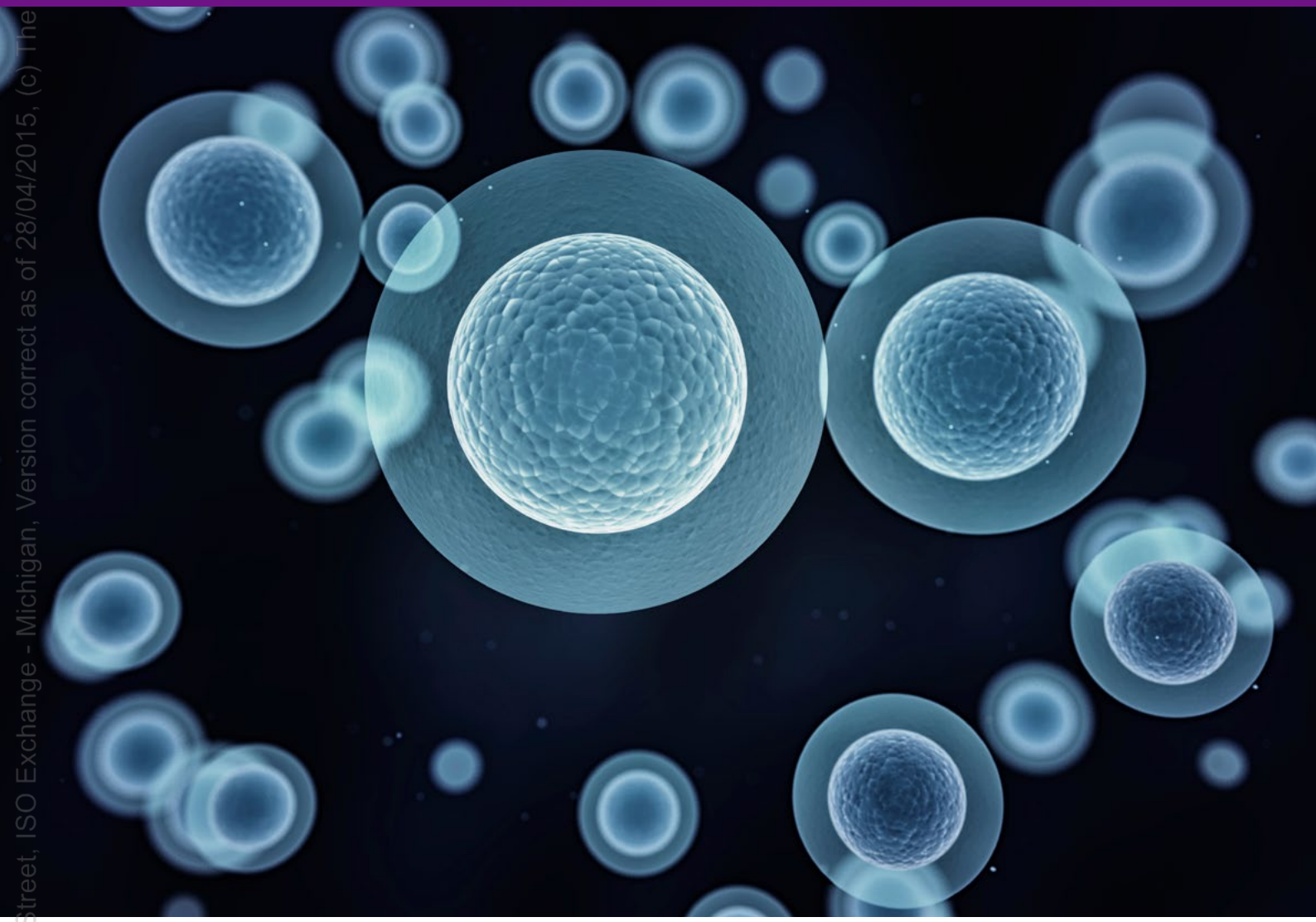
PAS 157:2015

Evaluation of materials of biological origin used in the production of cell-based medicinal products – Guide



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Foreword

This PAS was sponsored by Innovate UK. Its development was facilitated by BSI Standards Limited and it was published under licence from The British Standards Institution. It came into effect on 31 March 2015.

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Acknowledgement is given to Patrick Ginty of Cell Therapy Catapult, as the technical author, and the following organizations that were involved in the development of this PAS as members of the steering group:

- CellData Services
- Cell Medica
- Consulting on Advanced Biologicals Limited
- GlaxoSmithKline (GSK)
- National Institute for Biological Standards and Control (NIBSC)
- Roslin Cells
- University College London

Acknowledgement is also given to the members of a wider review panel who were consulted in the development of this PAS.

This PAS is not to be regarded as a British Standard. It will be withdrawn upon publication of its content in, or as, a British Standard.

The PAS process enables a guide to be rapidly developed in order to fulfil an immediate need in industry. A PAS can be considered for further development as a British Standard, or constitute part of the UK input into the development of a European or International Standard.

Relationship with other publications

This PAS builds on the content of three previous related PAS documents:

PAS 83, *Developing human cells for clinical applications in the European Union and the United States of America – Guide,* PAS 84, *Cell therapy and regenerative medicine – Glossary* and PAS 93, *Characterization of human cells for clinical applications – Guide*. PAS 83 provides a detailed description of the development pathway and accompanying regulatory framework applicable to cellular therapy products for clinical use whereas PAS 84 provides a glossary of terms for cell therapy and regenerative medicine. PAS 93 provides guidance on the characterization of human cells for clinical applications within a regulatory context.

Use of this document

As a guide, this PAS takes the form of guidance and recommendations. It should not be quoted as if it were a specification or a code of practice and claims of compliance cannot be made to it.

It has been assumed in the preparation of this PAS that the execution of its provisions will be entrusted to appropriately qualified and experienced people, for whose use it has been produced.

Presentational conventions

The guidance in this standard is presented in roman (i.e. upright) type. Any recommendations are expressed in sentences in which the principal auxiliary verb is "should".

Commentary, explanation and general informative material is presented in smaller italic type, and does not constitute a normative element.

Contractual and legal considerations

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

Compliance with a PAS cannot confer immunity from legal obligations.

Innovate UK statement

Innovate UK – the new name for the Technology Strategy Board – is the UK's innovation agency. We fund, support and connect innovative businesses to accelerate sustainable economic growth.

Timely, consensus-based use of standards plays a vital role in ensuring that the knowledge created in the UK's research base is commercialized and brought to market and plays an important part in driving innovation.

Innovate UK is working with BSI, Research Councils and Catapults to establish new standards earlier in the development of technologies. We are collaborating in four areas of innovation to define standards that will accelerate the development of technologies and services to provide UK businesses with a competitive "first mover advantage", including the subject of this document that will enable the evaluation of materials of biological origin to be used in the production of cell-based medicinal products.

We have also established the Cell Therapy Catapult as a centre of excellence in innovation, with the core purpose of building a world-leading cell therapy industry in the UK. Its mission is to drive the growth of the industry by helping cell therapy organizations across the world translate early stage research into commercially viable and investable therapies. For more information see **https://ct.catapult.org.uk**.

More widely, health and care is a key priority area in our work – with major innovation programmes to stimulate the development of new technologies, products and services, building on the UK's world-class science and technology base and its global presence in the biopharmaceutical and health technology sectors.

Read more about Innovate UK and our plans in health, care and other areas here: **https://www.innovateuk.gov.uk** or contact **support@innovateuk.gov.uk**

Introduction

The quality of any material used in the production of a cell-based medicinal product can have implications with regard to the safety and efficacy of that product. Cell-based medicines are often complex and exert their therapeutic effects via a mechanism or mechanisms of action that are not fully understood. The need to manufacture a consistent product makes it imperative to reduce as many sources of process variability as possible in order to reduce variability in the final product. The materials used during the processing and manufacture of the final product, especially those of biological origin, are significant sources of variability. In addition, they have the potential to introduce contamination with adventitious agents. However, in the development of cell-based medicinal products, the role of biological materials in processing and manufacturing steps, can be critical in determining the cellular growth characteristics as well as the viability, purity and potency of the final product.

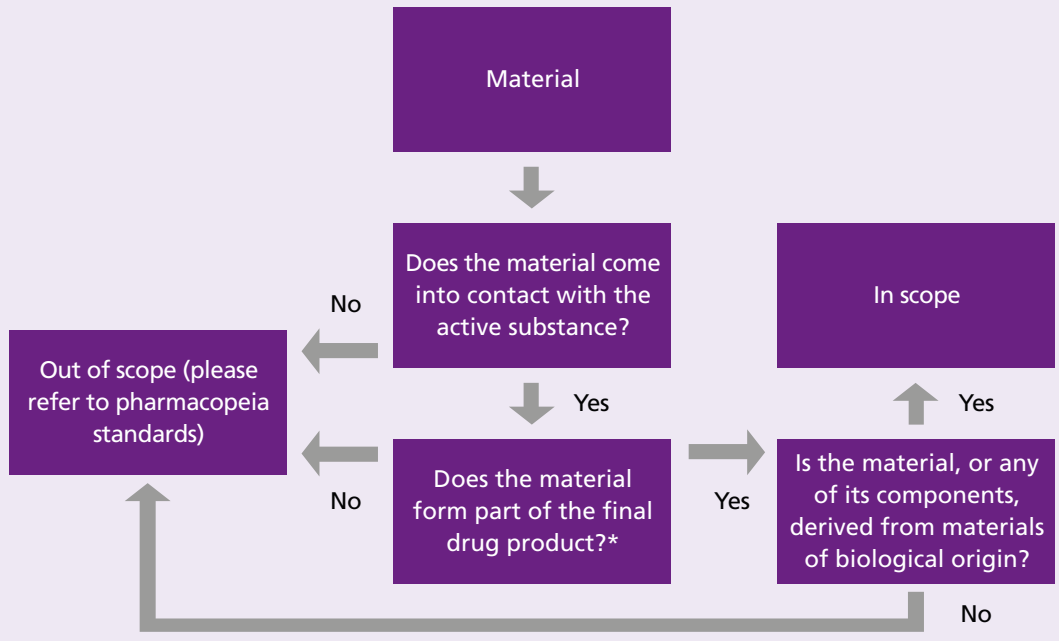
In the European Union (EU), the European Economic Area (EEA) and the United States of America (US), the regulatory requirements around the selection and qualification of these materials reflect the need for flexibility in the approach taken by developers of cell-based medicines, but also demand that the scientific rationale for the selection and qualification of these materials is robust. These requirements, along with differences in expectations of regulatory authorities, combine to make compliance challenging. However, perhaps the most challenging aspect, is the limited availability of biological materials that are manufactured to recognized quality standards, e.g. pharmacopeia grade. Many materials, particularly those of biological origin, are only available in forms for "research" or "*in vitro*" use or, the manufacturers state that the material is not for human use, complicating the qualification of these materials for use in the production of medicinal products.

Therefore, the main objective of this PAS is to provide guidance that aims to help developers improve the consistency and quality of the materials used in the production of cell-based medicinal products, with a view to eliminating/mitigating potential risks to product quality and patient safety and therefore enhance the probability of success at each stage of development and ultimately leads to product licensing.

This PAS builds on a series of previously published PAS documents (PAS 83, 84 and 93) to provide a body of information and guidance that supports the development of cell-based medicinal products in the UK.

NOTE *Figure 1 contains a decision chart that indicates whether or not a material is in scope of this PAS.*

Figure 1 – Decision chart demonstrating the rationale applied to the scope of PAS 157



*Starting material or excipient as defined in Directive 2001/83/EC and therefore out of scope of this PAS.

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1 Scope

This PAS gives guidance on the evaluation of materials of biological origin used in the production of cell-based medicinal products for human use; including those gene therapy products whereby the cells form part of the final drug product.

This PAS also includes guidance on identifying, assessing and controlling risks to patients associated with materials of biological origin.

This PAS covers the evaluation of all materials of biological origin that come into contact with the cellular active substance.

This PAS focuses primarily on materials of human and animal origin and their potential impurities and contaminants. However, reagents derived from diverse biological sources including plants, insects and marine organisms are also used in the development of cell-based medicinal products. Therefore the fundamental principles of risk management also apply for these materials.

This PAS also covers legislation for cell-based medicinal products and is intended for developers who wish to undertake clinical trials and/or license products in both the EU and the US.

This PAS does not cover the selection, assessment or control of cellular active substances, nor the starting materials as defined in Directive 2001/83/EC [1] and excipients. However, it is anticipated that these are still covered by general risk management procedures.

This PAS does not cover biological materials that are used in the development of any other biological medicinal product.

This PAS is applicable for product developers at all stages of development; however maximum benefits can be gained by the implementation of recommendations in this PAS in the early stages of development.

This PAS is intended for use by organizations and individuals with an interest in the development of cell-based medicinal products for clinical applications.

2 Terms, definitions and abbreviations

2.1 Terms and definitions

For the purposes of this PAS the terms and definitions given in PAS 84 apply with the following modifications/ exceptions.

NOTE *The accepted EU terminology and definitions are used as a default throughout the document but where the US terminology differs from this, the appropriate terms may be used. The broad definition of raw materials provided in PAS 84:2012 is used throughout but excludes starting materials as defined in PAS 84.*

2.1.1 ancillary material

material used in the manufacture of a **cell based medicinal product** (**2.1.2**) that comes into contact with the cell or tissue product during manufacturing, but is not intended to be part of the final product formulation

{SOURCE: United States Pharmacopoeia (Chapter 1043) [2]}

NOTE *Ancillary materials can include tissue culture flasks, bags, tubing, pipettes, needles and all plastic-ware that comes into contact with the cell or tissue.*

2.1.2 cell-based medicinal product

medicinal product containing cells as the active substance

NOTE *In European law, cell-based medicines are regulated as Advanced Therapy Medicinal Products (ATMPs) as defined in Directive 2001/83/EC [1]. However, in the United States Code of Federal Regulations (CFR) [3], these products are known as "Section 351" Human Cells, Tissues and Cellular and Tissue-based Products (HCT/Ps) as they are regulated under section 351 of the Public Health Service Act [4] (as defined in 21 CFR Part 1271 [3]. However, in the interests of clarity,* ***cell-based medicinal products*** *are be used as a collective term for both ATMPs and Section 351 HCT/Ps throughout.*

2.1.3 developer

entity that is ultimately responsible for the development of the **cell-based medicinal product** (**2.1.2**)

2.1.4 drug master file

submission to the US Food and Drugs Administration (FDA) that may be used to provide confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs