run it you get the same product when using the same conditions, or at least some feedback control to give you similar conditions but the same product, it could work.

The bigger barrier is patient-to-patient variability. I don't think it's insurmountable, and as we understand more about what patient attributes lead to different process outcomes, and ultimately product attributes, we can control that and characterize the patient up front. Then we can put them in a general category so that they can go into Program A, B or C, and get the same product every time. But that's an absolutely huge proposition that's going to be very hard to meet.

Q How important will in-house facilities be for cell and gene therapy manufacturers moving forward? And what would you consider the most critical considerations for anyone considering establishing a new in-house facility today?

DA: The current environment we see with constrained capacity and very complicated manufacturing processes, and the speed with which we need to be able to both provide therapies and react to changes, is a very big driver to having internal manufacturing capacity if you don't have a really tight partnership with a contractor partner. It's a question of the needs of your business and how you can overcome that. Sometimes you're going to have to spend a lot of money either way: either you spend a lot of money on working with a contract partner to secure capacity, or you spend money up front to build out your own internal manufacturing. CMOs are building as fast as they can to try to keep up with demand, but right now the

capacity is simply lagging behind the demand we have.

One of our key considerations at bluebird as we commercialize our therapies and learn about supplying products at a commercial scale, is that when you're building internal manufacturing, especially for smaller and earlier phase biotechnology companies, you need to understand what are you building that facility for. Are you aiming for that facility to simply support clinical proof of concept? Or are you going to build it for commercial scale? Because that means something completely different, and I think that most traditional biotechnology companies wildly underestimate the commercial complexities, the amount of focus you need, and the amount of capital that you need to be able to do it at a commercial scale.

EG: I agree – as mentioned previously, I'm convinced that having direct control on at least part of your manufacturing gives you an advantage. It gives you flexibility in your scheduling, but also to quickly adapt to changes. It gives you knowledge, by facilitating your discussion between your R&D and production teams, supporting continuous improvement of your process. And it also gives you a real control of your product quality. Clearly this was Ceylad's choice to start with, and it was a real advantage for the fast transition to the clinic, and swift increasing of our production pipeline.

Besides the obvious considerations when you establish your own facility – such as where to put it in proximity to airports, or if there is a risk of Mother Nature in certain areas and so on – I would say that one of the key points is the ability to recruit the real experts in the field. In some areas these might be easy to find, but you might need to fight with competitors. Being able to pay for the cost of recruitment is also a factor to consider when establishing your own facility.

GR: Emilie nicely summed up the advantages of in-house manufacture for flexibility, control, the learnings you gain by seeing it yourself, and the co-efforts between development, manufacturing and research. It lets you solve problems quickly, make changes, and to have a vision of where you're going and to stick to it.

However, it's also important to have the flexibility to have a CDMO. You may need to flex sometimes and plan for more capacity, especially in the autologous space. It's good to have that option as well. And for a small company like Century that is starting out, it depends on your resources and where you want to allocate them. It is expensive to build in-house, and it takes time and certain expertise. If you don't have all of

those things, sometimes you may have to start with a CDMO until you do, and that's fine. If it is a strong relationship and you feel comfortable you can stick with it. But ultimately, for the reasons we discussed, having your own in-house manufacturing is something everyone should really strive towards.

EF: Roche CustomBiotech continues to see more and more companies moving towards in-house facilities. We've seen this being done to build up extensive QC capabilities to have greater control on quality, to have close-to-real-time data available to further understand their manufacturing process, and also to reduce product release timelines and cost.

JL: I see a bit of a misalignment between early stage biotechnology companies, cell therapy and the CDMO model. For early stage biotechnology companies in this space, every patient is a critical piece of data, and frankly a critical piece of evaluation for the company. The ability to flex and respond to patient needs is crucial. This can take a little bit more risk, and whether it's looking at the logistics side or changing the process, there's an incentive for the companies to learn everything they can.

Whereas for the CDMO, it's a margin on one particular manufacturing run, and you're one client amongst a huge order book. For most small companies at an early phase, every patient is the future of the company. I could see a CMDO becoming part of our network in the later stages, when things are a bit more established.

Regarding Derek's point about commercial scale and underestimating those needs, we've spent a couple of years implementing our own manufacturing. We've also made a real investment in IT systems, whether it's the chain of custody, chain of identity, electronic batch records, or electronic lab systems. This is something I would never have done in a prior life in an early stage biotech. Now, it's looking like a smart decision, because it takes years to do this. As an early stage company, if you do have access to the resources, then it makes sense to do these things much earlier than you would at any other biotechnology or pharmaceutical company.

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> - **Emilie Gauthy**

Q How important are CMOs and CROs to manufacturing business models in the future, and do you expect to see the advanced therapies service sector continue to develop in step with the commercializing advanced therapy field?

EF: Even though we're seeing more manufacturers utilize in-house facilities or move towards in-house facilities, I think CMOs and CROs will continue to play a critical role in manufacturing cell and gene therapies in the future. Contract manufacturing capabilities need to continue to increase with

the market growth that we're anticipating, especially as more advanced therapies commercialize.

With market expansion and more commercial successes, my hope is that suppliers, including Roche CustomBiotech, will continue to innovate and provide advanced solutions that will be implemented at CMOs and CROs, and in-house facilities. This will allow for more standardization and advancement.

"Having standardized parts of the process helps everyone, including letting regulators understand us better."

- Derek Adams

EG: As mentioned earlier, at some point in moving towards commercialization you will need to multiply your manufacturing sites, both to increase your production capacity and to de-risk supply failures. When you go for commercialization, the demand for your product will not be completely predictable at the start. Seeing how companies will make use of CDMOs at that stage to deal with fluctuation will be interesting.

CDMOs also play a big role in manufacturing key materials. A classic question is whether you should internalize or outsource manufacturing of vectors, for instance. On the one hand, outsourcing might bring you new knowledge and expertise that would be costly to integrate. You need to create a strong partnership and collaborate with your CDMO to bring their production to the level of your commercial needs. Your partner will need to be ready to work on developing its infrastructure and intensifying its production.

On the other hand, this might become very binding, and you don't want to get stuck in a business position where you don't have alternatives and you rely on your CDMO's production availability. For this reason, keeping some internal production assets remains important.

DA: To build on what Evonne said about driving standardization, I think that's one of the biggest ways that partnerships with contractor manufacturers can help the industry.

A partner of ours at one of our CMOs said, "We want to get good at manufacturing everybody's secret grandma cookie recipe". That is where we are today, but part of what will help the industry and patients in the future is if we start to align on standards for processes that aren't necessary for being competitive. Many of us have been at conferences and heard the history of other biotechnology processes that have coalesced around some standards, such as monoclonal antibodies. Having standardized parts of the process helps everyone, including letting regulators understand us better. Contract manufacturers have a huge part to play in helping lay that groundwork and bringing early phase manufacturing and sponsors into a template that will help the whole industry move forward. We can't underestimate how much we need CDMOs to help us create standards.

GR: The future remains really bright for cell therapies – we've only begun to scratch the surface of how wonderful they can be.

Anybody that knows the autologous CAR T clinical data and commercialization stories of Kymriah® and Yescarta® knows that these therapies truly save lives. There may have been some challenges along the way, but they're just going to get better. As we understand the science more, I believe they can become curative, and will go on to affect many other types of cancer.

Solid tumors are a big challenge, but it's certainly a challenge worth undertaking. I believe we're going to get there, but I don't know

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how fast. For hematological malignancies, the effect of these therapies is going to become greater and greater, and the cost is going to become less as we learn and understand more. That means the demand is going to go up, and that's where CDMOs are going to come in, because I don't know if people can keep up internally. They'll want to, but having that capacity at your disposal will allow you to flex very quickly and meet the increasing demand.

Q How will the manufacturing model evolve with the ongoing emergence of allogeneic therapies, and their progress towards commercialization?

EG: The allogeneic manufacturing model will be quite different from the current design and infrastructure developed for autologous manufacturing. Allogeneic manufacturing will be much closer to classical manufacturing design, with continuous production and no planning based on patient apheresis schedules. Of course, de-risking of allogeneic therapies may still require multiplying manufacturing facilities, and CDMOs will likely play a big part in supporting the increasing demand.

However, new constraints are emerging, and could become real issues, as we aim to treat large indications with allogeneic therapies. The availability of the raw and starting materials comes to mind –the market for some key materials is already tense, so with the emergence of new allogeneic therapies, we may see a huge increase in demand that would put additional pressure on supplies. My fear is that this could become a critical problem if the costs start to rise, as materials are already a big part of the cost of the cell and gene therapies. This could ultimately jeopardize patient access to drugs if the cost becomes prohibitively high.

From a technology perspective, fill and finish technology will become a new constraint with allogeneic therapies. Finally, one point that we sometimes underestimate is the potential issues linked with the storage of a large amount of cryopreserved product. We need to consider who will manage them, and where. Will hospitals be able to provide these storage capacities?

GR: Scale up is a big challenge, as is the expandability of the cells. You want to make large enough batches to make this worthwhile – if it's only marginally better than autologous in terms of the number of doses you can make per batch, it's not going to be cost effective.

Then there is the cryopreservation challenge. Where are these products going to be stored? If they're going to be stored at the hospitals, do the hospitals have the infrastructure to store these, or can we build the infrastructure? If we do, how are we going to maintain and qualify it? Things are going to have to change somehow in order to accommodate that. The alternative is that you ship just in time, which is not quite as bad as an autologous because your product will always be ready, but it's a challenge in itself.

If we can get away from cryopreservation, even just to dry ice shipping, that would change things a lot. We could use minus 80

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freezers, or if you want to be more futuristic than that, perhaps freeze dried cells. That could be a huge game changer.

These challenges are not easy to overcome, but they can be overcome with time.

DA: For the autologous cell field, the allogeneic approach feels like both a threat and an opportunity. The amount of infrastructure the autologous world requires presents a lot of different challenges that allogeneic therapies don't necessarily have to tackle.

How long it will be before allogeneic takes over as the dominating technology is a question everybody has. What we know right now is that the autologous approaches are probably ahead, and most of the data seems to indicate they're doing amazing things for patients. For those of us who have to try to think about and predict the future, the allogeneic world does seem to fit much more with traditional models of making and distributing biopharmaceuticals. It has a lot of compelling features that make us think if we can only get there, we won't have to worry about the complexities of the autologous world. But right now, the autologous world is providing such great clinical benefits that there's still a need to invest in those as well.

GR: In addition to that, the autologous world is not just a little ahead, it's very far ahead. We know it works incredibly well, whereas the allogeneic space is completely unproven.

I predict that allogeneic therapies will eventually get there and will work. But it's a matter of time, and also a matter of cell quality. Not all allogeneic cells will be equal, and not all will work well. We know that not all autologous therapies are equal in the sense that some patients just can't produce cells that are good enough.

That's also why I think this field is still very promising, because as we move these hematological trials into earlier therapies, where patients and their cells are not as beaten up, they're likely going to work even better. For these reasons, there's going to be a place for both for a long time. Allogeneic therapies will work in certain cases for certain products, but autologous therapies are going to continue to work very well.

JL: In my mind there is a race – the operational development of autologous therapy as we get better at the execution of a complex supply chain, versus the developing science of allogeneic therapies.

Greg mentioned the point of earlier line therapies. When you're working on a therapy for a patient in second or third line of treatment who has failed everything, vein-to-vein time is critical. In an earlier line therapy, it may not be as important.

There is also the concept of 'off-the-shelf' autologous therapy: if you're a second line therapy you can collect the material initially, the patient can go on the first line therapy while you manufacture, then you have off-the-shelf autologous product available if that patient progresses.

This presents a business risk, but it has happened serendipitously in some of our trials. We've received a patient's material, made the cells, and then they're not ready for them. Later, they are ready for their cells and within a week they're being treated. This is a powerful mode of operation, although whether or not there's a business model that can support it is something to consider. Operationally, it was pretty exciting to have an investigator call us and ask for the patient's cells and be able to say yes, we have stability data, we have them in the freezer, and we'll send them to you tomorrow.

"as a biomanufacturer ... It's your absolute duty to monitor, measure, and mitigate risk, whenever possible."

- John Lunger

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Q Where do you see the sector's focus fall in terms of cost control moving forward, in both autologous and allogeneic setting?

JL: For material costs, we're getting there. With things like vectors, costs are coming down precipitously as yields get better, and as scale grows. I think vector will ultimately become a lower element event, not to mention that there are other gene transfer technologies which may do away with vector all together in the future.

Another component is the labor that's involved in manufacturing. Automation will help with this, as will different utilization of facilities. However, for larger markets in the autologous space we don't have an inventory to account for varying demand, so instead we have people. We consider it almost like a volunteer fireman position: you have to wait for the cells to come in, and you have to be there when they do. Once you have a higher volume of demand, that becomes a much higher utilization.

In these two areas as we get to more patient indications, costs will come down. Automation will come as we understand our processes better. So in this race between allogeneic and autologous therapies, if you look at the cost element, the gap will continue to close over time.

EF: As a supplier of critical raw materials, we can continue to create structures like master service agreements, or supply agreements, with CMOs or manufacturers to create tiered pricing structures that reduce costs of these materials for manufacturers. Commercialization will increase economies of scale for suppliers, and this will then reduce running costs.

GR: When you think about both allogeneic and autologous therapies and their raw materials we are considering cytokines, growth factors, some of the more expensive reagents, and disposables. Disposables might be tougher to drive down, just because the cost is the cost, but for reagents there could be opportunities to make those cheaper. Providers should be looking at ways to make materials affordable, because market demand is going to go up. This will be a big need in the allogeneic space in particular.

> "Continuing to keep these conversations open in order to enhance partnerships will allow the industry to grow together."
>
> - **Evonne Fearnot**

Q How are regulators influencing both manufacturing and commercial business model decision making? And how does the incorporation of risk-based approaches in much of the recent regulatory guidance play into these decisions?

EF: Both regulators and the addition of the risk-based approaches and newer guidances are driving centralized models, in my opinion. Regulators are interested

in quality and they inspect on quality. Additionally, regulatory compliance costs money to uphold quality and/or remediation. Again, this will influence companies towards choosing a centralized model.

Traditionally regulators will tell you their requirements, you will demonstrate you have met them, and you will be given approval. But with risk-based approaches, the manufacturer has to do lot more work up front to identify their procedures, their risks, and how they are going to control them, and then present that to the regulators. A centralized model makes it easier to create risk assessments and to create procedures to address those, as well as to create and retain records.

Q What are the key elements that every manufacturer needs to consider when approaching commercialization to in order manage risk and cost, and achieve sustainable commercial success?

EG: You should start thinking about what your commercial product manufacturing should look like, and what the easiest route towards commercialization would be, as early on in your product development as possible.

I strongly believe that building first on your in-house manufacturing is key to moving quickly through the initial stages and facilitating swifter implementation of process improvement. However, moving closer to commercialization, you need to ensure you bring the right partners and suppliers along with you.

Another key aspect is to secure raw materials with the right quality, and strong contracts that will ensure supply and avoid unpredictable costs. You need to identify the right alternatives to support fluctuation in your product demands, and address supply risk without impacting your product quality. This is not an easy task when dealing with cell-based products and very complex materials, so I would suggest starting with the most critical supplies using a risk-based approach. This will probably bring you to work with your suppliers to make sure they address your specific needs and support them to intensify their production. Finally, you should keep in mind that the ultimate goal is to secure the availability of your drugs to the patients who require them.

JL: The idea of an infrastructure for growth is important, particularly for personalized therapies, where a thousand patients equals a thousand batches. Invest early in things at scale –that's everything from training systems, electronic batch record systems, bar coding systems, to electronic environmental monitoring. Think of everything that you need for doing thousands of batches. Even in my history in small molecules we didn't do thousands of batches at a time, and we had huge systems. You have to be thinking about the infrastructure that you can scale, because it takes years to get that infrastructure in place.

GR: Invest early on in process characterization and assay characterization. The more you understand about the process and the product attributes, the better a job you can do at scaling up, scaling out, tech transfers, and more. It gives you more strength in the probability of success of these various things.

For assay characterization, make sure you have assays that are reliable early on. If you don't know what you're measuring, then nothing you do really matters.

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DA: To commercialize a therapy remember that you have to approach it with your eyes and your check book wide open. You have to have a lot of humility knowing you're going from amateur to professional status, and there's not a lot of wiggle room there.

There's a lot of speed in the early phases to get clinical data, and then the clinical data look amazing. But when you reach commercialization, there are more barriers that have to be surmounted. The clinical data may be awesome, but you need to be able to address the risks, and this is not something regulators have a sense of humor about.

EF: I would add that we should continue to focus on strong partnerships. I think that this goes beyond just CDMOs and therapeutic manufacturers and includes both regulators and suppliers. Continuing to keep these conversations open in order to enhance partnerships will allow the industry to grow together, and get to where it needs to be.

AUTHORSHIP & CONFLICT OF INTEREST

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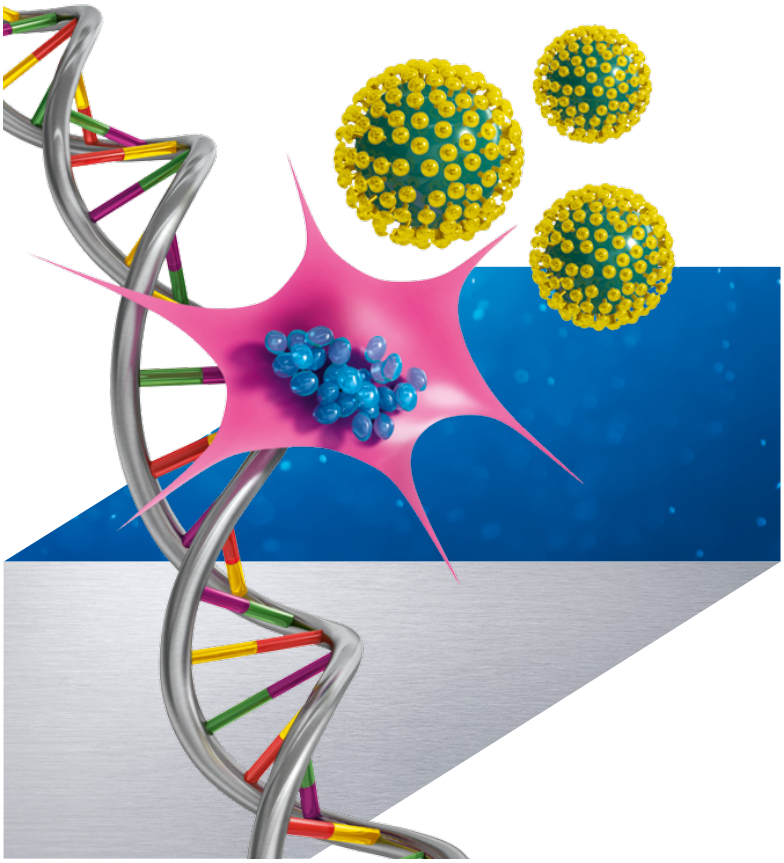
MycoTOOL Mycoplasma Real-Time PCR Kit

Rapid and accurate testing

Mycoplasma are common sources of contamination in biopharmaceutical production, cell therapy, and tissue engineering, with contamination rates reported between 15 and 35% according to recent industry data.*

The Roche MycoTOOL Real-Time PCR Kit makes mycoplasma testing fast, easy and reliable. Avoid the 28-day culture test and obtain results in just a few hours.



Achieve high sensitivity and specificity through improved tests

- ≤10 CFU/ml, meeting regulatory requirements
- No cross reactivity with closely related bacterial species

Rely on an accurate, and robust test procedure

- Measures ~150 culturable and non-culturable mycoplasma species
- Optimized controls and validated reagents (mycoplasma free)

Save time with easy-to-use kit and proven real-time PCR technology

- Automated workflow using automated sample preparation and Real-Time PCR
- <5 hours, including sample preparation**

Characteristics

MycoTOOL Mycoplasma Real-Time PCR Detection Kit	
Sample prep	1 ml cell culture from high throughput or manual sample preparations.
Control concept	Recovery of sample preparation is controlled using an internal control.
Enhanced specificity	~150 mycoplasma species can be detected. The probe format ensures that nonspecific amplicons are **not** detected**.
All reagents included	Supplied and ready-to-use reagents jump start your assay.
High cell densities	Unprocessed bulk of standard cell concentrations (*e.g.*, 5 x 10^6 CFU/ml) processed directly.
High quality	Roche is certified according to ISO 13485. Change notification available upon request.

*Armstrong SE, Mariano JA, Lundin DJ. The scope of mycoplasma contamination within the biopharmaceutical industry. *Biologicals*. 2010 Mar;38(2):211-3. https://www.ncbi.nlm.nih.gov/pubmed/20362237. Date accessed: Jan 11, 2017. **Data on file.

For use in quality control/manufacturing process only.

CUSTOMBIOTECH

The MycoTool Mycoplasma Real-Time PCR Kit is easily combined with the MagNA Pure 96 Automated Sample Preparation System and the LightCycler® 480 Real-Time PCR Instrument for high throughput automated workflows.

Application	Batch testing Flexible sample volume	Evaluation Single samples	Real Time PCR
Instrument	**MagNA Pure 96 Instrument** 	**Manual Extraction** 	**LightCycler® 480 Instrument II (96 well version)** 
Catalog number	06 541 089 001		05 015 278 001 (96 well)
Kit	MagNA Pure 96 DNA and Viral NA Large Volume Kit	QC Sample Preparation Kit	MycoTOOL Mycoplasma Real-Time PCR Kit (160 PCR reactions)
Catalog number	06 374 891 001	08 146 829 001	06 495 605 001

Odering information

Product	Catalog number
MycoTOOL Mycoplasma Real-Time PCR Kit (160 PCR reactions)	06 495 605 001

Additional Quality Control or In-Process Manufacturing Kits	
QC Sample Preparation Kit	08 146 829 001
MycoTOOL Mycoplasma Detection Amplification Kit	05 184 240 001

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