CELL & GENE THERAPY INSIGHTS

TRENDS & OPPORTUNITIES IN RAW MATERIAL SOURCING

CHANNEL CONTENT

INTERVIEW

Key considerations and risk management best practice for placenta-derived cell therapy raw materials

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Q Can you introduce us to the specific raw materials-related considerations for Pluristem's product pipeline?

RG: According to EMA Draft Guideline on Quality, non-clinical and clinical requirements for investigational advanced therapy products in clinical trials (2019), starting materials are for example, 'donated cellular material (cells or tissue) from single or multiple donors, once processed' and 'additional substances (e.g. scaffolds, matrices, devices) when combined as an integral part with the manipulated cells'. The source material for the manufacture of Pluristem's investigational products is a placenta donated by a woman who has undergone elective caesarian section following a full-term pregnancy. Placentae are used for research purposes, for process development or for the manufacture of a clinical-grade product suitable for clinical trials. The manufacturing process of the clinical-grade product is detailed in a Biological, Chemical and Pharmaceutical Quality document that is submitted and approved by relevant regulatory authorities.

All Medical Centers donating placentae are required to have the approval of their local Ethic Committee (EC), and, if required by EC, approval from Israeli Ministry of Health (MoH). Prior to donating a placenta, the donor will sign an Informed Consent form before any procedure is performed.

The donor eligibility process includes screening of the donor for the risk of communicable diseases via a questionnaire, physical examination, review of medical records, and testing of the donor's blood sample for detection of infectious diseases.

Raw materials (RMs) used in manufacturing of clinical products should be purchased from the user's approved suppliers. RMs approval should be based on a qualification program. Qualification of RMs should be based on the risk assessment of each raw material, as assessed by R&D and QA departments. The goal of raw material risk assessment is to proactively identify risks that could contribute to an interruption of raw material sourcing, raw material performance, or the material qualification essential to the supply of safe and efficacious final cell therapy products. Risk assessment should employ a quantitative approach – for example, assigning a point value to each risk parameter for a RM, which results in cumulative scores that prioritize effort and resources for decreasing the risks associated with RMs. Based on the risk assessment, a qualification classification should be designed for each RM.

As biological raw materials are more difficult to characterize, because they have complex biological activities and high variability from lot to lot, specific characterization testing may be needed to assess a variety of quality attributes.

> "Risk assessment should employ a quantitative approach..."
> Ruth Goldberg

Performance variability of such materials may have an impact on the potency and stability of the final cell therapy product. Examples of complex functionality testing for RMs may include, for example, growth promotion testing of individual lots of Fetal Bovine Serum (FBS) on cells used in manufacturing,

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and *in vitro* tissue culture toxicity assays for individual lots of Dulbecco's Modified Eagle Medium (DMEM).

Q Are there any particular materials that carry additional risk – for example, that are single-sourced – and what is your approach to mitigating this risk?

LR: In the cell therapy field almost every RM or disposable is single source. One of the reasons for this is the long process of assuring the quality and suitability of the material for clinical use. Furthermore, since the drug product of cell therapy is a live product that can react to changes in the process, the impact an alternative product could have on the characterization of the cell product is basically unknown. To mitigate the risk of single source materials, we created a cross-functional team composed of representatives from QA, supply chain, manufacturing, development, and QC. Using a risk assessment process, the team evaluates each material based on its risk to the supply chain and potential effect on product characterization. Based on that assessment, a mitigation plan begins to work on the highest risks.

If during the assessment of the alternative material gaps are detected in the level of quality, the QA team will work with the manufacturer to close these gaps. On the other hand, if gaps are detected on the operational level, customization of the product will be done. The work of the cross-functional team on the alternative material continues from the highest material risks to the lower ones in parallel to the product development steps, creating a continues process of supply chain risk reduction, and many times even cost reduction.

Apart from the risk of single source materials, additional risks to specific materials quality also come from the material transport and storage conditions. These risks, if not reduced, can have a significant impact on the process and product quality, reproducibility, and batch-to-batch consistency. Since our product is a live product that reacts to changes in the process, even small changes to the critical raw material specifications can have an impact on the product characterization. To mitigate these risks and increase the level of consistency and reproducibility, we test the critical raw materials and study how different storage and transport conditions (temperature, etc.) affect the product characterization. If gaps are detected, we work with the suppliers to adapt the storage and transport conditions.

This approach to raw material risk reduction increases our level of understanding and knowledge regarding the raw materials in use and allows us to better define the critical material attributes. During the COVID-19 pandemic we learned the importance of having this process well established, since it allowed us to search, test, approve, and source alternative raw materials when needed.

Q How have you sought to address any additional upstream supply chain issues that have been presented by the ongoing pandemic? And how will the pandemic change materials sourcing on an ongoing basis in your own particular sphere?

RG: Coronavirus 2019 (COVID-19) has caused significant disruption to the cell and gene therapy industry, which has generally encountered complexities in supply of materials, and logistics processes. The supply chains have had to face new challenges as the disease rapidly has evolved.

The first challenge comes from the shortage of supplies of materials to the cell and gene therapy industry. Disruptions were also observed for cell collection from patients (human-to-human contact), visits to medical centers, shipments of cell material to manufacturing sites, and transportation of products to administration centers.

The first manufacturing step at Pluristem is collecting donated placentae at the time of delivery of healthy, full-term babies, from elective cesarean operations. As cesarean operations weren't drastically limited during the pandemic, and the placentae were collected with minimal human-to-human contact, no disruption was observed in this field. In addition, as part of a risk-based approach adopted by our company in order to mitigate the main risks of COVID-19 related to drug safety or quality, screening of the donors for SARS-CoV-2 before giving birth and at the day of discharge from the hospital was added to the overall viral control strategy.

On the other hand, we experienced long delivery times for plastic components and biological supplies, and sometimes found ourselves short of manufacturing or laboratory equipment such as personal protective equipment, disinfectants for cleaning rooms, single-use consumables, and biological raw materials.

Consequently, the pandemic had led us to re-evaluate our supply chain and manufacturing strategies. We considered strategic partnerships with key suppliers and identified and qualified at least two potential suppliers for critical raw materials, rather than relying on just one.

In addition, because of travel restrictions and physical-distancing guidelines, we adopted digitalization tools and prepared our company for remote working during the early days of the pandemic. For example, digitalization of signing on documentation allowed for remote access and a reduced need for onsite personnel. Also, digitalization of our suppliers remote site inspections and virtual audits did not hamper suppliers' evaluation and qualification. Thus, trustworthiness and readiness for digitalization is valued highly during the current crisis when site inspections are restricted.

Q Stepping back for a moment, what are the most pressing priorities for the cell and gene therapy field as a whole in advancing the industrialization of raw material and consumables supply?

RG: One of the things the cell and gene therapy industry needs is more standardization of terms for quality statements.

A diversity of terms is used to describe raw materials and it would be great if standard terms (terminology) were harmonized. For example, statements such as: 'Laboratory grade'/'Research grade'; 'GMP'/'cGMP'/'manufactured under GMP'/'GMP-compliant'; 'GMP intended use for research only' or 'GMP intended use for further manufacturing'; 'Clinical–grade (approved drug)'/'for a specified intended use only'/'not approved for other "off-label" processing uses

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without qualification and approval from regulatory agencies'.

Developing a clinical-grade product according to FDA or EMA guidelines involves various elements and having cGMP-compliant raw materials is one of the most crucial ones to ensure the safety of the cell and gene therapies and eventually, of the patients. Having high-quality research and cGMP raw materials options smooths the transition from process development through clinical trials and commercial manufacturing of cell and gene therapy products. However, cGMP-compliant raw materials are not always readily available.

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> Ruth Goldberg

Suppliers do make efforts these days to perform validation of raw materials' manufacturing processes in order to meet robust specific specifications, which will predict a precise performance of the raw materials. Suppliers also make efforts to have quality systems that manage change controls, traceability, and investigations. They perform GMP QC analysis emphasizing sterility, impurities and other residuals testing. In order to be GMP compliant, regulatory certificates are also important to have, for example: certificates of analysis, certificates of origin, stability reports, extractable and leachable study reports, and others certificates depending on the raw material type.

The demand for single-use technology has also increased, which in turn has led to a greater expectation that suppliers should have an expanded single-use network that will help cell and gene therapies to scale-up from research and development to commercialization. Single-use solutions will provide productive strategies in effectively scaling up and reduce risks and costs. Single-use technology will also offer a more flexible and safer approach to sterile fluid handling (closed system solutions) in cell and gene therapy manufacturing compared to traditional methods in place today. Cell and gene manufacturing requires small batch sampling under aseptic conditions to preserve the limited material for the patients, whilst complying with regulatory standards and having representative results. Manufacturers will benefit from collaboration with suppliers to tailor single-use systems and technology to the individual manufacturing requirements in the sampling process, which will allow for even better efficiency and process security [1].

Continuous investment in improvement and partnerships is required, and suppliers can make valuable contributions to cell and gene therapy production based on their existing knowledge, technology capabilities, and obligation to provide solutions.

Q Where and how is progress being made in increasing consistency, scalability, and standardization – and reducing costs – of allogeneic cell starting materials?

LR: It has become apparent in the last few years that efforts need to be made to increase process consistency and reduce the cost of processing and manufacturing,

to make cell therapy products viable in the real world. Our aim as cell product candidate developers and manufacturers is to develop a process that will yield an active, viable, and affordable product, remaining cognizant of the fact that the cell manufacturing process and product quality are strongly affected by the quality and consistency of all starting materials. In allogeneic cell therapies, among all starting materials, the cells themselves have the highest impact on process reproducibility. Over recent years, an effort has been made throughout the industry to develop industrialized solutions based on closed systems, standardized protocols, and automation in order to increase the level of consistency, scalability, and reproducibility of cell collection steps. Furthermore, studies have been performed in order to learn how different conditions can affect the cell starting materials during transport. Based on the increasing body of knowledge, new approaches and technologies are being developed to increase the starting material stability. It will probably take a few more years to learn what the best conditions for each product type are, but the industry, the clinicians, and the cell collection sites understand the importance and the effect of the cell collection step and are willing to contribute to the learning effort. Once standardized, the process will even deliver cost reductions due to a reduced failure rate in the cell starting materials. At Pluristem, we collect the donated placentae directly from the hospitals and we manufacture the product in-house. Through the years, we have conducted various studies on the different parameters affecting the donated starting material stability and quality. Based on that work, close collaboration, and teaching the hospital staff, we were able to increase the fresh starting material stability to over 24 hours, which allows greater flexibility in our manufacturing.

Another recent effort has been made in the field of media and media components. It has been commonly accepted for years now that a shift to serum-free media is needed to reduce risk and increase the consistency of manufacturing compared to the use of fetal bovine serum. Based on this understanding, many off-the-shelf serum-free media were developed by different companies. The consequent increase in availability of serum free media allowed cell therapy manufacturers to test them, better understand what is important, and give feedback to the media developers, driving a process of continuous improvement. We have ultimately seen a process of quality and consistency improvement in parallel to cost reduction.

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>
> Lior Raviv

Furthermore, since cell manufacturing companies understand the impact of media and media components on their product, we now see a trend of companies customizing their own media formulations using media components bought from different suppliers. Based on our experience at Pluristem, in-house formulation development increases consistency, creates a dramatic cost reduction, and allows us to have full control over the cost and the source of the media components. At Pluristem, in parallel to our media

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development efforts, we performed an extra step to reduce cost and switched from suppliers' custom solutions to in-house solutions preparation. Because we work in a closed environment and everything needs to be sterilized before entering the clean rooms, the standard approach is to work with the supplier to have custom designed packaging suitable for the process. This process increases the overall cost. In parallel to the development of serum-free media, we established a team that filters each solution we purchase in-house and adapts it for our process needs. This gives us the ability to buy any packaging for the raw materials that we need off-the-shelf and to design the container in-house. Designing the container in-house increases the availability of the specific raw material, which then increases our independence – thus, the risk of not having the raw materials available when we need them is reduced.

"In parallel to the development of serum-free media, we established a team that filters each solution we purchase in-house and adapts it for our process needs."
Lior Raviv

Q Concern over regulatory uncertainty and disharmony around requirements for raw materials seems to be on the increase. Are there any specific aspects that are considerations for Pluristem as you approach the challenge of ensuring regulatory compliance on a global basis?

RG: Raw materials used in cell and gene therapies are not common raw materials with monographs, made in GMP environments, and there are no compendia documents available for these materials.

Terminology is the first subject to take into consideration. There are various terms for materials used in manufacturing of cell and gene therapy products: 'materials' in EU Directive 2001/83/EC; 'ancillary materials' in ISO Standard ISO/TS 20399-1 Biotechnology; 'raw materials' in European Medicines Agency (EMA) guidelines; and 'ancillary materials' in USP <1043> (ancillary materials). As terminology varies in different countries, ICH terminology may be recommended as a good option to use, as their terms are internationally accepted and applied across the pharmaceutical, biotechnology, and cell and gene therapy industries. However, despite the differences in terminology, the definitions according to the U.S. FDA regulatory guidance, EU Directive, and ISO Standards are all consistent in stating that the RMs are not intended to be present in the final product.

Although there are regulations that describe both quality and regulatory requirements for the manufacture of cellular therapies, the regulations do not specifically describe quality requirements for RMs. However, they do provide a framework for strategies to control these RMs. Guidance on RM use is available from the U.S. FDA (USP <1043> and specific chapters for fetal bovine serum, cytokines, growth factors), US FDA directives in Title 21 CFR,

the International Conference on Harmonization (ICHQ10), the European Medicines Agency (EMA) (Annex I, part IV of Directive 2001/83/EC) and the EP 5.2.12. Most of the guidance is relevant to medicinal products (small molecules) and biologic drug products (blood or blood products), and does not apply directly to cellular and gene therapeutics. However, as the industry has grown, more specific standards and relevant cGMP regulations for cell and gene therapy RMs have arrived.

Ensuring that the biological RMs used are human/animal origin-free (AOF) is one of our main concerns. A certificate of origin (CoO) is much desired because it helps to reduce adventitious agents risk concerns, which are one of the main regulatory deficits for cell and gene therapy companies. A certified animal origin-free product allows us to not have to prove viral safety of biological-derived raw materials or their components used during manufacturing. What we do need is a consistent definition of AOF to be agreed by the regulatory agencies. Users should obtain AOF statements that include as much detailed data as possible relating to the supply chain of components involved in the manufacturing of biological RMs

A new ISO draft for Ancillary Materials ISO/CD 20399 (current ISO/TS 20399, 2018) is anticipated. This document will provide guidance to suppliers and users of RMs to improve the consistency and quality of RMs of biological (human and animal) and chemical origin used in the production of cellular therapeutic products and gene therapy products for human use. It will help the suppliers and users of RMs to achieve and maintain an appropriate level of documented lot-to-lot consistency in the aspects of identity, purity, storage and stability, biosafety, and performance.

As there are regulatory requirement differences – and some regulatory guidance may have more detailed requirements on viral safety testing or characterization, leading to confusion – Pluristem's objective is to choose well characterized, high quality RMs intended for use in cell and gene therapy manufacturing, which meet the current regulatory guidance in the major markets (such as USA and Europe). Whenever available, FDA- and EMA-approved GMP or Clinical Grade materials are used at Pluristem. The use of such materials should eliminate the need to make subsequent changes to materials.

Q How do you weigh up the pros and cons for in-house development and production of critical raw materials versus outsourcing? And do you see the balance changing in this regard?

LR: This is indeed a hot topic in cell therapy. Our approach is based on what will affect the 'day after approval'.

Pluristem works through the development stages of the company and the product with Phase 3 and market approval in mind. We will be measured not only on gaining market approval, but mainly on the day after when we need to deliver actual commercial cell therapy products to patients. If we are not able to supply the product, or the product is too expensive, this will affect our success. Pluristem is a cell therapy developer, and our aim is to invest our efforts in producing our products, not to develop RMs. However, wherever we saw that a RM

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(or any other element needed by the manufacturing process) had the potential to disrupt our manufacturing, we decided to develop an in-house solution.

For every new product or process we are developing, we assess the criticality of the different starting materials and other RMs in terms of their availability, cost, consistency, complexity, and more. Using this assessment, we categorize the risk of this outsourced material and the related cost in commercial manufacturing. If we identify a potential risk, we develop a mitigation that will be either outsource or produce in-house. For example, during the development of our second product (PLX-R18), we realized that working with fetal bovine serum had a crucial impact on our ability to manufacture and on our product cost, so we implemented a project for switching our products to serum-free media. Once we started working with off-the-shelf serum-free media, we noticed that our cost of goods (COG) significantly increased. Assessing the risk, we implemented methods in our process development to understand the critical material attributes and we realized that we could design our own formulation of serum-free media. By doing this, we created a solution with full control of our sourcing material, costs, and the capabilities of the in-house serum-free media to support the process. At the end of the mitigation process, we managed to increase yield of our product, to reduce the cost, and to gain operational independence.

In the RMs field, we performed many development studies and gathered a lot of information and knowledge about what critical material attributes are. Therefore, if we have a specific component that we believe is needed for the manufacturing process and it has only one supplier, increasing our understanding allows us to potentially work with alternative suppliers and materials. By creating the ability to work with alternatives, you can reduce the cost and increase the availability of specific RMs.

Ultimately, there is no right or wrong answer to the question of 'outsource vs in-house'. At Pluristem, we believe that manufacturing, process development, quality, and product data collection and interpretation must all be in-house to allow us to fully understand the product. All other elements could be either in-house or outsourced, providing they don't increase risk and cost to the process compared to the alternative solution.

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