Active Pharmaceutical Ingredients

GMP for Active Pharmaceutical Ingredients

WHO TRS 957, 2010, Annex 2

World Health Organization

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There are 3 parts to this training.

In Part 1, we will discuss good practices relating to:

- Introduction and scope of the GMP guideline and this training
- 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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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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Introduction and scope

- GMP for APIs - appropriate system for managing quality
- APIs to meet quality and purity requirements
- “Manufacturing” includes all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls
- Not covering safety aspects for personnel or environment protection

1.1

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Introduction and scope

- Applies to the manufacture of APIs for use in finished pharmaceutical products (FPPs)
- Sterilization and aseptic processing of sterile APIs are not covered here
- The guide covers APIs that are manufactured by chemical synthesis, extraction, cell culture or fermentation, by recovery from natural sources, or by any combination of these processes – but the training here focuses on chemical synthesis

1.3

- Excludes vaccines, whole cells, whole blood and plasma etc.

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Introduction and scope

- Appropriate GMP applied from the point at which the API starting material is normally introduced into the process
- Includes the validation of critical process steps determined to impact the quality of the API
- The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification and packaging
- GMP implemented in physical processing (e.g. granulation, coating) and manipulation (e.g. milling and micronizing)

1.3

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Introduction and scope

- An “API starting material” is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in house.
- API starting materials normally have defined chemical properties and structure. The company should designate and document the rationale for the point at which production of the API begins.

1.3

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Quality management

- Quality is the responsibility of all persons
- Establish, document and implement an effective quality management (QMS). All quality-related activities should be defined and documented.
- QMS to cover organizational structure, procedures, processes and resources – ensuring APIs meet specifications
- Quality unit(s) covering quality assurance (QA) and quality control (QC) responsibilities – and independent of production

2.10 – 2.14.

- Identified authorized persons to release intermediates and APIs

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Quality management

- Activities recorded at the time of action
- Any deviation documented and explained. Critical deviations investigated to identify the reason (root cause)
- Materials released by QU before used. (Release under quarantine not the norm see 10.20)
- Communication to management in a timely manner of e.g. regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls and regulatory actions)

2.15. – 2.18.

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Change control

- A formal change control system (written SOP) covering production and control:
  - identification, documentation, appropriate review, and approval of changes in:
    - raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software
- Drafted, reviewed and approved by units and approved by QU
- Potential impact evaluated. A classification procedure to determine level of testing, validation and documentation needed to justify changes to a validated process

13.10

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Change control (2)

- Minor or major) changes
- Changes impact also on documents – ensure revision
- Evaluation of the first batches produced or tested under the change
- Accelerated stability programme where critical changes affect established retest or expiry dates
- Inform manufacturers of the current dosage form where changes from established production and process control procedures can impact the quality of the API

13.10

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Complaints and recalls

- All quality-related complaints recorded and investigated (SOP)
- Complaint records should include:
  - name and address of complainant;
  - name (and, where appropriate, title) and telephone number of complainant;
  - nature of the complaint (including name and batch number of the API);
  - date the complaint was received;
  - action initially taken (dates and identity of person taking the action);
  - any follow-up action taken;
  - response provided complainant (incl. date response was sent); and
  - final decision on intermediate or API batch or lot.

15.

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Complaints and recalls

- Complaint records kept - evaluate trends, product-related frequencies and severity. Take additional/immediate action
- Written procedure that defines the circumstances under which a recall of an intermediate or API is considered
- Recall procedure specifies
  - responsible people
  - how a recall should be initiated,
  - who should be informed about the recall
  - how the recalled material should be treated.
- Serious or potentially life-threatening situation – Authorities

15.

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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

2.22.

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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

2.22.

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Responsibility for production activities

- Preparing, reviewing, approving and distributing production instructions
- Producing APIs and intermediates (preapproved instructions)
- Review production batch records (completed and signed)
- Reporting and evaluating production deviations. Investigating critical deviations – recording their conclusions
- Cleanliness and disinfecting of production facilities

2.3

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Responsibility for production activities (2)

- Ensuring calibrations are done: and records are kept
- Ensuring maintenance of premises and equipment
- Review and approval of validation protocols and reports
- Evaluating proposed changes in product, process or equipment
- Ensuring qualification of new and, when appropriate, modified facilities and equipment

2.3

Internal audits (self-inspection)

- Companies should perform regular internal audits
- SOP and schedule followed
- Audit findings and corrective actions documented
  - Brought to the attention of the responsible management of the firm.
- Agreed corrective actions should be completed in a timely and effective manner.

2.4.

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Product quality review

- Regular quality reviews (e.g. annually) to verify consistency of the process. Cover:
  - critical in-process control and critical API test results;
  - all batches that failed to meet established specification(s);
  - all critical deviations or non-conformances and related investigations;
  - any changes carried out to the processes or analytical methods;
  - results of the stability monitoring programme;
  - quality-related returns, complaints and recalls; and
  - adequacy of corrective actions.
- Review and evaluate results – determine corrective action, revalidation

2.5

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Personnel

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Personnel

- Adequate number of personnel, qualified, trained, experienced
- Written responsibilities (job descriptions)
- Regular training which covers e.g. operations and GMP with periodic assessment of training
- Training records maintained. Training should be periodically assessed.

3.1.

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Personnel hygiene

- Practice good sanitation and health habits
- Wear clean clothing, change when appropriate
- Include covers for head, face, hands and arms when necessary
- Avoid direct contact with intermediates or APIs
- No smoking, eating, drinking, chewing
- Storage of food restricted to certain designated areas
- Infectious disease – and open lesions

3.2.

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Consultants

- Sufficient education, training, and experience
- Records of their name, address, qualifications and type of service provided

3.3

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Buildings and facilities

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Buildings and facilities: Design and construction

- Located, designed, and constructed to facilitate cleaning, maintenance and operations
- Minimize potential contamination including limited exposure to objectionable microbiological contaminants (where appropriate)
- Adequate space ensuring orderly placement of equipment and materials to prevent mix-ups and contamination
- Closed or contained systems can be located outdoors

4.1.

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Buildings and facilities: Design and construction

- Flow of materials and personnel
  - prevent mix-ups or contamination.
- Defined areas or other control systems for:
  - Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;
  - Quarantine before release or rejection of intermediates and APIs;
  - Sampling of intermediates and APIs;
  - Released materials and rejected materials;
  - Production operations;
  - Packaging and labelling operations; and
  - Laboratory operations.

4.1.

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Premises

- Adequate, clean washing and toilet facilities
  - separate from, but easily accessible to, manufacturing areas
- Laboratory areas and operations separated from production areas
- In-process controls can be located in production areas
  - production process do not adversely affect laboratory measurements, and
  - laboratory and its operations do not adversely affect production

4.1.

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Sanitation and maintenance

- Buildings properly maintained and repaired – kept clean
- Written procedures for sanitation describing
  - cleaning schedules, methods, equipment and materials to be used in cleaning buildings and facilities.
- Written procedures for the use of
  - suitable rodenticides, insecticides, fungicides, fumigating agents and cleaning and sanitizing agents
- Used in a manner not to contaminate equipment, raw materials, packaging or labelling materials, intermediates and APIs

4.7.

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Lighting

- Adequate lighting should be provided in all areas to facilitate cleaning, maintenance and proper operations

Sewage, refuse and other waste

- E.g. solids, liquids, or gaseous byproducts from manufacturing - disposed of in a safe, timely and sanitary manner
- Containers and/or pipes for waste clearly identified

4.5. – 4.6.

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Containment

- Highly sensitizing materials, such as penicillins or cephalosporins:
  - Dedicated production areas, facilities, air handling equipment and/or process equipment , should be employed in the production of.
- Material of infectious nature or high pharmacological activity or toxicity such as certain steroids or cytotoxic anti-cancer agents:
  - Dedicated production areas (unless validated inactivation and/or cleaning procedures are established and maintained)
- Measures to prevent cross-contamination
- No handling, production or storage of highly toxic non-pharmaceutical materials such as herbicides and pesticides

4.4.

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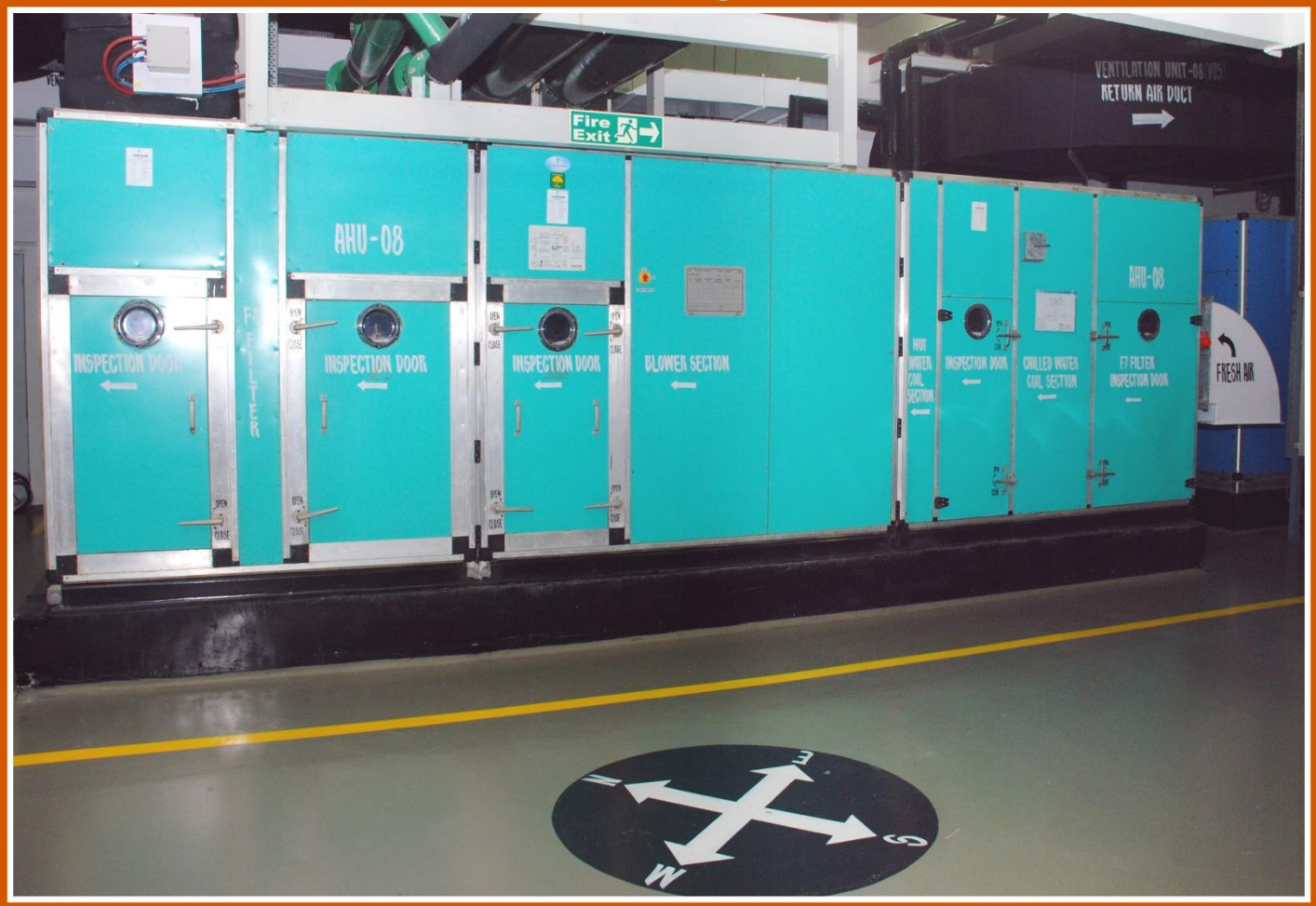
Air handling unit



Utilities

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Utilities

- Qualification of utilities that could impact on product quality
  - e.g. steam, gases, compressed air, HVAC
- Monitoring and action in case of OOL
- Drawings for these utility systems should be available
- Adequate ventilation, air filtration and exhaust systems where appropriate
- Designed and constructed to minimize risks of contamination and cross-contamination

4.2.

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Utilities

- Control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture
- Control risks of contamination and cross-contamination if air is recirculated to production areas
- Identify permanently installed pipework
  - Identifying individual lines, documentation, computer control systems etc.
  - Pipework located to avoid risks of contamination of the intermediate or API
- Drains of adequate size and provided with an air break

4.2.

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Water

- Demonstrate that water used is suitable for its intended use
- At minimum - WHO guidelines for drinking (potable) water quality
- Other chemical and/or microbiological water quality specifications can be used - appropriate specifications for physical and chemical attributes, total microbial counts, objectionable organisms and/or endotoxins established
- Validated water treatment process: water monitored with appropriate action limits

4.3

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See also separate training modules on HVAC systems and water for pharmaceutical use

Principles are the same in FPP and API production and control