TECHNICAL BULLETIN

Raw Material Qualification – A Fundamental Overview

Raw Material Qualification: Where to Begin?

Introduction

Raw materials are a critical part of the manufacturing process for cell therapy products. However, selecting and qualifying raw materials can be challenging and confusing for cell therapy manufacturers. For example, definitive regulations for raw materials have not yet been developed, resulting in regulatory ambiguity for both cell therapy manufacturers and raw material suppliers. Similarly, there is no single "raw material-grade" manufacturing standard or any standardization of compliance claims, such as ancillary-grade, clinical-grade, Good Manufacturing Practice (GMP)-grade, and animal-component-free. For reasons such as these, it can be difficult for cell therapy manufacturers to determine the qualification regime required for a particular raw material. In order to help clarify these issues, this technical bulletin discusses the fundamentals of raw material qualification with reference to a publication in the journal Cytotherapy.[1]

What Are Raw Materials?

Raw materials are components, reagents, and materials used during the manufacture of cell therapy, gene therapy, or tissue-engineered products that are not intended to be part of the final product. Raw materials include cell isolation reagents, culture and cryopreservation media, and disposables such as plasticware and bioprocessing bags. The term "raw materials" is not globally recognized by regulators and nomenclature varies among regions (for example, raw materials are called "ancillary materials" in North America).

Even though raw materials are not intended to be present in the final product, they can still affect its safety, efficacy, and consistency. Therefore, it is important for raw materials to be carefully scrutinized in terms of their chemical and biological characteristics, as well as their effects on the final cell therapy product.

What Type of Qualification Is Required for Raw Materials?

"Raw material qualification" refers to the process of establishing the source, identity, purity, biological safety, and general suitability of a given raw material. The specific qualification process required for a raw material depends on many factors, including the type of raw material, the type of cell or gene therapy product or tissue-engineered product being manufactured, and the stage of manufacture in which the raw material is used. Therefore, it is impossible to provide a "one-size-fits-all" qualification program suitable for every situation. Instead, manufacturers must design their own qualification programs using a risk-based approach and an understanding of applicable guidelines and regulations.

While there are still no specific and definitive regulations for raw materials, chapter <1043> of the United States Pharmacopeia (USP), provides guidelines for developing appropriate raw materials qualification programs. Such programs should focus on five areas: (1) identification, (2) selection and suitability for use in manufacturing, (3) characterization, (4) vendor qualification, and (5) quality assurance and control. For more information on each of these areas, consult USP <1043>, Ancillary Materials for Cell-, Gene-, and Tissue-Engineered Products.

The level of risk associated with a raw materials will affect the qualification activities that are necessary. USP <1043> provides a framework for classifying raw materials into four different tiers based on risk. For a raw material in Tier 1 (low-risk, highly qualified), the manufacturer may need to request a Regulatory Support File, obtain certificates of analysis (CoA) and certificates of origin (CoO), assess removal from the final product and the effects of lot-to-lot variability, and conduct stability studies. For a raw material in Tier 4 (high-risk, minimally qualified), the manufacturer would need to carry out all the activities listed above, as well as more extensive qualification, such as confirming critical CoA results, conducting adventitious agent testing, and possibly working with the supplier to upgrade the raw material manufacturing process to cGMP standards.

The outline above is only a very high-level overview of raw material qualification. For more details, see USP <1043>, ISO/TS 20399-1, 2, 3, Ph.Eur. General Chapter 5.2.12 and Solomon et al.[1]

What "Grade" of Raw Material Is Required for Cell Therapy Manufacturing?

Contrary to widespread belief, globally there is no particular grade of raw materials that is required for use in cell therapy manufacturing. However, raw materials that are manufactured under robust quality management systems and strictly controlled processes reduce the qualification burden for a cell therapy manufacturer. For this reason, it can be preferable to source raw materials that are manufactured under cGMP, or that are themselves approved, cleared, or licensed therapeutic products or medical devices.

Note, however, that even an approved therapeutic product used as a raw material must be validated for applications outside of its intended use. A manufacturer may not need to repeat tests that the raw material supplier has already carried out in the course of material qualification, but they will still need to evaluate its stability and performance in the manufacturing process, as well as the impact of lot-to-lot variability on the final product.

How Can Manufacturers and Raw Material Suppliers Work Together to Streamline Raw Material Qualification?

While raw material qualification is ultimately the responsibility of the cell therapy manufacturer, it can be made much more efficient through close partnership with the raw material supplier. Suppliers can assist manufacturers in many ways, such as by providing robust quality documentation, permitting audits of their facility, notifying manufacturers of changes to a raw material before such changes take effect, preparing and submitting a Regulatory Support File (RSF), and providing increased levels of testing or custom formulations. Table 2 in Solomon et al.[1], summarized on the right, provides a clear overview of the respective accountabilities of cell therapy manufacturers and raw material suppliers.

Manufacturers should establish strong working relationships with raw suppliers at an early stage. With clear communication between the two parties, it is often possible to anticipate and resolve issues or concerns related to the use of a raw material. Table 3 in Solomon et al.[1] reviews several case studies in which manufacturers and raw material suppliers were able to work together to resolve quality or regulatory issues.

Summary

This document provides only a general overview of raw material qualification. For a more in-depth discussion of these topics, see Solomon et al.[1], which reviews the current state of raw materials regulations from a global perspective. Note, however, that it is critical for manufacturers to familiarize themselves with USP <1043>, ISO/TS 20399-1, 2, 3, Ph.Eur. General Chapter 5.2.12 and other applicable guidelines, preferably engaging directly with regulatory authorities at an early stage in the product development process.

User and Supplier Accountabilities for Raw Material Use

Qualification Activity	Supplier	User
Performance in the intended application		X
Provide CoA, CoC, CoO for raw material	X	
Verify country of origin to assure raw material is safe with respect to source-relevant animal diseases (e.g. BSE/TSE)	X	X
Conduct a risk assessment for use of raw material, based on information provided by supplier, or in collaboration with the supplier, for example, failure modes and effects analysis		X
Establish and implement qualification plan for raw material		X
Confirm CoA test results critical to the cell product (e.g. functional assay)		X
Characterization testing of raw material and set specifications (e.g. identity, purity, functionality, viral contraw materialination, animal origin, etc.)	X	X
Assess effect of lot-to-lot variation of raw material on the final cell product		X
Determine if biocompatibility, biodistribution, cytotoxicity or adventitious agent testing is needed (or testing results might be available from supplier, if applicable)		X
Assess presence of residual raw material in the final cell product		X
Assess stability of raw material	X	X
Qualify the supplier of the raw material (e.g. supplier audit)		X
Execute quality and supply agreement	X	X
Implement higher manufacturing standards, custom formulation or replacement of substandard components	X	X
Upgrade manufacturing process for raw material under cGMP compliance (i.e. in some instances, there may be requirements for shared costs and risk)	X	X
Inform the user of any changes in the manufacturing process of the raw material or design/formulation of the raw material (e.g. under a quality agreement)	X	
Prepare and submit a master file for raw material, if applicable	X	

References

1. Solomon J et al. (2016) Current perspectives on the use of Ancillary Materials for the manufacture of cellular therapies. Cytotherapy 18(1): 1–12.