



Good Manufacturing Practice for ATMPs

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Overview

- ▶ Regulation of ATMPs in the EU
- ▶ GMP for ATMPs: challenges
- ▶ The development of GMP for ATMPs Guideline
- ▶ Questions addressed to MS
 - (1) *How to deal with non-substantially manipulated ATMPs?*
 - (2) *What requirements for investigational ATMPs?*
 - (3) *Where to set the bar?*
- ▶ Conclusions



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1. Regulation of ATMPs in the 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.
- Hospital exemption.

1. Regulation of ATMPs in the 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).

▶ 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.

2. GMP for ATMPs: challenges

- ▶ Guidelines should ensure adequate manufacturing conditions to preserve quality, safety and efficacy of the ATMPs.
- ▶ Guidelines should be well-adapted to the characteristics of ATMPs:
 - scarcity of starting materials: limited material for sampling and testing;
 - short shelf-life: analytical results from testing may not be available prior to administration;
 - high degree of variability (due to differences in cells/tissues from different donors) to be factored in when considering requirement of consistent production.
- ▶ Guidelines should impose proportionate obligations:
 - small batches (for autologous products, each unit is a different batch);
 - market constraints regarding raw materials;
 - R&D mainly conducted by university hospitals and SMEs.

3. The development of GMP for ATMPs Guideline.

- ▶ Stakeholder consultation (23 Jul -12 Nov '15):
 - ▶ strong support, in particular from hospitals, academia and SMEs;
 - ▶ additional flexibilities/clarifications requested.
- ▶ Drafting group:
 - ▶ chaired by COM;
 - ▶ experts from CAT and IWG (as well as other national experts representing both inspectors and assessors of ATMPs).
- ▶ Work progress after the end of the consultation:
 - ▶ 8 teleconferences and 1 physical meeting (since the end of the consultation);
 - ▶ 10 sections of the document discussed in detail;
 - ▶ draft Guideline expected to be ready for consultation by the summer.
- ▶ Adoption expected by the end of the year.



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4. The questions addressed to MS

- ▶ In addition to consulting with experts in drafting group, COM would like to have the view of the competent authorities on the following issues:
 - How to deal with non-substantially manipulated ATMPs?
 - What is the right level of regulation for investigational ATMPs used in early phases of clinical trials?
 - Setting the bar of regulatory burden at the right level: what is your experience?

(1) How to deal with non-substantially manipulated ATMPs?

- ▶ Cells/tissues that are used for a different essential function in the recipient as in the donor are ATMPs.
 - ▶ Level of processing is similar to transplantation setting.

- ▶ Many hospitals in the EU perform transplant of cells/tissues under regulatory framework of transplant legislation.
 - ▶ Operation under a different framework with different requirements may be challenging.



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(1) How to deal with non-substantially manipulated ATMPs? (cont.)

- ▶ Alignment of the GMP requirements for non-substantially manipulated ATMPs to the quality requirements for the transplantation of cells/tissues?
- ▶ Should specific flexibilities be recognised (in line with requirements under the transplantation legislation)?
 - ▶ Quality of air.
 - ▶ Qualification of premises and equipment.
 - ▶ Process validation.
 - ▶ Quality control obligations.
 - ▶ Environmental monitoring obligations.
 - ▶ Other?
- ▶ No distinction vis-à-vis substantially manipulated ATMPs?



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(2) What requirements for investigational ATMPs?

- ▶ Some current obligations deemed disproportionate (in particular by hospitals):
 - ▶ e.g. more simulations to demonstrate aseptic processing (media fill tests) than number of ATMPs actually produced.
- ▶ Flexibility requested for GMPs requirements applicable to ATMPs used in early phases of CTs, e.g.:
 - ▶ manufacturing in A/C room (as opposed to A/B room);
 - ▶ qualification of premises and equipment
 - ▶ quality controls
- ▶ The international perspective:
 - ▶ compliance with GMPs not required in the US (for early phases of clinical trials).

(3) Where to set the bar?

- ▶ Too low GMP requirements entail risks for patients; too high requirements may prevent the development of the field and deprive patients of safe and effective medicinal products.
- ▶ MS experience in the application of the GMP requirements for ATMPs can provide valuable input:
 - ▶ it is argued that lower manufacturing costs are incurred when manufacturing under the hospital exemption;
 - ▶ it is argued that ATMP manufacturers have to comply with different GMP requirements depending on MS:
 - ▶ e.g.: strict approach to sampling and testing in some MS (amount of cells/tissues used for quality control exceed the actual amount of cells/tissues administered to patients) v. pragmatic approach in other MS.

5. Conclusions

- ▶ The GMP for ATMPs Guideline is seen very positively by those involved in the development of ATMPs.
- ▶ The development of the GMP for ATMPs Guideline is an opportunity to:
 - ▶ reduce burdens to facilitate the development of the field, while maintaining a high level of patient protection;
 - ▶ clarify what is expected from manufacturers of these products in a manner that is harmonised across the EU.
- ▶ The involvement of MS (through the drafting group and your responses to the questionnaire) is important.



Thank you!

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