Good Manufacturing Practice for ATMPs

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1. Legal framework for ATMPs in EU

- ATMPs:
  - Gene therapy
  - Somatic cell therapy
  - Tissue engineering
- ATMPs are regulated as medicinal products
  - Marketing authorisation granted on the basis of quality, safety and efficacy criteria.
  - Single assessment/authorisation across EU.
  - Specialised committee within EMA: the Committee for Advanced Therapies ("CAT").
  - GMPs, pharmacovigilance, and other "pharma" obligations apply.

1. Legal framework for ATMPs in EU (cont.)

Because of the novelty, complexity and technical specificity of advanced therapy medicinal products, specially tailored and harmonised rules are needed to ensure the free movement of those products within the Community, and the effective operation of the internal market in the biotechnology sector. (Regulation 1934/2007, recital 5).

- Adaptations already implemented for ATMPs:
  - Content of technical requirements for MAA (COM Directive 2009/120).
    - Possibility to apply a risk-based approach to the quality, preclinical and clinical data required to obtain a MA.

1. Legal framework for ATMPs in EU (cont.)

- Article 5 of Regulation 1934/2007:

  The Commission shall, after consulting the Agency, draw up detailed guidelines in line with the principles of good manufacturing practice and specific to advanced therapy medicinal products.

- Additional GMP principles for ATMPs were added to Annex 2 of the GMP Guidelines (“Manufacture of biological active substances and medicinal products for human use”).
  - Annex 2 does not derogate from the general framework: the general Chapters and other annexes of the GMP guidelines are also applicable to ATMPs.

2. Quality challenges of ATMPs:

- Starting materials
  - Cells/tissues are scarce materials – limited material for sampling and testing.
- High degree of variability
  - Differences in cells/tissues of different donors.
- Small batches
  - For autologous products, each product is a different batch.
- Short shelf-life
  - Analytical results from testing may not be available.
- Manufacturing process is key
  - Safety and efficacy profile may be altered by small changes in culture conditions, raw materials used, *etc*.

2. Other challenges for the development of ATMPs

- R&D conducted by university hospitals and SMEs:
  - Clean rooms typical of pharma development (A in background A/B) not always available.
  - However, hospitals operate under quality and safety systems required for transplantation.
  - Not familiar with pharma GMP requirements.

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3. GMP specific for ATMPs: Objectives

- Adaptation of GMP requirements to specific characteristics of ATMPs.
- Reduction of burdens.
  - Public health should, however, not be compromised.
- To facilitate the understanding of relevant obligations for ATMP developers.

4. The consultation paper

- **Adaptation of GMP to specific characteristics of ATMPs:**
  - Supply chain specific features: role of Tissue Establishments:
    - Identity testing.
    - Level of supervision.
  - Inherent variability and scarcity of cells/tissues:
    - Testing requirements.
    - Sampling of biological starting materials.
    - Validation obligations.
  - Addressing reconstitution by doctors in hospitals.

4. The consultation paper (cont.)

- **Reduction of burdens:**
  - Possibility to accept clean rooms with a background C or D.
    - This flexibility would not apply for commercial manufacturing or pivotal clinical trials.
  - Additional flexibilities for ATMPs: *e.g.* no trending.
  - In general, more emphasis on outcome and less detailed requirements:
    - Flexibility for manufacturers to apply measures best suited to the specific product.

4. The consultation paper (cont.)

- Reduction of burdens <u>without compromising public health:</u>
  - Some requirements on key aspects of the manufacturing process have been reinforced:
    - For cell-based products, cleaning validation between manufacture of different batches.

4. The consultation paper (cont.)

- **Making GMP requirements more understandable and accessible**:
  - Single document with all requirements relevant to ATMPs.
  - Current provisions streamlined (overlaps, requirements not relevant to ATMPs will be removed).
  - Text drafted with specific focus on ATMPs.

5. Specific GMPs for ATMPs: the process

- Consultation with EMA experts (CAT and IWG GMDP) started in February 2015.
  - 19 meetings (virtual and face to face).
- Consultation document drafted by COM on basis of input from EMA experts.
  - The consultation document does not represent any official position from the European Commission.
  - It is a tool to seek the views of stakeholders.

5. Next steps

- Evaluation of comments from stakeholder consultation
  - Deadline for comments: November, 12.
- Drafting of GMP Guideline for ATMPs.
  - COM will continue to rely on the expertise of EMA (CAT and IWG GMDP) to draft the Guidelines.
- Discussion at Pharmaceutical committee and possible further consultation of stakeholders.

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Thank you!

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