Active Pharmaceutical Ingredients

Part 2

WHO TRS 957, 2010, Annex 2

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In Part 1, we discussed good practices relating to:

- Quality Management
  - Change control
  - Complaints and recalls
  - Rejection and re-use of material
- Personnel
- Buildings and facilities

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In Part 2, we will discuss good practices relating to:

- Equipment and materials
- Documentation
- Production and storage
- Validation

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Fluid Bed Dryer

Jet mill for micronisation of API

Equipment

World Health Organization

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Process equipment - Design and construction

- Appropriate design and adequate size, closed systems (or precautions). Drawings available. Equipment suitably located for:
  - use, cleaning, sanitization and maintenance
- Suitable Material of Construction (MOC)
- Used within its qualified operating range
- Major equipment (e.g. reactors, storage containers) and permanently installed processing lines appropriately identified.
- Lubricants, heating fluids or coolants controlled

5.1.

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Equipment maintenance and cleaning

- SOP and schedules for the preventive maintenance of equipment
- SOPs for cleaning of equipment and its subsequent release for use
- Detailed cleaning SOPs to enable operators to clean each type of equipment in a reproducible and effective manner. Cover:
  - assignment of responsibility for cleaning of equipment;
  - cleaning schedules, including, where appropriate, sanitizing schedules;
  - a complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;
  - when appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;

5.2.

Equipment maintenance and cleaning

- Detailed cleaning SOPs to enable operators to clean each type of equipment in a reproducible and effective manner. Cover:
  - instructions for the removal or obliteration of previous batch identification;
  - instructions for the protection of clean equipment from contamination prior to use;
  - inspection of equipment for cleanliness immediately before use, if practical; and
  - establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

5.2.

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Equipment and utensils – prevent contamination

- Cleaned, stored (sanitized or sterilized when needed)
- Also in continuous or campaign production of successive batches
- Between production of different materials to prevent cross-contamination
- Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents defined and justified
- Equipment identified as to its contents and its cleanliness status by appropriate means e.g. label.

5.2.

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Calibration of equipment

- Control, weighing, measuring, monitoring and test equipment - calibrated according to written SOP and an established schedule
- Performed using standards traceable to certified standards
- Calibration records maintained
- Current calibration status known and verifiable
- “Out of calibration” instruments should not be used, and deviations investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration

5.3

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Computerized systems

- GMP-related systems validated, including IQ, OQ – suitability of hardware and software
- Controls to prevent unauthorized access or changes to data, prevent omissions in data - record of any data change made
- SOPs for operation and maintenance of computerized systems
- Manual entries require additional check on accuracy of the data
- Incidents recorded and investigated
- Changes through change control procedure and remain validated

5.4.

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Control panel for Reactor

Do we need to control access to the control panel for the reactor?

What controls do you think?

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Computerized systems

- System breakdowns or failures
  - permanent loss of records
- Back-up system in place
- A means of ensuring data protection

Data can be recorded by a second means in addition to the computer system.

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Materials management (General)

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Materials management (General)

- SOPs for receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials
- Procedure for evaluating the suppliers of critical materials
- Materials purchased against an agreed specification, from a approved suppliers
- Name and address of manufacturer should be known in cases where materials are supplied through another party
- Changing the source of supply of critical raw materials should be done according to change control procedure

7.1.

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Receipt and quarantine

- Visual examination upon receipt and before acceptance
  - correct labelling, damage, broken seals, tampering, contamination
- Under quarantine – sampled and examined or tested
- Before mixing with existing stocks (e.g. solvents or stocks in silos), identified, tested, released
- Procedures to prevent discharging incoming materials wrongly
- Bulk deliveries from non-dedicated tankers - assurance of no cross-contamination from the tanker.

7.2.

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Tankers:

- certificate of cleaning;
- testing for trace impurities;
- audit of the supplier.

Solvent charging from tanker to underground tank

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Receipt and quarantine

- Large storage containers, attendant manifolds, filling and discharge lines appropriately identified
- Containers / batches of materials given distinctive code, batch or receipt number
- System to identify the status of each batch

7.2.

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Storage of materials

- Handling and storage in a manner to prevent degradation, contamination and cross-contamination
- Stored off the floor, suitably spaced to permit cleaning and inspection. Oldest stock used first
- Storage conditions and storage period no adverse affect. Controlled
- Outdoor storage – provided labels remain legible and containers are appropriately cleaned before opening and use
- Rejected materials identified and access controlled

7.4.

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Re-evaluation

- Materials re-evaluated as appropriate
- To determine their suitability for use (e.g. after prolonged storage or exposure to heat or humidity)

7.4.

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Returns

- Returned intermediates or APIs identified and quarantined
- When doubts:
  - Storage, shipping (before or during return) conditions
  - Condition of containers (quality)

THEN reprocess, rework or destroy as appropriate.

- Records of returned materials include e.g.:
  - name and address of the consignee;
  - intermediate or API, batch number and quantity returned;
  - reason for return; and
  - use or disposal of the returned intermediate or API.

14.5.

Documentation and records

6.1.

Documentation and records - System and specifications

- Documents prepared, reviewed, approved and distributed (SOP)
- Issuance, revision, superseding and withdrawal – controlled with maintenance of revision histories.
- SOP for retaining documents (e.g. development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records and distribution records)
- Appropriate retention periods of documents

6.1.

Active Pharmaceutical Ingredients

Documentation and records (System and specifications) (2)

- Production, control and distribution records kept at least one year after the expiry date of the batch. For APIs with retest dates, for at least three years after the batch is completely distributed
- Entries in records indelible. In spaces provided for such entries, directly after performing the activities. Person identified
- Corrections to entries dated and signed, original entry readable
- Records kept on site or be promptly retrieved from another location
- Originals or as true copies

6.1.

Active Pharmaceutical Ingredients

Documentation and records (System and specifications) (3)

- In case of microfilming or electronic records - suitable retrieval equipment and a means to produce a hard copy
- Specifications for raw materials, intermediates, APIs, labels, and packaging materials. Also (where necessary) for process aids, gaskets or other materials that could critically impact on quality
- Acceptance criteria for in-process controls
- Electronic signatures to be authenticated and secure

6.1.

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Equipment cleaning and use record

- Cleaning, sanitization and/or sterilization and maintenance records to show the date, time (if appropriate), product and batch number, person
- Dedicated equipment - individual equipment records are not necessary. Records of cleaning, maintenance and use can be part of the batch record or maintained separately

6.2.

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Raw material, intermediate, API labelling and packaging material records to show e.g.:

- name of the manufacturer, identity and quantity of shipment of each batch of raw materials, intermediates or labelling and packaging materials for APIs; the supplier; supplier's control (or other) number; the number allocated on receipt; and the date of receipt;
- results of any test or examination done, conclusions derived; use of materials;
- examination and review of API labelling and packaging material
- final decision regarding rejected materials
- Master (approved) labels maintained for comparison

6.3.

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Master production and control instructions/ records

Prepared, checked, dated and signed instructions. Include:

- the name of product being manufactured, document reference code,
- complete list of raw materials and intermediates designated by names or codes to identify any special quality characteristics;
- quantity or ratio of each raw material or intermediate to be used
- production location and major production equipment to be used

6.4.

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Detailed production instructions, including:

- sequences to be followed,
- ranges of process parameters to be used,
- sampling instructions, in-process controls, acceptance criteria,
- time limits (individual processing steps and/or the total process)
- expected yield ranges at appropriate phases of processing or time;
- special notations, precautions, cross-references;
- storage instructions, labelling, packaging materials, storage conditions

6.4.

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Batch production records (batch production and control records)

- Prepared for each intermediate and API with unique batch or identification number, dated and signed
  - complete information
  - checked before issuance
- Record includes:
  - dates and times; major equipment (e.g., reactors, driers and mills) used;
  - specific identification of each batch (including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;
  - actual results recorded for critical process parameters;
  - any sampling performed;
  - signatures of the persons performing and directly supervising or checking

6.5.

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Batch production records (batch production and control records)

- Record includes (2):
  - in-process and laboratory test results;
  - actual yield at appropriate phases or times;
  - description of packaging and label for intermediate or API;
  - representative label of API or intermediate if made commercially available;
  - any deviation, its evaluation, investigation;
  - results of release testing
- Written SOP followed for investigating critical deviations or the failure of a batch of intermediate or API
- Investigation to extend to other batches when needed

6.5.

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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

6.7.

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Production and in-process controls

- Raw materials weighed under appropriate conditions using suitable devices
- Subdivision of material in container with information e.g.:
  - material name and/or item code;
  - receiving or control number;
  - weight or measure of material in the new container; and
  - re-evaluation or retest date if appropriate.
- Critical weighing, measuring or subdividing operations witnessed
- Verification of materials by production prior to use

8.

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Production and in-process controls

- Critical activities witnessed or subjected to an equivalent control
- Actual yields versus expected yields
  - at designated steps
  - Ranges established (previous laboratory, pilot scale or manufacturing data)
- Deviations documented and investigated
- Processing status of major units of equipment indicated
- Control materials to be reprocessed or reworked. Prevent unauthorized use

8.

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Time limits

- Meet time limits as in BMR to ensure the quality of intermediates and APIs

- Deviations documented and evaluated

8.2.

Active Pharmaceutical Ingredients

Time limits

- Meet time limits as in BMR to ensure the quality of intermediates and APIs
- Deviations documented and evaluated
- Time limits may be inappropriate when processing to a target value (e.g. pH adjustment, hydrogenation or drying to a predetermined specification) because completion of reactions or processing steps are determined by inprocess sampling and testing
- Intermediates held for further processing stored under appropriate conditions to ensure their suitability for use

8.2.

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Rejection and reuse of materials

- Intermediates and APIs failing to meet established specifications identified and quarantined - may be reprocessed or reworked. Final disposition of rejected materials recorded

Reprocessing

- Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g. distillation, filtration, chromatography, milling) that are part of the established manufacturing process

14.1. – 14.2.

Rejection and reuse of materials

Reprocessing

- Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. (This is not considered to be reprocessing)
- Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely affected due to the potential formation of by-products and overreacted materials

14.1. – 14.2.

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Reworking

- Batches that do not conform to established standards or specifications – investigate reason for non-conformance – then decision on reworking
- Reworked batches subjected to appropriate evaluation, testing, stability testing if warranted and documentation including concurrent validation
- Procedures for comparing the impurity profile of each reworked batch with batches manufactured by the established process
- Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used

14.3.

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Recovery of materials and solvents

- Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates or the API acceptable according to approved procedures
- Recovery procedures for solvents controlled and monitored
- Recovered materials meet specifications suitable for their intended use
- May combine fresh and recovered solvents and reagents
- Use of recovered solvents, mother liquors and other recovered materials should be adequately documented

14.4

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Validation

12.

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Validation

- Policy, intentions and approach to validation documented and should cover e.g. production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems

- Critical parameters and attributes identified (development stage or from historical data) and the ranges defined
  - API critical product attributes;
  - process parameters that could affect CQA;
  - range for each critical process parameter (CPP)

12.

- Validation: Operations critical to the quality and purity of the API.

Validation protocol and report

- Protocol: Written, reviewed, approved
  - Specify critical process steps and acceptance criteria
  - Type of validation and the number of process runs
- Report: Cross-references the protocol, summarizes the results, deviations, conclusions, recommendations
- Variations from the validation protocol documented with appropriate justification

12.2.

Qualification

- Before starting process validation - critical equipment and ancillary systems including utilities, facilities
- Design qualification (DQ)
- Installation qualification (IQ)
- Operational qualification (OQ)
- Performance qualification (PQ)

12.3.

Approaches to process validation (PV)

- Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

- Traditional approach – three types
  - Prospective validation
  - Concurrent validation
  - Retrospective validation (exceptional cases)

12.4.

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Approaches to process validation (PV)

- Retrospective validation only when:
  - Critical quality attributes and critical process parameters have been identified.
  - Appropriate in-process acceptance criteria and controls have been established.
  - There have not been significant process or product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability.
  - Impurity profiles have been established for the existing API.
- Batches selected to be representative of all batches made during the review period, including failed batches. Sufficient number to prove process consistency

12.4.

New Approaches to process validation (PV)

Stage I, II and Stage III validation

- Stage I – process design (development)
- Stage II – qualification and continuous process performance verification
- Stage III – continued process performance verification

- Lifecycle approach with continuous improvement

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Process validation programme

- Number of process runs depends on the complexity or magnitude of the process/change
- Prove consistency of the process (e.g. complex API processes or API processes with prolonged completion times)
- Critical process parameters controlled and monitored
- Confirm that the impurity profile of API is within limits specified
- Impurity profile comparable to or better than historical data / profile determined during process development or for batches used for pivotal clinical and toxicological studies.

12.5.

Periodic review of validated systems

- Periodic evaluation of systems and processes
- Objective is to verify that they are still operating in a valid manner
- Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation
- Concept of risk based approach can be followed

12.6.

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Cleaning validation

- Cleaning procedures validated, focus on situations or process steps where contamination or carry-over of materials poses the greatest risk to API quality
- Early production - may not be necessary to validate where residues are removed by subsequent purification steps
- Reflect actual equipment usage patterns
- Representative intermediate or API can be selected for cleaning validation. Selection based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity and stability

12.7.

Cleaning validation

- Cleaning validation protocol includes:
  - equipment, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled and analytical methods, type of samples, collection and labelling of samples
- Validated analytical methods
  - sensitivity , detection limit , recovery .
  - residue limits practical, achievable and verifiable

12.7.

Cleaning validation

- Sampling to include:
  - swabbing, rinsing or alternative methods (e.g. direct extraction)
  - sampling methods capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning

12.7.

Cleaning validation

- Include microbiological and endotoxin where appropriate
- Monitor cleaning procedures at appropriate intervals after validation
- Ensure that these procedures are effective when used during routine production by
  - analytical testing
  - visual examination
- Visual inspection can allow detection of gross contamination concentrated in small areas

12.7.