EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Workshop on quality support to early access approaches (PRIME & Breakthrough)

Session 4: GMP-compliance

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An agency of the European Union

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Overview

Why GMP is important?

Good Manufacturing Practice (GMP) is that part of Pharmaceutical Quality System (PQS) ensuring:

- Medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorization (MA), Clinical Trial Authorization or product specification

- Medicinal products do not place patients at risk due to inadequate safety, quality or efficacy.

PRIME and GMP: GMP Compliance is an important part of the PRIME to enable faster development and approval in areas of unmet medical need/major public health need **without compromising quality**, safety and efficacy.

Overview: principles and guidelines of GMP in the EU

EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

- Regulation No.1252/2014, Directive 2003/94/EC (Reg. No.2017/1569 and Dir. 2017/1572) ,
  - applying to active substances, investigational medicinal products and medicines for human use.
- Directive 91/412/EEC
  - applying to medicines for veterinary use.
- Reg. 1394/2007, Directives 2001/83/EC, 2001/82/EC lay down related provisions.

- Interpretation of key principles and guidelines are provided in part I, II, III, IV.
- Related annexes provide clarifications on specific type of products or topics.
- GMP global harmonization (PIC/S, MRAs)

GMP topics raised during the evaluation of PRIME applications

Submission of conditional Marketing Authorisation Applications based on clinical trial data generated with products manufactured in a facility that did not meet full GMP requirements (e.g. academic laboratory)

- The manufacture of investigational medicinal products or ATMPs should be in compliance with GMP.
- For medicinal imported from third countries, the importer shall ensure that the products have been manufactured in accordance with standards which are at least equivalent to the GMP standards laid down by the Community. The QP should determine that equivalent standards of GMP apply through knowledge (audit) of the quality system employed at the manufacturer.
- The application of GMP is intended to ensure that subjects are not placed to undue risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture.
- Marketing Authorisation should include data from clinical studies conducted using a product with known and controlled manufacturing process and quality.

GMP topics raised during the evaluation of PRIME applications

Comparability Assessment Plan: should include the evaluation of GMP gaps, e.g.:

- Evidence of PQS (including possibility for receiving an inspections at the non GMP site).
- Risk assessment.
- Deviations, OOS, OOT handling systems.
- Validation and qualification system (e.g. room classification, environmental monitoring).
- Analytical and microbiological testing evaluation.
- Stability studies.
- Change systems (e.g. change in manufacturing and testing).
- Documentation handling (e.g. batch records, procedures, records traceability, etc.).
- Manufacturing Process description, variability and performance.
- Clinical batches evaluation and Comparability data between manufactured batches.
- Starting material and vendor audit system evaluation.

GMP topics raised during the evaluation of PRIME applications

Concurrent validation

- May be acceptable in exceptional circumstances (strong benefit-risk ratio for the patient - due to the limited availability of the starting materials (ATMPs)).
- Regulatory Authority involvement.
- Decision must be justified, documented in the Validation Master Plan and approved by authorized personnel.
  - Robust validation strategy: protocol, definition of CQA and CPP and associated acceptance criteria (based on development data and process knowledge – historical data and manufacturing experience)
  - Overview of all production processes versions used for the all non-clinical and clinical studies, including data supporting process validation and comparability exercises.
  - Reviews of data from the manufacture of batches to confirm that the manufacturing process is able to ensure consistent product quality and that the defined specifications are complied with.
  - The results and conclusion should be formally documented and available to the QP prior to batch certification.

GMP topics raised during the evaluation of PRIME applications

Out Of Specification (OOS)

- Any OOS should be fully recorded and investigated with the objective of determining the root cause and implementing appropriate corrective and preventive actions.
- The impact of any deviation should be assessed in accordance with a quality risk management
- The certifying Qualified Person (QP) should consider:
  - OOS results (most probable cause determined) in the batch or lot disposition decision
  - consideration to include the affected batches into stability
  - the potential for a batch specific variation also needs considering.
- Any decision to release a batch, in spite of an initial OOS result that has not been invalidated, should come only after a full investigation has shown that the OOS result does not reflect/impact the quality, safety and efficacy of the batch. In making such a decision, Quality Assurance/QP should always be on the side of caution and strongly justify the decision.

GMP topics raised during the evaluation of PRIME applications

Out Of Specification (OOS)

Administration of out of specification products (EU GMP Part IV)

- 11.53. Exceptionally, the administration of cells/tissues that are contained in a cell/tissue based ATMP that is OOS may be necessary for the patient. …..To avoid an immediate significant hazard to the patient and taking into account the alternative options for the patient and the consequences of not receiving the cells/tissues contained in the product, the supply of the product to the treating physician is justified.
- 11.54. ……the manufacturer should provide the treating physician with its evaluation of the risks and notify the physician that the out of specification product is being supplied to the physician at his/her request. The confirmation of the treating physician to accept the product should be recorded by the manufacturer. ……the manufacturer should immediately notify the sponsor/MAH of such events….the sponsor/MAH should inform the relevant competent authority. For marketed products.
- 11.42 …… In case of recurrent deviations, the need for changes to the manufacturing process should be assessed.

GMP topics raised during the evaluation of PRIME applications

Master Cell Bank (MCB) and Working Cell Bank (WCB) not manufactured under GMP

- The establishment of new seed/cell lots/banks and viral seed stocks should be done in accordance with GMP (EU GMP Annex 2, Part IV)
- The use of no GMP cell stocks/cell banks and viral seed stocks could only be accepted in exceptional cases and provided that there is extensive characterisation and testing.
- A risk analysis should be conducted to identify the testing requirements necessary to ensure the quality of the starting material.
- In all cases, the overall responsibility for the quality (as well as the impact thereof on the safety and efficacy profile of the product) lies with the manufacturer and/or the sponsor or marketing authorisation holder.
- The competent authorities should agree to the strategy.

GMP topics raised during the evaluation of PRIME applications

Batch release from a laboratory based in a third country (e.g. USA)

- EU GMP Annex 16 (Directive 2001/83/EC Article 51 (1)(b))

  The QP is responsible for ensuring that each finished medicinal product batch has been manufactured in accordance with GMP and the MA. Unless an MRA or similar agreement is in place between the EU and the exporting country, the QP is also responsible for ensuring that the finished medicinal product batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products is in accordance with the requirements of the marketing authorisation.

- EU GMP Part IV ATMPs

  It may be justified to rely on testing performed in the third country in cases where the limited amount of material available (e.g. autologous products) or the short shelf-life impedes double release testing. In such cases, the testing in the third country should be conducted in GMP-certified facilities (in the case of authorised ATMPs) or under GMP conditions equivalent to those applicable in the EU (in the case of investigational ATMPs).

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Any questions?

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