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Regulating Raw Materials Testing

Efforts are already underway to harmonize standards and regulatory approaches for testing of raw and ancillary materials, but continuous improvement is required.

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The global cell and gene therapy market is predicted to grow significantly by 2024, according to market research (1). Drivers for this growth include an increasing prevalence of chronic diseases, expansion in available clinical evidence proving efficacy and safety the therapies, new product launches, regulatory favor, and enhanced manufacturing expertise (1).

The manufacture of cell and gene therapies and advanced therapeutic medicinal products (ATMPs), however, is particularly sensitive and requires a comprehensive understanding of the materials used in the manufacturing processes to ensure a safe and quality finished product. "The quality, safety, and efficacy of cell therapies and ATMPs are critically influenced by the raw and ancillary materials used in the manufacturing process," explains Bernd Leistler, vice-president production, CellGenix. "Successful cell therapy manufacturing is therefore dependent on the use of high quality raw and ancillary materials."

ESSENTIAL COMPONENTS

"The terms 'raw material' and 'ancillary material' have been used interchangeably in different geographies, but they refer to different classes of starting materials—including cells, recombinant proteins, and growth media, among others—used in the development and manufacture of advanced therapies," says Claudia Zylberberg, CEO of Akron Biotechnology.

According to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q7 guidance, raw materials are starting materials, reagents, and solvents that are used in either the production of an intermediate or an API (2). Whereas, ancillary materials are defined by the *United States Pharmacopeia* (*USP*) as reagents and materials used in the manufacturing process of ATMPs that are not present in the final product (3).

"The process of manufacturing an advanced therapy is a complex train of unit operations, many of which are just now beginning to be bundled into closed systems," continues Zylberberg. "Regardless of how far down the path of system closure and automation we go, starting material integrity and consistency will remain critical, as one cannot sterilize the final drug product. Ensuring batch-to-batch consistency and sterility of raw and ancillary materials is paramount for ensuring the production of a safe, efficacious, and cost-effective advanced therapy."

As a result of the critical nature of raw and ancillary materials in ATMP manufacturing, a secure supply chain is imperative, notes Leistler. "A delay in delivery or change in product quality could lead to delays in production, not only increasing costs but also putting precious patient samples in jeopardy," he says. "Because the global demand for high-quality good manufacturing practice (GMP) raw and ancillary materials is rapidly growing, as more promising cell therapies approach market authorization and commercialization, a reliance on well-prepared suppliers and negotiation on supply agreements for critical raw and ancillary materials are recommended."

REGULATORY CHALLENGES

Regulatory guidance documents for raw and ancillary materials are, essentially, recommendations rather than guidelines and are not aimed at the manufacturers of the raw and ancillary materials but the manufacturer of the advanced drug product. "All current regulations and guidance documents assign ultimate responsibility for quality and suitability of the raw and ancillary materials to the user (cell and gene therapy [CGT] manufacturer)," adds Leistler. "Therefore, the CGT manufacturers need to work in close cooperation with their supplier to get support."

As a result of the onus for quality and suitability of raw and ancillary materials being placed on the therapy manufacturer, most decide to perform identity and purity testing as control tests, asserts Leistler. "Potency testing for raw and ancillary materials is more difficult, especially as there is a large variability and poor comparability of the available biological assays," he says.

"Standardization of raw and ancillary materials testing is required, and reference materials may be needed in some cases," confirms Zylberberg. "Both elements, standardization and reference materials, will bring much needed regulatory harmonization and expected consistency."

Additionally, geographical discrepancies can make regulatory considerations more complex. "Each region has its own regulatory agencies that view cell and gene products and ATMPs under different lenses," states Zylberberg. "The harmonization that we have seen in the biopharmaceutical world through ICH has yet to emerge for the advanced therapy industry."

Nevertheless, Zylberberg remarks that efforts to harmonize standards, especially those around raw and ancillary materials, are gaining momentum. "These efforts are being pursued through pharmacopeia (principally US, European Union, and Japan) as well as International Organization for Standardization (ISO), which uses a consensus-based approach, and other supranational entities," she says. "The Standards Coordinating Body (SCB) for Regenerative Medicine (4) has been coordinating these efforts within different standard-setting organizations globally to ensure that different aspects of the industry and the manufacture of these ATMPs can be covered appropriately." Some of the latest work being performed by SCB includes the coordination of working group discussions on the potential standardization of chain of custody/chain of identity identifiers and efforts into the standardization of tissue engineering terms (4).

In concurrence, Leistler emphasizes that various initiatives are being witnessed regarding the harmonization of regulatory guidelines for raw and ancillary materials. "ISO issued the first global guidance for raw and ancillary materials suppliers and

Practical tips for a successful partnership for raw and ancillary materials

The success of an advanced therapy development program can be impacted by the raw and ancillary materials supply chains. A relationship between materials suppliers and developers is, therefore, of great import. As such, *BioPharm International* asked Claudia Zylberberg, CEO of Akron Biotechnology, and Bernd Leistler, vice-president production, CellGenix, to provide some practical tips for a successful partnership.

Close relationship

"The relationship between ancillary materials suppliers and advanced therapy developers should be more intimate than an arms-length relationship," explained Zylberberg. "There needs to be a close partnership between the two in order to create opportunities for improvement on both sides."

Open dialogue

"It is important to build a trustful partnership with your supplier and share forecasting information to prevent supply issues," said Leistler.

"The need for data and documentation on the ancillary materials employed in a developer's manufacturing process is increasing, which requires greater openness and dialogue between parties," added Zylberberg. "It is important to maintain an open dialogue, ensuring that issues are addressed early on, and both parties work together to meet common goals."

Security of supply

"Security of supply is a critical issue for advanced therapy developers. It is imperative to ensure that your ancillary materials provider can scale alongside you and provide the regulatory support you need," emphasized Zylberberg. "This is a two-way street, as developers must provide accurate forecasts and clear directives regarding testing and documentation requirements to ensure timely delivery and support."

"In this regard, it is advisable to set up supply and quality agreements for critical raw and ancillary materials," confirmed Leistler.

—Felicity Thomas

users—ISO Technical Standard 20399 (5)—which has currently been processed into an ISO standard to improve global reach and acceptance," he confirms.

Another initiative has involved the Alliance for Regenerative Medicine (ARM), which approached the European Directorate for the Quality of Medicines (EDQM) about the possibility of setting up a certification scheme for raw materials according to *European Pharmacopoeia* (*Ph. Eur.* 5.2.12) (6), adds Leistler. "This initiative is of critical importance because compliance to this general chapter is already demanded by regulators," he says. "Hence, a certification scheme would ease the regulatory burden for CGT manufacturers."

Furthermore, the European Medicines Agency (EMA) is evaluating the possibility of introducing a master file system, continues Leistler. "Drug master files (DMF) for raw materials are currently only available in the US and Japan," he notes.

COST OF REGULATORY DISCREPANCIES

The global pharmacopeias have different structures and procedures, which can lead to compendial variances regarding testing requirements for critical raw materials, asserts Leistler. "This can be prohibitive on the path towards global compliance and global availability of a new CGT," he says. "Therefore, raw materials and ancillary materials should be chosen for which all global regulatory expectations have been considered in their set of quality parameters and release specifications."

Further explaining the discrepancies facing advanced therapy manufacturers, Zylberberg raised the example of ancillary materials derived from human plasma, which are subject to different regulatory testing requirements depending on the geographic region in which they are being used. "The need to adjust testing to match requirements set by several different competent authorities raises costs and increases complexity for manufacturers," she states. "Employing GMP-compliant ancillary materials saves advanced therapy developers time and money because batch-to-batch consistency allows for greater planning and simplifies manufacturing. Nonclinical-grade material may lack batch-to-batch consistency and the safety profile necessary once a developer enters the clinic, raising costs and increasing risk."

Additionally, if the choice of appropriate raw and ancillary materials is made at a late stage of clinical development, costs can be significantly impacted, confirms Leistler. "This cost increase is primarily driven by the need to perform time-consuming clinical comparability studies to prove the raw material changes do not alter the final cell therapy product. This [step] is mandatory at a late stage in clinical development," he stresses.

CONTINUOUS IMPROVEMENTS

As the market demands increase for advanced therapies, raw and ancillary materials must also be areas of continuous improvement, where further compliance and increased regulatory requirements will come into force as a result of the fact that ATMPs cannot be sterilized, asserts Zylberberg. "The cost associated with raw and ancillary materials and the improvements suppliers may make could easily be absorbed by creating more transparent relationships between sponsors and suppliers," she says.

"Each group of raw materials has its own challenges and hurdles and it is important to understand and address those as the industry matures," concludes Zylberberg. "The regulatory agencies creating a framework around them will help the manufacturing of ancillary materials to always be ahead of the curve."

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