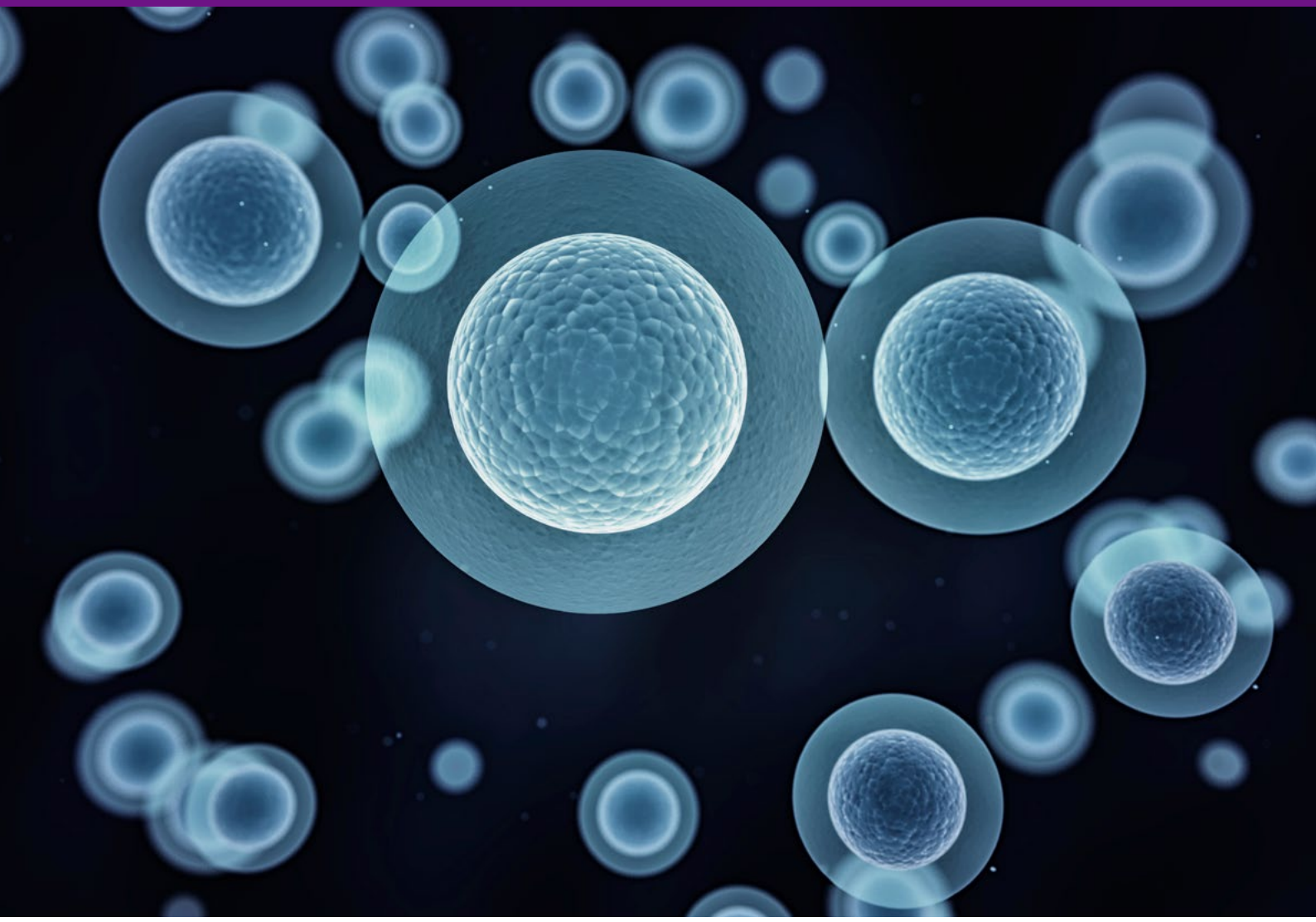
PAS 157:2015

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:

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- 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 It will be withdrawn upon publication of its content in, or as, a British Standard.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.

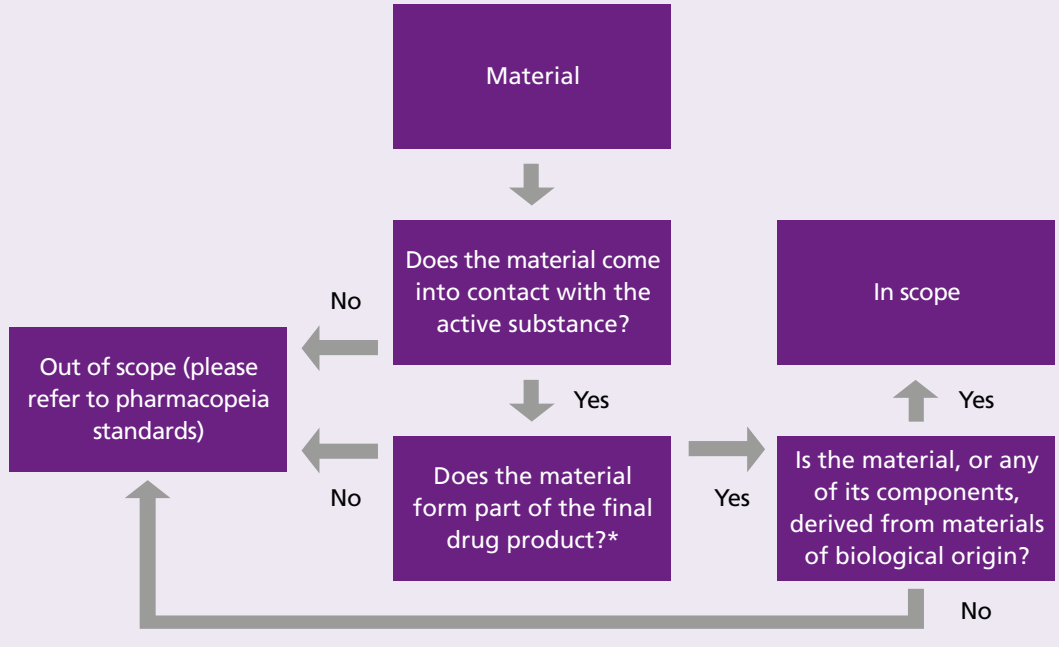
In the European Union (EU), the European Economic Area (EEA) and the United States of America (US), the regulatory requirements around the selection and qualification of these materials reflect the need for flexibility in the approach taken by developers of cell-based medicines, but also demand that 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

2.1.5 excipient

any constituent of a medicinal product other than the active substance and the packaging material

[SOURCE: European Directive 2001/83/EC [1]]

2.1.6 manufacturer

organization responsible for the production of the final product

NOTE *This can be a separate entity from the developer.*

2.1.7 raw material

substances used for manufacturing or extracting the active substance(s) but from which the active substance is not directly derived

NOTE 1 *Examples include reagents, culture media and sera.*

NOTE 2 *The term **raw materials** is not used in the CFR [3]. Instead, the term **ancillary materials** (see **2.1.1**), as defined in the United States Pharmacopoeia (USP) (Chapter 1043) [2] is used to describe all materials used in the manufacture of cell-based medicinal products that "come into contact with the cell or tissue product during manufacturing, but are not intended to be part of the final product formulation". Therefore the definition of ancillary materials also includes materials used during the manufacture of cell-based medicinal products (**2.1.2**) such as; tissue culture flasks, bags, tubing, pipettes, needles and all plastic-ware that comes into contact with the cell or tissue but these non-biological materials are not within the scope of this PAS. Therefore, for the purposes of this PAS, the term **raw material** as defined above includes only those ancillary materials that are of biological origin and are not intended to form part of the drug product.*

2.1.8 supplier

entity that supplies biological materials for use in the production of a **cell-based medicinal product** (**2.1.2**)

2.2 Abbreviations

For the purposes of this PAS, the following abbreviations apply.

AM	ancillary material
ASMF	active substance master file
ATMP	advanced therapy medicinal product
BLA	biologics licence application
CAPA	corrective and preventative action
CBMP	cell-based medicinal product
CEP	certificate of suitability
CFR	US Code of Federal Regulations
CoA	certificate of analysis
CoO	certificate of origin
DMF	drug master file
EC	European Commission
EDQM	European Directorate for the Quality of Medicines and Healthcare
EEA	European Economic Area
EMA	European Medicines Agency
FDA	US Food and Drugs Administration
GMP	good manufacturing practice

NOTE *In the US the term "current good manufacturing practice (cGMP)" is used.*

HCT/P	human cells, tissues, and cellular and tissue-based products
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IP	intellectual property
IVUO	in vitro use only
MAA	marketing authorization application
NDA	new drug application
Ph.Eur.	European Pharmacopoeia
QC	quality control
RUO	research use only
TSE	transmissible spongiform encephalopathy
USP	United States Pharmacopoeia

3 Regulatory requirements and guidance applicable to biological materials used in the production of cell-based medicinal products (EU and US)

3.1 Key differences between the EU and the US Food and Drugs Administration (FDA)

3.1.1 General

There are a number of differences between the regulatory landscape in the EU and the US and this is reflected in the regulatory requirements and guidance related to materials used in the development of cell-based medicinal products.

These differences and the potential impact they have are described and summarized in Table 1 and described in **3.1.2** and **3.1.3**.

3.1.2 Drug master files

In the US, developers have the option of filing and maintaining a drug master file (DMF) as described in 21 CFR 314.420 (Applications for FDA Approval to Market a New Drug) [3]. A DMF is a submission to the 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.

Table 1 – Key differences in regulatory landscape and terminology in the EU and US

Terminology	EU	US
Drug master file (DMF)	No.	Yes.
Active substance master file	Yes (but not applicable to biologicals).	Yes (as part of DMF).
Regulatory definition of materials in the scope of this PAS	"Materials used during the manufacture of the active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance shall be considered as raw materials" (Medicinal Products Directive 2001/83/EC [1]). The definition of raw materials is found in the EU legislation for medicinal products, and specifically for ATMPs. The definition of raw materials in the legislation does not exclude tissue culture plastics, needles, etc. but they are not specifically mentioned in the text as examples of raw materials.	"The defining property of ancillary materials is that they are not intended to be present in the final product. They are materials used as processing and purification aids or agents that exert their effect on the therapeutic substance". Ancillary materials definition also includes "helper" viruses and "helper" plasmids when they are not intended to be part of the final product. Definition taken from USP Chapter 1043 as "ancillary materials" term is not used in the US Code of Regulations (CFR) [3]. The term ancillary materials is used exclusively for HCT/Ps and does not apply to any other drug or biologic. Synonyms found in the CFR include "components" and "reagents".

There are five types of DMF:

a) Type I Manufacturing Site, Facilities, Operating Procedures, and Personnel.
b) Type II Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product.
c) Type III Packaging Material.
d) Type IV Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation.
e) Type V FDA Accepted Reference Information.

A type II DMF can be used to hold proprietary information on the drug substance, drug product or any materials used in their preparation and/or manufacture, i.e. raw materials.

In the EU, there is an active substance master file (ASMF) that is covered by an EMA guidance document (CHMP/QWP/227/02: Guideline on Active Substance Master File Procedure, Rev 2012) [5]. However, unlike the DMF in the US, the ASMF cannot be used for biological active substances such as those used in ATMPs.

3.1.3 Terminology

NOTE *The scope of this PAS is not exclusive to the manufacturing steps in the generation of a cell-based medicinal product as the principles of this PAS can apply equally to any processing steps involving the cellular active substance that may occur prior to any manufacturing steps. However, the legal and regulatory terminology can be specific to the manufacture of a cell-based medicinal product and can vary depending on the country and the piece of legislation in question. Therefore, this subclause discusses the use of the regulatory terminology used during the manufacturing phase of development in both the EU and the US. For example, the terms "raw materials" in the EU and "ancillary materials" in the US (see* ***2.1.7****).*

The term raw materials is not used in the US. Instead, most of the materials that would be considered raw materials in the EU are classified as ancillary materials. References to ancillary materials are made in the United States Pharmacopoeia (USP) [2] and not the US Code of Federal Regulations (CFR) [3] (see **3.2.2**).

3.2 Regulatory requirements and guidance applicable to the manufacture of medicinal products

3.2.1 EU legislation and guidance

NOTE 3.1.3 *refers to the specific terminology that appears in the regulatory requirements/guidance in the EU/US.* ***3.2*** *uses that terminology to identify the parts of the EU/US requirements/guidance that are most applicable to the development of cell-based medicinal products.*

Annex A provides a comprehensive list of regulatory requirements and/or guidance related to the quality of raw materials for the manufacture of ATMPs and/or medicinal products in the EU. This is not an exhaustive list of references to raw materials quality but it covers legislation and guidance which is applicable when considering cell-based medicinal products. Specific references to the requirements related to raw materials have been underlined in Annex A.

Recurring themes in the excerpts from the EU legislation for medicinal products include:

a) traceability of raw materials;
b) control of raw materials during manufacture and distribution;
c) documentation of raw material from origin through manufacture and distribution;
d) sourcing of animal- and human-derived raw materials;
e) the risk of contamination (particularly transmissible spongiform encephalopathy (TSE) and viruses);
f) the need for supplier audits; and
g) risk associated with animal- and human-derived materials.

NOTE *In addition to the EU legislation for the manufacture of medicinal products, the European Commission also provides separate legislation for those steps that may occur prior to any manufacturing steps, i.e. the donation, procurement, testing, processing, preservation, storage and distribution of cells and tissues that are going to be manufactured into cell-based medicinal products. Attention is drawn to parent Directive 2004/23/EC [6] and the two technical Directives 2006/17/EC [7] and 2006/86/EC [8]. These Directives do not refer to raw materials but do make reference to materials that come into contact with the active substance and therefore the principles of this guidance may be applied on a case-by-case basis during these pre-manufacturing steps.*

3.2.2 US regulations and guidance

Ancillary materials were first discussed under the synonym ancillary products in the US Food and Drug Administration Notice, "application of current statutory authorities to human somatic cell therapy products and gene therapy products" (Federal Register 58 (197), October 14, 1993, pp. 53248–53251 [9]). This document established the FDA's authority to regulate human somatic cell therapy products and gene therapy products. The FDA guidance documents provide limited detail on how manufacturers can develop and execute ancillary material (AM) qualification programmes. However, general guidance on the qualification of ancillary materials can be found in the USP [2] (Chapter 1043: ancillary materials for cell, gene and tissue engineered products). This guidance uses a four-tiered risk classification system to guide the appropriate level of qualification, which is summarized in Table 2.

There are no specific references to either raw materials or ancillary materials in 21 CFR [3]. However, the US requirements do contain the terms "components" and "reagents" which both overlap with the definition of AMs. The term component is defined in 21 CFR Part 210 [3] (current good manufacturing practice (cGMP) in manufacturing, processing, packing, or holding of drugs; general) as follows:

"(3) *Component* means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product."

Therefore the term "component" is synonymous with the definition of both a raw material and an ancillary material. This term is used in 21 CFR 211.80 [3] through 211.94 and 211.101(b) and (c). 21 CFR Part 211 (current good manufacturing practices for finished pharmaceuticals) [3].

Table 2 – Summary of risk levels applied to ancillary (raw) materials in the US (adapted from USP 1043)

Risk tier	Examples/comments
1 – Lowest risk (highly qualified).	Licensed biologic, approved drug, approved or cleared medical device or biomaterial.
2 – Low risk (well characterized).	Intended for use in drug, biologic, device manufacture. Made under most relevant current good manufacturing practices (cGMPs) and normally excludes animal derived materials.
3 – Moderate risk (greater qualification required than for tiers 1 and 2).	Intended for *in vitro* diagnostic use only and not for cell, gene and tissue engineered products.
4 – Highest risk (extensive qualification necessary).	Materials not manufactured under cGMP, not for cell, gene and tissue engineered products. Highly toxic substances with biological mechanisms of action and also includes most complex animal derived fluid materials not subjected to adventitious viral removal or inactivation procedures.

Ancillary materials can also be considered as "supplies and reagents", a term that is used in 21 CFR Part 1271.210 and 1271.260 (human cells, tissues and cellular and tissue-based products) [3] but there is no clear definition provided.

***NOTE** Attention is drawn to 21 CFR Part 1271 [3] which contains the requirements that are applicable during the manufacture of a cell-based medicinal product and those steps that occur prior to manufacture, i.e. donation, procurement and handling practice of cells and tissues.*

3.3 Quality declarations for manufactured biological materials used in the production of cell-based medicinal products

A number of different quality declarations can be applied by manufacturers to the biological materials they market.

Table 3 provides a list of manufacturers' quality declarations that confirm that the material has been approved by a regulatory body and/or complies with a recognized quality grade. However, compliance with any grade/standard does not necessarily mean that the material is suitable for a specific process, even if it is of demonstrable quality. The developer should ensure that the product has the requisite properties, e.g. functionality profile.

Table 3 – Recognized quality declarations used by suppliers of materials used in the production of cell-based medicinal products

Quality declaration	Technical and regulatory description
Licenced medicinal product/drug	By definition, a licensed medicinal product/drug has demonstrated quality, safety and efficacy for its intended use and can therefore be viewed as the highest standard in terms of quality. In Europe, this is demonstrated by having an approved market authorization application (MAA), whereas in the US, this is demonstrated by having a biologics licence application (BLA) or a new drug application (NDA).
Pharmacopeia grade	If a material used in the manufacture of a cell-based medicinal product has a monograph in the European Pharmacopoeia (Ph.Eur) [10] or the USP [2], the developer can reference it as a way of demonstrating conformance with a level of quality deemed sufficient for use in the manufacture of a medicinal product. Chapters may contain more general measures for groups of materials but they are not measures that relate to specific materials.
CE-marking	CE-marking is a symbol demonstrating that a product has met all the European directives applicable to it and may be sold in the EU and EEA (Directive 93/42/EEC [11]). A CE-marking provides developers with confirmation that the product has been manufactured under a quality management system, i.e. BS EN ISO 13485 but the suitability of the product for a specific purposed must be qualified irrespective of this approval.
510(k) (pre-market notification)	In the US, cell culture media can fulfil the criteria for being Class II medical devices (medium risk) and therefore can be approved under the 510(k) pre-market notification pathway. 510(k) refers to the specific section of the Food, Drug and Cosmetic Act (21 CFR Part 807) [3] under which Class II medical devices are regulated. Under the provision, manufacturers can gain approval for a device by showing substantial equivalence with a Class II device that has already been approved. As with the CE-marking process above, the 510(k) notification demonstrates that the product has been manufactured under a quality management system, i.e. 21 CFR 820 [3].

Table 3 – Recognized quality declarations used by suppliers of materials used in the production of cell-based medicinal products *(continued)*

Quality declaration	Technical and regulatory description
European Directorate for the Quality of Medicines and Healthcare (EDQM) Certification of Suitability to the European Pharmacopeia (Ph.Eur.)	***NOTE*** *The procedure for achieving certification of suitability to the monographs of the European Pharmacopoeia was established in 1994 to control the chemical purity of pharmaceutical substances. In 1999, the procedure was extended to include products with a risk of TSE.* In order for a manufacturer (a supplier of a biological material in this context) to be granted a certificate of suitability (CEP) the EDQM appoint a panel of assessors to review a detailed dossier that contains a description of the manufacturing process and the tests performed on the materials used along with the final substance. The manufacturer must demonstrate that their product complies with the quality standards required by the Ph.Eur. [10] and European regulations and must also demonstrate the suitability of the Ph.Eur. monograph to control the quality of their product. The applicant must also agree to comply with the relevant good manufacturing practice (GMP) and to accept a site inspection at any time at the request of the EDQM. The CEP is recognized in all EU member states and some additional non-EU countries such as Canada, New Zealand and Australia.

Table 4 contains examples of quality declarations that are used by suppliers of biological materials used in the production of cell-based medicinal products. The descriptions provided are commonly used but there is no consensus on the meaning of the terms used within it and this table is not intended to endorse these descriptions.

Materials bearing these quality declarations should still be assessed for their quality and suitability.

Table 4 – Frequently used quality declarations made by suppliers of materials used in the production of cell-based medicinal products

Quality declaration	Description
GMP or cGMP grade	Manufacturing a material in compliance with GMP requirements (e.g. Directive 2003/94/EC [12] in Europe and 21 CFR Part 211 [3] in the US) demonstrates that the material has been manufactured under a robust quality assurance system. However, GMP compliance is not a quality grade of material, as GMP does not apply to the quality of the product itself, but the systems, processes and procedures used to manufacture it. Some form of regulatory oversight, e.g. inspection, is required to demonstrate that a manufacturing process is GMP compliant, as is the case for the manufacture of medicinal products and active pharmaceutical ingredients. If there is no regulatory oversight, the supplier should only claim to comply with the principles of GMP.
Clinical grade	The term "clinical grade" is used to describe a material that is suitable for clinical application, i.e. use in humans. However, the term "clinical grade" in isolation is not a recognized quality grade and the use of this term by suppliers of materials is discretionary and a thorough quality and risk assessment should still be carried out.
Research use only (RUO) grade	RUO is the grade of material that is commonly supplied by manufacturers and it makes no claims about being suitable for human or clinical application. Sometimes referred to as "in vitro use only" (IVUO). It may also specifically state that the material is not suitable for clinical or human use. Therefore, the suitability of a RUO material for use in clinical applications must be assessed on a case by case basis (see **Clause 4**). Any material that carries the RUO label should undergo a risk assessment by the developer before it is considered for use (see **4.2.3**).
ATMP/HCT/P grade	Suppliers sometimes use regulatory definitions such as "ATMP" or "HCT/P" grade, "ready", etc. as measures of quality. However, the use of these terms by suppliers of materials is discretionary and a thorough quality and risk assessment should still be carried out.
Xeno-free	In the context of human cell-based medicinal products, the term xeno-free implies the absence of non-human animal components e.g. in cell culture media formulations.
FDA approved	FDA approval can only be declared when the manufacturer has a recognized licence or approval for the material in question, e.g. 510(k), BLA, etc. and so "FDA approved" is not a guarantee of quality when used in isolation. If a material in question has been approved for a similar use/ application, e.g. by another developer this does not automatically qualify it for use in a different process.

4 Evaluation criteria and mitigation of risk

4.1 Evaluation criteria

A number of different grades of materials, certificates, terminologies and compliance with quality management systems which can be applied/used by suppliers when supplying their product (see Table 3 and Table 4). However, a number of factors should be considered by developers when evaluating a biological material for its suitability in development of a cell-based medicinal product, irrespective of the grade or quality standard that is claimed by the supplier of that material (see Table 5).

Table 5 – Key factors and considerations when evaluating biological materials for use in the production of cell-based medicinal products

Factor	Key considerations and guidance	Key questions
Source	The need to ensure the identity, activity, purity and quality of materials discussed in **4.1**, begins with the sourcing or provenance of those materials. Materials of biological origin present additional risks including transmission adventitious agents or the introduction of biological impurities. Process development should have the objective of keeping the use of all such materials to a minimum. The use of a risk-based approach to selection of essential materials is encouraged. Attention is drawn to the following guidance and information: • Chapter 5-2-12 of Ph.Eur. raw materials for the production of cell-based and gene therapy medicinal products (draft). • EMEA/410/01 Rev. 3 July 2011) (2011/C 73/01) [13]. • EMA/CHMP/BWP/303353/2010 (2011) [14]. • European Commission Decision 2007/453/EC [15], 2009/830/EC [16] and subsequent amendment to 2007/453/EC [15] (2012/111/EU [17]). • Regulation (EC) No. 1774/2002 [18].	Is the material from source that reduces the risk of adventitious agents? For example, bovine material from countries with negligible risk of TSE, such as Australia or New Zealand. Can the material be replaced with another that has a lower risk profile? For example, porcine-derived trypsin replaced by recombinant trypsin. Is the material from source that reduces the risk of adventitious agents? For example, bovine material from non-TSE countries such as Australia or New Zealand.

Table 5 – Key factors and considerations when evaluating biological materials for use in the production of cell-based medicinal products *(continued)*

Factor	Key considerations and guidance	Key questions
Manufacture	Developers should always seek the maximum level of information related to the manufacturing process applied to a material of biological origin. For example, a material may not be of biological origin but the manufacturing process for that material may still have involved the use of a material of biological origin.	Is the product manufactured in a dedicated facility? For example, to minimize possible contamination issues. If the material is not used in a dedicated facility, what safeguards are in place to avoid the contamination of that material? For example, line clearance procedures, cleaning. Have any biological materials been used in the manufacturing process for the material? If a recombinant protein, was the protein manufactured using a mammalian or bacterial expression system?
Testing	The principles of ICH Q5A [19] (see **B.3**) including testing of materials for viruses, viral clearance capability of manufacturing process and testing of product for contaminating viruses, should be applied. Irradiation or heat inactivation of materials, e.g. cell culture media, serum, is often applied but may suffer from variation in irradiation dose/heat inactivation through the batch of bottles.	What characterization is carried out on the material to show identity, purity and activity levels? Has the supplier of the material performed adequate viral inactivation steps/safety testing on the material before release? Can the consistency of irradiation/heat inactivation be demonstrated amongst batches?
Traceability	Information on the traceability of the material (from source to supplier) should be as complete as possible to ensure that any subsequent steps along the supply chain have not introduced further risk to the safety or quality of that material, e.g. through contamination.	Does the supplier have a complete record of the material and all of its components? Is the material manufactured under a quality system? If so, is the quality system appropriate?
Continuity of supply	Once a material has been identified, it is important to ensure that the supplier can meet the requirements for the consistent and reliable supply of that material. Any failure on their part to supply the requisite material at the requisite level of quality may have a negative impact on the manufacture of a cell-based medicinal product. The extent to which alternative supplies of a material can be considered equivalent must be evaluated by the developer. Qualification of biological functionality may be necessary as well as material quality. Where the material is not commercially available at a suitable quality it may be necessary to manufacture it in-house or under contract. However, the consistency of supply needs to be weighed against the ability (in terms of cost and time) required for full material quality control (QC) that would be provided if the material was purchased through a commercial supplier.	What alternatives are available should a material no longer be available? What characterization is necessary to ensure an alternative material can be considered equivalent? If a suitable alternative is not available, can the material be manufactured in-house?

4.2 Mitigation of risk

4.2.1 Scientific approach

Once a material of biological origin has been procured from the supplier, the responsibility of ensuring that the material is fit for purpose lies solely with the developer. It is for this reason that a number of considerations should be taken into account when using that material in the processing and/or manufacture of a cell-based medicinal product.

Table 6 contains a list of factors and considerations that should be taken into account by developers of cell-based medicinal products to mitigate risks associated with materials of biological origin, irrespective of the grade or quality standard that is claimed by the supplier of that material.

4.2.2 Supplier audit and questionnaires

One method of increasing the developer's confidence in the quality of a material is through supplier audit. Supplier audit provides the developer with an opportunity to ensure that all of the information required to demonstrate traceability from the origin of the material(s) to the final distribution is present and that these documented records provide sufficient information that is recorded. If the supplier is operating to a certified quality management system, e.g. BS EN ISO 9001, this can provide further assurances to the developer that a system of record keeping is being maintained and procedures are in place to ensure a state of control, i.e. corrective and preventative action (CAPA). These audits are used to assess the entire manufacturing process, the shipment and distribution procedures, along with any testing procedures. For example, for each test carried out by the supplier (e.g. in process testing, final quality control (QC) testing) a standard operating procedure should be in place along with an associated training record for each member of staff that carries out the test in question.

Table 6 – Key factors and considerations for the mitigation of risks associated with biological materials used in the production of cell-based medicinal products

Factor	Key considerations	Key questions
Validation for the specific application/ process in question	A single material can be used in multiple different and often complex manufacturing processes in order to generate a multitude of different cell-based medicinal products. For example, certain cytokines and/or growth factors are present in a wide variety of cell culture processes and products. However, it should not be assumed that because a material can be used for one process, it is fit for purpose when applied to another. For this reason, validation studies that measure the effects of the biological material on final product quality when applied to a particular process should be considered.	Has the material been validated for use in a similar process? What are the specific risks/ impacts on the final product quality if the material is not fit for purpose?
Testing/ characterization	A biological material that does not present a direct safety risk may still not be suitable for use if it does not consistently provide levels of biological activity that are sufficient for its intended purpose. The specification in the certificate of analysis (CoA) provided by the supplier of the biological material can be used as a starting point for this but it should not be the sole basis for ensuring quality as a CoA often only contains basic information such as sterility and purity. It is the responsibility of the developer to test and characterize the incoming material to ensure that it is fit for purpose and each batch is consistent. For analytical test methods with direct implications to safety such as detection of adventitious agents, these methods should be validated from the outset. All methods should be demonstrated to be fit for purpose.	Which are the attributes of the material that are most critical to final product quality? How is the material going to be tested and are the methods/ reagents used fit for purpose? Has the potential for batch to batch variability been taken into account?

Developers should audit suppliers before the procurement of a new material, and then at periodic intervals afterwards to ensure that the same levels of quality are being maintained. Although supplier audit is not mandated by the regulators in the EU or the US, attention is drawn to Annex II, part B5 of *EudraLex* Volume 4 [20] (see Annex A).

Developers can share the audit by undertaking it with another developer that also utilizes that material. However, a material can be better qualified for use in the processing/manufacture of one cell-based medicinal product over another, and the developer should take this into account when considering combining forces with another developer to do this, in addition to any concerns over intellectual property (IP).

Before undertaking an audit of a supplier, the developer should submit a questionnaire to the supplier that contains a number of key questions that allows the developer to evaluate the suitability and quality of the material in question and then also assess the need for an audit.

The supplier questionnaire can be used to extract information related to the material in question, and should be comprehensive enough to ensure that any obvious safety risks are assessed.

Materials of biological origin should come under additional scrutiny, in addition to any claims that are made by the manufacturer regarding quality. Table 7 contains sample questions that the developer can include in a supplier questionnaire.

The developer should request a certificate of analysis (CoA) and a certificate of origin (CoO), that demonstrate the specifications, composition and provenance of the material.

Table 7 – Example questions that can be included in a supplier questionnaire for the evaluation of a biological material for use in the production of cell-based medicinal products

Example questions applicable to all materials
a) Where is the material manufactured and is it segregated from other materials during manufacture?
b) What characterization of the product is carried out, e.g. release tests/specifications?
c) If applicable, what sterilization or other decontamination measures have been applied?
d) Is the material manufactured under a specific quality system, to conform to the pharmacopeia, to meet a quality standard, etc?
Example questions specific to animal-derived materials
a) Are there any animal components in the material, and if so please specify the type?
b) If bovine, please specify the source (country) of the animal from which the material is derived?
c) What viral testing was carried out on the material and have any viral clearance steps been carried out?
d) If bovine material is present, have any steps been taken to minimize the risk of TSE transmission?
NOTE *If using bovine serum, attention is drawn to EMA guidelines on the use of bovine serum in the manufacture of human biological medicinal products [21].*
Example questions specific to human-derived materials
a) What is the type and tissue source of the human material?
b) What level of donor testing was carried out?
c) In what country does the donor reside?
d) Was the donation and procurement of the material carried out under the applicable regulatory requirements, e.g. EU Tissues and Cells Directives [6] [7] [8], 21 CFR [3] Part 1271?

4.2.3 Risk assessments

The developer can use the information provided by the supplier of a biological material as the basis for a risk assessment. The aim of a risk assessment in instances such as this, is to use a systematic and consistent procedure to assess both the likelihood of occurrence and severity of the outcome associated with a specific risk for a specific material. One such approach to assessing risk is described in the guidance provided in ICH Q9 (quality risk management) [22] (see **B.3**).

The developer should determine what is an acceptable level of risk and risk mitigation. The threshold of what is a low, medium or high risk material should be justified and the methodology applied should be weighted as such to ensure that a low risk status is more difficult to achieve than a medium or high risk. Equally, the degree of risk mitigation applied to the material in question should be justified using a robust scientific rationale.

Risk assessments can be used to support the use of a material in clinical and commercial manufacture of a cell-based medicinal product. Therefore it can be useful to include these in regulatory submissions. However, it should be noted that the risk assessment is carried out to assess the safety and quality risks associated with a material and does not provide any assessment of the biological functionality and any resultant impact on product quality and efficacy.

5 Characterization of biological materials

The impact on the quality of cell-based medicinal product made by the inclusion of a single material of biological origin in the processing and manufacture of that product, cannot be assessed without robust characterization of the biological material in question. For example, when there is a requirement to replace a material during development, in order to make that change, an equivalent replacement material should be sought and which has both scientific and regulatory implications (see **6.1**). This emphasizes the need for characterization.

The developer and the supplier share the responsibility for testing/characterization to ensure the quality of the material meets their criteria, although the degree of supplier responsibility is very much dependent upon the agreement in place between the supplier and the developer (see **6.2**). However, once the developer has accepted the material, the responsibility for the continued control and characterization of that material lies with them. This responsibility includes any validation and/or comparability studies that may have to be carried out to demonstrate that the material has not changed the quality, safety and efficacy of the product, beyond levels that are acceptable to the developer and the regulator, i.e. when changing suppliers, lots, storage conditions.

The frequency, type and level of characterization applied depends upon the nature of the biological material in question, but the developer should apply a level of characterization that is proportional to the type and criticality of that material (a risk-based approach). Typically, a material could be tested to provide further information on a number of characteristics, but the extent of these tests will depend on the level of testing carried out by the manufacturer and the robustness of the data they provide. A brief summary of these characteristics include:

a) appearance – a short description of what the material looks like;
b) identity – a test to confirm the presence of the substance of interest;
c) purity – a measure of how pure the substance is;
d) impurities – these can be divided into:
    1) product-related impurities – typically break-down products of the material, but with biological materials this can include other unwanted substances that were part of the original material;
    2) process-related impurities – residues from the manufacturing process;
    3) contaminants – any substance that was not intended to be there, typically bacterial (sterility, endotoxin) and adventitious agents, but can include solvents, leachates, etc.;
e) content (quantity) – the amount/concentration of the intended substance in the container;
f) biological activity – where the material is biologically active, e.g. enzyme activity and units of cytokine activity; and
g) other relevant characteristics – e.g. pH, osmolality, conductivity, volume, mass, density, moisture content, visible/sub-visible particles and inclusions.

NOTE 1 *This list does not refer to the cellular material that forms the active substance of the cell-based medicinal product CBMP, as described in PAS 93. However, many of the general principles of PAS 93 can be applied to the characterization of biological materials.*

NOTE 2 *More detailed information on the quality requirements for cell-based medicinal products is provided in draft Chapter 5-2-12 of the Ph.Eur. [10].*

6 Managing changes to materials

6.1 The regulatory impact of changes to materials

In order to ensure the quality of the final medicinal product is maintained, the materials used in the processing and manufacture of that product should themselves be manufactured to consistent levels of quality. The need for consistency of quality of a material is emphasized if a supplier:

a) changes the manufacturing process (including composition of the biological material); or
b) ceases to manufacture the material; or
c) changes the manufacturing site.

Any changes to the process or composition of biological materials at any stage during development, including pre-clinical, are likely to have an impact on the quality of the cell-based medicinal product. This can impact the validity of previous studies undertaken before the change.

Changes made once the product has entered the clinical phase of development should be assessed for their impact on regulatory compliance. The data required to justify these changes should always be proportional to the stage of development and the level of risk.

6.2 Supplier agreement considerations

In the event of a change being made to the manufacturing process or composition of a biological material by the supplier, it is important that the developer is aware of these changes prior to them being effected. Equally, the developer of the cell-based medicinal product should identify an alternative supplier of the biological material, as the preferred supplier may cease to manufacture the material. As such, the quality agreement executed by the developer should have a clear clause relating to continuity of supply.

In addition to having a suitable characterization package to allow comparability studies to be carried out with a replacement or modified biological material, the developer should also incorporate clauses into the original agreement with the supplier of the biological material in question, mandating that if changes to the manufacturing process for that material are to occur, sufficient notice must be given by the supplier of the biological material to the developer.

Annex A (informative)
Excerpts of EC legislation that refer to raw materials

Regulation EC 1394/2007 [23] (The Advanced Therapy Medicinal Products Regulation)

Article 15 Traceability (1)

The holder of a marketing authorisation for an advanced therapy medicinal product shall establish and maintain a system ensuring that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used.

Directive 2001/83/EC [1] as amended by Directive 2009/120/EC [24]

ANNEX I Part I Standardised Market Authorization Dossier Requirements

3.2.1. Active substance(s)

3.2.1.1. General information and information related to the raw and starting materials

b)

Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials.

3.2.1.2. Manufacturing processes of the active substance(s)

b)

Raw materials shall be listed and their quality and controls shall also be documented.

3.2. Content: basic principles and requirements

(3) This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.

ANNEX I PART IV ADVANCED THERAPY MEDICINAL PRODUCTS

3. SPECIFIC REQUIREMENTS REGARDING MODULE 3

3.1. Specific requirements for all advanced therapy medicinal products

A description of the traceability system that the marketing authorisation holder intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used, shall be provided.

The traceability system shall be complementary to, and compatible with, the requirements established in Directive 2004/23/EC of the European Parliament and of the Council (*), as regards human cells and tissues other than blood cells, and Directive 2002/98/EC, as regards human blood cells.

3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products

3.3.1. Introduction: finished product, active substance and starting materials

Materials used during the manufacture of the active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance shall be considered as raw materials.

Eudralex Volume 4, Annex II – Part A [20]

Animals

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In addition to compliance with TSE regulations, other adventitious agents that are of concern (zoonotic diseases, diseases of source animals) should be monitored by an ongoing health programme and recorded. Specialist advice should be obtained in establishing such programmes. Instances of ill-health occurring in the source/donor animals should be investigated with respect to their suitability and the suitability of in-contact animals for continued use (in manufacture, as sources of starting and raw materials, in quality control and safety testing), the decisions must be documented. A look-back procedure should be in place which informs the decision-making process on the continued suitability of the biological active substance or medicinal product in which the animal sourced starting or raw materials have been used or incorporated. This decision-making process may include the re-testing of retained samples from previous collections from the same donor animal (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source/donor animals must be documented and used to determine the removal of those animals from the programme for defined periods.

Documentation

26

Starting and raw materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, to assure an appropriate level of control including their microbiological quality.

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Where human cell or tissue donors are used, full traceability is required from starting and raw materials, including all substances coming into contact with the cells or tissues through to confirmation of the receipt of the products at the point of use whilst maintaining the privacy of individuals and confidentiality of health related information. Traceability records must be retained for 30 years after the expiry date of the medicinal product. Particular care should be taken to maintain the traceability of medicinal products for special use cases, such as donor-matched cells. Directives 2002/98/EC and Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events apply to blood components when they are used as starting or raw materials in the manufacturing process of medicinal products. For ATMPs, traceability requirement regarding human cells including haematopoietic cells must comply with the principles laid down in Directives 2004/23/EC and 2006/86/EC. The arrangements necessary to achieve the traceability and retention period should be incorporated into technical agreements between the responsible parties.

Starting and Raw Materials

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The source, origin and suitability of biological starting and raw materials (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors) should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available, the risk of using a potentially failed material and its potential impact on other batches should be clearly understood and assessed under the principles of QRM. In such cases, release of a finished product is conditional on satisfactory results of these tests. The identification of all starting materials should be in compliance with the requirements appropriate to its stage of manufacture. For biological medicinal products further guidance can be found in Part I and Annex 8 and for biological active substances in Part II.

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The risk of contamination of starting and raw materials during their passage along the supply chain must be assessed, with particular emphasis on TSE. Materials that come into direct contact with manufacturing equipment or the product (such as media used in media fill experiments and lubricants that may contact the product) must also be taken into account.

Quality Control

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For biological medicinal products with a short shelf life, which for the purposes of the annex is taken to mean a period of 14 days or less, and which need batch certification before completion of all end product quality control tests (e.g. sterility tests) a suitable control strategy must be in place. Such controls need to be built on enhanced understanding of product and process performance and take into account the controls and attributes of starting and raw materials.

Eudralex Volume 4, Annex II – Part B1 [20]

3

Control measures for starting or raw materials at establishments such as abattoirs should include appropriate elements of a Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency. These measures may be drawn from sources outside EU GMP but should be shown to provide equivalent levels of control.

4

Control measures for starting or raw materials should be in place which prevent interventions which may affect the quality of materials, or which at least provides evidence of such activities, during their progression through the manufacturing and supply chain. This includes the movement of material between sites of initial collection, partial and final purification(s), storage sites, hubs, consolidators and brokers. Details of such arrangements should be recorded within the traceability system and any breaches recorded, investigated and actions taken.

5

Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture. Issues must be investigated to a depth appropriate to their significance, for which full documentation should be available. Systems should also be in place to ensure that effective corrective and preventive actions are taken.

Eudralex Volume 4, Annex II – Part B10 [20]

Somatic Cell Therapies and Tissue Engineered Products

1

Where they are available, authorised sources (i.e. authorised medicinal products or CE marked medical devices) of additional substances (such as cellular products, bio-molecules, bio-materials, scaffolds, matrices) should be used in the manufacture of these products.

EMEA/CHMP/410869/2006

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS – 2009 [25]

4.2.1

Starting and raw materials

The manufacturing process of CBMP usually does not include terminal sterilisation, purification steps, viral removal and/or inactivation steps. Therefore, stringent sourcing requirements and acceptance criteria for all materials derived from human or animal origin should be adequately defined according to their intended use.

4.2.1.2. Other materials, reagents and excipients

Each substance used in the procedure should be clearly specified and evaluated as to its suitability for the intended use. The microbial purity and low endotoxin level of these materials should be ensured.

The quality of biologically active additives in culture media such as growth factors, cytokines and antibodies, should be documented with respect to identity, purity, sterility and biological activity and absence of adventitious agents. It is recommended to keep the use of such materials to a minimal and to avoid the use of reagents with sensitisation potential e.g. βlactam antibiotics.

For viral safety aspects, the guidelines on viral safety and Eudralex vol. 2B should be taken into consideration. The principles laid down in the general text of the European Pharmacopoeia on viral safety should be followed for every substance of animal and human origin that is used during the production.

When the raw materials, reagents and/or excipients have a marketing authorisation or mentioned in a Pharmacopoeia, appropriate references may be given.

A. Human derived materials

Reagents of human origin (e.g. albumin, immunoglobulins) should be evaluated for their suitability in a manner identical to that employed for plasma-derived products as recommended in the CPMP Note for guidance on plasma-derived medicinal products. The use of synthetic alternatives should be investigated. If serum is required in the culture media, the use of serum isolated from the same individual who donated the cells is preferred, where possible, to alternate allogeneic serum.

B. Animal derived material

Where cells or tissues of animal origin are used e.g. as supportive cells, the guidance given in "Points to consider on Xenogeneic Cell Therapy Medicinal Products" should be followed.

Animal derived reagents may harbour infectious agents and may increase undesirable immunological responses in the recipient. When applicable, the use of animal reagents should be avoided and replaced by non-animal derived reagents of defined composition.

When bovine serum is used, the recommendations of the Note for Guidance on the "Use of Bovine Serum in the Manufacture of Human Biological Medicinal Product" should be followed. The use of irradiated sera and/or alternative synthetic media is encouraged and should be considered.

For viral safety testing of materials of other animal species, the table of extraneous agents to be tested for in relation to the general and species-specific guidelines on production and control of mammalian veterinary vaccines and Note for Guidance on Production and Quality Control of Animal Immunoglobulins and Immunosera for Human use should be consulted.

4.2.3

Characterisation

3

Adventitious agents

A critical aspect is to establish that CBMP are free from adventitious microbial agents (viruses, mycoplasma, bacteria, fungi). The contamination could originate from the starting or raw materials (see above), or adventitiously introduced during the manufacturing process. A risk assessment should be performed to evaluate the possibility of reactivation of cryptic (integrated, quiescent) forms of adventitious agents. A thorough testing for the absence of bacteria, fungi and mycoplasma shall be performed at the level of finished product. These tests should be performed with the current methodologies described in the European pharmacopoeia for cell-based products. In cases where the short shelf life of the CBMP is prohibitive for the testing of absence of bacteria under the Ph.Eur. requirements, alternative validated testing methods may be acceptable, if justified.

EMA/CAT/GTWP/671639/2008

Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (2012) [26]

5.1.2. Other materials, reagents and excipients

Materials and reagents used for the transduction process and subsequent steps should be of appropriate quality, including testing for sterility, absence of adventitious agents and endotoxin among other controls, in order not to compromise the quality, safety and efficacy of the final product. Viral safety as well as measures taken to minimise the risk of transmitting agents causing TSE of any reagent or material of animal origin should be demonstrated. Recombinant proteins such as enzymes, antibodies, cytokines, growth or adhesion factors should be characterised and controlled, where appropriate and relevant.

Annex B (informative) Regulatory documents and guidance referenced in this guide

B.1 Europe

European Commission Decision 2007/453/EC of 29 June 2007, 2009/830/EC and subsequent amendment to 2007/453/EC (2012/111/EU), establishing the BSE status of Member States or third countries or regions thereof according to their BSE risk.

Regulation (EC) No 1774/2002 of the European Parliament and of the Council of 3 October 2002 laying down health rules concerning animal by-products not intended for human consumption.

Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

Council Directive 93/42/EEC of 14 June 1993 concerning medical devices as amended by Directive 2007/47.

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use as amended by Directive 2009/120.

Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells.

Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells.

Eudralex Volume 4 Good Manufacturing Practice (GMP) Guidelines: Annex II Manufacture of Biological active substances and Medicinal Products for Human Use.

EMA/CAT/GTWP/671639/2008 Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (2012).

EMEA/CHMP/410869/2006 Guideline on human cell-based medicinal products (2009).

EMEA/410/01 Rev. 3 July 2011 (2011/C 73/01) Notes for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (2011).

EMA/CHMP/BWP/303353/2010 CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products (2011).

CHMP/QWP/227/02 Guideline on Active Substance Master File Procedure, Rev 2012.

B.2 United States of America

Title 21 Code of Federal Regulations Part 211 Current Good Manufacturing Practices for Finished Pharmaceuticals.

Title 21 Code of Federal Regulations Part 314 Applications for FDA Approval to Market a New Drug.

Title 21 Code of Federal Regulations Part 807 Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices.

Title 21 Code of Federal Regulations Part 820 Quality System Regulation.

Title 21 Code of Federal Regulations Part 1271 Human Cells, Tissues and Cellular and Tissue-Based Products.

U.S. Food and Drug Administration Notice, "application of current statutory authorities to human somatic cell therapy products and gene therapy products" (Federal Register 58(197), October 14, 1993, pp. 53248–53251).

B.3 Other

ICH Q5A(R1) Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin.

ICHQ9 Quality Risk Management.

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PAS 84, *Cell therapy and regenerative medicine – Glossary*

PAS 93, *Characterization of human cells for clinical applications – Guide*

BS EN ISO 9001, *Quality management systems – Requirements*

BS EN ISO 13485, *Medical devices – Quality management systems – Requirements for regulatory purposes*

Other publications

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