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Biotechnology — Analytical methods — General requirements and considerations for the testing and characterization of cellular therapeutic products

Biotechnologie — Méthodes analytiques — Exigences et considérations générales pour les essais et la caractérisation de produits de thérapie cellulaire

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 276, *Biotechnology*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

The emergence of cellular therapeutic products has increased the need for high quality, robust, and validated measurements for the characterization and testing of products containing cells as the active substance. These products are regulated by regional health authorities who evaluate product quality in terms of their quality attributes (QAs) via appropriate biological, physical and chemical assays (analytical methods).

Analytical methods are performed on cellular starting materials, in in-process testing and as a part of product conformance testing, comparability studies, and stability testing. These analytical methods are used to assess attributes associated with product quality features and manufacturing controls (in-process controls), and are performed to establish identity, purity, cell count, viability, potency, and stability in all phases of clinical study and commercialization. Quality attributes are used to ensure that only product lots that meet defined specifications are released. Quality attributes are also used for stability testing and trending purposes as well as in-process indicators.

Analytical methods also underpin the development of new cellular therapeutic products by providing insight into biological mechanisms of action and facilitating the research and development that advances manufacturing. In addition, analytical methods are used to evaluate and compare cellular therapeutic products from different batches that have, for example, been produced on different days, at different locations, or via a changed manufacturing process.

Quantitative measurement of a cellular therapeutic product is challenging due to the complex and highly dynamic nature of viable cells and cell samples, the varying vulnerability of cell types and processing steps, a lack of understanding of fundamental cell biology, and the large number of parameters associated with bioprocessing and measurement processes. Biological variability further complicates measurements. Additionally, different donor samples can have different susceptibilities to processing steps, making the need for in-process controls during the measurement process even more critical. As such, analytical methods are key to evaluate cellular therapeutic products, as well as the cellular starting material and intermediate, although the specific performance criteria can be different from those of the final cellular therapeutic products.

This document provides a general approach to design fit for purpose analytical methods to measure and assess quality attributes of a cellular therapeutic product. Aspects of this document can also be applicable to the testing and characterization of cells used in viruses, exosome, and antibody production. The general process to select and design fit for purpose analytical methods can be applied to cellular starting material, intermediates, cell end products, control cells, feeder cells, and cells used in assays (e.g. target cells). It also provides general approaches to understand, minimize, and monitor sources of variability. Acceptable levels of accuracy and precision are guided by the biological implications of the measurement result and the practical limitations of the measurement process.

This document also provides general considerations for setting specifications for the testing of a final cellular therapeutic product. General considerations are also provided for establishing analytical methods and analytical strategies (including analytical method matrix approaches) for common categories of critical quality attributes (CQAs) (i.e. attributes used to establish identity, cell count, purity or impurity, potency or relevant biological activity, viability, sterility, stability, and maturation profile).

This document was developed to provide additional technical guidance on cell characterization and specifically outlines approaches for strategic development of analytical methods cellular therapeutic product characterization and testing (see Annex A for schematic outline of concepts presented in this document).

Biotechnology — Analytical methods — General requirements and considerations for the testing and characterization of cellular therapeutic products

1 Scope

This document provides general requirements for the testing of cellular therapeutic products intended for human use.

This document also provides considerations for the characterization of cellular therapeutic products, including approaches to select and design analytical methods that are fit for purpose.

Such considerations can be used to establish critical quality attributes for a cellular therapeutic product.

This document is applicable to cellular starting materials (including those for tissue engineered products) and intermediates of cellular therapeutic products.

This document is not applicable to tissues used in transplantation.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
acceptance criteria
numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures which the product or materials at other stages of manufacture is intended to meet

3.2
adventitious agent
microorganisms unintentionally introduced into the manufacturing process

Note 1 to entry: Microorganisms can include bacteria, fungi, mycoplasma or spiroplasma, mycobacteria, rickettsia, protozoa, parasites, transmissible spongiform encephalopathy (TSE) agents and viruses.

Note 2 to entry: Adventitious agents are a subset of impurity for *cellular therapeutic product* (3.15).

3.3
analytical method
investigative procedure for qualitatively or quantitatively measuring or assessing the presence, amount, or functional activity of a target entity (the analyte)