EU-GMP-Guide
Annex 16: Certification by a Qualified Person and Batch Release

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Termin zur Stellungnahme: **5. November 2013**

Kommentare zur Weiterleitung bis spätestens
11. Oktober 2013 an **AQPA**

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1. Scope:

- *QP certification and batch release within EEA*
- *Human or veterinary medicinal products*
- *Also for exported products*
- *Also for investigational medicinal products*
- *Nothing in this Annex should be taken as overriding basic arrangements as defined by marketing authorisation (MA)*

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2. General principles:

- *Ultimate responsibility lies with the MAH*
- *Responsibility to ensure particular batch manufactured acc. MA, EU GMP (or equivalent), and in compliance with the laws in country of certification as well as **country of destination** lies with the QP*
- *Batch release process:*
  - *Manufacture and testing in accordance with defined release procedure*
  - *Certification by a QP that batch complies with MA and EU-GMP*
  - *Assigning release status taking QP certification into account (release status could be done by another person, delegation in SOP or contract)*
- *Purpose of controlling batch release:*
  - *Compliance with MA*
  - *Compliance with EU-GMP or equivalent*
  - *Compliance with any other relevant legal requirements (e.g. of the destination country)*
  - *In case of investigation or recall, to ensure certifying QP is readily identifiable*

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3. The process of certification:

- *Each batch of finished product: certified by a QP within the EEA (before sale or for export)*
- *Certification only by a QP of a license holder named in the MA*
- *QP must have detailed knowledge and should be able to demonstrate knowledge (product type, production processes, tecnical advances and changes to GMP)*
- *Regardless of how many sites involved, the certifying QP of finished product must ensure all necessary steps completed through an agreed QMS*
- *Manufacturing at sites in EEA:*
  - *Each site must have at least one QP (confirm operations by the site)*
  - *QP has access to the necessary details of the MA*
  - *QP certifying finished product may assume full responsibility for all stages or this may be shared with other QPs (same or different MAH)*
  - *Any division of responsibilities amonst QPs defined in a written agreement or in a procedure*

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3. The process of certification (cont‘d):

- *Manufacturing sites outside the EEA:*
  - *Certification for all medicinal products released for EEA markets, or for export (irrespective of complexity of supply chain and global locations of sites involved)*
  - *Importation inlcudes at least: receiving, sampling, storage, QC-testing, certification and release (conducted by authorised sites in the EEA)*
  - *QP may take into account confirmation by other QPs (site in the EEA and defined in the MA)*
  - *Take into account: conditions of storage and transport*
  - *Unless MRA or similar agreement in place, each batch has undergone in a Member State analysis acc. requirements of the MA*
  - *Sampling of imported product taken after arrival in the EEA (specific samples taken in third country (e.g. for sterility testing) should be technically justified (same shipping conditions, demonstrate that samples are representative))*

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3. The process of certification (cont‘d):

- *Manufacturing sites outside the EEA (cont‘d):*
  - *Different finished poduct batches originating from the same bulk batch:*
    - *QP may certify the different finished product batches based on testing of another batch originating from the same bulk batch provided the ID and assay testing are conducted on each occasion within the EEA and secured evidence that:*
      - *Finished product originates from same bulk batch*
      - *Finished product stored and transported in similar conditions*
      - *Bulk product stored in similar conditions before packaging*
      - *Samples tested are representative of the whole batch*

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3. The process of certification (cont‘d):

- *QP must personally ensure:*
  - *Certification is permitted under terms of MIA*
  - *Any additional requirements of national legislation are complied with*
  - *Certification recorded in a register or equivalent document*
- *Ensure the following points (may be delegated to appropriately trained personnel or third parties). QP will need to rely on QMS (QP should have on-going assurance that this reliance is well founded)*
  - *All activities in accordance with EU GMP*
  - *Entire supply chain is documented and available to the QP. Preferably a comprehensive diagram*
  - *All sites of manufacture, analysis and certification are compliant with the MA*
  - *All manufacturing and testing activities are consistent with the MA*
  - *Source and specifications of starting materials and packaging materials compliant with the MA. A supplier quality management system is in place.*
  - *APIs have been manufactured in accordance with GMP and imported/distributed in accordance with GDP and Art. 46b of Dir. 2001/83/EC* (= Schriftliche Bestätigung bei nicht anerkannten Drittstaaten)

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3. The process of certification (cont'd):

- *Excipients have been manufactured in accordance with the appropriate level of GMP (Art. 46 (f) of Dir. 2001/83/EC)*
- *TSE status of all materials compliant with the MA*
- *All records complete and endorsed by appropriate personnel. All required IPC and checks have been made.*
- *All manufacturing and testing processes remain in validated state. Personnel trained and qualified, where required.*
- *QC data complies with registered specification, or where authorised, the Real Time Release Testing programme*
- *Any post marketing commitments have been addressed. On-going stability data continues to support certification*
- *Impact of any change has been evaluated and any additional checks and tests are complete*

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3. The process of certification (cont'd):

- *All investigations pertaining to the batch being certified (including OOS and adverse trend investigations) have been completed to a sufficient level to support certification*
- *Any on-going complaints, investigations or recalls do not negate the conditions for certification*
- *Required technical agreements are in place*
- *Self inspection programme is active and current*
- *Appropriate arrangements for distribution and shipment are in place*
- *Product for EU market has required safety features (Art. 54 of Dir. 2001/83/EC)*

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3. The process of certification (cont‘d):

- *Special guidance may apply for certain products such as Annex 3 for Radiopharmaceuticals*
- *Parallel importation & distribution*
  - *QP should confirm compliance with national and EU rules for parallel import and parallel distribution*
  - *QP of the MIA holder has to certify that re-packaging in accordance with relevant Authorisation and GMP*
  - *Re-packager should ensure product has been obtained from authorised supply chain and that each sourced batch has undergone QP-certification prior to ist release into the supply chain*
  - *Re-packager must ensure authenticity by verifying safety features*

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3. The process of certification (cont'd):

- *Recording of the certification:*
  - *Certification is recorded in a register or equivalent document*
  - *Record should show each batch satisfies provisions of Dir. 2001/83/EC or 2001/82/EC*
  - *Record kept up to date as operations are carried out*
  - *Records must remain at the disposal of the competent authority*
  - *Records must be kept for at least five years*
  - *Control report or another proof of certification of an equivalent system should be made available in order o be exempted from the controls when entering another Member State*

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4. Relying on GMP assessments by third parties e.g. audits:

- *Should be in accordance with Chapter 7 (EU GMP)*
- *Should focus on approval of audit reports, e.g.*
  - *General GMP requirements*
  - *QMS*
  - *All relevant production and QC procedures*
  - *All audited areas accurately described*
  - *Manufacture and QC follows GMP*
  - *Outsourced activities comply with the MA*
  - *QP should ensure written final assessment and approval of audit reports according to company‘s requirements*
  - *QP should be aware of outcome of audits with critical impact before certifying relevant batches*
  - *Repeated audits in accordance with principles of QRM*

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5. Handling of unplanned deviations:

- *All registered specifications for API, excipients and finished products must be met*
- *Product may be considered to meet the requirements when:*
  - *Deviation is unexpected, unplanned and relates to MA*
  - *Risk assessment concludes no adverse effect on quality, safety or efficacy*
  - *Need for inclusion in the on-going stability porgramme evaluated*
  - *Biological products – effect of even minor changes resulting in unexptected impact of safety or efficacy considered*
  - *QP should be aware and take into consideration any deviations which have potential impact for compliance with GMP or the MA*

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6. The release of a batch:

- *Release only after QP certification. Until a batch is released it should remain at the site of the manufacturer or be shipped under quarantine to another authorised site*
- *Safeguards to ensure uncertified batches are not released (physical (segregation and labelling) or electronic (validated computerised system))*
- *Safeguards to prevent premature release should remain when uncertified batches are moved to another site*
- *Notification by a QP to the releasing site should be formal and unambiguous and subject to requirements of Chapter 4 (EU GMP)*

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Kommentare,

die die AQPA an die EMA weiterleiten soll ?

(Frist: 5. November 2013)

Falls erforderlich bitte bis <u>11. Oktober 2013</u> an die AQPA

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Kommentare:

1. ***Zu 2.2: Anstelle von den Gesetzen im Bestimmungsland sollte die QP ausschließlich die Produktzulassung im Bestimmungsland und die dort lizensierten Spezifikationen für die Freigabe berücksichtigen.***
2. **…**
3. **…**