Cytotherapy, 2015; ■■: ■■–■■

International Society for Cellular Therapy
ISCT®

Current perspectives on the use of ancillary materials for the manufacture of cellular therapies

JENNIFER SOLOMON[1], LYNN CSONTOS[1], DOMINIC CLARKE[2], MARK BONYHADI[3], CLAUDIA ZYLBERBERG[4], IAN MCNIECE[5], JOANNE KURTZBERG[6], ROSEMARIE BELL[7] & ROBERT DEANS[8]

[1]STEMCELL Technologies Inc, Vancouver, BC, Canada, [2]Charter Medical Ltd, Winston-Salem, NC, USA, [3]Juno Therapeutics, Seattle, WA, USA, [4]Akron Biotech LLC, Boca Raton, FL, USA, [5]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA, [6]Robertson Clinical and Translational Cell Therapy Program, Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA, [7]QIMR Berghofer Institute of Medical Research, Brisbane, Queensland, Australia, and [8]Rubius Therapeutics Inc, Cambridge, MA, USA

Abstract

Continued growth in the cell therapy industry and commercialization of cell therapies that successfully advance through clinical trials has led to increased awareness around the need for specialized and complex materials utilized in their manufacture. Ancillary materials (AMs) are components or reagents used during the manufacture of cell therapy products but are not intended to be part of the final products. Commonly, there are limitations in the availability of clinical-grade reagents used as AMs. Furthermore, AMs may affect the efficacy of the cell product and subsequent safety of the cell therapy for the patient. As such, AMs must be carefully selected and appropriately qualified during the cell therapy development process. However, the ongoing evolution of cell therapy research, limited number of clinical trials and registered cell therapy products results in the current absence of specific regulations governing the composition, compliance, and qualification of AMs often leads to confusion by suppliers and users in this field. Here we provide an overview and interpretation of the existing global framework surrounding AM use and investigate some common misunderstandings within the industry, with the aim of facilitating the appropriate selection and qualification of AMs. The key message we wish to emphasize is that in order to most effectively mitigate risk around cell therapy development and patient safety, users must work with their suppliers and regulators to qualify each AM to assess source, purity, identity, safety, and suitability in a given application.

Key Words: *ancillary materials, cellular therapy, cGMP, raw materials, regulation, stem cell research, translational medical research*

Introduction

Interest continues to grow in the development and commercialization of cellular therapies because of their potential to resolve a large number of unmet clinical indications [1,2]. Consequently, as new therapies advance through clinical trials, there is increasing scrutiny of the materials and processes used in the manufacture of the intended cell therapy product. A wide variety of starting materials may be used in the manufacturing process, some of which are integral to the final product, and in some cases, contribute to its composition or are found in the final cell product as active ingredients or as excipients. Whereby some materials used with the manufacturing process are ancillary materials, which, by definition, are components, reagents or materials used during manufacture that exert an effect on the cell product but are not intended to be part of the final cell product. It should be noted that the term ancillary material (AM) is not globally recognized by regulators and is commonly referred to as raw material in some jurisdictions, such as in Europe; however, for the sake of clarity, this paper will use the term AM throughout to describe such materials. Examples of AMs include but are not limited to: cell separation reagents, cell culture media, cryopreservation agents and disposables such as plasticware and bioprocessing bags. Many grades and compositions of AMs exist, and typically these are not approved or intended for clinical administration or use (eg, are labeled as "research use only"). Because an AM does come in contact with cells destined for clinical administration, the quality of the AM used can affect the safety, potency and purity of the cell product. As such, the long-term appropriateness of reagents and materials for use as AMs in a clinical setting must be

Correspondence: **Jennifer Solomon**, PhD, Suite 500, 1618 Station Street, Vancouver, BC, Canada V6A 1B6. E-mail: jennifer.solomon@stemcell.com

(Received 3 February 2015; accepted 21 September 2015)

http://dx.doi.org/10.1016/j.jcyt.2015.09.010

considered under a phased and risk-based approach at each stage along the development process of a cellular therapeutic and evaluated on the basis of various criteria, including but not limited to suitability in the given application, composition, compliance, cost, availability and. ultimately, risk to patient safety.

Currently, no AM-specific regulations exist in worldwide regulatory frameworks. A growing number of guidance documents reference AM use from several national and international organizations [3–6], and, although these organizations provide a framework for strategies to control AMs, raw materials, components and starting materials, they do not precisely define the regulatory or quality requirements for AMs. More specifically, regulators provide limited guidance to cell therapy manufacturers (herein referred to as AM users) surrounding compliance requirements, generation and execution of qualification programs and the accountabilities of AM users compared with AM suppliers along development paths. Furthermore, AM suppliers do not consistently classify and name reagents intended for use as AMs, leading to further challenges to compliance. As a result, there is much confusion and mismatched expectations pertaining to the requirements for both users and suppliers. The intent of this paper is to bring further awareness to existing regulatory guidance and assist in clarifying some common misunderstandings as they relate to AMs. Moreover, this paper should serve as a resource to aid in the process of qualification and final selection of AMs for use in cellular therapy applications and ultimately to facilitate the development and commercialization of cellular therapies worldwide. Although the scope of this paper is limited, we will provide a starting point for communication between AM users, suppliers and regulators by defining commonly observed terminology, highlighting current applicable regulations and key guidance references, defining compliance and how it relates to AM use at various stages of cellular therapy development and, finally, outlining key responsibilities and accountabilities surrounding AM qualification on the basis of our combined experiences. We anticipate that this paper will be the first of a series that evaluate and help to establish standards for AM requirements globally.

Terminology

The terminology and quality or compliance claims used to describe AMs for cellular therapies can often be confusing because of inconsistent classification, naming or labeling for intended use. Very few of the more common terms are aligned across industry or region, which makes it exceedingly difficult for end-users to confidently select AMs at critical stages of the development process. In some instances, the terminology may simply be a variation in labeling or marketing techniques between different manufacturers of similar products. Such is the case with laboratory-grade and research-grade terminology frequently used to describe the same AM offered by separate suppliers. However, more frequent misunderstanding arises around current Good Manufacturing Practice (cGMP) labeling, such as products labeled as GMP, cGMP-compliant, or manufactured under cGMP, the interpretation of the requirements to label products as such and the understanding of the intended use (for example, GMP AMs labeled as research use only). Other parties have provided some guidance related to definition of terms in specific regions or as part of independent initiatives that can be leveraged [7]. However, given the criticality of the components and processes required to develop cell therapies, it is important to understand the terminology and highlight the potential differences as they relate to AMs, and materials in general, on a more global perspective. Table 1 defines the more commonly used quality and regulatory terms that describe AMs used for cell therapies that are based on existing guidances and opinion within the industry. It is recognized that there are international differences and discrepancies that are based on intended use of the AM (eg, in research versus clinical applications) and that this table does not recognize all opinions globally, despite the authors' best efforts.

It is important for AM users to investigate and fully understand the claims made by suppliers. Because of the lack of governance and consistency around AM labeling and naming, it is common that suppliers have different definitions and interpretations of standard terms for quality claims. Early and continuous communication between the users and suppliers is critical to align expectations. Furthermore, it is anticipated that dialogue between the users and their regulators will enhance user qualification requirements, and, ultimately, hold suppliers accountable for AM labeling and marketing claims.

However, to further complicate the qualification process, AM manufacturing processes and formulations are generally considered proprietary, and many suppliers are not able or willing to disclose confidential yet necessary information despite vigilant due diligence by AM users. Recognizing this dilemma, many regulatory agencies allow suppliers to submit confidential manufacturing information directly to the agencies in the form of a master file. Master files are, however, neither necessary nor required. With the United States used as an example, a device or drug master file (DMF) for a specific AM can be submitted to the US Food and Drug Administration (FDA) by the supplier, which users can then reference in their regulatory submissions upon obtaining permission from the DMF owner (ie, the supplier). Yet, a common