Quality control and batch release aspects of Advanced Therapy Medicinal Products

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QUALITY CONTROL AND BATCH RELEASE ASPECTS OF ADVANCED THERAPY MEDICINAL PRODUCTS

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INTRODUCTION

Background: Biological medicinal products are products with an active substance produced or extracted from a biological source. Advanced Therapy Medicinal Products (ATMPs) are medicinal products based on genes, cells or bioengineered tissues that have been regulated in the European Union from 2007. Dedicated Good Manufacturing Practice (GMP) guidelines have been established from the European Commission in order to guarantee their quality, efficacy and safety from the development to the marketing authorisation. Consequently, GMP guidelines covering manufacture of *biological active substances and medicinal products for human use including biological active substances* (hereafter "biologicals") have been revised in June 2018 to prevent overlapping scope. The manufacturing of biologicals and ATMPs has to comply with guidelines that are established by the European Commission.

Research question: We hypothesized that due to biological nature of ATMPs, similarities in part of these guidelines related to quality control and batch release aspects could be evidenced in the texts. This analysis will help to understand why two different texts have been elaborated by analyzing whether they are actually based on specific considerations in terms of quality control and batch release arising from the nature of the products and the processes differences between ATMPs and other biological medicinal products.

Methods: We conducted a comparative analysis of the two following regulatory texts : *Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (focuses on from chap. 10 QUALIFICATION to the end)* and *Manufacture of Biological active substances and Medicinal Products for Human Use.* In a first systematic approach, we identified the similarities and the specificities of texts outline (paragraph and section titles). Then, we analysed contents based on chosen relevant key words that may be diversely used in two texts (control, quality control, strategy of control, certification, release, in process control, quality risk management, analytical technics/methods, testing etc) in order to highlight similarities and specificities in all aspects related to quality control and batch release.

RESULTS

SIMILAR REQUIREMENTS

Starting and raw materials
- Compliance with legislations on quality, safety and traceability of human tissues/cells, blood/blood components, and genetically modified cells, (donation, procurement and testing)
- Appropriate level of control and requirements
- Possibility to process starting materials before the results of their testing, but release of finished product conditioned by satisfactory results

Premises and equipment for quality control
- Apart from production.
- Prevention of mix-ups and cross-contamination during testing.
- Storage space (samples and records

Primary containment
- Safe & respect products' characteristics.
- Maintaining quality and prevent spillage.
- Compatibility of labels with ultra-low storage temperatures

Seed lot and cell bank system

To prevent drift of properties during handling and storage:
- Appropriate specifications (number of generations,…)
- Risk of adventitious agents and cross contamination

Batch certification, release

Initial and final certification based on :
- Environmental & analytical testing
- Defined specifications (market authorization, clinical trial authorization)

By qualified person
Management of "out of specifications"

Documentation
- Specifications, instructions, records/reports.
- On the source, origin, distribution chain, methods and controls.
- Traceability records (30 years).

Retained samples for QC retesting
- "Look-back procedure" attesting for the continued suitability of the biological active substance.
- Re-testing of retained samples from previous collections ➔ "last negative donation"

In-process control
- Ensures quality consistency
- Happens at appropriate stages of productions.

Hazard identification/quality risk
- Quality risk management and risk-based approach to minimise variability of biological processes and materials and to reduce/control contaminations.
- Subjects are animals, biological agents, premises, equipment and control operations

Considerations for microbiological risk
- Level of bioburden or need to be sterile defined in MA and CTA for substances and materials at various stages
- Sterilization process allowing to preserve the activity of materials and excipients
- Aseptic process and strategies minimizing the risk of contaminants introduction (quality of starting materials, adapted environmental monitoring, use of closed system, cleaning, use of antimicrobials or antibiotics without interference

Legend

Existing or combined sections of each text

Disseminated requirements within each text

SPECIFICITIES

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (2017)

Validation of analytical methods

➢ Suitability for the intended purpose
- Sterility
- Safety attributes
- Critical quality attributes
- Release criteria
- Stability testing

Additional in vitro assays
- ➢ « potency testing (or proliferation assays …)
- ➢ After batch release as supporting data for process validation »

Cell stocks
- ➢ Obtained from a limited number of passages,
- ➢ Do not cover the entire life cycle of the product
- ➢ Control and release conditions in accordance with principles of cell banks

On-going stability program
- ➢ For finished products with shorter shelf-life
- ➢ After the marketing authorisation
- ➢ Stability of specifications during the shelf-life

Novel aspects justified by specific challenges of cell-based therapy

- **Complexity of products & processes + limited batch series + variability of the starting materials (especially in autologous setting) ➔ Flexibility and "Risk-based approach" for appropriate measures of quality control**
- **At the authorized and investigational stages, from the raw material to the final production**

Guidelines on the Manufacturing of Biological active substances and Medicinal Products for Human Use (2018)

Quality of starting materials or non human origin Animal sources

➢ **2 types of sources**:
- Live groups (monkeys, horses, sheeps, goats, hamsters, cattle…)
- Animal materials derived post-mortem

➢ To comply with TSE regulations: suitability of sources/donors, traceability identification system to to control all hazards

➢ Strictly controlled selection of donor animals.
- Healthy
- Specific pathogen free (SPF)
- Raised in SPF conditions
- Bred in captivity specifically designed for the purpose of the research

Controls & Testing using animals

➢ Animals used in quality control assays
- Generic assays, e.g., pyrogenicity,
- Specific potency assays

- **Quality controls and certification aspects: measures emphasizing procurement and quality of starting materials of animal origin, mitigation of a higher risk of low purity and microbiological contamination, and of greater variability of biological analytical techniques ➔ "risk quality management principles" for appropriate measures of quality control**
- **Focus on the process, from raw material (principally extracted from animals or donors) to the active substance**

DISCUSSION/CONCLUSION

Similar spirit of the two texts
- Based on the crucial role of manufacturing and control processes in determining the quality of such types of medicinal products
- To ensure measures related to the biological origin and the related inherent variability of such medicinal products are adopted regarding the requested standards of quality, a major determinant of safety and efficacy for the patients

→ Large set of similarities in their content on quality control and batch release, based on their common biological nature and related risks in terms of quality of starting human and raw materials, traceability, sustainability of quality, compatibility of containments, importance of process controls, strategy for initial and final certification and batch release.

Explicit Rationale for differences in the two texts
- Substantial specificities due to specific risks, as presented in the scopes and general principles of the texts
- Very detailed text of 90 pages for ATMPs dated of 22/11/2017, and briefer text of 25 pages for biologicals dated of 26/06/2018 that has been revised in order to take into account the new guidelines on ATMPs.

→Exclusive Guidelines: it is explicitly stated that the text on biologicals does not apply to ATMPs which are covered by specific guidelines.

Questioning the relevance of having two distinct and exclusive texts
- As ATMPs are a specific category of biologicals, the levels of similarities and differences regarding quality control and batch release are variable, e.g., The "risk-based approach" for ATMPs seems matched to the "risk quality management principles" for biologicals, but the former is more prospective with the idea to anticipate and control current poorly known risks.
- Some specific requirements solely expressed in the ATMPs guidelines may be relevant to other biologicals, e.g., the validation of biological methods used for quality control and testing.
- Some specific requirements solely expressed in the text on Biologicals may be relevant to ATMPs: Because ATMPs could also in the future be designed based on xenogeneic cells and are prone to necessitate the use of raw materials of animal origin (such as cell culture or extraction reagents etc..), it can be anticipated that details of recommendations on animal sources warrant further considerations in ATMP guidelines as it is currently for biologicals.
- The rationale for some style/form differences is unclear: The vocabulary used in the two texts is very different while they have been adopted with a 7 months interval only, and it often refers to the same ideas.

The two texts are presented as exclusive, but they share common aspects.

They share common aspects related to the biological nature of the product.
They could benefit from being formulated in a more similar manner to facilitate full understanding and implementation by stakeholders, especially manufacturers.

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