Good Manufacturing Practice (GMP)

Dr. Isra Dmour
Credit: Prof. Dr. Nizar Al-Zoubi

What is Good Manufacturing Practice (GMP)?

- A system for ensuring that products are consistently produced and controlled in accordance to the standards appropriate to their intended use and the product specification.
- GMP are regulations that describe the methods, equipment, facilities and controls required for producing.
- GMP regulations establish mandatory, **minimum** requirements
- –Compliance is not a matter of choice
- –Complying with GMP is the **lowest** acceptable quality standard

System for Quality

- Remember! Last lecture we said we CAN'T test quality! WHY?

What is tested is not sold

What is sold in not tested

Hence,

Quality is not testing of a product.

It Should be built in each stage of process/ operation

- **GMP is based on a number of principles, such as:**

– Quality must be built into the product, not tested into it.

– **Quality assurance** is a shared responsibility of everyone involved in the production process.

– **Quality control** is a continuous and systematic process that monitors and verifies the quality of the product at every stage.

– **Quality risk management** is a proactive approach that identifies, assesses and mitigates potential risks to the quality of the product.

– **Documentation** is an essential tool that records and demonstrates the compliance with GMP.

GMP CONCEPT

Provides a high level of assurance that medicines are manufactured in a way that ensures their safety, efficacy and quality

Medicines are manufactured to comply with their marketing authorization

Quality is built in

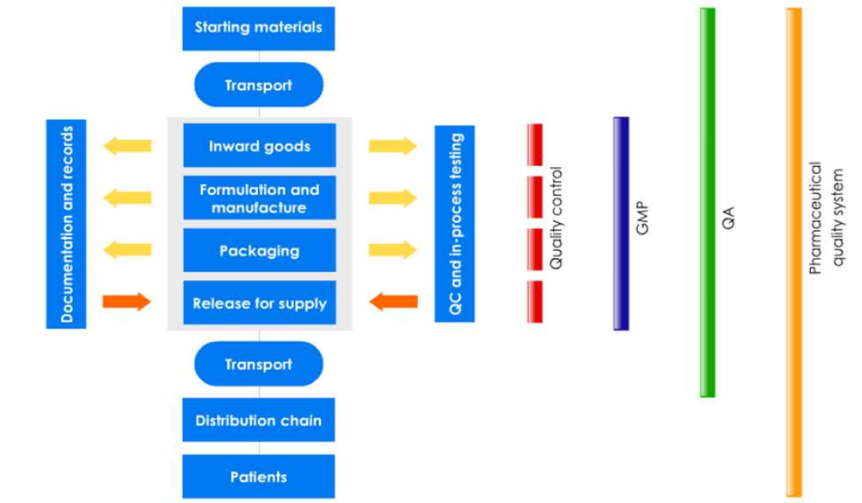
GMP is enforced by regulatory authorities in different countries and regions, such as the Food and Drug Administration (FDA) in the United States, the European Medicines Agency (EMA) in the European Union, and the World Health Organization (WHO) at the global level.

These authorities conduct inspections and audits to verify that the manufacturers comply with GMP and other relevant regulations. Non-compliance with GMP can result in serious consequences, such as product recalls, fines, sanctions or even criminal charges.

GMP covers the following:

- Quality Management
- Personnel
- Premises and equipment
- Documentation
- Production
- Quality Control
- Contract Manufacture and Analysis
- Complaints and Product Recall
- Self Inspection

How do QA, GMP and QC Fit Together ?



PHARMACEUTICAL QUALITY SYSTEM

- To achieve quality objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System.
- This system incorporates Good Manufacturing Practice and Quality Risk Management.

9

PHARMACEUTICAL QUALITY SYSTEM

- ICH guidelines Q10

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL QUALITY SYSTEM
Q10

10

PHARMACEUTICAL QUALITY SYSTEM

Product lifecycle

1) Pharmaceutical Development:

- Drug substance development;
- Formulation development (including container/closure system);
- Manufacture of investigational products;
- Delivery system development (where relevant);
- Manufacturing process development and scale-up;
- Analytical method development.

11

PHARMACEUTICAL QUALITY SYSTEM

Product lifecycle

2) Technology Transfer:

- New product transfers during Development through Manufacturing;
- Transfers within or between manufacturing and testing sites for marketed products.

12

PHARMACEUTICAL QUALITY SYSTEM

Product lifecycle

3) Commercial Manufacturing:

- Acquisition and control of materials;
- Provision of facilities, utilities, and equipment;
- Production (including packaging and labelling);
- Quality control and assurance;
- Release;
- Storage;
- Distribution (excluding wholesaler activities).

13

PHARMACEUTICAL QUALITY SYSTEM

Product lifecycle

4) Product Discontinuation:

- Retention of documentation;
- Sample retention;
- Continued product assessment and reporting.

14

PHARMACEUTICAL QUALITY SYSTEM

- Quality Management is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product.
- It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use.
- Quality Management therefore incorporates Good Manufacturing Practice.

15

PHARMACEUTICAL QUALITY SYSTEM

A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:

1. Product realisation is achieved by designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;
2. Product and process knowledge is managed throughout all lifecycle stages;
3. Medicinal products are designed and developed in a way that takes account of the requirements of GMP;
4. Production and control operations are clearly specified and Good Manufacturing Practice adopted;
5. Managerial responsibilities are clearly specified;

16

PHARMACEUTICAL QUALITY SYSTEM

6. Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is from the approved supply chain;
7. Processes are in place to assure the management of outsourced activities:
   - Assessing the suitability and competence of the other party to carry out the activity or provide the material
   - Defining the responsibilities and communication processes
   - Monitoring and review of the performance of the contract acceptor or the quality
   - Monitoring incoming ingredients and materials

17

PHARMACEUTICAL QUALITY SYSTEM

8. A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality.
9. The results of product and processes monitoring are taken into account in
   - batch release,
   - the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future.
10. All necessary controls on intermediate products, and any other in-process controls and validations are carried out;

18

PHARMACEUTICAL QUALITY SYSTEM

11. Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge.
12. Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required;

19

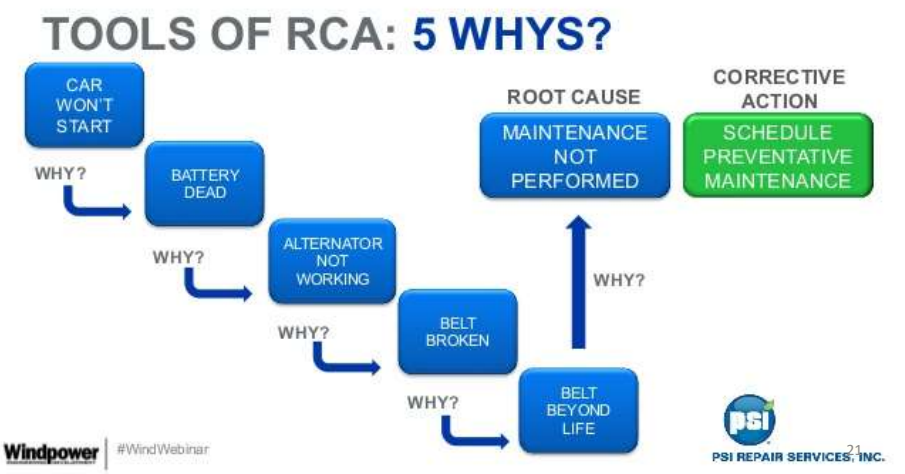
PHARMACEUTICAL QUALITY SYSTEM

13. After implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality;
14. An appropriate level of root cause analysis (RCA) should be applied during the investigation of deviations, suspected product defects and other problems.

20

PHARMACEUTICAL QUALITY SYSTEM

What is RCA?



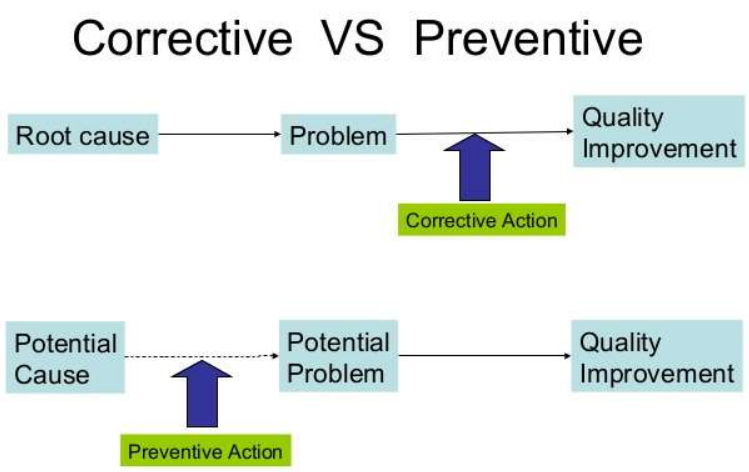
21

PHARMACEUTICAL QUALITY SYSTEM

- In cases where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most **likely** root cause(s) and to addressing those.
- Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system based errors or problems have not been overlooked, if present.
- Appropriate **corrective actions and/or preventative actions (CAPAs)** should be identified and taken in response to investigations.

22

PHARMACEUTICAL QUALITY SYSTEM



23

PHARMACEUTICAL QUALITY SYSTEM

15. Medicinal products are not sold or supplied before a Qualified Person (QP) has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products;
16. Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;
17. There is a process for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Pharmaceutical Quality System.

24

PHARMACEUTICAL QUALITY SYSTEM

- The Pharmaceutical Quality System should be defined and documented.
- A Quality Manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities.

25

PHARMACEUTICAL QUALITY SYSTEM

Quality Control

- Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that:
  - the necessary and relevant tests are actually carried out and,
  - that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

26

PHARMACEUTICAL QUALITY SYSTEM

Quality Control

The basic requirements of Quality Control are that:

1. adequate facilities, trained personnel and approved procedures are available for sampling and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
2. samples are taken by approved personnel and methods;
3. test methods are validated

27

PHARMACEUTICAL QUALITY SYSTEM

Quality Control

4. records are made, manually and/or by recording instruments, which demonstrate that:
   - all the required sampling, inspecting and testing procedures were actually carried out.
   - any deviations are fully recorded and investigated;
5. the finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorisation or Clinical Trial Authorisation, are of the purity required, and are enclosed within their proper containers and correctly labelled;

28

PHARMACEUTICAL QUALITY SYSTEM

Quality Control

6. records are made of the results of inspection
7. testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
8. no batch of product is released for sale or supply prior to certification by a Qualified Person.
9. sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the sample is retained in the final pack.

29

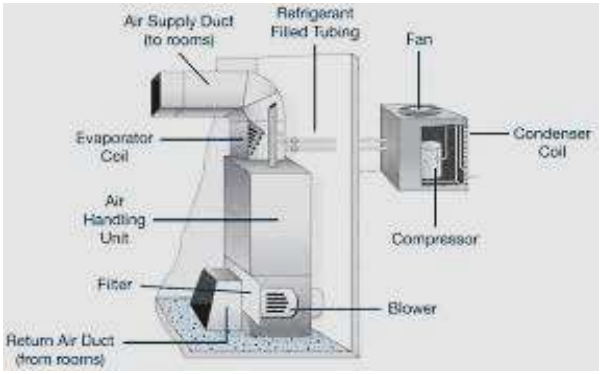
PHARMACEUTICAL QUALITY SYSTEM

Product Quality Review

- Regular periodic or rolling quality reviews of all authorised medicinal products should be conducted with the objective of verifying the consistency of the existing process:
  - A review of all batches that failed to meet specification(s)
  - A review of all quality-related returns, complaints and recalls and the investigations performed at the time
  - The qualification status of relevant equipment and utilities, e.g. HVAC (heating, ventilation, and air conditioning), water, compressed gases
  - A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken

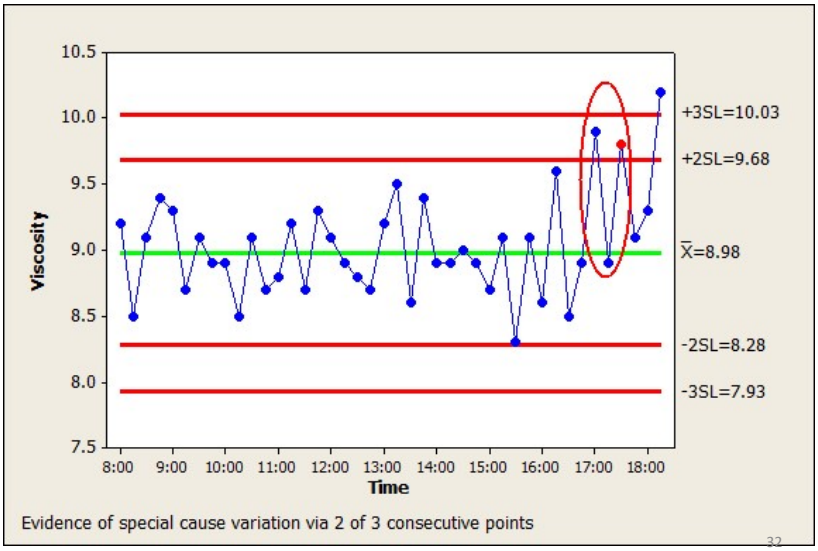
30

HVAC system



31

PHARMACEUTICAL QUALITY SYSTEM



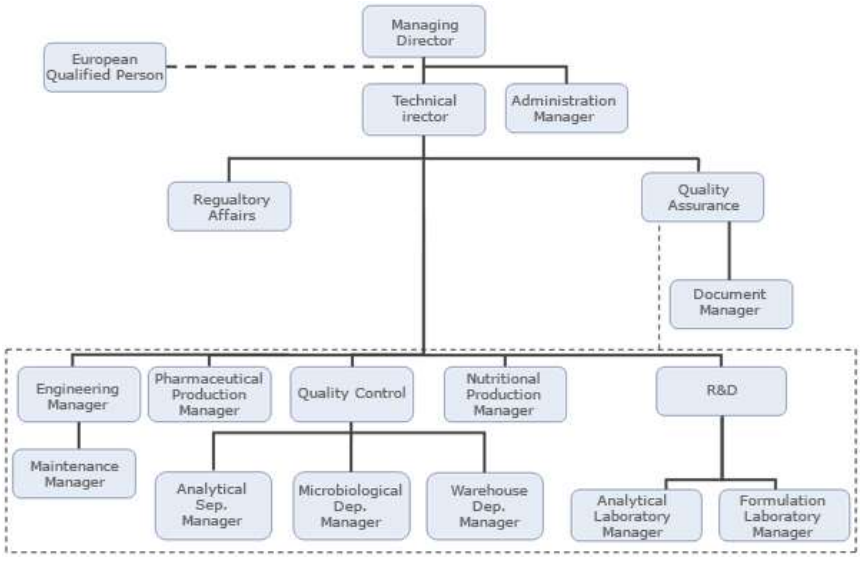
Evidence of special cause variation via 2 of 3 consecutive points

32

PERSONNEL

- The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience.
- The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.
- The manufacturer must have an organization chart in which the relationships between the heads of Production, Quality Control and where applicable Head of Quality Assurance or Quality Unit and the position of the Qualified Person(s) are clearly shown in the managerial hierarchy.

33



34

PERSONNEL

- People in responsible positions should have
  - specific duties recorded in written job descriptions
  - adequate authority to carry out their responsibilities
- There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.
- Senior management has the ultimate responsibility to ensure:
  - an effective quality management system is in place to achieve the quality objectives,
  - roles, responsibilities, and authorities are defined, communicated and implemented throughout the organization.

35

PERSONNEL

Key Personnel

- Senior Management should appoint Key Management Personnel including the head of Production, the head of Quality Control, and Qualified Person(s)
- Normally, key posts should be occupied by full-time personnel.
- The heads of Production and Quality Control must be independent from each other.
- For medicinal products manufactured within the European Union, a Qualified Person must ensure that each batch has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorization.

36

PERSONNEL

Key Personnel

The **head of the Production Department** generally has the following responsibilities:

- To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
- To approve the instructions relating to production operations and to ensure their strict implementation;
- To ensure that the production records are evaluated and signed by an authorised person;
- To ensure the qualification and maintenance of premises and equipment in his department,;
- To ensure that the appropriate validations are done;
- To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

37

PERSONNEL

Key Personnel

The **head of the Quality Control Department** generally has the following responsibilities:

- To approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products;
- To approve specifications, sampling instructions, test methods and other Quality Control procedures;
- To approve and monitor any contract analysts;
- To ensure :
  - that all necessary testing is carried out and the associated records evaluated;
  - the qualification and maintenance of his department, premises and equipment;
  - that the appropriate validations are done;
  - that the required initial and continuing training of his department personnel is carried out and adapted according to need.

38

PERSONNEL

Key Personnel

- The heads of Production and Quality Control and where relevant, Head of Quality Assurance or Head of Quality Unit, generally have some shared, or jointly exercised, responsibilities relating to quality. These may include:
  - The monitoring and control of the manufacturing environment
  - Plant hygiene
  - Training
  - Process validation
  - The retention of records

39

PERSONNEL

Training

- The manufacturer should provide training for all the personnel whose duties take them into production and storage areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.
- Training include:
  - the theory and practice of Good Manufacturing Practice,
  - Training appropriate to the duties assigned to personnels
- Training programs should be available, approved by either the head of Production or the head of Quality Control, as appropriate.
- Training records should be kept.

40

PERSONNEL

Training

- Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, should be given specific training.
- Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing.

41

PERSONNEL

Personnel Hygiene

- Detailed hygiene programmes should be established and adapted to the different needs within the factory.
- They should include procedures relating to the health, hygiene practices and clothing of personnel.
- All personnel should receive medical examination upon recruitment.
- Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.

42

PERSONNEL

Personnel Hygiene

- Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out
- Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited.
- Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.
- Personnel should be instructed to use the hand-washing facilities.

43

PREMISES AND EQUIPMENT

- Premises should be situated in an environment which, presents minimal risk of causing contamination of materials or products
- Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products.
- Premises should be cleaned and, where applicable, disinfected according to detailed written procedures.

44

PREMISES AND EQUIPMENT

- Lighting, temperature, humidity and ventilation should be appropriate for the manufacture and storage of medicinal products and the accurate functioning of equipment.
- Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.
- Steps should be taken in order to prevent the entry of unauthorised people.

45

PREMISES AND EQUIPMENT

Production Area

In order to minimize the risk of a serious medical hazard due to crosscontamination, dedicated and self contained facilities must be available for the production of particular medicinal products, such as:

- highly sensitizing materials (e.g. penicillins)
- biological preparations (e.g. from live microorganisms).
- Certain antibiotics,
- certain hormones,
- certain cytotoxics,
- certain highly active drugs and non-medicinal products

46

PREMISES AND EQUIPMENT

Production Area

- For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made.
- The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products

47

PREMISES AND EQUIPMENT

Production Area

- Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to:
  - minimise the risk of confusion between different medicinal products or their components,
  - to avoid cross-contamination
  - to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

48

PREMISES AND EQUIPMENT

Production Area

- Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should:
  - be smooth
  - be free from cracks and open joints
  - not shed particulate matter
  - permit easy and effective cleaning and, if necessary, disinfection.
- Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean.
- As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

49

PREMISES AND EQUIPMENT

Production Area

- Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.
- Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.
- In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.

50

PREMISES AND EQUIPMENT

Production Area

- Production areas should be well lit, particularly where visual on-line controls are carried out.
- In-process controls may be carried out within the production area provided they do not carry any risk for the production.

51

PREMISES AND EQUIPMENT

Storage Areas

- Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products:
  - starting and packaging materials,
  - intermediate, bulk and finished products,
  - products in quarantine,
  - released, rejected, returned or recalled.
- Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

52

PREMISES AND EQUIPMENT

Storage Areas

- Storage areas should be designed or adapted to ensure good storage conditions:
  - clean and dry
  - Maintained within acceptable temperature limits.
  - Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

53

PREMISES AND EQUIPMENT

Storage Areas

- Highly active materials or products should be stored in safe and secure areas.
- Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.
- There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

54

PREMISES AND EQUIPMENT

Quality Control Areas

- Normally, Quality Control laboratories should be separated from production areas.
- There should be adequate suitable storage space for samples and records.
- Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

55

PREMISES AND EQUIPMENT

Quality Control Areas

- Laboratories for the control of biologicals, microbiologicals and radioisotopes, should be separated from each other.
- Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

56

PREMISES AND EQUIPMENT

Ancillary Areas

- Rest and refreshment rooms should be separate from other areas.
- Facilities for changing clothes, and for washing and toilet purposes should be easily accessible and appropriate for the number of users.
- Toilets should not directly communicate with production or storage areas.

57

PREMISES AND EQUIPMENT

Ancillary Areas

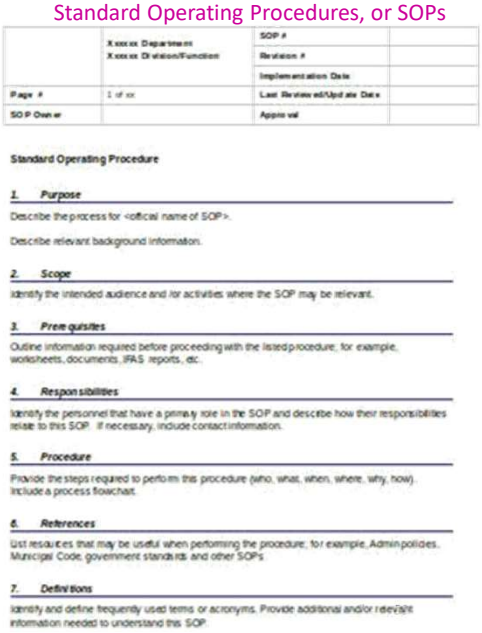
- Maintenance workshops should as far as possible be separated from production areas.
- Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
- Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

58

DOCUMENTATION

- Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements.
- There are two primary types of documentation used to manage and record GMP compliance:
  - instructions (directions, requirements)
  - records/reports.

Standard Operating Procedures, or SOPs



	Xxxxx Department Xxxxx Division/Function	SOP #	
		Revision #	
		Implementation Date	
Page #	1 of xx	Last Reviewed/Update Date	
SOP Owner		Approval	

Standard Operating Procedure

1. Purpose

Describe the process for <official name of SOP>.

Describe relevant background information.

2. Scope

Identify the intended audience and /or activities where the SOP may be relevant.

3. Prerequisites

Outline information required before proceeding with the listed procedure; for example, worksheets, documents, IFAS reports, etc.

4. Responsibilities

Identify the personnel that have a primary role in the SOP and describe how their responsibilities relate to this SOP. If necessary, include contact information.

5. Procedure

Provide the steps required to perform this procedure (who, what, when, where, why, how). Include a process flowchart.

6. References

List resources that may be useful when performing the procedure; for example, Admin policies, Municipal Code, government standards and other SOPs

7. Definitions

Identify and define frequently used terms or acronyms. Provide additional and/or relevant information needed to understand this SOP.

DOCUMENTATION

Required GMP documentation

- Site Master File: A document describing the GMP related activities of the manufacturer.
- Instructions (directions, or requirements) type:
  - Specifications
  - Manufacturing Formulae, Processing, Packaging and Testing Instructions
  - Procedures: (Otherwise known as Standard Operating Procedures, or SOPs), give directions for performing certain operations.
  - Protocols: Give instructions for performing and recording certain discrete operations
  - Technical Agreements: Are agreed between contract givers and acceptors for outsourced activities

60

DOCUMENTATION

Required GMP documentation

- Record/Report type:
  - Records: Provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution.
  - Certificates of Analysis: Provide a summary of testing results on samples of products or materials together with the evaluation for compliance to a stated specification.
  - Reports: Document the conduct of particular exercises, projects or investigations, together with results, conclusions and recommendations.

61

DOCUMENTATION

Generation and Control of Documentation

- Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorisation dossiers, as appropriate.
- Documents should have unambiguous contents and be uniquely identifiable.
- The effective date of document should be defined.

62

DOCUMENTATION

Generation and Control of Documentation

- Documents containing instructions should be approved, signed and dated by appropriate and authorised persons.
- Documents should not be hand-written; although, where documents require the entry of data, sufficient space should be provided for such entries.
- Documents within the Quality Management System should be regularly reviewed and kept up-to-date.

63

DOCUMENTATION

Good Documentation Practices

- Handwritten entries should be made in clear, legible, indelible way.
- Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.
- Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded

64

DOCUMENTATION

Retention of Documents

- It should be clearly defined which record is related to each manufacturing activity and where this record is located.
- Specific requirements apply to batch documentation which must be kept for:
  - one year after expiry of the batch to which it relates or
  - at least five years after certification of the batch by the Qualified Person,

  whichever is the longer.
- For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used.

65

DOCUMENTATION

Retention of Documents

- For other types of documentation, the retention period will depend on the business activity which the documentation supports.
- It may be considered acceptable to retire certain documentation (e.g. raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data.
- Secure controls must be in place to ensure the integrity of the record throughout the retention period.

66

DOCUMENTATION

Specifications

- There should be appropriately authorised and dated specifications for:
  - starting and packaging materials, and finished products.

67

DOCUMENTATION

Specifications for starting and packaging materials

Specifications for starting and primary or printed packaging materials should include or provide reference to, if applicable:

(a) A description of the materials including:

- The designated name and the internal code reference;
- The reference, if any, to a pharmacopoeial monograph;
- The approved suppliers and, if reasonable, the original producer of the material;
- A specimen of printed materials;

(b) Directions for sampling and testing;

(c) Qualitative and quantitative requirements with acceptance limits;

(d) Storage conditions and precautions;

(e) The maximum period of storage before re-examination.

68

DOCUMENTATION

Specifications for intermediate and bulk products

- Specifications for intermediate and bulk products should be available for critical steps or if these are purchased or dispatched.
- The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

69

DOCUMENTATION

Specifications for finished products

Specifications for finished products should include or provide reference to:

(a) The designated name of the product and the code reference where applicable;

(b) The formula;

(c) A description of the pharmaceutical form and package details;

(d) Directions for sampling and testing

(e) The qualitative and quantitative requirements, with the acceptance limits;

(f) The storage conditions and any special handling precautions, where applicable;

(g) The shelf-life.

70

DOCUMENTATION

Manufacturing Formula and Processing Instructions

- Approved, written Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured.
- The Manufacturing Formula should include:

(a) The name of the product, with a product reference code relating to its specification;

(b) A description of the pharmaceutical form, strength of the product and batch size;

(c) A list of all starting materials to be used, with the amount of each, described; mention should be made of any substance that may disappear in the course of processing;

(d) A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

DOCUMENTATION

Manufacturing Formula and Processing Instructions

The Processing Instructions should include:

(a) A statement of the processing location and the principal equipment to be used;

(b) The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);

(c) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use;

(d) Detailed stepwise processing instructions [e.g. checks on materials, pretreatments, sequence for adding materials, critical process parameters (time, temp etc)];

(e) The instructions for any in-process controls with their limits;

(f) Where necessary, the requirements for bulk storage of the products; including the container, labeling and special storage conditions where applicable;

(g) Any special precautions to be observed.

DOCUMENTATION

Packaging Instructions

- Approved Packaging Instructions for each product, pack size and type should exist. These should include, or have a reference to, the following:

(a) Name of the product; including the batch number of bulk and finished product

(b) Description of its pharmaceutical form, and strength where applicable;

(c) The pack size expressed in terms of the number, weight or volume of the product in the final container;

(d) A complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;

73

DOCUMENTATION

Packaging Instructions

(e) Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;

(f) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use.

(g) Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;

(h) A description of the packaging operation, including any significant subsidiary operations, and equipment to be used;

(i) Details of in-process controls with instructions for sampling and acceptance limits.

74

DOCUMENTATION

Batch Processing Record

- A Batch Processing Record should be kept for each batch processed and should contain the following information:

(a) The name and batch number of the product;

(b) Dates and times of commencement, of significant intermediate stages and of completion of production;

(c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

(d) The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);

75

DOCUMENTATION

Batch Processing Record

(e) Any relevant processing operation or event and major equipment used;

(f) A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;

(g) The product yield obtained at different and pertinent stages of manufacture;

(h) Notes on special problems including details, with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions;

(i) Approval by the person responsible for the processing operations.

76

DOCUMENTATION

Batch Packaging Record

A Batch Packaging Record should be kept for each batch or part batch Processed and should contain the following information:

(a) The name and batch number of the product,

(b) The date(s) and times of the packaging operations;

(c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

(d) Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;

(e) Details of the packaging operations carried out, including references to equipment and the packaging lines used; 77

DOCUMENTATION

Batch Packaging Record

(f) Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;

(g) Notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Packaging Instructions;

(h) The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

(i) Approval by the person responsible for the packaging operations 78

DOCUMENTATION

Procedures and records: Receipt

- There should be written procedures and records for the receipt of each delivery of each starting material, (including bulk, intermediate or finished goods), primary, secondary and printed packaging materials.
- There should be written procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

79

DOCUMENTATION

Procedures and records: Receipt

The records of the receipts should include:

(a) The name of the material on the delivery note and the containers;

(b) The “in-house” name and/or code of material (if different from a);

(c) Date of receipt;

(d) Supplier’s name and, manufacturer’s name;

(e) Manufacturer’s batch or reference number;

(f) Total quantity and number of containers received;

(g) The batch number assigned after receipt;

(h) Any relevant comment.

80

DOCUMENTATION

Procedures and records: Sampling

- There should be written procedures for sampling, which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

Procedures and records: Testing

- There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

81

DOCUMENTATION

Procedures and records

There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:

1. Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training.
2. Validation and qualification of processes, equipment and systems;
3. Equipment assembly and calibration;
4. Technology transfer;
5. Maintenance, cleaning and sanitation;
6. Environmental monitoring;
7. Pest control;

82

DOCUMENTATION

Procedures and records

There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:

1. Complaints;
2. Recalls;
3. Returns;
4. Change control;
5. Investigations into deviations and non-conformances;
6. Internal quality/GMP compliance audits;
7. Summaries of records where appropriate (e.g. product quality review);
8. Supplier audits.

83

DOCUMENTATION

Procedures and records

- Records should be maintained for the distribution of each batch of a product in order to facilitate recall of any batch, if necessary.
- Logbooks should be kept for major or critical analytical testing, production equipment, and areas where product has been processed.
- They should be used to record in chronological order, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

84

PRODUCTION

- Production should be performed and supervised by competent people.
- All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.
- All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

85

PRODUCTION

- Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.
- Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.
- Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

86

PRODUCTION

- All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.
- Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or crosscontamination.
- At every stage of processing, products and materials should be protected from microbial and other contamination.

87

PRODUCTION

- When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.
- At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

88

PRODUCTION

- Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format.
- It is often helpful in addition to the wording on the labels to use colors to indicate status (for example, quarantined, accepted, rejected, clean,…).
- Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

89

PRODUCTION

- Any deviation from instructions or procedures should be avoided as far as possible.
- If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.
- Access to production premises should be restricted to authorized personnel.
- Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

90

PRODUCTION

Prevention of Cross-contamination in Production

Cross-contamination should be avoided by appropriate technical or organizational measures, for example:

(a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;

(b) providing appropriate air-locks and air extraction;

(c) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

(d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed;

(e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of crosscontamination;

(f) using "closed systems" of production;

(g) testing for residues and use of cleaning status labels on equipment.

91

PRODUCTION

Validation

- Validation studies should be conducted in accordance with defined procedures. Results and conclusions should be recorded.
- When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing.
- The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.
- Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.
- Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

92

PRODUCTION

Starting Materials

- The purchase of starting materials should involve staff who have a particular and thorough knowledge of the suppliers.
- Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer.
- For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.
- If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

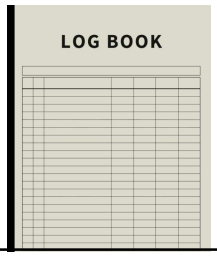
93

PRODUCTION

Starting Materials

Labels should bear at least the following information:

1. the designated name of the product and the internal code reference where applicable;
2. a batch number given at receipt;
3. where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
4. where appropriate, an expiry date or a date beyond which retesting is necessary.



94

PRODUCTION

Starting Materials

- There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material.
- Only starting materials which have been released by the QC Department and which are within their shelf life should be used.
- Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
- Each dispensed material and its weight or volume should be independently checked and the check recorded.

95

PRODUCTION

Processing Operations: intermediate and bulk products

- Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.
- Intermediate and bulk products should be kept under appropriate conditions.
- Critical processes should be validated.
- Any necessary in-process controls and environmental controls should be carried out and recorded.
- Any significant deviation from the expected yield should be recorded and investigated.

96

PRODUCTION

Packaging Materials

- Attention similar to that given to starting materials.
- Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access.
- Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups.
- Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

97

PRODUCTION

Packaging Operations

- Particular attention should be given to minimising the risk of:
  - cross-contamination
  - mix-ups
  - substitutions
- Different products should not be packaged in close proximity unless there is physical segregation

98

PRODUCTION

Packaging Operations

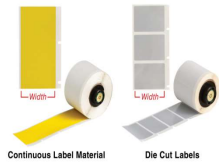
- Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation.
- The line-clearance should be performed according to an appropriate check-list.
- The name and batch number of the product being handled should be displayed at each packaging station or line.
- All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

99

PRODUCTION

Packaging Operations

- Containers for filling should be clean before filling
- Normally, filling and sealing should be followed as quickly as possible by labelling.



- If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.
- Special care should be taken when using cut-labels and when over-printing is carried out off-line.
- Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.
- Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
- Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing

100

PRODUCTION

Packaging Operations

On-line control of the product during packaging should include at least checking the following:

(a) general appearance of the packages;

(b) whether the packages are complete;

(c) whether the correct products and packaging materials are used;

(d) whether any over-printing is correct;

(e) correct functioning of line monitors.

➢Samples taken away from the packaging line should not be returned.

101

PRODUCTION

Packaging Operations

- Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel.
- Detailed record should be kept of this operation.
- Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.
- Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded.
- A documented procedure should be followed if uncoded printed materials are returned to stock.

102

PRODUCTION

Finished Products

- Finished products should be held in quarantine until their final release under conditions established by the manufacturer.
- After release, finished products should be stored as usable stock under conditions established by the manufacturer.

103

PRODUCTION

Rejected, Recovered and Returned Materials

- Rejected materials and products should be clearly marked as such and stored separately in restricted areas.
- They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed.
- Whatever action is taken should be approved and recorded by authorised personnel.
- The reprocessing of rejected products should be exceptional and is only permitted:
  - if the quality of the final product is not affected,
  - if the specifications are met
  - if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved.
- Record should be kept of the reprocessing.

104

PRODUCTION

Rejected, Recovered and Returned Materials

- The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.
- Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure.

105

QUALITY CONTROL

GMP for QC is concerned with the following aspects:

- sampling,
- specifications
- testing
- organisation,
- documentation
- release procedures

The main aims of GMP for QC is to:

- ensure that the necessary and relevant tests are carried out,
- and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory

106

QUALITY CONTROL

- Each holder of a manufacturing authorisation should have a Quality Control Department.
- This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal.
- Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.
- Quality Control personnel should have access to production areas for sampling and investigation as appropriate

107

QUALITY CONTROL

Documentation

The following details should be readily available to the Quality Control Department:

- specifications;
- sampling procedures;
- testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- analytical reports and/or certificates;
- data from environmental monitoring, where required;
- validation records of test methods, where applicable;
- procedures for and records of the calibration of instruments and maintenance of equipment

108

QUALITY CONTROL

Documentation

❑The following details should be readily available to the Quality Control Department:

- specifications;
- sampling procedures;
- testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- analytical reports and/or certificates;
- data from environmental monitoring, where required;
- validation records of test methods, where applicable;
- procedures for and records of the calibration of instruments and maintenance of equipment

❑For some kinds of data (e.g. analytical tests results, yields, environmental controls) it is recommended that records are kept in a manner permitting **trend evaluation**.

109

QUALITY CONTROL

Sampling

The sample taking should be done in accordance with approved written procedures that describe:

- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;
- instructions for any required sub-division of the sample;
- the type and condition of the sample container to be used;
- the identification of containers sampled;
- any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
- the storage conditions;
- instructions for the cleaning and storage of sampling equipment.

110

QUALITY CONTROL

Sampling

- Reference samples should be representative of the batch of materials or products from which they are taken.
- Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).
- Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn

111

QUALITY CONTROL

Testing

- Analytical methods should be validated.
- All testing operations described in the marketing authorization should be carried out according to the approved methods.
- The results obtained should be recorded and checked to make sure that they are consistent with each other.
- Any calculations should be critically examined.

112

QUALITY CONTROL

Testing

The tests performed should be recorded and the records should include at least the following data:

(a) name of the material or product and, where applicable, dosage form;

(b) batch number and, where appropriate, the manufacturer and/or supplier;

(c) references to the relevant specifications and testing procedures;

(d) test results, including observations and calculations, and reference to any certificates of analysis;

(e) dates of testing;

(f) initials of the persons who performed the testing;

(g) initials of the persons who verified the testing and the calculations, where appropriate;

(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

113

QUALITY CONTROL

Testing

- All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.
- Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them.
- The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions.
- In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.

114

QUALITY CONTROL

Testing

- Animals used for testing components, materials or products, should, where appropriate, be quarantined before use.
- They should be maintained and controlled in a manner that assures their suitability for the intended use.
- They should be identified, and adequate records should be maintained, showing the history of their use.

115

QUALITY CONTROL

On-going stability program

- After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate program that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile).
- The purpose of the on-going stability program is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.

116

QUALITY CONTROL

On-going stability program

- Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis.
- The equipment used for the on-going stability program (stability chambers among others) should be qualified and maintained.

- The on-going stability program should be described in a written protocol.

117

QUALITY CONTROL

On-going stability program

The protocol should include the following parameters:

- number of batch(es) per strength and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container closure system(s);
- testing intervals (time points);
- description of the conditions of storage (standardized ICH conditions for long term testing, consistent with the product labelling, should be used);
- other applicable parameters specific to the medicinal product..

118

QUALITY CONTROL

On-going stability program

- The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis.
- Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability program (unless none are produced during that year).
- An on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

119

QUALITY CONTROL

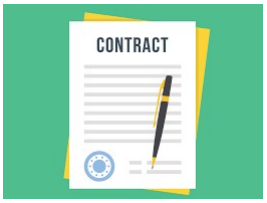
On-going stability program

- Results of on-going stability studies should be made available to key personnel and, in particular, to the Qualified Person(s).
- Out of specification or significant atypical trends should be investigated.
- Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities.

120

OUTSOURCED ACTIVITIES

- Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality.
- There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party.



121

COMPLAINTS AND PRODUCT RECALL

Complaints

- A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him.
- If this person is not the Qualified Person, the latter should be made aware of any complaint, investigation or recall.
- There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

122

COMPLAINTS AND PRODUCT RECALL

Complaints

- Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated.
- All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected.
- Complaints records should be reviewed regularly.

123

COMPLAINTS AND PRODUCT RECALL

Complaints

- Special attention should be given to establishing whether a complaint was caused because of counterfeiting.
- The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product.

- **Follow until resolution**

124

SELF INSPECTION

- Self inspections should be conducted in order to monitor the implementation and compliance with GMP principles and to propose necessary corrective measures.
- Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged program in order to verify their conformity with the principles of Quality Assurance.

125

SELF INSPECTION

- Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company.
- Independent audits by external experts may also be useful.
- All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures.
- Statements on the actions subsequently taken should also be recorded.

126

Glossary

BATCH (OR LOT)

- A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

BATCH NUMBER (OR LOT NUMBER)

- A distinctive combination of numbers and/or letters which specifically identifies a batch

127

Glossary

BULK PRODUCT

- Any product which has completed all processing stages up to, but not including, final packaging.

FINISHED PRODUCT

- A medicinal product which has undergone all stages of production, including packaging in its final container.

INTERMEDIATE PRODUCT

- Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

128

Glossary

CLEAN AREA

- An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

CONTAINED AREA

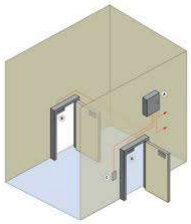
- An area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area.

129

Glossary

AIR-LOCK

- An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.



RECONCILIATION

- A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.

130

Glossary

CALIBRATION

- The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

CROSS-CONTAMINATION

- Contamination of a material or of a product with another material or product.

131

Glossary

STARTING MATERIAL

- Any substance used in the production of a medicinal product, but excluding packaging materials.

PACKAGING MATERIAL

- Any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

132

Glossary

QUARANTINE

- The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.

REPROCESSING

- The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

133