PAS 157: The selection of materials of biological origin used in the design and development of cell-based medicinal products for clinical application – Guide

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Standards or “Standards?”

Standards are the cornerstone of the Medical Device and Pharmaceutical Industries

Cells:
- Complex, varied and highly specified functionality
- Specified manufacturing processes
- Sensitive to micro-environment
- Cannot be characterised by simple physico-chemical methods
So, how do standards fit in?

- BSI works closely with the Catapult, UK research base, academia, regulatory bodies and other relevant organizations (in both the public and private sector) to develop best practice in regenerative medicine and cell therapies.

- Formed Regenerative Medicine-1 (RGM-1) committee of cell therapy experts in 2009.

- BSI has published several guidance (PAS) documents in the area:
  - **PAS 83** – a guide to the regulatory considerations product developers need to take account of in Europe and the US.
  - **PAS 84** - a glossary of terms used in cell therapy and regenerative medicine.
  - **PAS 93** - a best practice in characterization of human cells for clinical applications.

- PAS (publically available specifications) are not standards in traditional sense but promote best practice within a regulatory context.

- Available at: [https://ct.catapult.org.uk/regulatory-documents](https://ct.catapult.org.uk/regulatory-documents)
Regulatory Guidance – PAS 83

• Describes + compares regulatory pathways for cell-based medicines in EU and US
• Definitions and key differences between EU and US
• Annex features relevant guidance, pharmacopeia monographs and chapters
• Technical author: Christopher Bravery (Consulting on Advanced Biologicals)
Table 3 Summary of EU regulatory authority responsibilities for CBMPs

<table>
<thead>
<tr>
<th>NCA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing (GMP) licence</td>
<td>✔️</td>
</tr>
<tr>
<td>EUTCD</td>
<td>✔️</td>
</tr>
<tr>
<td>Orphan designation</td>
<td>✔️</td>
</tr>
<tr>
<td>Innovation Task Force</td>
<td>✔️</td>
</tr>
<tr>
<td>SME registration</td>
<td>✔️</td>
</tr>
<tr>
<td>Classification</td>
<td>✔️</td>
</tr>
<tr>
<td>Certification</td>
<td>✔️</td>
</tr>
<tr>
<td>Scientific advice</td>
<td>✔️</td>
</tr>
<tr>
<td>CTA</td>
<td>✔️</td>
</tr>
<tr>
<td>MAA</td>
<td>✔️</td>
</tr>
<tr>
<td>Variations (post MAA)</td>
<td>✔️</td>
</tr>
<tr>
<td>Pharmacovigilance</td>
<td>✔️</td>
</tr>
</tbody>
</table>

Key to Table 3

1 National competent authority of the country in which the activity takes place.

2 The NCA for medicines and EUTCD are not necessarily the same, this differs between Member States.

3 The NCA will determine whether the product is a medicinal product, and can provide a national opinion on whether it is an ATMP. The EMA (CAT) will determine whether a medicinal product is an ATMP.

4 Applicable to SMEs developing ATMPs only.
Characterisation Challenges – PAS 93

• Provides regulatory context to characterisation of cell-based therapies
• Annex features comprehensive description of cell characterisation techniques
• Practical considerations and best practice
• Technical author: Alison Wilson (Cell Data Services)
3 The need for characterization

3.1 Scientific need for characterization

Characterization of cells used for clinical application involves an integrated assessment of the identification and properties of the cells, both as a cellular starting material and as the cellular active substance for a cell therapy product. The characterization of cellular starting materials and cellular active substances is a key part of the development of cell therapy products. Its place in the overall development is exemplified in PAS 93.

There is a need to characterize both the cellular starting material and the cellular active substance, as a clear understanding of how the cells behave throughout the manufacturing process is essential in assessing the impact of processing changes or changes in the materials used on the cells and thus the finished cell therapy product. The quality, safety and efficacy of the product is intricately linked to the manufacturing process. Because cells cannot be fully characterized in the laboratory, developers should optimize product consistency, quality, and purity by ensuring that the manufacturing process remains the same over time and that any necessary changes are made in a controlled manner. At the same time, the developer should develop tools (assays) that can be used as evidence towards confirming that the critical characteristics of the cells have not been altered.

Characterization is required for:

a) product development – to ensure that the relevant properties of the cellular starting material and the cellular active substance are adequately understood and can be controlled; and

*NOTE it is important to understand the attributes of the cells that are most important for the function of the cell therapy product, and the effects that changes in the manufacturing process may have upon them. The extent to which critical properties can vary without affecting the overall cell therapy product needs to be evaluated.*

b) comparability – to establish whether changes (for example, scale-up of manufacture, introduction of a new material) are likely to impact upon the safety or efficacy of the cell therapy product.

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Table A.2 – Application of cell characterization techniques – Whole cell analysis (continued)

<table>
<thead>
<tr>
<th>Technique</th>
<th>Identity</th>
<th>Purity</th>
<th>Biological activity</th>
<th>Stability</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td>Flow cytometry</td>
<td></td>
<td>O</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Automated cell counter</td>
<td>0</td>
<td>O</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total DNA</td>
<td>0</td>
<td>O</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hoechst/DAPI/PI</td>
<td>0</td>
<td>O</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Impedance spectroscopy</td>
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<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Key:
- 0 Characterization techniques applicable to isolated cells
- X Characterization techniques applicable to cells embedded in a 3D matrix
- 0 When used with cells in a 3D matrix, the optical properties of the matrix have to be considered as well as the barrier to mass transfer, which can affect the ability to incorporate fluorescent labels.
- X Requires sectioning to visualize cells embedded in a matrix.
PAS 157: Selection of raw materials used in the design and development of cell-based medicinal products for clinical application
Raw Material – EU Regulatory Definition

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.

Product = only as strong as its weakest point
Rationale for PAS 157

- PAS-157: Selection of raw materials used in the design and development of cell-based medicinal products for clinical application
- EMA recognized that raw materials used in development of ATMPs often not of acceptable quality or impact on process / product not assessed

<table>
<thead>
<tr>
<th>SA recurrent quality questions asked:</th>
<th>MAA Major quality objections asked:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of active substance vs. finished product;</td>
<td>Active substance vs. Finished product have not been defined appropriately;</td>
</tr>
<tr>
<td>Acceptability of the raw materials used;</td>
<td>Impact of raw materials used in the ATMP manufacture;</td>
</tr>
<tr>
<td>Acceptability of characterisation of the AS and FP;</td>
<td>Insufficient characterisation of the AS and FP;</td>
</tr>
<tr>
<td>Acceptability of markers;</td>
<td>Potency assay not sufficiently correlated to biological activity;</td>
</tr>
<tr>
<td>Acceptability of the potency assay;</td>
<td>No correlation between markers and clinical outcome</td>
</tr>
<tr>
<td>Acceptability of the comparability data;</td>
<td>Lack of comparability data;</td>
</tr>
<tr>
<td>Acceptability of purity and identity tests, etc...</td>
<td>Purity and identity tests not adequate, etc..</td>
</tr>
</tbody>
</table>

Slides taken from EMA presentation
Recurrent major objections raised during the evaluation of ATMP

- Quantitative and qualitative information of the raw materials composition should be provided.
- Raw materials of “research” or “in-vitro grades” not acceptable.
- Impact and effect of raw materials used on the ATMP final quality profile...

Think about contractual agreement between raw materials manufacturers and ATMPs developers!
Conclusions?

- RM are common quality deficiency at licencing stage
- Many biological materials used in development of ATMPs are non-compendial - only research grade materials are available to developers
- EMA – EDQM looking to create more monographs for materials but monographs take time
- EMA – EDQM Ph.Eur. Chapter 5.2.12 on raw materials in preparation but this will have a different focus (to be discussed later)
- Currently little guidance for developers, especially those who are early stage / academic-led
- Room for guidance to allow manufacturers to make informed decisions on the materials / quality standards that currently exist
- A “best practice guideline” in a similar vein to PAS-93
- Approach should compliment Ph.Eur. Chapter and not conflict
Content

- To include guidance on:
  - Regulatory and quality definitions for raw materials
  - Considerations for selection of raw materials and risk assessments
  - Supplier evaluation e.g. questionnaires, audits
  - Characterisation of materials and managing process change
  - Appropriate regulatory legislation and guidance (EU, US, ICH)
  - List of raw materials with quality certificates, monographs or chapters

- Due for publication Q1 2015
- Requires regular expert input with multiple iterations
  = Expert Steering Group
## Steering Group Composition

<table>
<thead>
<tr>
<th>Organization</th>
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<tbody>
<tr>
<td>Cell Data Services</td>
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<tr>
<td>Cell Medica</td>
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<td>Cell Therapy Catapult</td>
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<td>Consulting on Advanced Biologicals</td>
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<tr>
<td>GlaxoSmithKline</td>
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<tr>
<td>Miltenyi Biotec</td>
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<tr>
<td>National Institute for Biological Standards and Control</td>
</tr>
<tr>
<td>Roslin Cells</td>
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<tr>
<td>University College London</td>
</tr>
</tbody>
</table>
Process for Publication

1. **1st Draft**
   - Scope, title agreed with steering group

2. **2nd Draft**
   - Steering group review & comment

3. **3rd Draft**
   - Public consultation

4. **Publication**
   - Agreement within steering group

We are here

Title & scope change

Q1 2015
PAS-157: The selection of **materials of biological origin** used in the design and development of cell-based medicinal products for clinical application – Guide

Started out as **raw** materials but several issues with this:

1. Raw materials is a term used in EU legislation but not in the US CFRs (guide is EU / US compatible)
2. Limits the scope to EU regulatory terminology – some materials may not meet the definition of a raw material (e.g. used prior to GMP manufacture) but still impact on quality / safety / efficacy of final product
3. Terms **raw** and **starting** materials are sometimes used interchangeably
4. Guidance specific to the qualification of **raw materials** in Europe is to be included in the Ph.Eur.

Scope was restricted to **materials of biological origin** because:

1. Biological materials commonly used in ATMP manufacture but very few of Ph.Eur. / USP grade, etc.
2. Biological materials can carry additional risks e.g. prions, bacterial, viral, etc.
Scope of PAS 157

Examples: Cytokines, sera, enzymes, etc. used during processing or manufacture of cell-based medicinal products
Chapter 5.2.12. RAW MATERIALS FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

Scope

- Applies to raw materials of biological origin used for the production of cell-based/gene therapy medicinal products. They are used in the manufacture of active substances but the active substance itself is not directly derived from them. This general chapter applies to the following classes of raw materials:
  - sera and serum replacements;
  - proteins produced by recombinant DNA technology such as growth factors, cytokines,
  - hormones, enzymes and monoclonal antibodies;
  - proteins extracted from biological material such as enzymes and polyclonal antibodies;
  - vectors.

- The principles of this general chapter may also be applied to other classes of biological raw materials where appropriate.

- Chemically synthesised raw materials out of scope
### PAS 157 and Chapter 5.2.12 – Key differences

<table>
<thead>
<tr>
<th><strong>PAS 157</strong></th>
<th><strong>Chapter 5.2.12</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aimed at early stage SMEs / academics as a “good practice” guide with worked examples</td>
<td>Less specific regarding target audience and provides methodology for raw material characterization and qualification</td>
</tr>
<tr>
<td>Covers US and EU regulatory terminology and sources of information as reference annex</td>
<td>EU only and uses EU regulatory terminology</td>
</tr>
<tr>
<td>Provides general technical material characterisation guidance + guidance on material selection criteria, risk assessment / mitigation and supplier considerations</td>
<td>Focuses on characterisation and quality attributes of sera, proteins and vectors.</td>
</tr>
<tr>
<td>Includes descriptions of quality declarations made by suppliers of materials e.g. pharmacopeia grade, GMP grade, research grade, etc.</td>
<td>Is a pharmacopeia chapter in its own right</td>
</tr>
<tr>
<td>Scope does not include ((in \text{ vivo})) gene therapies</td>
<td>Covers all ATMPs</td>
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</table>

**Aim:** to provide guidance that compliments that of EMA / EDQM and does not conflict / confuse developers
PAS 157 – Examples of Content
# Quality Declarations – Descriptions

<table>
<thead>
<tr>
<th>Quality Declaration</th>
<th>Technical and Regulatory Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GMP or cGMP grade</strong></td>
<td>Manufacturing a material in compliance with GMP requirements (e.g. Directive 2003/94/EC in Europe and 21 CFR Part 211 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.</td>
</tr>
<tr>
<td><strong>Clinical grade</strong></td>
<td>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 recognised quality grade nor evidence of a regulatory approval.</td>
</tr>
<tr>
<td><strong>Research use only (RUO) grade</strong></td>
<td>Research use only 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 section 5). Any material that carried the RUO should undergo a risk assessment by the developer before it is considered for use (see section 5.3).</td>
</tr>
<tr>
<td><strong>ATMP / HCT/P grade</strong></td>
<td>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 thought quality and risk assessment should still be carried out.</td>
</tr>
</tbody>
</table>
## Selecting Materials

<table>
<thead>
<tr>
<th>Factor</th>
<th>Key Considerations and Guidance</th>
<th>Key Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source</strong></td>
<td>The need to ensure the identity, activity, purity and quality of materials 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. Notes for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 3 July 2011) (2011/C 73/01) European Commission Decision 2007/453/EC, 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.</td>
<td>Is the material from source that reduces the risk of adventitious agents? E.g. bovine material from non-TSE countries such as Australia or New Zealand. Can the material be replaced with another that has a lower risk profile? E.g. porcine-derived trypsin replaced by recombinant trypsin. Is the material from source that reduces the risk of adventitious agents? E.g. bovine material from non-TSE countries such as Australia or New Zealand. Can the material be replaced with another that has a lower risk profile? E.g. porcine-derived trypsin replaced by recombinant trypsin.</td>
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</table>

- **Traceability**
- **Manufacture**
- **Testing**
- **Continuity of Supply**
# Mitigating Risk

<table>
<thead>
<tr>
<th>Factor</th>
<th>Key Considerations</th>
<th>Key Questions</th>
</tr>
</thead>
</table>
| **Appropriate testing / characterisation** | A 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 manufacturer of the 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 pH.  

It is the responsibility of the manufacturer to test and characterise the incoming material to ensure that it is fit for purpose and each batch is consistent. | 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?  

What batch acceptance procedures are in place? |
| **Validation for the specific application / process** | 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 examples, 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 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? |
Other Content

- Sample content for supplier questionnaires
- Supplier audit / agreements
- Sample risk assessments for individual materials
- Guidance on managing process change and characterization
- Regulatory context:
  - EU vs US (terminology, general approach)
  - Provision of / references to, key legislation and guidance (EU / US)
  - List of Eur.Ph / USP grade materials (monographs) and appropriate chapters
Acknowledgements

- Ben Sheridan, Alex Price and Sophie Hamza (BSi)
- Alison Wilson, Christopher Bravery, Berndt Schroeder, Alexis Cockroft, Amanda Skulte, Glyn Stacey, Edward Samuel (Steering Group)
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