Quality by Design Planning in ATMPs

A Guide to Selecting the Right Starting Materials

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Advanced therapy medicinal products (ATMPs) represent a new frontier in precision medicine. From cancer cures to treatments for "untreatable" genetic disorders, they're poised to define the next generation of medical care.

And, fortunately for patients, this brighter future of medicine is nearly here:

- Up to 21 cell therapy launches and 31 gene therapy launches are expected in 2024.[1]
- More than 3,500 cell and gene therapies (CGTs) are in development.[2]

"With these therapies, we're giving very sick patients a vehicle for the road to health, and we want to make sure we're giving them the best car to speed their journey," said Sun Ra Bullins, Vice President of Operations at Excellos. "We're not just looking for yield; we're not just looking for approval. We want to give patients the best lifesaving therapies they can get."

However, finding ways to ensure the safety and efficacy of these novel therapies, all while speeding time to market, is critical to deliver on the promise of ATMPs. That starts with sourcing the optimal raw materials: ones that lay the foundation for consistent processes that yield effective and safe therapeutics and help developers avoid costly delays that slow time to market — or, worse, sink their program entirely.

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There are sourcing considerations and regulatory requirements for these starting materials that cell- and tissue-based advanced therapy developers will need to follow later in the development pipeline. If developers do not plan that far ahead when selecting a provider for their starting materials, they will be forced to change suppliers by Phase 2, necessitating requalification, regression testing, additional product validation and potentially repeating PPQ.

In the following pages, we'll share how CDMOs and therapeutic firms can evaluate their needs and select the raw and cellular starting materials that will set their programs up for success. **You'll learn how raw materials affect the consistency of your process and product, what the essential components of a robust GMP framework are, and which strategies help you find a trusted vendor that can propel your program forward.**

For Many Therapeutics Firms, Finding Consistent Raw Materials Remains a Challenge

The cellular starting materials used to make ATMPs — cell and tissue raw materials — are the most variable materials in the process. And, perhaps not surprisingly, therapeutics firms and CDMOs still struggle with a lack of standardization for suppliers across the industry.

"One of the issues I hear about across the industry is variability in starting materials," Bullins said. "When we work with different suppliers, we find we need them to define exactly what it is they'll deliver in terms of appropriate documentation, appropriate labeling and appropriate testing, because there's no standard that every supplier follows."

With few industrywide standards, it falls on CDMOs and therapeutics firms to critically evaluate suppliers, keeping consistency top of mind. And, while some organizations have the bandwidth and expertise to perform extensive ongoing quality control — Bullins' organization, Excellos, for example, developed an enhanced characterization program called Excellos 360 — many do not. As a result, finding the right partner is key to a program's success.

"Because cellular raw materials are the most variable raw materials in the process of producing an advanced therapy, it's essential that they come from a supplier who is truly GMP- and GTP-compliant," said Matt Chorley, Vice President of Global Quality at BioIVT. "That means they follow a robust quality-management system as well as a manufacturing framework that's consistent and reproducible and stands up to regulatory scrutiny across the entire life cycle of the advanced therapy."

What Does it Mean to Follow a Robust GMP Framework?

Strong end-to-end GMP frameworks are based in partnership between vendors and their clients. Here's how to ensure consistency across the life cycle of your raw materials.

Documentation: The key ingredient for consistency

In a robust GMP and GTP framework, each step is **validated, controlled and documented** to demonstrate consistency and minimize variability.

The quality of your raw materials can affect your process at any stage of development. But it becomes especially critical as you enter Phase 2 and Phase 3 clinical trials.

Phase 2: Transitioning for Research Use Only (RUO) to GMP Materials

CDMOs and therapeutics firms face their biggest challenge when entering Phase 2 clinical trials, the point at which regulatory authorities and national standards organizations (e.g., USP, EP, JP) expect and require the use of GMP materials.

"By the time you're mandated to work with GMP suppliers, you've already put a lot of work and qualification into your program," Chorley explained. "Switching vendors at that point is very cumbersome. And if your vendor can't provide consistent GMP materials, it can bring your program to a halt or minimally slow progress."

Finding quality GMP materials at this point requires reevaluating and auditing vendors, and the most time-consuming work begins when those materials arrive. You'll need to complete regression testing and validation to demonstrate concordance with your initial process, Chorley said. In addition, much of the work you put into performance qualification will need to be repeated in many cases and/or additional concordance studies will have to be completed.

As a result, therapeutics firms and CDMOs often face costly delays at this stage as they adapt their processes around new products and develop new internal quality control protocols. Plus, they may face further delays recruiting the specialized talent needed to complete this work.

"Overall, you're slowing down your product from getting on market, you're taking on extra costs, and you're taking on validation efforts you may not have the capability to do on your own," Chorley explained. "If you had qualified a supplier who is GMP and GTP compliant from the beginning, they'd have done the heavy lifting in quality control and validation to help you make the switch more easily and keep your program on track."

Phase 3: Sourcing Raw Materials at Scale

The second-biggest hurdle arises as firms enter Phase 3 clinical trials, and their patient population — and the volume of raw materials they require — increases exponentially.

"Your needs increase at each phase of development, and by Phase 3, you need to be able to meet the needs of your large and extensive patient enrollment," Chorley said. "If you don't have a consistent vendor who can supply you throughout that whole process, it's nearly impossible to avoid a negative impact on your therapeutic time to market."

Not having enough raw and cellular starting materials to scale may mean finding and qualifying additional vendors, the long validation process that follows, and, potentially, batch-to-batch inconsistencies in the end product.

Finding a GMP-Qualified Vendor from the Start Sets You Up for Success

Although quality control and validation are essential for any therapeutics firm and CDMO, selecting the right vendor helps streamline your program and minimizes the risk of delays. You'll get the best results by opting for a vendor that can supply both RUO and GMP materials — and qualifying vendors by assessing their GMP framework from the outset, Bullins advised.

"When we were sourcing materials, we found vendors who said they did GMP, but they didn't provide documentation that would withstand regulatory scrutiny," he explained. "Our CEO had to do a lot of work sourcing starting materials that could support GMP manufacturing."

The ideal partner should offer both RUO and reliable GMP materials. That way, it's likely to have the expertise needed to help you transition seamlessly between the two when you need to. You'll also be able to develop your process around a robust GMP and GTP framework from the beginning, minimizing the risk of variability or regulatory hurdles later on. Finally, selecting the right vendor from the start gives you a chance to build long-lasting relationships and get support at each stage of development.

Selecting the Optimal Cellular Starting Materials for ATMPs

Three strategies to evaluate vendors and find the right fit:

1. Ask how vendors reduce variability for cellular starting material. Grappling with variability adds costly complexity to your process development and may affect the efficacy of the resulting therapeutic. Therefore, it's important to have a strong sense of a vendor's quality control and quality assurance programs to choose the right partner.

The right vendor should be able to explain how it maximizes consistency at every step of the process, starting with robust donor screening and medical questionnaires through to leukapheresis, apheresis, and storage and shipping conditions.

Crucially, it should be able to provide the supporting documentation to match — both to support your internal process development and facilitate conversations with regulators.

Location, Location, Location

Consistency in transport and receiving play a key role in reducing variability across your program. And Bullins takes turnaround times into account by considering vendors' location when making his sourcing decisions.

"Many of our clients have stringent ground requirements for timing to make sure the cells are viable before moving on to process," he explained. "Having someone who's local enough to provide cells within 24 hours is a bonus — otherwise, longer turnaround times necessitate more stability studies."

As you evaluate your options, ask vendors whether they can consistently service your location, and consider the risk of shipping delays to find your optimal partner.

2. Seek out vendors that can scale along with you. It's normal for many therapeutics developers to experience growing pains as they scale — but they can be especially acute when developing ATMPs. Finding a sufficiently deep donor pool is the biggest bottleneck to scaling, Bullins said. As a result, it's important to keep your long-term needs in mind when selecting a vendor.

As you assess potential vendors, ask how they plan to meet your needs as you move through each phase of development. The ideal partner should have a large geographic footprint with depth in supply and offer access to materials from a robust and reliable donor-management network.

3. Look for technical partnership and deep industry expertise. In a fast-evolving field such as ATMPs, in-depth expertise is a significant competitive advantage — and the ideal vendor should offer technical partnership in addition to quality raw materials.

These insights can prove invaluable for anticipating regulatory issues early and helping ensure compliant processes from the get-go, Chorley said. "The right vendor can help you understand the technicalities around what regulatory requirements you must follow and help you identify any requirements you may have missed."

But the benefits go far beyond regulatory compliance. A team of cell-isolation experts can, for example, conduct in-depth cell characterization to assess the viability of the cells and offer insights to extend stability, while tech operations experts can help overcome challenges in manufacturing.

As you qualify potential vendors, ask about the breadth and depth of scientific expertise that will be available to you, Bullins said. "Not every vendor will be able to understand the next step in your process and anticipate what your needs are, which is especially important when you're talking about GMP."

Request case studies or illustrative examples for how they've helped similar clients in the past, and share your technical challenges during the evaluation process to ensure the vendor has the expertise you need.

Client Service is Critical

Assessing a vendor's technical expertise can double as an opportunity to gauge its approach to client care. Besides a technical partnership, it should have a dedicated team to offer client support and, ideally, a dedicated point of contact to serve as an extension of your team.

Vendor evaluation checklist

Use this evaluation matrix to narrow your shortlist and find the optimal partner.

Material Availability

Vendor:

- Offers both RUO and GMP materials.
- Can reliably transport materials to your location in an appropriate time frame.
- Recallable donors for your therapeutic.

Documentation

Vendor Offers the Following to Demonstrate Adherence to GMP Sstandards:

- Medical questionnaires/donor screening forms that follow IRB protocols.
- Master batch records for each leukapheresis and apheresis center.
- Storage-condition records (controlling, monitoring, verification).
- Shipping-condition records (controlling, monitoring, verification).
- Validation documentation.
- GMP-training records and dedicated support staff.
- Demonstration of compliance with GTP's.

Scalability

Vendor Offers:

- Access to recallable donor pools.
- Sufficient for your needs during Phase 3 clinical trials and commercialization.
- Ability to consistently scale the donor pool across multiple sites.

Subject Matter Expertise

Vendor Offers:

- Technical manufacturing support.
- Scientific support.
- Regulatory support.
- Process design support.
- Client support.
- Dedicated point of contact.
- Responsive team.
- Track record of success/Client success stories.

Deliver on the promise of ATMPs with the optimal raw materials

Succeeding in the complex world of ATMPs requires consistency — and raw materials make the difference between a safe, effective and life-changing therapeutic and projects that languish in the pipeline.

"At the end of the day, we want patients to have the safest and most effective therapeutics possible. These are silver bullets, and we want them on market," Chorley said. "I'm in this business to help developers get the materials and expertise they need to change patients' lives."

References:

1. Alfano, S., Gotham, A., Loche, A., Salazar, P. (2022, September 20). Eight Imperatives for Launching Cell and Gene Therapies. McKinsey & Company. Retrieved from Mckinsey & Company.
2. Saleh, S., Dabbous, O., Sullivan, S.D. *et al*. A practical approach for adoption of a hub and spoke model for cell and gene therapies in low- and middle-income countries: framework and case studies. *Gene Ther* (2023). Retrieved from Gene Therapy.

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How BioIVT Can Help

BioIVT's experts understand developers' challenges and can assist with sourcing the right solutions for your specific needs.

With our extensive footprint of multiple donor centers near biotech hubs in the U.S., U.K. and EU, the company provides seamless RUO-to-GMP support for cell and gene therapy companies. This includes fresh or cryopreserved leukopaks from a diverse pool of normal and diseased donors, including over 600 HLA-typed recallable donors — who can transition from RUO to GMP within your clinical therapeutic pipeline. In addition, BioIVT offers mobilized leukopaks, isolated CD34+ cells, and RUO and GMP human AB serum to maximize cell expansion, as well as a wide range of other biospecimen preparations, including a variety of mononuclear cells.

BioIVT's GMP-grade leukopaks are processed in a 21 CFR-compliant cGMP framework with full compliance regarding all necessary quality and regulatory requirements and collected in FDA-registered sites under 21 CFR Part 1271. All of BioIVT's biospecimens are collected following strict quality and ethical policies to meet regulatory requirements and applicable laws. You can learn more about **BioIVT's CGT solutions here.**

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