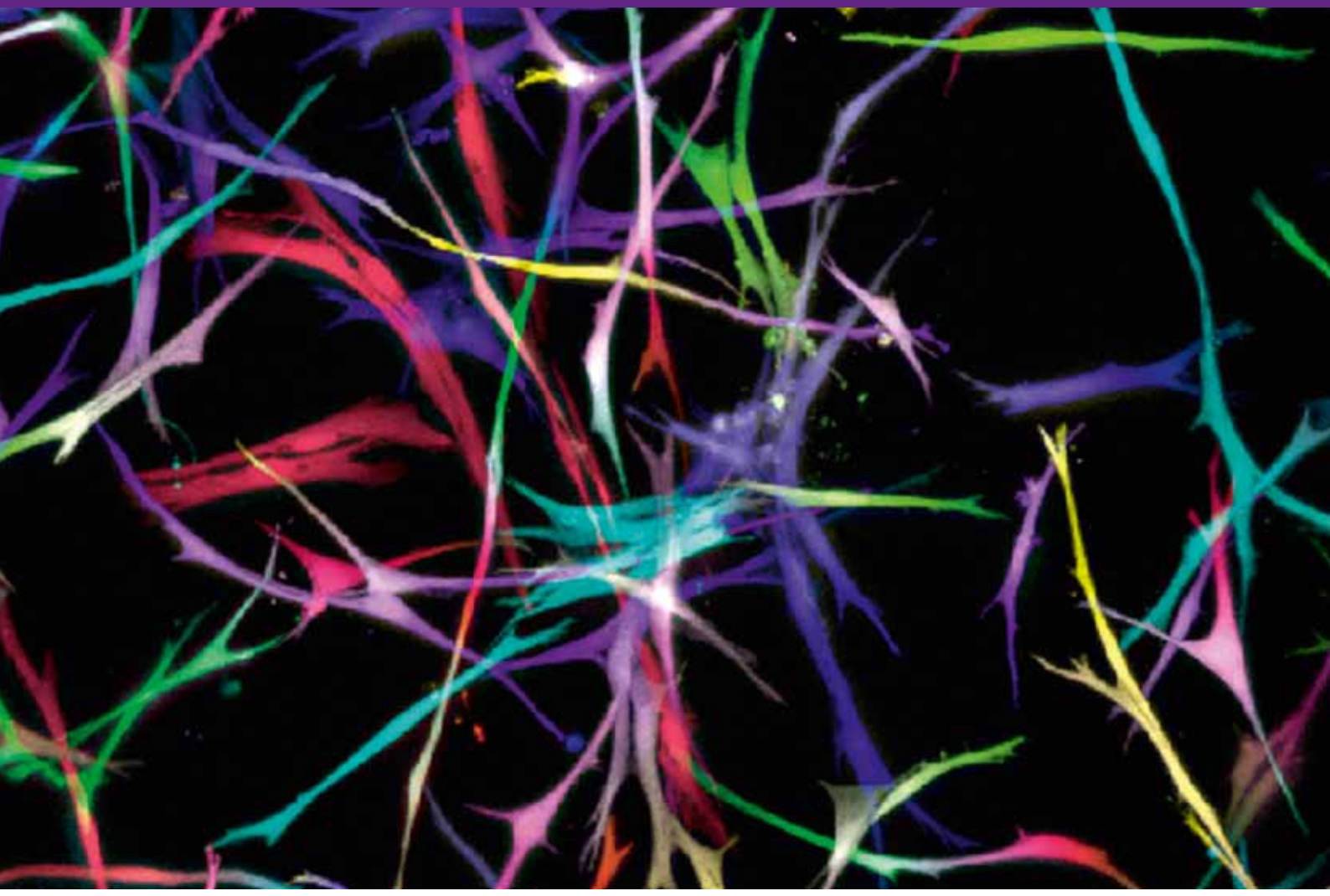
PAS 93:2011

Characterization of human cells for clinical applications

Guide



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Ministerial statement

I am delighted to introduce this new BSI publication that follows on from the successful previously published PAS 83 and PAS 84. It is of great importance to the UK that we not only provide new and innovative medicinal and healthcare products to an ageing population, but also develop the wealth creating industries that will serve this growing need.

The field of cell therapies, including regenerative medicine, is rapidly advancing and the UK has particular strengths in this area, as demonstrated by a recent report from the Office for Life Sciences "Taking Stock of Regenerative Medicine in the UK". The Government intends to bolster and grow the UK's global position in the technology and to support its translation into practical medical therapies.

PAS 93 is a crucial repository of knowledge that will guide developers of new cell therapy products towards successful commercialization and adoption of the technology. It is the first of its kind in the world and is a good example of how UK academia, industry and Government can work in partnership to deliver real economic and social benefits through standardization. BSI has a crucial role to play in harnessing and delivering such knowledge and I encourage all relevant stakeholders to consider how they could use standardization to deliver benefits such as this.

Rt Hon David Willetts MP
Minister for Universities and Science

Foreword

This Publicly Available Specification (PAS) was commissioned by the Department for Business Innovation & Skills (BIS) and its development was facilitated by the British Standards Institution (BSI). It came into effect on 31 August 2011.

Acknowledgement is given to Alison Wilson as technical author, Damian Marshall for developing the annexes on the cell characterization techniques, and the following organizations that were involved in the development of this PAS as members of the steering group:

- BioPharmaceutical Solutions Ltd
- Cell Data Services
- Consulting on Advanced Biologicals
- Department for Business Innovation & Skills (BIS) – Office for Life Sciences
- Department of Health
- LGC
- Loughborough University – Centre for Biological Engineering
- National Physical Laboratory
- University College London
- University of Sheffield – Centre for Stem Cell Biology

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 specification to be rapidly developed in order to fulfil an immediate need in industry. A PAS may 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 complements PAS 83, *Guidance on codes of practice, standardised methods and regulations for cell-based therapeutics – From basic research to clinical application* [1)], which exemplifies the place of characterization in the context of the overall development process for a cell therapy product.

The terms and definitions given in PAS 84, *Regenerative medicine – Glossary* [1)], apply to this PAS.

Presentational conventions

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

Commentary, explanation and general informative material is presented in 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.

[1)] Under revision.

Introduction

This PAS is designed to provide guidance on the characterization of human cells for clinical applications. It complements PAS 83, which exemplifies the place of characterization in the context of the overall development process for a cell therapy product.

An overview of the scope of PAS 93 is illustrated in Figure 1.

Terms used in this PAS are defined in PAS 84, a glossary for cell therapy and regenerative medicine.

For clarity, this PAS differentiates between the terms "cell therapy product", "medicinal product" and "advanced therapy medicinal product" (ATMP).

Cell therapy product is the broadest term used in the PAS and aspects discussed in the context of cell therapy products are applicable to all products consisting of or containing human cells.

In the EU, a medicinal product is one that is subject to the regulatory framework set out in European Directive 2001/83/EC [1] for the authorization, control and marketing of medicines. Medicinal products require prior approval from regulatory authorities before they can be used in clinical trials or sold in any country of the European Economic Area.

An ATMP is a cell-based (or gene-based) product that is subject to the general provisions of the regulatory framework for medicinal products and also to the specific provisions of Regulation (EC) No 1394/2007 [2].

The PAS also includes reference to US requirements. The US regulates most cell therapy products as biologics. This legal category is distinct from drugs (US) but the requirements are broadly comparable, and biologics require prior approval from the Food and Drug Administration (FDA) under Section 351 of the Public Health Services Act (PHS Act) [3] and relevant sections of the Food, Drug and Cosmetics Act (FD&C Act) [4] before they may be used in clinical trials or marketed in the US.

The US also recognizes human cell/tissue products (HCT/Ps) which are not subject to pre-marketing approval but are regulated solely under Section 361 of the PHS Act [3] and Title 21, Part 1271 of the Code of Federal Regulations (21CFR1271) [5] (establishment registration, donor eligibility requirements and good tissue practices). The information in this PAS could be of interest to developers of HCT/Ps, however, there is no current regulatory requirement for the characterization of HCT/Ps. Cell therapy products as covered in this PAS are not specifically defined by US legislation but are regulated under the category of biologics.

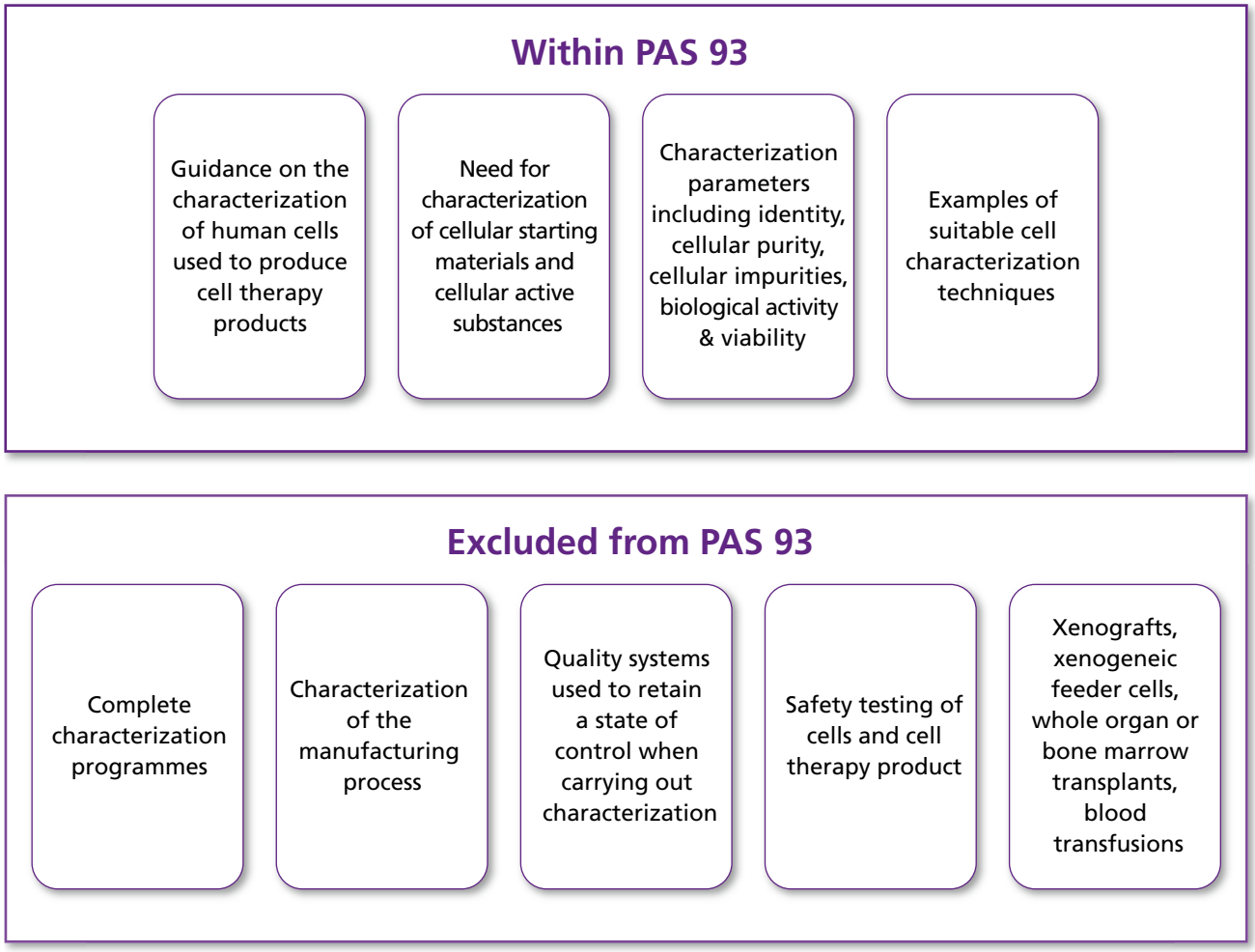
This PAS provides general guidance applicable to all cell therapy products and also guidance specific to licensed biologics and ATMPs.

Approval of a medicinal product requires the submission of a marketing authorization application to the appropriate regulatory authority. The application contains all of the known information concerning the quality, safety and efficacy of the medicinal product.

In the EU, the Marketing Authorisation Application (MAA) is submitted to the relevant authority: the European Medicines Agency is responsible for authorization of ATMPs in Europe.

In the US, the application is known as New Drug Application (NDA) for products regulated as drugs, and a Biologics Licence Application (BLA) for products regulated as biologics. The scientific information requirements are similar to those expected in the EU. The relevant authority is the Food and Drug Administration. Description of the regulatory frameworks in the EU and the US is beyond the scope of this PAS.

Figure 1 – Overview of PAS 93 scope



1 Scope

This PAS gives guidance on the characterization of human cells being developed for clinical applications.

This PAS is not a regulatory guideline, but gives guidance on the need for characterization of cells and key current, available cell characterization techniques. The choice of characterization techniques needs to be made by the developer on a case-by-case basis depending on the intended use of the cells.

This PAS covers the need for the characterization of cellular starting materials and cellular active substances and the characterization parameters (including identity, purity, cellular impurities, biological activity and viability).

This PAS is intended for use by organizations and individuals with an interest in the development of human cells for clinical applications including academic groups, small and medium sized enterprises (SMEs) and larger industrial manufacturers and the general public.

The guidance in this PAS is applicable to the characterization of human cells in the context of EU and US regulation of cell therapy products, but it will be broadly relevant to all regions/markets that accept or refer to International Conference on Harmonisation (ICH) guidance in the regulation of biological medicinal products including cell therapy products.

This PAS is not a manual for developing a cell therapy product and does not cover:

a) complete characterization programmes;

b) characterization of the manufacturing process;

c) quality systems used to retain a state of control when carrying out characterization;

d) safety testing of cells and cell therapy products; and

NOTE *Requirements for safety testing of cells and cell therapy products are addressed in detail in relevant legislation and guidance documents.*

e) xenografts, xenogeneic feeder cells, whole organ or bone marrow transplants and blood transfusions.

2 Terms, definitions and abbreviated terms

2.1 Terms and definitions

For the purposes of this PAS the terms and definitions given in PAS 84 apply.

2.2 Abbreviations

ATMP	advanced therapy medicinal product (EU)
BLA	biologics licence application (US)
CBER	Center for Biologics Evaluation and Research (US)
CBMP	cell-based medicinal products
CDER	Center for Drug Evaluation and Research (US)
CHMP	Committee for Medicinal Products for Human Use (EU)
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
FD&C Act	Food, Drug and Cosmetic Act (US)
HCT/P	human cells, tissues and cell and tissue-based products (US)
HSC	haematopoietic stem cell
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MAA	Marketing Authorisation Application (EU)
MSC	mesenchymal stem cell
NDA	New Drug Application (US)
PHS Act	Public Health Services Act (US)