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CAT considerations for minimally manipulated ATMPs and the use of RBA for such products

EMA – EuropaBio Information day

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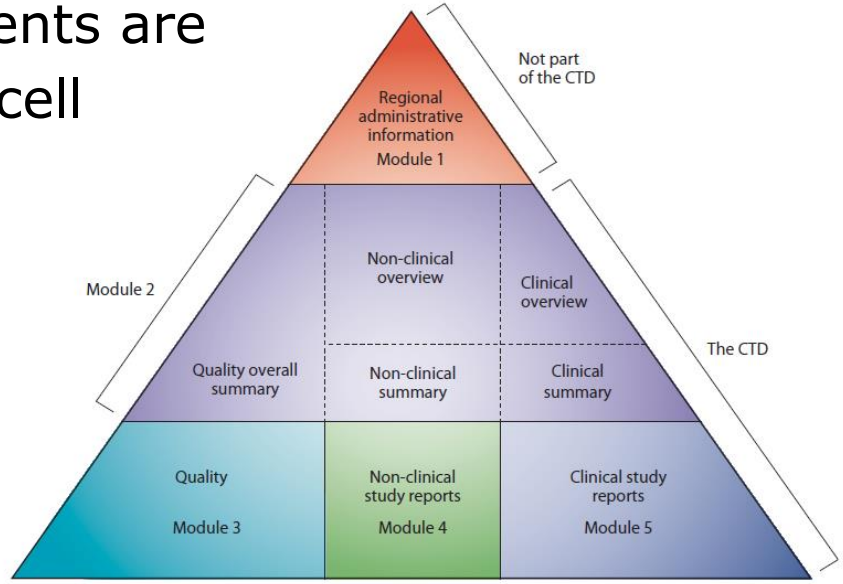
Problem statement (1)

Minimally manipulated cells intended for a different function in donor & recipients are defined as ATMPs (TEP or somatic cell therapy product).

Therefore, the Quality, Non-clinical and Clinical requirements apply as for all ATMPs.

CTD Triangle



The CTD triangle. The Common Technical Document is organized into five modules. Module 1is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Problem statement (2)

CAT is fully aware that the standard ATMP dossier requirements need to be adapted to those minimally manipulated ATMPs:

For example:

- Quality development: product characterisation likely more limited / wide specification range due to variability of starting material
- Non clinical and clinical development different due to product variability

How to solve this problem?

Make maximal use of the flexibility offered by the ATMP Regulation: **use of the Risk Based Apprach**!

However, the concept of RBA is not easy to understand for unexperienced developers, especially in the case of minimally manipulated ATMPs…

➔ CAT is developing a Question & Answer document

Q/A document for minimally manipulated ATMPs is under preparation

The AIM

- To introduce developers how to use the RBA when they started with the ATMP which contains minimally manipulated cells (MMC)
- To help developers to identify risks and risk factors and so ease risk profiling and B/R assessment
- To enhance development of MMC by showing flexibility when RBA is used

What issues shoud be addressed when start development of the product?

- What do I need to know about the product for the intended use?
- How to use RBA for product development?
- How to determine the risk/risk factors associated with manufacturing / product characterisation?
- What are the risks associated with the product (with regard to safety / efficacy)?
- How to determine the risk factors associated with safety and efficacy of the product?
- Where and how is RBA adding flexibility to the system – what are advantages to use RBA?

RISK-BASED APPROACH

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How to identify various risks associated with the clinical use of the product and risk factors inherent to the product with respect to quality, safety and efficacy ?

Step 1.

Risk identification

Step 2.

Risk factors identification

Step 3. Risk profiling

1. To identify risks associated with the clinical use of the product
2. To identify product specific risk factors contributing to each identified risk
3. To map the relevant data for each identified risk factors against each of the identified risks
4. To conclude on the risk factor – risk relationships

An example

Autologous peripheral blood mononuclear CD34+ cells - Indication: Chronic heart failure

Step 1: Risk identification

Quality

- ❑ Infection → YES
- ❑ Immunogenicity → ?
- ❑ Treatment failure → YES

Safety

- ❑ Adverse events:
  - Infection → YES
  - Tumourigenicity → NO (autologous, non-manipulated cells)
  - Immunogenicity → ?
  - Thrombotic events → ?
  - Any others?

Efficacy

- ❑ Treatment failure → YES

Step 2: What risk factors could be related to the product?

Cell starting material/cell population, heterogeneity

- Sourcing of the cells
  - Autologous, mix-up of a product
- Product composition and purity:
  - Total cell number and amount of CD34+ cells
  - Cell purity
  - Cell viability
- Manufacturing process-related:
  - Processing of the cells
  - Process-related impurities

Microbiological purity

- Starting and raw materials
  - Quality of the starting and raw materials
- Manufacturing process
  - Aseptic processing
- Final Product
  - Quality of the final product

Step 3: How should the risks and risk factors be addressed?

Cell starting material

- Proper labelling throughout the manufacture, from starting materials up to the final product
- Characterisation studies, process validation, release testing

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Microbiological purity

- Testing of the starting and raw materials
- Validation of the aseptic process, control of the manufacturing (GMP)
- Sterility testing of the final product (limitation: short shelf-life → how to address sterily before administration?)

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Step 2: What non-clinical risk factors could be related to the product?

Proof-of-principle

- pharmacodynamics, mode of action
- dose
- mode of administration

Safety

- dose
- mode of administration
- biodistribution
- persistence of the cells

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Step 3: What testing possibilities do we have?

Non-clinical studies to demonstrate **proof-of-principle** of the product:

In vitro

- Major cellular functions (viability), mode of action

In vivo

- Mechanistic studies! (the exact mechanism of CD34+cells unknown); small animal models
- Functionality testing
- Disease models; large animal models
- Dose finding studies - no adequate »dose-effect« animal model at the moment

Non-clinical studies to demonstrate **safety** of the product:

In vivo

- The studies of biodistribution (migration and persistence) of the cells (due to imaging/technical advantages); small animal models
- route of administration; large animal models
- Adverse events: thrombotic events, immunogenicity (?)

Step 2: What risk factors could be related to the efficacy and safety of the product?

Proof-of-concept

- Pharmacodynamics, mode of action

Early and pivotal studies

- Mode of administration
- Dose
- Biodistribution (migration and persistence of the cells)

Step 3: What testing possibilities do we have?

Pharmacodynamic studies - structural/histological assays

- Cardiac Morphological Imaging (cardiac MRI, CT scan, echocardiography and nuclear studies to determine regional wall thickness)
- Cardiac Functional Imaging (ECHO, cMRI and CT scan for volumes and EF fraction)

Dose finding studies

Migration-persistence studies - direct and non-direct labeling techniques using:

- magnetic resonance imaging (MRI)
- nuclear imaging - positron emission tomography (PET) or single photon emission computer tomography (SPECT) ?

Step 3: continued…

Clinical safety studies:

- The surgical procedure to administer the product should be evaluated
- The safety issues arising from the non-clinical development should be addressed especially in the absence of an animal model (thrombotic events, immunogenicity…)

Clinical efficacy studies: efficacy endpoints (LFEV, NT-proBNP, 6-minute walk test…?)

Follow up with regard to long term efficacy and safety…

Limitations:

- Different pathophysiology of chronic heart failure
- Different clinical presentation of chronic heart failure

Presentation of the outcome of RBA

STEP 1

Risk / Risk factor	Tumour formation	Unwanted immunogenicity	Treatment failure	Disease transmission	Unwanted tissue formation	Toxicity
Cell starting material	hESC have inherent capability for teratoma formation. Risk addressed in other sections of this table and in CTD 3.2.S.2.3 - Control of Materials	Possible HLA mismatching. Controlled by donor screening and selection. CTD 3.2.R – Regional information.		Information on cell origin not complete. Lack of information on donor and derivation addressed through viral testing. CTD - 3.2.S.2.3 - Control of Materials (control of HSA used in IVF medium), CTD 3.2.A.2 - Adventitious Agents Safety Evaluation		
Culture / feeder cells and growth factors	Culture with GFs or hormones to enhance proliferation/trigger differentiation may induce tumour formation. Process related impurities controlled - CTD 3.2.S.2.3 - Control of Materials; 3.2.S.2.5 -	Possible immune reaction to animal derived materials, feeder cells - impurities controlled in CTD 3.2.S.2.3 - Control of materials; 3.2.S.3.2 - Impurities.		Potential for disease transmission from cell source, animal derived materials / feeder cells. Viral safety testing of relevant starting and raw materials. CTD 3.2.S.2.3 - Control of materials; 3.2.S.3.2 - Impurities.		

STEP 2

STEP 3

Conclusion - Risk-based approach is:

- **A tool for pro-active identification of the investigations / testing during product development**

- **A tool for justification of the presence / absences of data in the MAA and thus ease B/R assessment and MA procedure**

- **Is intended to provide flexibility to regulation of ATMPs and not a rigid classification system of different risks**

- **Is intended to help developers and not to burden them**

How to do the risk/risk factor profiling?

- **Consult that Guideline on risk-based approach (EMA/CAT/CPWP/686637/2011) and the examples of RBA for substantially manipulated ATMP**

- **Q/A document on RBA for minimally manipulated ATMPs is under preparation**
  - **Expected to be published in first half of 2016**

- **Request Scientific Advice on your product development on basis of RBA**

Further informations: http://www.ema.europa.eu

- **Information from the CAT: public agenda, minutes and monthly reports**

  Go to: Committees → CAT

- **Summaries of scientific recommendations on classification of ATMP**

  Go to: Advanced therapies
  ATMP classification
  Summaries

Review

Regenerative Medicine

Manufacturing, characterization and control of cell-based medicinal products: challenging paradigms toward commercial use

During the past decade, a large number of cell-based medicinal products have been tested in clinical trials for the treatment of various diseases and tissue defects. However, licensed products and those approaching marketing authorization are still few. One major area of challenge is the manufacturing and quality development of these complex products, for which significant manipulation of cells might be required. While the paradigms of quality, safety and efficacy must apply also to these innovative products, their demonstration may be demanding. Demonstration of comparability between production processes and batches may be difficult for cell-based medicinal products. Thus, the development should be built around a well-controlled manufacturing process and a qualified product to guarantee reproducible data from nonclinical and clinical studies.

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CELL & GENE THERAPY INSIGHTS

NAVIGATING THE GLOBAL ATMP REGULATORY LANDSCAPE

SPOTLIGHT

REGULATORY REVIEW

Regulatory viewpoints on the development of advanced stem cell–based medicinal products in light of the first EU-approved stem cell product

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Thank you for your attention!