EU Regulatory Activities and Experience

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Guidance

European Medicines Agency

London, 21 May 2008

COMMITTEE FOR MEDICINAL PRODUCT FOR HUMAN USE (CHMP)

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS

DATE FOR COMING INTO EFFECT | 1 September 2008

Guideline for Investigational ATMPs
Drafting stage

Committee for Advanced Therapies (CAT)

European Medicines Agency

Reflection paper on stem cell-based medicinal products
Adoption by CAT | 14 January 2011

Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee
Final
Adoption by CAT | 16 April 2010

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Raw materials

• Potential risks
  - Characterization
    o Unexpected impact on the product
  - Consistency
    o Reproducibility of the manufacturing process (i.e. amount interleukin added)
    o Impact of a change of vendor (source)
  - Safety aspects
    o Adventitious agents
    o compromized product
    o Harm to patient
Raw materials of biological origin for the production of cell-based and gene therapy medicinal products:

-.. applies to the following classes of raw materials
  - sera and serum replacements;
  - recombinant proteins, i.e. growth factors, cytokines, hormones, enzymes and mAbs
  - proteins extracted from biological material, i.e. enzymes and polyclonal Abs
  - vectors

-.. other classes of biological raw materials, where appropriate

Out of scope: Medical devices, plastics and chemically synthesised raw materials, i.e. basal media, synthetic peptides/polynucleotides
Developing process and specifications

Process establishment and validation can be done using cells from healthy donors, in many cases, this is the only option.

**BUT** consider representativeness!

- Patients might be heavily pretreated and the characteristics of their cells might differ → i.e. degree of adherence, expression of markers
- Proof-of-concept studies might not yield the same result
- Impact on critical product parameters
- Batch failures during clinical trials
- Impact on dose?
Defining specifications

- Human cell-based medicinal products (CBMPs) are heterogeneous with regard to the origin and type of the cells and to the complexity of the product
  - cells may be self-renewing stem cells, more committed progenitor cells or terminally differentiated cells
  - cells may also be genetically modified with newly established genotype/phenotype for the intended therapeutic effect
  - cells may be used alone, associated with biomolecules or other chemical substances or combined with structural materials that alone might be classified as medical devices (combined ATMPs)

→ A one-size fits all approach is not reasonable nor feasible
Defining specifications

• Selection of tests is product-specific and has to be defined by the manufacturer; Specifications should be appropriate to the stage of product development, justified (already for FIH) and subject to review during development

• Specifications are to be based on relevant development data, batches used in non-clinical and/or clinical studies and data from stability studies

• Justification to address how quality attributes and acceptance criteria are relevant for the performance of medicinal product

• Acceptance criteria should be presented as quantitative limits, ranges, or other attributes or variables for the tests described
Specifications during development

- Acceptance criteria and tests are to ensure sufficient control of the active substance
- Quality control tests to be performed at DP level, unless justification can be provided based on DS testing
- If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process tests, this needs to be justified
- References to the Ph.Eur., the pharmacopoeia of an EU Member State, USP or JP may be applied
Specifications - DP

• Same principles as for setting DS specification should be applied for DP

• Tests and their acceptance criteria should be defined to enable sufficient control of quality of the product
  - Tests for contents, identity, purity are mandatory
  - Tests for sterility, endotoxin are mandatory for sterile DPs
  - Suitable potency assay should be developed ASAP and in place before FIH clinical trials

• Analytical methods and limits for content and bioactivity should ensure correct dosing

• Upper limits required for impurities taking safety considerations into account
Specifications

Requirements:

- Identity
- Purity
- Potency
- Impurities
- Sterility/Bioburden
- cell viability
- total cell number

Are the markers unique?
What else is in the preparation?
How long will cells be cultured?
Are specifications covering all manipulations i.e. Loading of cells with proteins/DNA?
Content - Dose

Setting the dose - Self-limitation by the applicant

- Dose needs to be justified and measureable
  - Consideration should be given to “adequate dose”, not just in terms of batch release/batch failure, but also in regards to efficacy

Identity - Purity

- Microscopic appearance is not a solid criterion
- Which cell populations are present in the DS/DP and how can they be identified?
Impurities

• Outline process and product-related impurities and assess their impact ← risk based approach

• To the extent possible, characterization should address the potential impact of the impurities, specifically cell populations (in vitro experiments)

• Investigate the consistency of cell population distribution

• Providing dilution factors of impurities might aid the discussion
Potency assay

- Suitable potency assay to be in place for release of material for FIH clinical trial and validated prior to pivotal clinical trials (although it may evolve)

- ICH 6QB Potency is the quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties → drawn from characterisation (and preclinical studies)

- Assay demonstrating biological activity should be related to the clinical response

- The potency assay is a valuable tool to provide assurance of unaltered biological characteristics of the product throughout development, particularly after manufacturing changes
Potency Assay - Considerations

- Potency may evolve during development ➔ define reference preparations
- Potency assay required for consistency, comparability, stability
- Potency of active substance if final product not possible
- Functional assay might not be quantitative but can serve to cross validate potency measurement of surrogate markers – mixed approaches possible and often necessary
- cells and induced differentiation / engraftment / ex vivo use might need kinetic studies to validate relevant biological activity(ies)
Confounding aspects to potency testing

- insufficient knowledge on the active component(s)
- limited sample size / shelf life (autologous, primary cells)
- Unclear mode of action / lack of appropriate biological attribute
- Structural complexity / Multifactorial actions - poor specificity
- Interfering substances / poor parallelism - poor accuracy
- inappropriate tools – acceptance criteria / specifications too wide
- non linearity – characterisation under dynamic conditions
Adventitious Agents/Sterility
What is the overall strategy?

- Differentiation between starting material-related (hardly avoidable) and process-related (avoidable) adventitious agents
- Compliance with EU Directive 2006/17/EC required
- Details on safety-relevant parameters for raw materials
- Alternative methods for control of microbiological quality (Ph. Eur. 5.1.6) when appropriate and where time is limited
- If sterility test results cannot be available before administration
  - Sterility evaluation on product intermediates
  - Risk-based approach: appropriate measures on how to deal with contamination with regards to patient treatment should be part of the risk assessment/CT dossier
Stability

Clearly describe what is expected of the product

• Time to patient application of fresh preparations
• How long will the product be cryopreserved?
• What is the duration after thawing until patient application?
• Issues of transport

• Generate data with test samples if possible and enlarge data pool during the clinical trial!

• Explore if material left over after patient treatment be used to generate data
Biological Assay vs Potency Assay

• Biological assays may not always be suitable for release testing (limited time) → combination of different types of assays may be needed to confirm the potency of cell based product

• Biological Assay = methods use for biological characterisation – broad definition; can be *in vitro* or *in vivo* / qualitative or quantitative / functional or analytical

• Potency Assay or Bioassay = biological assay(s) required for consistency (release) + comparability + stability - can be
  - QUANTITATIVE functional *in vivo* or *in vitro* assay
  or
  - QUALITATIVE functional *in vivo* + QUANTITATIVE analytical *in vitro* assay
Possibilities
(if correlated with biological activity)

- Expression of relevant biological substances
  e.g. (recombinant) protein, glyco- or lipo-protein, growth factors, enzymes, cytokines
- mRNA, if correlated with protein expressed
- Formation of cell/extra cellular matrix/structures
- Cell interactions (e.g. immune activation/inhibition)
- Measurement of differentiation/self-renewing capacity/migration
- Regeneration/repair = measured effect / time period
- Quantification of mRNA - complement with expressed protein
- Kinetic studies of relevant biological activity(ies) may be needed
## Specifications - Example

### Autologous Dendritic Cells

<table>
<thead>
<tr>
<th>Tests</th>
<th>Methods/Reference</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total viable DCs</td>
<td>Flow count flow cytometry</td>
<td>30–60 × 10⁶ viable DCs/mL (CD45+ 7-AAD-HLA-DR+ CD11c+) (after thawing)</td>
</tr>
<tr>
<td>Number of doses</td>
<td>Count</td>
<td>4–20 vials</td>
</tr>
<tr>
<td>Viability</td>
<td>Flow cytometry (CD45+ 7-AAD)-</td>
<td>≥ 60%</td>
</tr>
<tr>
<td>% viable DCs</td>
<td>Flow cytometry (CD11c+ HLA-DR+ 7AAD-)</td>
<td>For information only</td>
</tr>
<tr>
<td>Sterility</td>
<td>Ph.Eur. 2.6.27 Direct inoculum Method</td>
<td>No microbial contamination</td>
</tr>
<tr>
<td>Endotoxin</td>
<td>Ph. Eur.2.6.14 Chromogenic kinetic method</td>
<td>Pass per Ph.Eur criteria &lt; 250 IU/mL</td>
</tr>
<tr>
<td>Appearance</td>
<td>Visual inspection</td>
<td>Not grossly clotted or clumped, vial closure appears normal</td>
</tr>
<tr>
<td>Container labelling</td>
<td>Clerical check</td>
<td>Donor identifiers and other required content</td>
</tr>
<tr>
<td>Volume</td>
<td>Visual inspection of the vial</td>
<td>Visual confirmation of vial and ≥ 1 mL mark</td>
</tr>
<tr>
<td>% Non-DC:</td>
<td>Flow cytometry</td>
<td>For information only percentage of CD3+ (T cells), CD19+ (B cells), and CD16+/CD56+ (NK cells) in CD45+ cells</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Flow</td>
<td>For information only</td>
</tr>
<tr>
<td>Mannan binding and uptake</td>
<td>Flow cytometry (mannan-FITC)</td>
<td>&gt; 5% positive (geometric mean, for information only)</td>
</tr>
<tr>
<td>Potency</td>
<td>MLR bioassay</td>
<td>&gt;= 10%</td>
</tr>
<tr>
<td>Potency</td>
<td>COSTIM bioassay</td>
<td>&gt;1</td>
</tr>
</tbody>
</table>

### Standardization?

- **One-dimensional FACS?**
- **The whole cell mix?**
Specifications

- Specifications are parameters that are defined to ensure quality and safety of the product, which includes fulfilling the proposed mechanism of action
- „For information only“ cannot be used for specifications that assure patient safety or/and are defined by the MoA, because...
  - ... the regulator cannot verify patient safety is ensured
  - ... consistency evaluation
  - ... NO batch would be rejected → patient safety??

In early development specifications are necessarily wide, therefore the emphasis is on batch data
Scientific/data based justifications required
Specifications – additional parameters

- Product characteristics that are not completely defined at a certain stage of development or for which the available data is too limited to establish relevant acceptance criteria, should also be recorded.

Such product characteristics could be included in the specification, without pre-defined acceptance limits.

The results should be reported in the Batch Analyses section (S.4.4). These parameters could only be additions to existing specifications, but not replace them.
Combined ATMP – Dossier content

Information relevant for device aspect evaluation to be provided:

• choice and intended function of MD, demonstration of compatibility with other components
• evidence of MD conformity with legal requirements
• evidence of MD BSE/TSE requirement compliance
• results of any assessment of the MD part by NB

• Where MDs used during the surgical procedures for application, implantation or administration of the ATMP may have an impact on the efficacy or safety of the ATMP, information on these devices shall be provided
Scientific issues for ATMPs with device aspects

- How is the dose defined?
- How are cells impacted by the combination?
- Long term effect in the body (membrane degradation?)
- How can potency be expressed/measured in the final product?
- Do in vitro conditions mimic in vivo behavior?
- Biocompatibility, toxicity, biodistribution, stability vs. turnover etc.

Co-development of analytical tools is needed to analyze combination products
Do not submit a clinical trial unless ..

- You can characterize your product
- You identified the mechanism of action with reasonable certainty and can support this by data
- Specifications are in place that support the mechanism of action
- Analytical tools are proven suitable
- A strategy is in place to fill knowledge gaps during the CT stage

→ A clinical trial can only generate valid data, if the product is sufficiently defined
Thank you for your attention!
Questions?

Questions

• What techniques/processes are useful to narrow down the critical quality attributes from exhaustive characteristic analysis?

• How many product lots are necessary to set acceptance criteria for starting cells/tissues and products?

• To what extent should the manufacturing conditions (e.g. raw materials, processes, scale and equipment) be fixed before manufacturing of products for non-clinical studies? How about products for clinical trials?

• What manufacturing changes are acceptable during development? What techniques/processes are available to assess comparability of cell-based products?
ATMPs are not generic drugs!

- **Chemical** active substances, single characterization methods possible; Generic concept

- **Biologic** medicinal products „the process is the product“; orthogonal methods; Biosimilar concept

- **ATMPs** are highly complex biological products where minor changes in the manufacture can have significant impact. Each product requires independent proof of quality/efficacy/safety; implicit extrapolation across manufacturing processes and/or products is not legitimate

  → i.e. just because one dendritic cell therapy has been approved, this does not mean that ALL dendritic cell products are efficacious
PharmEur Chapter 5.2.12

- Risk assessment
- General requirements:
  - Origin – Traceability
  - Production - suitable quality management system and production facilities
  - Predefined quality requirements for identity, purity and biological activity; reference material
  - Shelf life/storage conditions
  - Labelling - expiry date, conditions for storage and use and any code that may be required for traceability
- Specific texts for sera, recombinant proteins, extracted proteins and vectors