GOOD MANUFACTURING PRACTICE

Introduction

- The first WHO draft text on good manufacturing practices (GMP) was prepared in 1967 by a group of consultants at the request of the Twentieth World Health Assembly (resolution WHA20.34). It was subsequently submitted to the Twenty-first World Health Assembly under the title “Draft requirements for good manufacturing practice in the manufacture and quality control of medicines and pharmaceutical specialties” and was accepted

General considerations

- Licensed pharmaceutical products (marketing authorization) should be manufactured only by licensed manufacturers (holders of a manufacturing authorization) whose activities are regularly inspected by competent national authorities.
- This guide to GMP shall be used as a standard to justify GMP status, which constitutes one of the elements of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce, through the assessment of applications for manufacturing authorizations and as a basis for the inspection of manufacturing facilities.
- It may also be used as training material for government medicines inspectors, as well as for production, QC and QA personnel in the industry.

General considerations

- The guide is applicable to operations for the manufacture of medicines in their finished dosage forms, including large-scale processes in hospitals and the preparation of supplies for use in clinical trials.
- The good practices outlined below are to be considered general guides, and they may be adapted to meet individual needs.
- The equivalence of alternative approaches to QA, however, should be validated.

General considerations

- The guide as a whole does not cover safety aspects for the personnel engaged in manufacture or environmental protection: these are normally governed by national legislation.
- A new concept of hazard analysis related to the risks in production and personnel safety is also newly recommended (Annex 7).
- The manufacturer should assure the safety of workers and take the necessary measures to prevent pollution of the external environment.

General considerations

- International Nonproprietary Names (INN) for pharmaceutical substances designated by WHO should be used when available, together with other designated names.

Quality assurance

- *Principle.* QA is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. QA, therefore, incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

- The system of QA appropriate to the manufacture of pharmaceutical products should ensure that:

- pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP) and good clinical practice (GCP)

- production and control operations are clearly specified in a written form and GMP requirements are adopted;
- managerial responsibilities are clearly specified in job descriptions;
- arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;
- the finished product is correctly processed and checked, according to the defined procedures;

- The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy

- The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company's suppliers, and the distributors.
- To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of QA incorporating GMP and QC. It should be fully documented and its effectiveness monitored.
- All parts of the QA system should be adequately staffed with competent personnel, and should have suitable and sufficient premises, equipment and facilities.

Good manufacturing practices for pharmaceutical products

- GMP is that part of QA which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP are aimed primarily at diminishing the risks inherent in any pharmaceutical production.
- Such risks are essentially of two types: cross-contamination (in particular of unexpected contaminants) and mix ups (confusion) caused by, for example, false labels being put on containers.

- Under GMP:
- all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
- qualification and validation are performed;
- all necessary resources are provided, including:

- ✓ appropriately qualified and trained personnel;
- ✓ adequate premises and space;
- ✓ suitable equipment and services;
- ✓ appropriate materials, containers and labels;
- ✓ approved procedures and instructions;
- ✓ suitable storage and transport;
- ✓ adequate personnel, laboratories and equipment for in-process controls;

- instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
- operators are trained to carry out procedures correctly;
- records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected;
- any significant deviations are fully recorded and investigated;

- records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- the proper storage and distribution of the products minimizes any risk to their quality;
- a system is available to recall any batch of product from sale or supply;
- complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

Sanitation and hygiene

- A high level of sanitation and hygiene should be practiced in every aspect of the manufacture of medicines products.
- The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product.
- Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene.

Qualification and validation

- In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.
- The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan.

Qualification and validation

- Qualification and validation should establish and provide documentary evidence that:
- the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP design qualification or DQ);
- the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ);
- the premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification or OQ);
- a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation or PV, also called performance qualification or PQ).

- Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.
- Qualification and validation should not be considered as one-off exercises. An ongoing programme should follow their first implementation and should be based on an annual review.
- The commitment to maintain continued validation status should be stated in the relevant company documentation, such as the quality manual or validation master plan.

- The responsibility of performing validation should be clearly defined.
- Validation studies are an essential part of GMP and should be conducted in accordance with predefined and approved protocols.
- A written report summarizing the results recorded and the conclusions reached should be prepared and stored.
- Processes and procedures should be established on the basis of the results of the validation performed.
- Particular attention should be paid to the validation of analytical test methods, automated systems and cleaning procedures.

Personnel

- All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.
- All personnel should be motivated to support the establishment and maintenance of high quality standards.

Personal hygiene

- All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.
- All personnel should be trained in the practices of personal hygiene
- Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials or medicines products until the condition is no longer judged to be a risk.

Personal hygiene

- All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.
- Direct contact should be avoided between the operator’s hands and starting materials, primary packaging materials and intermediate or bulk product.
- To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering.

Personal hygiene

- Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.
- Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines should not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.
- Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or nonemployees, e.g. contractors' employees, visitors, senior managers and inspectors.

MANUFACTURE OF STERILE MEDICINAL PRODUCTS

Principle

- The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogenic contamination.
- Much depends on the skill, training and attitudes of the personnel involved.
- Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure.
- Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

- The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials.
- Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

- The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area.
- Manufacturing operations are divided into two categories; firstly those where the product is terminally sterilized, and secondly those which are conducted aseptically at some or all stages.

- Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment.
- Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbial contamination of the product or materials being handled.

- For the manufacture of sterile medicinal products 4 grades can be distinguished:
- Grade A
- Grade B
- Grade C and D

- Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections.
- Normally such conditions are provided by a laminar air flow work station.
- Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications. The maintenance of laminarity should be demonstrated and validated

- Grade B: For aseptic preparation and filling, this is the background environment for the grade A zone.
- Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

Terminally sterilized products

- Preparation of components and most products should be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilization.
- Where the product is at a high or unusual risk of microbial contamination, (for example, because the product actively supports microbial growth or must be held for a long period before sterilization or is necessarily processed not mainly in closed vessels), then preparation should be carried out in a grade C environment.

Terminally sterilized products

- Filling of products for terminal sterilization should be carried out in at least a grade C environment
- Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background.

Aseptic preparation

- Components after washing should be handled in at least a grade D environment. Handling of sterile starting materials and components, unless subjected to sterilization or filtration through a micro-organism-retaining filter later in the process, should be done in a grade A environment with grade B background.
- Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.

Aseptic preparation

- Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.
- Prior to the completion of stoppering, transfer of partially closed containers, as used in freeze drying should be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.

Personnel

- Only the minimum number of personnel required should be present in clean areas
- All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products.
- This training should include reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

Personnel

- High standards of personal hygiene and cleanliness are essential.
- Wristwatches, make-up and jewellery should not be worn in clean areas
- Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.
- The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination

Personnel

- The description of clothing required for each grade is given below:
- Grade D: Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.
- Grade C: Hair and where relevant beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.
- Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilized, non-powdered rubber or plastic gloves and sterilized or disinfected footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.

Premises

- In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.
- To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment.
- Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.
- False ceilings should be sealed to prevent contamination from the space above them.
- Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.

Premises

- Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture.
- Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing.
- Both airlock doors should not be opened simultaneously.
- A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively.
- It should be demonstrated that air-flow patterns do not present a contamination risk
- A warning system should be provided to indicate failure in the air supply.

Sterilization

- All sterilization processes should be validated. Particular attention should be given when the adopted sterilization method is not described in the current edition of the European Pharmacopoeia, or when it is used for a product which is not a simple aqueous or oily solution.
- Where possible, heat sterilization is the method of choice.
- In any case, the sterilization process must be in accordance with the marketing and manufacturing authorizations.

Sterilization

- Before any sterilization process is adopted its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

- For effective sterilization the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.
- Validated loading patterns should be established for all sterilization processes.
- Biological indicators should be considered as an additional method for monitoring the sterilization.

PHARMACEUTICAL MICROBIOLOGY

Introduction

- Pharmaceutical microbiology laboratories may be involved in:

— sterility testing;

— detection, isolation, enumeration and identification of microorganisms (bacteria, yeast and moulds) and testing for bacterial endotoxins in different materials (e.g. starting materials, water), products, surfaces, garments and the environment;

— assay using microorganisms as part of the test system.

Personnel

- Microbiological testing should be performed and supervised by an experienced person, qualified in microbiology or equivalent.
- Staff should have basic training in microbiology and relevant practical experience before being allowed to perform work covered by the scope of testing.
- The laboratory management should ensure that all personnel have received adequate training for the competent performance of tests and operation of equipment.
- Personnel should be trained in necessary procedures for containment of microorganisms within the laboratory facility.
- Personnel should be trained in safe handling of microorganisms

Environment

Premises

- Microbiology laboratories and certain support equipment (e.g. autoclaves and glassware) should be dedicated and separated from other areas, especially from production areas.
- Microbiology laboratories should be designed to suit the operations to be carried out in them.
- There should be separate air supply to laboratories and production areas.
- Access to the microbiological laboratory should be restricted to authorized personnel:

Environment

- **Premises**
- Personnel should be made aware of:

— the appropriate entry and exit procedures including gowning;

— the intended use of a particular area;

— the restrictions imposed on working within such areas;

— the reasons for imposing such restrictions;

— the appropriate containment levels.

Environment

Cleaning, disinfection and hygiene

- There should be a documented cleaning and disinfection programme.
- Results of environmental monitoring should be considered where relevant.
- There should be a procedure for dealing with spillages.
- Adequate hand-washing and hand-disinfection facilities should be available.

Validation of test methods

- Standard (pharmacopoeia) test methods are considered to be validated.
- Test methods not based on compendia or other recognized references should be validated before use. The validation should comprise, where appropriate, determining accuracy, precision, specificity, limit of detection, limit of quantitation, linearity and robustness.
- Potentially inhibitory effects from the sample should be taken into account when testing different types of sample.
- The results should be evaluated with appropriate statistical methods, e.g. as described in the national, regional or international pharmacopoeias.

Equipment

- Each item of equipment, instrument or other device used for testing, verification and calibration should be uniquely identified.
- As part of its quality system, a laboratory should have a documented program for the qualification, calibration, performance verification, maintenance and a system for monitoring the use of its equipment.

Equipment

Calibration, performance verification and monitoring of use

- The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument
- The frequency of calibration and performance verification will be determined by documented experience and will be based on need, type and previous performance of the equipment

Reagents and culture media

- Laboratories should ensure that the quality of a reagents and media used is appropriate for the test concerned.
- Laboratories should verify the suitability of each batch of reagents critical for the test, initially and during its shelf-life.
- Media may be prepared in-house or purchased either partially or fully prepared. Vendors of purchased media should be approved and qualified.

- **Labelling**
- Laboratories should ensure that all reagents (including stock solutions), media, diluents and other suspending fluids are adequately labelled to indicate, as appropriate, identity, concentration, storage conditions, preparation date, validated expiry date and/or recommended storage periods. The person responsible for preparation should be identifiable from records.

- **Organism resuscitation**
- Organism resuscitation is required where test methodologies may produce sublethally injured cells. For example, exposure to:

— injurious effects of processing, e.g. heat;

— antimicrobial agents;

— preservatives;

— extremes of osmotic pressure; and

— extremes of pH.

- Organism resuscitation may be achieved by:

— exposure to a liquid media like a simple salt solution at room temperature for 2 hours;

— exposure to a solid repair medium for 4–6 hours.

Reference materials and reference cultures

International standards and pharmacopoeia reference substances

- Reference materials and certified reference materials are generally used in a microbiological laboratory to qualify, verify and calibrate equipment.
- Whenever possible these reference materials should be used in appropriate matrices.
- International standards and pharmacopoeia reference substances are employed, for example, to:

— determine potency or content;

— validate methods;

— enable comparison of methods;

— perform positive controls;

— perform growth promotion tests.

- If possible reference materials should be used in appropriate matrices.