Cytotherapy, 2014; 16: 1187–1196

International Society for Cellular Therapy
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Reference materials for cellular therapeutics

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Abstract

The development of cellular therapeutics (CTP) takes place over many years, and, where successful, the developer will anticipate the product to be in clinical use for decades. Successful demonstration of manufacturing and quality consistency is dependent on the use of complex analytical methods; thus, the risk of process and method drift over time is high. The use of reference materials (RM) is an established scientific principle and as such also a regulatory requirement. The various uses of RM in the context of CTP manufacturing and quality are discussed, along with why they are needed for living cell products and the analytical methods applied to them. Relatively few consensus RM exist that are suitable for even common methods used by CTP developers, such as flow cytometry. Others have also identified this need and made proposals; however, great care will be needed to ensure any consensus RM that result are fit for purpose. Such consensus RM probably will need to be applied to specific standardized methods, and the idea that a single RM can have wide applicability is challenged. Written standards, including standardized methods, together with appropriate measurement RM are probably the most appropriate way to define specific starting cell types. The characteristics of a specific CTP will to some degree deviate from those of the starting cells; consequently, a product RM remains the best solution where feasible. Each CTP developer must consider how and what types of RM should be used to ensure the reliability of their own analytical measurements.

Key Words: *reference materials, cellular therapeutics, metrology, standards*

Introduction

The case for appropriate standardization is clear (1), and the craft-to-mass paradigm shift described by Griffiths (2) bears many similarities to the situation we have today with cellular therapeutic (CTP) manufacturing. The term "standard" can encompass a variety of meanings and may be interpreted differently by different people, ranging from social norms to formalized agreed documents to physical materials; this imprecision of language can lead to confusion and misunderstanding as to the nature of the standard being discussed. The focus of this discussion is manufacturing and quality in product development, much of which relates to in-house standardization. However, to bring conformity to manufacturing and comply with regulatory expectations, there is a need to apply external standards. Examples of the types of standards that are covered are given in Table I, but these examples are by no means exhaustive.

CTP are defined here as those cell therapy (including tissue engineered) products that are regulated as medicinal products (drugs) and thus subject to standardized quality systems, namely Good Manufacturing Practice, and similar systems in place for other aspects of development, such as Good Clinical Practice. These quality systems standards ensure minimum standards such as hygiene, traceability of documentation and calibration of equipment and ultimately contribute to product conformity, traceability and safety. Other written standards exist such as pharmacopeia, which provide quality criteria for certain raw materials, allowing suppliers to market material of the same generally acceptable quality to many different manufacturers, reducing in-house raw material testing and facilitating material changes. Pharmacopoeias also provide some standardized test methods (eg, sterility) with reduced or no need for validation, which also facilitates regulatory review because the results are recorded in standard units and thus their meaning is immediately understood by the regulator. As will be discussed later, pharmacopoeias also supply a range of reference materials.

With emerging fields such as CTP, there is often a need for standards beyond those imposed by regulation, for example, the need to agree to

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(Received 24 March 2014; accepted 30 May 2014)

http://dx.doi.org/10.1016/j.jcyt.2014.05.024

Table I. Examples of types of standards.

Example standard	Description and purpose
Base quantity	Foundation of the International System of Units (SI) Quantity, measuring unit (abbreviation) • Length, meter (m) • Mass, kilograms (kg) • Time, seconds (s) • Electric current, ampere (A) • Thermodynamic temperature, Kelvin (K) • Amount of substance, mole per liter (mol/L) • Luminous intensity, candela (cd) Of the seven base units, only the kg is not (yet) derived from a physical constant of nature.
Physical (material) standard	
Reference material	A material of known or arbitrary quantity used for a specific comparison purpose, for example, international prototype kilogram.
Certified reference material	A consensus agreed reference material produced by a recognized body such as the World Health Organization, United States Pharmacopoeia (USP), European Pharmacopoeia (Phur.Eur)
Gold standard	Historic reference of "commercial value" by which a currency unit (eg, $, £) had a value relative to a quantity of gold.
Product reference material	Example product material from a qualified process to be used for comparative quality purposes (usually in-house only).
Written standard	
Reference measurement procedure (reference method)	A consensus method that if conducted exactly as described will provide a suitably reliable measurement for the intended purpose.
Pharmacopoeia method	A regional/national standard method applied to pharmaceuticals that may be a reference measurement method or may require the use of a CRM. Its use may be mandatory.
National/international standard	Such as International Standards Organisation (ISO), European Committee for Standardization (CEN), British Standards Institution (BSI). Written standard that may or may not be mandatory for a particular industry. Such standards can, for example, describe processes (eg, quality system) or testing requirements (eg, medical device compliance).
Consensus standard	Industry or organizational agreed written standard, can cover codes of practice, standard operating procedures, agreed definitions (eg, International Society for Cell Therapy consensus definition of MSC).
Guideline	Usually non-binding recommendations and advice from a government agency (eg, European Medicines Agency (EMA), US Food and Drug Administration), industry group, and so on, covering a specific category or type of product.

These examples are descriptive and do not necessarily use standard terms and are used to convey a sense of the range and nature of standards available.

common terminology (3). The scientific community has, for instance, agreed on some minimum cell characteristics that define human multipotent mesenchymal stromal cells (MSC) (4). As with all standards, the purpose must be clearly stated and the standard not misapplied. Dominici *et al.* (5) specifically state that the criteria should only apply to research, and These identifying criteria should not be confused with release specifications for clinical studies. In a recent paper reflecting on 66 investigational new drug development submissions for MSC-based CTP, the US Food and Drug Administration acknowledges this last point but comments that many researchers seem to believe otherwise.

The objective of the following discussion is to identify the need for physical reference materials for quality control of CTP along with some of the issues faced in their preparation. The diversity of methods and products means that the individual needs of developers will differ, and many reference materials (RM) will need to be prepared in-house; consequent generalized solutions cannot be presented.

Reference materials

The concept of reference materials remains a fundamental principle in measurement; of the seven base units (Table I) of the international system of units (SI), only mass (the kilogram) is still dependent on a physical standard. Although a number of attempts have been made and are still under investigation to supersede this international prototype kilogram, all measurements of mass can be traced back through various copies to this one standard (6). Without standards, science would be very much less certain and observations from different labs could neither be compared nor replicated.

Two measurement results are only comparable if they can be traced to the same reference (7), which should ideally be internationally recognized (eg, SI units, certified reference material). This issue affects