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

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Scope:

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

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General principles:

- *Ultimate responsibility lies with the marketing authorisation holder (MAH)*
- *QP is responsible to ensure each individual batch manufactured acc. MA, GMP, and in compliance with the laws in country of certification*
- *Batch release process:*
  - *Manufacture and testing in accordance with defined release procedure*
  - *Certification by a QP that batch complies with MA and GMP*
  - *Transfer to saleable stock taking QP certification into account (if performed at another site, written agreement needed)*
- *Purpose of controlling batch release:*
  - *Compliance with MA*
  - *Compliance with GMP*
  - *Compliance with any other relevant legal requirements*
  - *In case of investigation or recall, to ensure certifying QP is readily identifiable*

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1. The process of certification:

- *Each batch of finished product: certified by a QP within the EU (before release for sale or supply in the EU or export)*
- *Certification only by a QP of the manufacturer and/or importer in the MA*
- *QP must have detailed knowledge and should be able to prove their continuous training (product type, production processes, technical advances and changes to GMP)*
- *Regardless of how many sites involved, the certifying QP of finished product must ensure all necessary steps completed under accepted quality system*
- *Manufacturing at sites in EU:*
  - *Each site must have at least one QP (confirm operations by the site)*
  - *QP should have 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 MIAH)*
  - *Any sharing of responsibilities amonst QPs must be defined in a formally agreed document (detailing responsibility for assessment of impact of deviations on compliance with GMP and the MA)*

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

- *Manufacturing sites outside the EU:*
  - *QP-certification for all medicinal products released for EU markets, or for export (irrespective of complexity of supply chain and global locations of sites involved)*
  - *QP may take into account confirmation by other QPs (site in the EU and defined in the MA)*
  - *Take into account conditions of storage and transport of batch and samples, if sent separately*
  - *Unless MRA or similar agreement in place, each batch has undergone in a Member State full analysis acc. requirements of the MA*
  - *Sampling of imported product either taken after arrival in the EU or be taken at the third country site in accordance with technically justified approach documented in quality system and defined in written agreement. Any samples taken outside EU shipped under equivalent conditions.)*

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

- *Sampling in a third country: technical justification should include QRM to identify and manage any risks. This should be documented and include at least:*
  - *Audit of the manufacturing activity including any sampling*
  - *Evaluation of subsequent transport steps of batch and samples*
  - *Ensure samples are representative of imported batch*
  - *Comprehensive scientific study including data to support any conclusions that samples are representative. Study should include at least:*
    - *Description of sampling process in third country*
    - *Description of transport conditions of samples and imported batch (differences should be justified)*
    - *Comparative analysis of samples taken in third country and samples after import*
    - *Consideration of time interval between sampling and import of batch and generation of data to support appropriate defined limits*
  - *Provision for random periodic analysis of samples after import (justify ongoing reliance on third country samples)*
  - *Review of any unexpected result or confirmed OOS (may have impact on reliance on sampling and should be **notified to Supervisory Authority** of certifying site; Such occurence should be regarded as potential quality defect and investigated in line with Chapter 8 of EU-GMP-Guide **(!!!)***

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1. *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 first imported batch provided that justification has been document based on QRM principles. This should take into account reliance on samples taken in third country. Evidence available to ensure integrity and identity of imported product has been established through documented verification of at least:*
      - *Relevant requirements for storage prior to packaging*
      - *Finished product stored and transported under required conditions*
      - *Consignment remained secure and no evidence for tampering during storage and transport*
      - *Correct identification of product has been established*
      - *Samples tested are representative of all batches derived from bulk batch*

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1. 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 GMP*
  - *Entire supply chain is documented and available for the QP. Preferably a comprehensive diagram*
  - *All audits (manufacture and testing of medicinal product and manufacture of API) have been carried out and audit reports are available to the certifying QP*
  - *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*

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1. 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 as appropriate*
- *QC data complies with registered specification, or where authorised, the Real Time Release Testing programme*
- *Any regulatory 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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1. 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(o) of Dir. 2001/83/EC), where appropriate*

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

- *Special guidance may apply for certain products such as Annex 2 for Biologicals and Annex 3 for Radiopharmaceuticals*
- *Parallel importation & distribution:*
  - *Any repackaging must be approved by competent authority of intended market*
  - *QP should confirm compliance with national and EU rules for parallel import and parallel distribution*
  - *QP of the (repackaging) MIA holder certifies that re-packaging in accordance with relevant authorisation and GMP*

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

- *Recording of QP 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 for release should be made available in order to be exempted from further controls when entering another Member State*

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

- *Should be in accordance with Chapter 7 (EU GMP)*
- *Special focus to approval of audit reports, e.g.*
  - *Address general GMP requirements*
  - *QMS*
  - *All relevant production and QC procedures*
  - *All audited areas accurately described in detailed audit report*
  - *Determined whether Manufacture and QC complies with GMP (in third countries at least equivalent to EU-GMP)*
  - *Outsourced activities comply with the MA*
  - *QP should ensure written final assessment and approval of audit reports*
  - *QP should have access to all documentation for audit outcome and continued reliance on outsourced audit activity*
  - *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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3. Handling of unexpected deviations:

- *All registered specifications for API, excipients, packaging materials and medicinal products must be met*
- *Product may be considered to meet the requirements when:*
  - *Deviation is thoroughly investigated and **root cause corrected (!)***
  - *For continued manufacture this may require submission of a variation*
  - *Impact of deviation assessed according QRM principles to include:*
    - *Evaluation of potential impact on quality, safety or efficacy and concluding impact is negligible*
    - *Consider need to include in ongoing stability programme*
    - *Biological products – consider that any deviations can have an unexpected impact on safety and efficacy*
  - *Certifying QP should be aware and take into consideration any deviations which have potential impact for compliance with GMP and/or the MA*

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4. The release of a batch:

- *Release only after QP certification. Until a batch is certified it should remain at the site of the manufacturer or be shipped under quarantine to another approved site*
- *Safeguards to ensure uncertified batches are not transferred to saleable stock (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 site where transfer to saleable stock is to take place should be formal and unambiguous and subject to requirements of Chapter 4 (EU GMP)*

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Glossary:

Confirmation: *A signed statement by a QP …*

Certification: *… by a QP*

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- **Bestätigungen von Herstellung außerhalb EU/MRA ?**
- **Darf eine QP „Zertifikate“ von nicht-QPs akzeptieren?**
- **Batch Record Review?**
- **Sämtliche Abweichungen?**
- **Change Control?**
- **Post Marketing Commitments?**
- **etc.**
- **…**

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Appendix I:

„Content of the confirmation of the partial manufacturing of a medicinal product“

Appendix II:

„Content of the Batch Certificate for Medicinal Products“