

# Ancillary Material Qualification – A Fundamental Overview

## Ancillary Material Qualification: Where to Begin?

### Introduction

Ancillary materials (AMs) are a critical part of the manufacturing process for cell therapy products. However, selecting and qualifying AMs can be challenging and confusing for cell therapy manufacturers. For example, definitive regulations for AMs have not yet been developed, resulting in regulatory ambiguity for both cell therapy manufacturers and AM suppliers. Similarly, there is no single “ancillary material-grade” manufacturing standard or any standardization of other 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 AM. To clarify these issues, this technical bulletin discusses the fundamentals of AM qualification with reference to a recent publication in the journal *Cytotherapy*.<sup>1</sup>

### What Are Ancillary Materials?

AMs are components, reagents, and materials used during the manufacture of cell therapy products but are not intended to be part of the final product. AMs include cell isolation reagents, culture and cryopreservation media, and disposables such as plasticware and bioprocessing bags. The term “ancillary material” is not globally recognized by regulators and nomenclature varies among regions (for example, AMs are called “raw materials” in Europe).

Even though AMs are not intended to be present in the final product, they can still affect its safety, efficacy, and consistency. Therefore, it is important for AMs 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 Ancillary Materials?

“Ancillary material qualification” refers to the process of establishing the source, identity, purity, biological safety, and general suitability of a given AM. The specific qualification process required for an AM depends on many factors, including the type of AM, the type of cell therapy product being manufactured, and the stage of manufacture in which the AM 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 AMs, chapter <1043> of the United States Pharmacopeia (USP) provides guidelines for developing appropriate AM 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>.

The level of risk associated with an AM will affect the qualification activities that are necessary. USP <1043> provides a framework for classifying AMs into four different tiers based on risk. For an AM in Tier 1 (low-risk, highly qualified), the manufacturer may need to cross-reference the Drug Master file (DMF; if available), obtain certificates of analysis (CoAs), assess removal from the final product and the effects of lot-to-lot variability, and conduct stability studies. For an AM 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 AM manufacturing process to current GMP standards.

The outline above is only a very high-level overview of AM qualification. For more detail, see USP <1043> and Solomon et al.<sup>1</sup>

## What “Grade” of Ancillary Material Is Required for Cell Therapy Manufacturing?

Contrary to widespread belief, in the United States there is no particular grade of AM that is required for use in cell therapy manufacturing. However, AMs that are manufactured under robust quality management systems with strictly controlled processes reduce the qualification burden for a cell therapy manufacturer. For this reason, it can be preferable to source AMs 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 an AM must be validated for applications outside of its intended use. A manufacturer may not need to repeat tests that the AM 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 Suppliers Work Together to Streamline Qualification?

While AM qualification is ultimately the responsibility of the cell therapy manufacturer, it can be made much more efficient through close partnership with the AM 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 an AM before such changes take effect, preparing and submitting DMFs, and providing increased levels of testing or custom formulations. Table 2 in Solomon et al.<sup>1</sup> provides a clear summary of the respective accountabilities of cell therapy manufacturers and AM supplier.

Manufacturers should establish strong working relationships with AM 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 an AM. Table 3 in Solomon et al.<sup>1</sup> reviews several case studies in which manufacturers and AM suppliers were able to work together to resolve quality or regulatory issues.

## Summary

This document provides only a general overview of AM qualification. For a more in-depth discussion of these topics, see Solomon et al.<sup>1</sup>, which reviews the current state of ancillary material regulation from a global perspective. Note, however, that it is critical for manufacturers to familiarize themselves with USP <1043> and other applicable guidelines, preferably engaging directly with regulatory authorities at an early stage in the product development process.

## 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.