EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Translating academic research into commercial products - regulatory considerations

Cell-based Therapy ATMPs

Manufacturing of cell-based therapy products: common issues & advice

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Disclaimer

✓*I attend this conference as an individual expert* and, although being a member of the CAT and BWP, my presentation might not be the view of the EMA and any of their Committees or working parties and neither of the French Medicines Agency (Afssaps).

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✓*No conflict of interest*

To set the scene

✓ cell-based products = medicinal products = "advanced therapy medicinal products" (ATMPs)

- To follow the regulation of medicinal products
  - need a marketing authorisation (MA) to reach the market
  - Same criteria for their evaluation
    – Quality - Safety - Efficacy
    → annex 1 dir. 2001/83
  - Some technical specificities in the criteria to be documented
    → part IV of annex 1

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

ANNEX I

ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

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PART IV

ADVANCED THERAPY MEDICINAL PRODUCTS

Advanced therapy medicinal products are based on manufacturing processes focussed on various gene transfer-produced bio-molecules, and/or biologically advanced therapeutic modified cells as active substances or part of active substances.

For those medicinal products the presentation of the Marketing Authorisation application dossier shall fulfil the format requirements as described in Part I of this Annex.

To set the scene

✓ cell-based products = medicinal products = "advanced therapy medicinal products" (ATMPs)

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  - need a marketing authorisation (MA) to reach the market
  - Same criteria for their evaluation
    - Quality - Safety - Efficacy (see annex 1 dir. 2001/83
  - Some technical specificities in the criteria to be documented (see part IV of annex 1)
- Same dossier structure (CTD) for MAA
  - Structure and template provided

Structure and format of the MAA dossier

European Medicines Agency

July 2003
CPMP/ICH/2887/99 - Quality

ICH Topic M 4 Q
Common Technical Document for the Registration of Pharmaceuticals for Human Use - Quality

Step 5

COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE
QUALITY OVERALL SUMMARY OF MODULE 2 AND MODULE 3: QUALITY
(CPMP/ICH/2887/99 - Quality)

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002725.pdf

Quality is a key parameter in the management of ATMP

- Very diverse nature of cellular product
- Specific (unique) mode of action
- Complex structure, difficult to know what contributes to the claimed/expected/observed clinical effet (or sometime negative effect)
- The process makes the product
  - From the « initial biopsy » up to the final product
  - Numerous steps, each being determinant for the final result
  - Use of reagents and other growth factors or cytokines
  - Use of matrix, scaffolds, medical device

➔ Important to get proper knowledge and mastering of the quality

Quality related issues -1-

- ✓ Active substance (drug substance)
  - Characterisation
  - Elucidation of structure / composition
  - Quality attributes needed for the activity

Quality related issues -2-

- Quality attributes
  - Identity (for all component of the product)
    - based on phenotypic and/or genotypic markers
    - relevant phenotypic markers
  - Purity / impurities, sterility
  - Potency assay
    - should be based on the intended biological effect and (ideally) related to the clinical response
    - should detect clinically meaningful changes in the product
    - in vitro or in vivo assays or assays based on surrogate markers
    - multiple assays if necessary
- Quality control strategy

Quality related issues -3-

- ✓ The manufacturing process
  - Relevant development to get the « target product profile »
  - Validation of the process and its critical steps
  - The In Process Controls
  - Consistency
  - Holding / storage period(s) and stability profile
  - The reagents and raw materials (→)

- ✓ The drug product
  - The critical steps of the formulation process
  - Release criteria
  - Storage/transportation
  - Stability
  - The final preparation step at the bedside

The reagents and other raw materials

- ✓ Culture media, growth factors, cytokines, sera
  - Quality documentation needed:
    - main steps of their manufacturing process
    - Quality control, consistency
    - Origin and viral/microbial qualification (incl. TSE agents)

- ✓ "GMP grade"
  - What does this mean?
  - It is the responsibility of the applicant, as final user,to assume (and investigate) the full quality, including viral safety aspects…

- ✓ Alternate suppliers and quality consistency for key reagents that impact the overall quality of the final product

Examples of issues identified -1-

✓For cell-based product xx

- Limited characterization
  - More cell markers
  - Purity: cell sub-populations
  - Definition of the product, correlation with clinical efficacy?
  - Functional assay to ensure consistency of the product used in patients
- Improve manufacturing process to reduce variability
- Establish consistency of manufacturing process

Examples of issues identified -2- Chondrocelect

Process validation and characterisation of Active Substance

The Applicant used a series of functional tests capable to characterise the cells and suitable to validate the manufacturing process. These functional assays include a cell culture (3D cell culture assay), an *in vitro* assay in animal models and cellular expression patterns of genes relevant for cartilage and chondrocyte biology.

The validation of the manufacturing process has been adequately performed. Some minor issues on the acceptance criteria for some parameters followed during the validation are still outstanding. The Applicant has committed to explore further the specification limits for the functional assay and to

In-process controls and specifications

The in-process controls of the manufacturing process have been clearly specified. Critical parameters have been included as in process controls to routinely confirm the quality of the Medicinal product by testing the biopsy and cell culture for aspects like e.g. medium appearance, pH, microbiology, cell morphology, purity, cell viability and cell yield. Appropriate operating ranges have been defined. As the manufacturing process is a continuous process and the active substance is not stored in between, no formal Active Substance specifications have been set.

Examples of issues identified -3- Chondrocelect (contd)

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of ChondroCelect Active Substance and Finished product have been presented in a satisfactory manner. The results of the tests carried out indicate satisfactory consistency and uniformity of the manufacturing process and finished product, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

At the time of CAT opinion, there were a number of minor unresolved quality issues related to the specification limits, biodegradable membrane and storage conditions (see above). These shortcomings, however, have no impact on the Risk-benefit balance of the product. The Applicant provided a Letter of Undertaking and committed to resolve these as follow-up measures after the opinion, within an agreed timeframe.

The guidelines

✓In comparison with "conventional" medicinal products, ATMPs deserve some specific technical adaptations to the Quality, Safety and Efficacy criteria

✓The CAT and its working parties have the mandate to elaborate guidelines or position statements to address these specific issues.

✓Guidelines should be read very carefully during the development phase of the ATMps

Technical Guidances available: Cell therapy

- Human cell-based medicinal products CHMP/410869/06
- Points to Consider on Xenogeneic Cell Therapy CHMP/1199/02
- Potency testing of cell based immunotherapy medicinal products for the treatment of cancer CHMP/BWP/271475/06
- Revision of the Points to Consider on Xenogeneic Cell Therapy Medicinal Products CHMP/165085/07
- Xenogeneic Cell-based medicinal products CHMP/CPWP/83508/09
- Reflection paper on *In-Vitro* cultured chondrocyte containing products for cartilage repair of the knee CAT/CPWP/288934/09

www.emea.europa.eu/htms/human/humanguidelines/biologicals.htm

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The risk based approach -1-

✓Due to the specific nature of advanced therapy medicinal products, a risk-based approach can be applied to determine the extent of Quality, Nonclinical and Clinical data (including RMP and PhV activities) to be included in the marketing authorisation application. The risk evaluation shall cover the entire development ….
(Dir. 2001/83/EEC, Annex I, part IV)

The risk based approach -2-

✓The following criteria can be used in the estimation of the overall risk of the product:

- origin (autologous - allogeneic);
- ability to proliferate and differentiate;
- ability to initiate an immune response (as target or effector);
- level of cell manipulation (in vitro/ex vivo expansion /activation / genetic manipulation);
- All aspects of manufacturing process including non-cellular components
- mode of administration (ex vivo perfusion, local, systemic)
- ……

Guideline under preparation

GMP question -1-

✓GMP: a Quality System concerned with the consistent manufacture of medicinal products of appropriate quality

✓GMP status required for establishments manufacturing ATMPs

✓EU GMP structure

- Part I: requirements for medicinal (finished) products
- Part II: requirements for AS used as starting materials (ICH Q7A)
- Annexes 1 – 20: supplementary guidance on specific topics

✓Annex 2: 'Manufacture of Biological Medicinal Products for Human Use' (current version from 1992), revision to be published soon, incorporates the ATMPs

GMP question -2-

✓GMPs contribute to the right execution of the process (environmental conditions, flow of materials and staff members, training, SOP, etc..)

✓GMPs are necessary

- to guarantee traceability of the batch records,
- review process,
- overall quality assurance system

✓However, GMPs make neither the product nor the process!

✓Important to dedicate also efforts on the process and product development….

Conclusion and advice -1-

✓Key elements in the Quality profile

- Knowledge of the product (as it evolves through its life cycle)
  - The "active substance"
  - The "product-related substances"
  - The impurities (process-related, reagents, etc.)
- Complexity of the process
  - Reproducibility despite complexity
  - Impact of any change (daily "adaptation" or on purpose) on the Efficacy/Safety profile → Product quality monitoring
- The reagents and materials used in the production process
- The control strategy
  - Validation of the process
  - Setting specification and limits based on the experience gained
    - Potency
    - Functionality
    - Stability indicating parameters

Conclusion and advice -2-

- ✓ Developers are encouraged
  - To read the guidelines and work with them all along the development of the product/process
  - to be in contact with EMA and its scientific committees as early as possible
  - Tools to be considered for assistance and early contact;
    - Innovation Task force (ITF)
    - CAT
      - Classification
      - **Scientific Advice**
      - Certification
    - PEDCO (for pediatric development)
    - COMP (Orphan designation)

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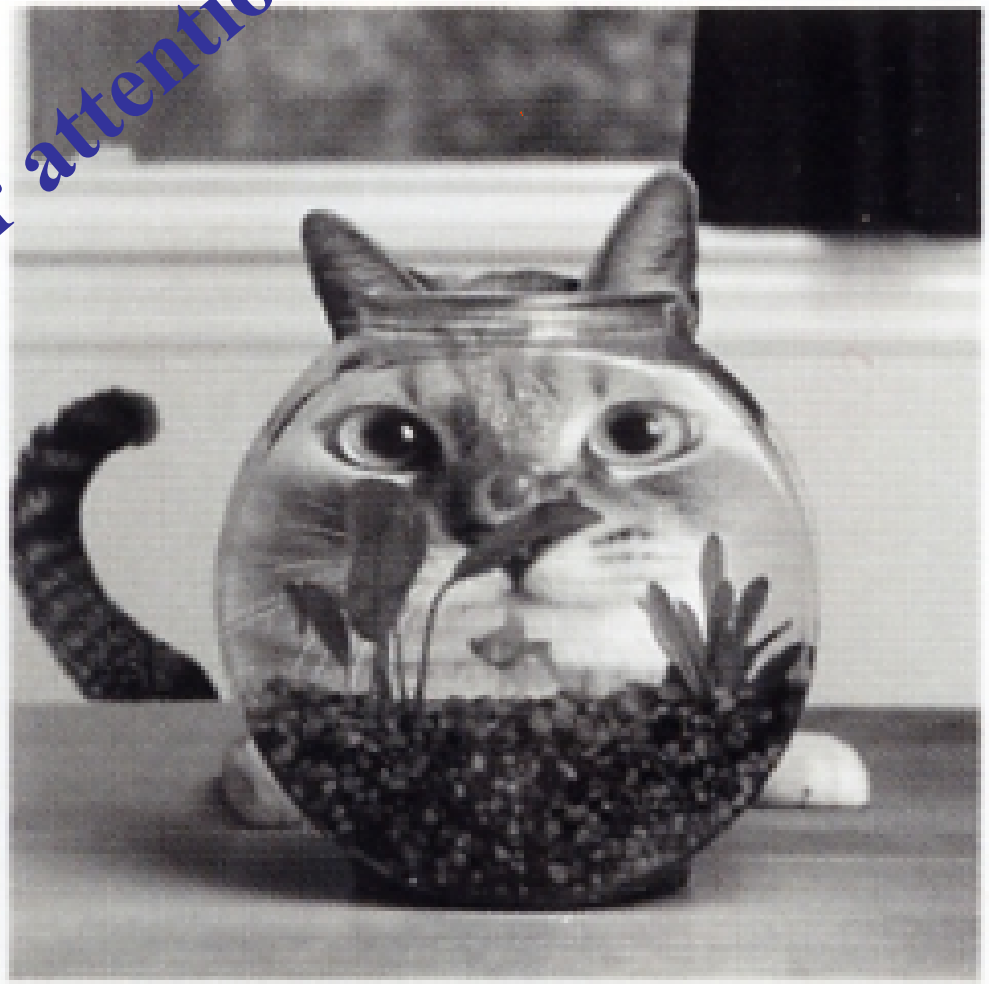
Thank you for your attention



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