EXPERT ROUNDTABLE

Overcoming Raw Material Challenges in Cell & Gene Therapy Manufacturing

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David has over 28 years of experience in the scientific, clinical and regulatory aspects of cells as therapeutic agents including the isolation, characterization and genetic modification of hematopoietic stem cells and T-cells for clinical applications. He has been instrumental in the creation of six GMP compliant biologics manufacturing facilities and associated quality systems, production and QC testing programs. Under his direction, plasmid DNA, CAR-T-cells, regulatory T-cells, engineered stem cell grafts and gene modified hematopoietic stem cell products have been manufactured and released for use in Phase I/II clinical trials.

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Bernd has a long track record as protein specialist. He joined CellGenix in 2003, and is currently responsible for all GMP and preclinical cytokine products for further manufacturing use, as well as process development for protein production which includes new packaging formats. Following his degree in chemistry he completed his dissertation on the structure, function, folding and assembly of oligomeric proteins. His professional career started at a leading manufacturer of diagnostic autoantibody immunoassays, where he managed the Biotechnology Department and developed it as a corporate service unit for recombinant and conventional human autoantigens and allergens.

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Q What risks should you look at when choosing a material supplier?

TW: You want to look at their physical capacity; what is their ability to produce to your forecast, not only in the short-term and in development, but in five or even ten years in the future? They need to have the technical ability to scale up to what is needed as you move into clinical and commercial applications.

You also need to have an understanding of financial risk, and of whether a supplier is financially healthy. Geographic risks must be considered too – are they built on the side of a volcano? Probably not, but are they in a location that may be subject to earthquake or tsunami issues?

And then there is political risk; whether there a chance the supplier may be subject to embargoes or increased tariffs. We all know tariffs have been up and down over the last two or three years, so understanding that sort of political risk is also key.

BL: The first risk I would like to mention is your sole source suppliers with single source materials. You should have a second source available whenever possible. But of course, typically this is not the case for customized products.

Next, it is good advice to think ahead in terms of quality. The quality of a material in use may be sufficient for early clinical trials, but you need to think ahead to the quality needs for a licensed medical product, and if your supplier is prepared for that.

Thirdly, think about supply security, and think about your needs a few years ahead. My recommendation would be to exchange rolling forecasts with your supplier on a regular basis.

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- **Bernd Leistler**

Q What information is needed to understand the risks related to supply, demand, and material supplier capacities?

DD: First you need to establish the manufacturer's production requirements. In order to assess risk, you need to know what you're asking of the supplier; in terms of volumes, cadence of delivery, and cadence of provision, as well as your raw materials specification – I think a lot of people underestimate the value of the raw material specification. For example, a supplier may say that they can give you 95% purity in a material, and that's okay for your purpose, unless the other 5% will interfere with your product.

Really understanding the critical quality attributes of your material, and the need for that material upfront, is going to be the basis for what we subsequently do, which is perform the equivalent of a failure mode analysis. We look at all the possible ways things can fail – on my list of considerations I have

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the size of the organization that's supplying, their financial history support, whether they are a stable company, and the turnover rate of employees too. If every time you call for a reagent there's someone new on the phone, it causes concern about the continuity of service.

Regarding capacity, a big issue is if you take a small company that makes an esoteric reagent, and they can supply you with 500 micrograms, and all of a sudden you want to move to 100 x scale, they may or may not have that capacity. You need to have an understanding of their ability to scale. And if they can scale, can they make the same product at scale? Oftentimes when you scale up a product the attributes of that product change.

These are all things you need to understand about the supply and demand of materials. Another way to look at the quality of the history of the materials to understand where they've had materials out of specifications. How often do they make a lot that doesn't meet criteria? If they quote a capacity but 30% of those lots fail, it impacts that capacity.

TW: This may be a smaller point but when you're talking with vendors, or talking internally, I think it's very important to use a common language for capacity, whether it's batches, milliliters, micrograms, and so on. This allows you to better compare and contrast both vendors, and your entire network situation, when you use common language.

BL: I would recommend asking about the production capacity, and whether stock levels are prepared for future demands while maintaining a high level of quality.

Next, I would ask about production lead times. Combining these, I would recommend exchanging regular rolling forecasts of both demand and capacity, in order to speak the same language as far as quality standards, in order to be prepared well in advance.

DD: A consideration we haven't brought up is that if your supplier is a sole source provider, meaning they are the only ones that manufacture an esoteric or custom reagent, it adds

"if your supplier is a sole source provider, meaning they are the only ones that manufacture an esoteric or custom reagent, it adds significantly to your risk profile."

- **David DiGuisto**

significantly to your risk profile and the considerations become different. In these cases you do not have the option of identifying backup vendors. This comes into play more often than you might think, and it's a major factor in risk assessment.

Q What do you think is the best approach to contingency planning in situations where there is a single supplier of a critical raw material – and how would you manage unique situations, such as the ongoing pandemic?

DD: The most important approach to contingency planning is to review the performance of a vendor, and then have a plan for what happens if that vendor goes away. What is the impact?

You can't control the vendor being there and also being able to meet capacity, but you can have a backup plan for your process – even if it's a challenging backup plan.

I've heard people having back up plans up to and including the purchase of the company, or an arrangement with the company that if they go out of business, the product line becomes the property of the client. That way, if they're unable to manage a business but they have a production technology you require, you can inherit the production technology. That's one way you can deal with a sole source provider – of course, not everyone will agree to it. But if they're small and esoteric, they may not be around in 3 to 5 years.

TW: Absolutely – especially for single or sole source materials, having a backup plan written into your contract is key. Speaking specifically to the situation today with COVID-19, we use a lot of CDMOs to manufacture our products, and we have some internal manufacturing. That presents a special challenge because we rely on the CDMOs to manage their inventory and understand risk. But as the IP holders, the company that is delivering these lifesaving therapies for patients, we have to be stewards of our own supply chain. Knowing your biller material, even if it's through a CDMO, is critical, and knowing where there may be risk is critical.

That means diving down into your biller materials: knowing of course what materials are there, but also going two or three steps further and being aware of what is being sourced from potential hotspots. That's very difficult, although there are some software solutions that can help.

BL: I consider contracts such as supply agreements and quality agreements to be very important elements. This can include stock levels and

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supply schemes, and on top of that as part of our mitigation plan and supply security plan we have a stock of product intermediate at each processing step to shorten the lead time, apart from what we have agreed with customers in terms of finished product forecasts.

Q How can the sterile connectivity between GMP raw materials and closed automated cell processing systems be improved?

BL: This is a frequently posed question. The ultimate goal is to have a sterile connectivity solution that can be operated outside the cleanroom. Today, I think weldable tubing is possibly the most broadly accepted and applicable technology. Secondly, there are sterile connectors, but the problem here is it requires standardization at both ends of the process, standardization of the raw materials and the cell culture system at the same time.

DD: We run into this all the time, where we might get something in a vial, and so it's an open process. What we've done where applicable is work with manufacturers on custom packaging. This involves identifying a unit of a material that we're going to use in a process, identify how we're using it in the process, and then asking them to package it in a way that allows us to make a sterile connection.

For example, we've had small bags of reagent with a segment of tubing that can be welded on to the automated production system. You may have to enter a supply agreement to justify the change to the manufacturer, but I think it's going to become more important for manufacturers to recognize that simply vialing may not work for all intended purposes, and that custom packaging – both in the size of the unit and the ability to do sterile connection – is extremely helpful to the client.

Q How can you streamline manufacture by reducing raw material handling requirements?

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- **Tom Walls**

DD: As we just discussed, packaging with sterile connections certainly helps, as does packaging in unit operations. For example, if I buy 100 milligrams but use 100 micrograms per reaction, I don't want to have to do that allocation myself. If I could instead buy the 100 milligrams in units per lot or per batch run, providing those specific package increments would be extremely helpful.

BL: One possibility would be to provide liquid reagents, specifically when considering freeze dried versus

lyophilized versus liquid cytokines. The big advantage of lyophilization is of course long-term stability – but as long as a shelf life of one or two years is sufficient, this could help to significantly reduce the workload of reconstituting and diluting the cytokines.

Another possibility would be customized mixes of reagents. It could be mixes of cytokines for a particular application. It could even be complete media by supplementing basal media with cytokines. This is of course very specific to the particular process or process step, but it is an achievable way of reducing manual workload in manufacturing.

DD: We've actually gone down that path, and two things came up: one was ensuring no interactions when you combine something formulated individually versus something stored and formulated as a compounded material. It may not have any interactions, but it's a question worth asking.

We also ran into an issue with lyophilized reagents. They have a stability as a lyophilized product of two years, and that's fabulous. But if we need to take that and compound it or formulate it to use it, we've now committed that lot, because we've made a new formulation. This means that stability of the compound changes completely and you have to rerun stability assays on your formulation, and the manufacturer cannot anticipate what your excipients or your matrix is going to be. So it may be less handling but it adds time and effort in re-establishing stability. When you're looking at reducing handling any impact it has on stability or interactions has to be considered.

Q What approach would you take to manage raw material variability in order to minimize its potential impact on bioprocessing?

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- **David DiGuisto**

DD: It is important to understand the quality attributes of your raw material outside of what's provided on the Certificate of Analysis (C of A), because you may have to include additional testing to what is provided by the manufacturer if it impacts the material. When it comes to consistency of quality of raw materials, there may be a burden on the user to analyses things that are not part of the C of A.

As I mentioned earlier, when scaling up you want to have a test lot at scale to make sure that the material has the same properties as when it was made at small scale. Properties often change upon scale up, or if you change the way you produce it, for example from an *E. coli* to a baculovirus, or some other change in methodology. You want to be sure that you have the same material by testing it in your production system.

BL: From a supplier perspective, you should really look at having a robust manufacturing process, and as David said, this has still to be true after scale-up and after any process changes. The critical steps have to be challenged

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by process validation, and these data must be available. If you have a significant process change, you have to revalidate the relevant process steps.

From the user perspective, I would recommend that you agree on appropriate specifications: you can negotiate adding one or two additional specifications, and agree that each new batch is tested against the new specifications. As I said earlier, this can all be written down in quality or supply agreements.

Q What particular issues have you encountered relating to the stability of critical reagents and other raw materials, and what is your advice on managing this particular aspect?

BL: Comprehensive stability data is a must and is required by all users. We have a multistep program – first we gather stress, accelerated and real-time stability data to demonstrate consistent quality over a long time, meaning several years. Secondly, additional supporting data are essential, such as in-use data, stability after reconstitution, and stability after a number of freeze-thaw cycles. This is tremendously helpful to the users in developing a robust and efficient manufacturing process, because they don't have to do it themselves.

DD: We try to ensure a supply chain by predicting our manufacturing capacity for a year at a time, and then acquire all those and hold all those supplies. This only works as long as the expiration date on the supplies does not exceed the year, of course. So one of the challenges is balancing your rate of purchase or acquisition of supplies with their intended use and expiry date. If I buy a years' worth of something and it expires in 6 months, it doesn't do me any good.

The other issue is shelf life. For example if with media you buy the raw components, but then you compound and test the media, you have to know what the shelf life of that media is once compounded.

So it is a supply issue, but it's downstream of the receipt of the supply, and more about the in-process life of something once compounded. You might not want to make media daily for a run that requires media exchanges but make a month's worth of media instead. The question becomes whether that compounded media is stable for the entire duration of its use.

Q Customization or standardization of raw materials: what are the pros and cons of either fundamental approach, and which do you prefer and why?

TW: I'm going to speak mainly to the pros on this one – as someone with a background in procurement and supply chain, of course I'm going to choose

standardization. That doesn't necessarily mean off the shelf or one size fits all, but within your process, I'm a big believer in standardizing wherever possible. It makes forecasting to the vendors simpler. It also makes dual sourcing more attractive for the second source if you have something that can be used across your process – and if it is off the shelf, so to speak, it makes it a lot more attractive for a secondary source because they're not making something specifically for you.

On the other hand, I do understand that there are needs for customization in certain types of packaging, but wherever possible, I would choose standardization.

BL: I think there is no generalized answer – the answer is highly process-specific, and there are always pros and cons.

Customized products are easier to use and may reduce labor, but you usually lose flexibility. Typically, you have a sole supplier, and you might be locked in to a particular reagent mixture which you cannot manipulate any more. Moreover, I think you should have a very stable and robust cell process to consider this option. Typically, customized articles are more costly due to additional development costs, and due to smaller batch sizes, so you should also have savings at the other end. The lead times should also be considered, as they may be longer than for off-the-shelf products which are usually always in stock.

It really depends on the maturity of the process and the state of development when you are considering whether customization is applicable or not.

DD: I agree with Tom that there are a lot of pros to standardization. If

you are looking at customization versus standardization, the caveats are understanding your requirements. When you say you want to standardize, what is the bandwidth of that? If you're too specific and too stringent, you're going to run into a few issues. One might be cost for your raw materials, and another consideration is the failure rate. Say you're using a material and you want to tighten the specs, and you go from 90% of the lots passing to all of a sudden 60% of the lots passing – this means your supply is diminished.

I think there's got to be a lot of care and understanding of the impact on materials when you standardize, of the stringency you impose, because it does have financial and supply chain effects in terms of availability.

Q Turning to the topic of regulation, what trends do you see evolving in terms of regulatory guidelines that impact the raw materials area? Are there any related national or global initiatives that may help with their ongoing development?

BL: I think the first generally accepted guidance document was the USP <1043>, which is currently being revised for the first time. This document established the idea of risk-based selection of raw materials, which is still today's thinking. The European Pharmacopeia is a bit more recent, with chapter 5.2.12 giving particular attention to biological raw materials. This has gotten binding in a way, in that it is referred to in part 4 GMP for ATMPs. This is another important step.

The first global initiative is from the ISO, which has launched a technical standard (ISO/TS 20399) which is today being transferred into an international standard, to gain more acceptance and to move towards being able to be certified against that.

The last trend I see, which is where we are contributing, is the initiative of the Alliance for Regenerative Medicine, which is trying to achieve a master file reference system for raw materials within the EU like the one that has existed for a long time in the US, the possibility to submit a DMF to the US-FDA and offer the possibility of cross-referencing.

These initiatives are fortunately growing in parallel and show the same thinking: risk assessment, risk mitigation, and particular attention to biological raw materials. This is all good to see – but we're still far from being harmonized globally.

TW: This doesn't speak to trends, but I will say that in previous labs in immature companies, people have sometimes mentioned vendor or brand names as part of raw material regulatory filings. It's not entirely applicable to this question, but this makes dual sourcing or multiple sourcing very tricky. I have found it's much better to be as generic as possible, keeping vendor and brand names out of any filings.

DD: In cell and gene therapy, oftentimes a raw material is a cell product harvested from a patient that then becomes part of the supply chain. And that is regulated: for example in the US 21 CFR 12 71, which addresses the requirements for donor material that are applicable to using that material. For example, if you're going to create an allogeneic cell therapy and you're using cord blood or some healthy donor product, the donor requirements help guide the standards and requirements for that type of raw material. This hasn't come up in our

discussion, but it's incredibly important for autologous and allogeneic cell based therapies where cells from a human are the starting point of the production.

Q When working with a CDMO partner, how can you manage supply risk without being overbearing?

TW: I spoke about this earlier in regards to the COVID-19 coronavirus situation, but I'm a big believer that as a biomanufacturer, someone who owns the IP and who is the ultimate steward for our patients, that you're also stewards of your supply chain. It's your absolute duty to monitor, measure, and mitigate risk, whenever possible.

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>
> - Tom Walls

This may feel a bit intrusive to a CDMO. When you get into a contract with a CDMO you are buying their expertise on supply chain management, and some are better than others. But again as a steward you have to monitor that risk and mitigate risk wherever you see it. We've talked about increased inventories – it may be a case of asking the CDMO or their tier 2 vendor to hold more inventories.

It may also mean reaching out directly to the tier 2 vendor to share forecasts across your entire network. We use a number of CDMOs, and some are very good at sharing forecasts while others are not that great. But when we present a forecast to a tier 2 vendor, we're presenting the entire universe of our demand, and that's a very powerful tool. This may involve non-disclosure agreements or confidential disclosure agreements or other types of supply agreements with vendors, because it's not necessarily your purchase order to the vendor, but you are sharing important information.

You don't want to be overbearing and you don't want to step in too much, but you need to understand the inventories of the CDMO, and you may sometimes want to reach back one link, at least, in the supply chain to talk with the vendor to your CDMO.

DD: If I'm going to go to a CDMO and put my production in their hands, and they have to manage supply chain, I'm going to audit them for their QMS system, how they manage supply chains and how they ensure continuity. This is the best way to come to an agreement a priori. That might then affect the supply and/or quality agreements for that CDMO.

I think having a written agreement upfront with a CDMO about obligations and expectations really helps clear the water, so there's not a discussion after the fact about what you thought they were going to do. Doing your due diligence up front is going to mitigate a lot of risk.

Q How are collaborative business models between cell and gene therapy developers and material suppliers evolving? What future trends and developments can we expect to see in this regard?

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DD: We've touched on a lot of these. The collaborative business models we've been working on include things we've been talking about like supply and quality agreements being absolutely essential, probably more essential for sole source providers than if you have multiple choices. And also service agreements with the CDMO outlining the expectations for service.

One possibility is to arrange for dedicated resources for a client. If you have a company and there's a product in high demand, and the CDMO has to make a large number of lots to service clients, you might ask to set up a production unit at the company to service your operation in particular, or ask to have a portion of their capacity dedicated to your efforts. That way you know you're not in a potentially variable position within a bigger queue. You might be able to pay for priority, for example by paying a premium for the service or supply to get a priority on distribution.

Finally, like I said earlier, another option is outright purchase of the supplier. The collaborative business model here is saying to them you're going to run as long as you can, and when you can't anymore, you become us. That's not always available to smaller biotechnology companies, but for larger biotechnology companies and smaller biopharmaceutical companies I think these are realistic emerging trends. We've seen people buy entire CDMOs to ensure their supply chain, so it's already happening now.

BL: As I said earlier, a very simple mode of collaboration is via supply agreement. What I predict is off-the-shelf and customized new raw material formats; in particular those that are adaptable and attachable to a sterile connectable closed system. This can be done in a co-development mode and be very customer specific. I predict co-development agreements for complex raw material products, for example media supplemented, or new innovative primary container systems.

"Build a trustful partnership by exchanging regular forecasts, and by being prepared in terms of production capacity for future demands."

- Bernd Leistler

TW: These are great points by all parties. To circle back, sharing information with those key critical sole vendors, sharing the forecasts, speaking common languages, and understanding their capacities are all crucial steps – and also considering their ability to flex capacities, and what that may cost.

As a start-up industry sometimes we may be a little short-sighted, but it's important to start thinking longer term and get ahead of problems by thinking years into the future, instead of just weeks and months.

What are the key elements of best practice for trouble shooting and securing supply? Particularly as both manufacturing scale and overall demand for raw material increases?

TW: Manage and mitigate risk wherever you see it in your supply chain. Work with vendors and CDMOs to share information. The cheapest way to mitigate risk is to share forecasting information. If you have to buy extra inventory, do it, but understand the dating and stability implications. And where you can, look to dual source.

BL: Build a trustful partnership by exchanging regular forecasts, and by being prepared in terms of production capacity for future demands. I would recommend auditing your suppliers on a regular basis and keep in regular contact. This helps you to understand each other's needs and capacities.

DD: I think that having a dedicated supply chain infrastructure or group at your company is really important. Asking manufacturing or quality to do it by themselves is not going to work, you need a dedicated supply chain group whose job it is to ensure this.

Knowing your book of business and knowing what you need before you go to a supplier is also key. Finally, it's important to be flexible and start early in securing your supply chain. Don't leave things until you're in the middle of production and suddenly start to have supply chain issues. Get all these contracts and agreements and supply chain specifics, such as raw materials specifications, worked out as far ahead of production as possible.

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