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Part 3

WHO TRS 957, 2010, Annex 2

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There are 3 parts to this training.

In the first two parts, we discussed good practices relating to:

- Quality Management and personnel
- Buildings, facilities and equipment
- Documentation
- Production and storage
- Validation

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In Part 3, we will discuss good practices relating to:

- Laboratory control
- Stability testing
- Contract manufacturing and testing
- Agents, brokers, and traders

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Responsibilities of the quality unit(s)

- Responsibilities described in writing - main responsibilities cannot be delegated. Involved in all quality-related matters
- Review and approve all appropriate quality related documents
  - E.g. SOPs, specifications, master production instructions
- Release or reject raw materials, intermediates, packaging etc.
- Releasing or rejecting intermediates and APIs
- Review of completed records (e.g. batch, laboratory control)
- Ensuring that critical deviations are investigated and resolved

2.20. – 2.21.

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Responsibilities of the quality unit(s)

- Ensure that self-inspections are done
- Approve intermediate and API contract manufacturers
- Approve quality impacting changes
- Review and approve validation protocols and reports
- Ensure investigation (and resolving) quality-related complaints
- Ensure effective systems for maintaining and calibrating critical equipment

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Responsibilities of the quality unit(s)

- Ensure that materials are appropriately tested and the results are reported
- Ensure stability data to support retest or expiry dates and storage conditions
- Perform product quality reviews

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Laboratory control

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Laboratory control records to include complete data derived from all tests conducted to ensure compliance with specifications and standards, including examinations and assays, as follows (e.g.):

- description of samples (name, batch number/code, date, quantity) and date the sample was received for testing;
- a statement of or reference to each test method used;
- weight or measure of sample used for each test as per method;
- data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions;

6.6

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Laboratory control records to include complete data derived from all tests conducted to ensure compliance with specifications and standards, including examinations and assays, as follows (e.g.): (2)

- Raw data (graphs, charts and spectra)
- Calculations performed (units of measure, conversion factors etc.)
- Test results and acceptance criteria comparison statement;
- Date of tests and signature of the person who performed each test;
- Date and signature of a second person who reviewed the original records for accuracy, completeness and compliance

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Complete records should also be maintained for:

- Any modifications to an established analytical method;
- Periodic calibration of laboratory instruments, apparatus, gauges and recording devices;
- All stability testing performed on APIs; and
- Out-of-specification (OOS) investigations.

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Batch production record review

- SOP followed for review and approval of batch production and laboratory control records, including packaging and labelling – by quality unit(s)
- Compliance with specifications before batch release - Reviewed and approved by the quality unit(s)
- All deviation, investigation and OOS reports also reviewed
- Delegation to the production unit for release of intermediates allowed excluding those shipped outside the control of the manufacturing company

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Sampling

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Sampling and testing of incoming production materials

- At least one test to verify the identity of each batch of material
- COA used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers
- Supplier approval includes
  - evaluation that provides adequate evidence (e.g. past quality history) of consistently providing material meeting specifications;
  - Full analyses on at least 3 batches before reducing testing
- Full analysis at appropriate intervals, COAs checked regularly

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Sampling and testing of incoming production materials

- No need for testing of processing aids, hazardous or highly toxic raw materials, other special materials – or materials transferred to another unit within the company
- Condition that COA shows compliance. Lack of on-site testing for these materials justified and documented
- Sampling procedure, sampling plan and sampling methods:
  - representative of the batch; number of containers to be sampled
  - which part of the container; amount of material
  - consider the criticality and variability of the material, past quality history of the supplier and the quantity needed for analysis.

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Sampling and testing of incoming production materials

- Sampling at defined locations
- Sampling procedures designed to prevent contamination of the material sampled and contamination of other materials

Containers from which samples are withdrawn

- Opened carefully
- Reclosed after sampling
- Marked to indicate that a sample has been taken

7.3

Validation:

Activities, policy and approach to validation as previously discussed

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Validation of analytical methods

- Validated - unless included in the relevant pharmacopoeia or other recognized standard reference
- Suitability of all testing methods used verified under actual conditions of use and documented
- Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.
- Complete records in case of any modification of a validated analytical method. (Reason for the modification and appropriate data to verify that the modification produces results that are accurate and reliable as the established method)

12.8.

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Contracted activities:

manufacturers and

quality control laboratories

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Contract manufacturers (including laboratories)

- Evaluated by the contract giver to ensure GMP compliance
- Written and approved contract or formal agreement
- Allows the contract giver to audit the contract acceptor's facilities
- Subcontracting – no third party without prior evaluation and approval of the arrangements
- Records kept on site and be readily available
- Change control system – prior approval

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Agents, brokers, traders, distributors, repackers and relabellers

17.1. – 17.2.

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Agents, brokers, traders, distributors, repackers and relabellers

- All to comply with GMP - and maintain complete traceability of the APIs and intermediates. Documents include:
  - identity of original manufacturer;
  - address of original manufacturer;
  - purchase orders; bills of lading (transportation documentation);
  - receipt documents; name or designation of API or intermediate;
  - manufacturer's batch number;
  - transportation and distribution records;
  - all authentic certificates of analysis, including those of the original manufacturer; and
  - retest or expiry date.

17.1. – 17.2.

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Quality management

- Agents, brokers, traders, distributors, repackers or relabellers to have an effective quality management system
- Repackaging, relabelling and holding of materials under appropriate GMP - avoid mix-ups and loss of identity or purity
- Repackaging under appropriate environmental conditions to avoid contamination and cross-contamination

17.3. – 17.4.

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- Stability studies to justify assigned expiration or retest dates if repackaged in a different type of container than that used by the manufacturer of the API or intermediate.
- Transfer all quality or regulatory information received from the manufacturer to the customer, and from the customer to the manufacturer of the API or intermediate
- Provide the name of the original manufacturer and batch number(s)
- Provide the identity of the manufacturer to regulatory authorities
- Certificates of analysis (see 11.4.)

17.5. – 17.6.

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Handling of complaints and recalls

- Maintain records of complaints and recalls (see 15.)
- May review the complaint with the manufacturer of material
- Investigation into the cause for the complaint or recall conducted and documented by the appropriate party
- Where a complaint is referred to the original manufacturer - record maintained (by e.g. the agents) to include any response received from the original manufacturer (including date and information provided)
- Returns (section 14.5.) - maintain documentation

17.7.

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- Case study