Draft Reflection Paper der EMA „GMP and MAH“

9. September 2020

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Allgemeine Informationen

- **14 January 2020**
- **EMA/457570/2019**
- **Deadline for comments: 17 July 2020**
- **31 Seiten**

https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-good-manufacturing-practice-marketing-authorisation-holders_en.pdf

Introduction, Purpose

- Applicability: MA applicants und MA-holder
- MAH can delegate certain activities to manufacturer or other party, but responsibilities stay with the MAH
- No reduced responsibilities / delegation whether MAH and manufacturer …
  - belong to same overall group of companies (but are different legal entities), or
  - are from separate and unrelated companies
- Guidance on expectation and explanation of responsibilities, but not on how to fulfill
- Inspection of MAHs by competent authorities empowered

Scope

- References:
  - EU GMP Guide Part I, II und Annexes
- Manufacturing includes laboratory testing (not only release testing, but also e.g. ongoing stability)
- All MAHs, also including:
    - Registration Holders
    - Traditional-use Registration Holders
    - ATMP-MAHs
- Not in scope:
  - GDP-requirements
  - Pharmacovigilance

MAH: Facilitating GMP- and MA-compliance

- Responsibilities relate to
  - Information of authorities, manufacturing sites and QPs
  - Collation of quality-information in manufacturing and distribution chain
- Assure that manufacturer own MIA and GMP-certificate
- Provide abbreviated version of CTD module 3 (for manufacturer and QPs):
  - Acceptable as long as sufficiently comprehensive and subject to Chance Control and oversight activities
- Communicate labelling and product information to the manufacturer (CTD module 1)
- Provide MA-variations to parties (incl. target implementation dates)
- Robust two-way communication system
  - MAH has adequate knowledge
  - Mfg sites and QPs have visibility on what is registered and any regulatory commitments made
  - MAH adequately informed of Change Management (regulatory impact assessment for relevant changes)
- Assure contracts according EU-GMP Part I, chapter 7
- System to assure data-integrity
  - GMP-activities
  - MA-variations
  - Long-term security, storage and archiving of MA-data

Outsourcing and Technical Agreements

- Only delegation of tasks/activities (in writing and agreed):
- Responsibility for compliance stays with the MAH
- Fragmented delegation:
  - Oversight function of MAH
- Qualification of third party:
  - MAH responsible to ensure that person or entity to whom any task or activity has been delegated possesses required competence, information and knowledge

Technical Agreements - Requirements

- Technical Agreement (TA)
  - even if different legal entities in **same group of company**
- MA-variation management
  - compliance in case of changes
- Segregation of responsibilities for PQR
  - including final compilation and evaluation
- Biological Products
  - sourcing of human derived starting materials
- Ionising radiation products
  - design of irradiation cycles, retaining their records
- Reference and Retention Samples
  - taking and storage
  - provisions in case of shutdown of storage site: proposed other arrangements to be consulted with CA in **each member state** where any unexpired batch has been placed on the market
- Document Retention:
  - Critical documentation, including raw data, which supports information in the MA should be retained whilst the MA remains in force

Qualification Activities and Audits

- QP-Declaration:
  - Responsibility: MA applicant
  - Personally signed by QP
  - Basis: audit of API-manufacturer
  - Re-audit: normally within 3 years
  - **Type 1A variation for „changes in the date of the audit“!!!**
    - **Gemäß Variations Guideline (EC guideline 2013/C 223/01) erforderlich!**
    - **Umfrage der EQPA: niemand hat das bislang gemacht**
    - **Situation unter Österreichischen QPs?**
    - **Kommentare diverser Verbände verlangen eine ersatzlose Streichung in der Guideline!**

Communication

- With manufacturers and authorities
- Robust two-way communication
- Focus: lifecycle MA compliance
- Arrangements for communication part of TA
- Essential tasks for communication:
  - Changes (regulatory notification or variation required?)
  - Quality defects and potential recalls
  - Ensuring continued supply
- Documentation:
  - Same overall group of company: SOPs
  - Different groups: detailed TA
- Scientific Advances:
  - Includes compliance with current Pharmacopoeia and quality guidelines
  - Includes ability of analytical methods to detect / quantify relevant impurities (ICH, VICH)
  - Submission of comments to EDQM if necessary

Product Quality Review (PQR)

- Final compilation and evaluation dedicated to MAH
- Full delegation to manufacturer not appropriate
- Segregated and shared responsibilities
- PQR data mostly delivered from manufacturer (GMP-data)
- MAH: focus on MA-compliance (e.g. variations, post-marketing commitments, recalls, etc.)
- Manufacturer: focus on GMP-compliance

Quality Defects, Complaints and Recalls

- MAH‘s responsibility: dedicated responsible person at MAH
  - Contact person as part of MA-application
  - Notification to and approval by authority
- Contact points of both parties in TA (for outsourced activities)
- Authority notification by MAH, in case of:
  - Quality defects and recalls
  - Suspect falsification (incl. distribution by illegal supply chain)

Maintenance of supply

- MAH to ensure appropriate and continued supplies
- Authority notification by MAH:
  - Restriction in supply (also if caused by manufacturer)
    - TA (or SOP) has to ensure information of MAH by manufacturer
  - Suspension of marketing and withdrawal from market, request on withdrawal, not applying for MA-renewal (including reason for such actions)
- Proactive prevention of shortage by MAH:
  - EMA-reflection paper references e.g. ISPE and PDS-documents

Falsified Medicines Directive (FMD)

- MAH responsible for implementation of Unique Identified (UI) and anti-tempering device (no delegation possible)
- Delegation of affixing safety features to manufacturer possible
- MAH responsible for upload and decommissioning of UI from repositories:
  - Delegation to third party possible, but only **physically located within EEA**
  - Segregation of responsibilities in TA
  - **CMO‘s not permitted to on-board to EU-hub**
- Decommissioning, MAH‘s responsibilities:
  - Ensure decommissioning of recalled or withdrawn products
  - Ensure decommissioning of stolen products
  - Indicate in repository that product was recalled, withdrawn or stolen
  - In **every** national or supranational respository!

aqpa
Austrian Qualified Person Association

Fragen???