Good Manufacturing Practice for ATMPs

Rocio Salvador Roldan
DG SANTE, Unit B5

This presentation only reflects the views of its author and does not necessarily reflect the opinion of the Commission

Health and Food Safety

European Commission

Overview

- Why a specific Guideline for ATMPs?
- Overview of the process
- What's in the Guidelines?
- Protection of public health
- Comments received

Health and Food Safety

1. Why a specific Guideline for ATMPs?

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).

- 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.

1. Why a specific Guideline for ATMPs?(cont.)

- Application of current GMP consistently identified as a problem for developers:
  - Lack of adaptation to specific characteristics of ATMPs:
    - Starting materials/finished products are limited and there is intrinsic variability.
    - Batches of very small size (often, one patient = one batch).
    - Low production (no factory that is constantly manufacturing the product).
    - Short shelf-life, which limits possibility for testing and also requires production close to patients (single factory to serve EU not feasible).
    - Reconstitution as per current Guidelines does not correspond to ATMP setting.
  - Divergent practices across EU.
  - More favourable environment in other jurisdictions.

2. Overview of the process

- Draft GMP for ATMP Guideline has been developed from input received from experts from MS, as well as input from EMA scientific advices:
  - All sections have been based on contributions from MS: National experts "sponsored" a section on volunteer basis:
    - AT, BE, CZ, DE, ES, FI, IE, IT, NL, PT
- 23 July- 12 November 2015: first stakeholder consultation
- Nov'15 – June'16: 10 teleconferences and 2 physical meetings.
- 28 June -26 September 2016: second stakeholder consultation.
- October'16- Janurary'17: 8 teleconferences and 2 physical meetings.

European Commission

2. Overview of the process (cont.)

- Drafting process has been challenging due to different views on certain aspects.
- Both types of expertise are important:
  - Specifications, manufacturing process, control strategy, release testing, process validation, *etc.* is part of marketing authorisation/clinical trial application and is also the core of GMP.
  - Scientific advices and content of marketing/clinical trial authorisations should be consistent with approach taken during inspections.

3. What's in the Guidelines?

- Explanation on how to apply risk-based approach:
  - RBA permits adaptation of quality requirements in MAA (including aspects therefore that fall under GMP).
  - Examples in Guidelines are based on questions from stakeholders and having regard to responses in scientific advices.
  - Clean air requirements for FIM trials/ non-substantially manipulated products : views of MS split.
- Gradual approach for investigational ATMPs:
  - Requirements increase as the clinical development progresses.
    - This approach is already embodied in EMA Guidelines and indirect references on current GMP: Guidelines clarify expectations.
    - Gradual approach to GMP is a key feature of US system
      - Draft Guidelines are however a bit more conservative than US approach.

3. What's in the Guidelines? (cont.)

- Adaptation to specific characteristics of ATMPs:
  - ***Sampling for autologous products***: *e.g.* recognition that samples cannot be retained (the full product must be administered to the patient).
  - ***Sterility testing***: Explanation of alternative strategies in cases of short-self life.
    - Current GMP recognise that administration to patient may need to take place before the results of the sterility testing are available but fails to provide guidance on alternative approaches that may be possible to try to get as much assurance as possible that product is not contaminated.
    - Approach consistent with scientific advices.
- Clarification of obligations:
  - Text of Guidelines adapted to the specific setting of ATMP manufacturing; *e.g:* the ***application of the concept of "shift"*** to ATMPs would pose unintended serious risks to public health.

European Commission

3. What's in the Guidelines? (cont.)

- Addressing novel questions, *e.g.*:
  - ***Multi-product facility***
  - ***Automated production***
  - ***Decentralised manufacturing***
  - ***Reconstitution***
  - ***Use of cell-lines established in the past***
- Reduction of administrative burdens:
  - Limited impact: in the context of the discussion in the drafting group, documentation obligations have been reinforced.

4. Protection of public health

- New Guidelines maintain a high level of protection for patients.
- No lowering standards but adaptation:
  - Different approaches may be valid to protect patients, *e.g.*:
    - Manufacturing in a grade C room with additional control measures and testing for sterility of every unit before it is given to the patient.
- Where necessary, Guidelines increase obligations, *e.g.*:
  - Validation of reconstitution process.
  - Obligations regarding raw materials and other critical materials (including medical devices used in combination products).

5. Responses received

- **Clean air requirements for non-substantially manipulated ATMPs:**
  - Agreement with COM proposal: AT/DE*/ES/IT/NL
  - Against COM proposal: None.
  - Other: UK

*DE: Need for flexibility, however, stressed, applying risk-based approach (*e.g.* manufacturing in semi-closed technologies and administration to patient within few hours).

Also noted that, currently, GLs provide for flexibility when processes are not closed: control measures to be applied having regard to risk taking into account "*the principles of Annex 1*", "*it is not the intention to force the manufacture of sterile product at a stage where low bioburden is appropriate and authorised*".

5. Responses received (cont.)

- **Clean air requirements for ATMPs used in FIM CTs:**
  - Agreement with COM proposal: AT/DE/IT*/NL**
  - Against COM proposal: ES, UK

** IT: Provided that it is clarified that this flexibility should only apply in case of life threatening pathologies for whom no therapeutic alternatives are available and that a detailed description of the approach applied should be described in the IMPD.

** NL: Provided that the risk assessment concerning the aseptic part of the process is required.

5. Other comments received

- PIC/s letter of 24th February 2017.
- Letter from IWG of 28th February 2017:
  - Concerns about process.
  - Concerns for patient's safety as result of lowered manufacturing standards.
  - Concerns that gradual approach to investigational ATMPs could delay translation of research into marketed products.
- ES: Objection to sections on RBA, reconstitution, decentralised manufacturing and semi-closed technologies.

European Commission

Thank you!

European Commission

Public Health information:

http://ec.europa.eu/health/index_eu.htm

Health and Food Safety