WHO GMP Guide for Specific Pharmaceutical Products

Quality Assurance of Pharmaceuticals

A compendium of guidelines and related materials Volume 2: Good manufacturing practices and inspection

Sterile pharmaceutical products
Biological products
Investigational pharmaceutical products for clinical trials in humans
Herbal medicinal products

Sterile pharmaceutical products

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Explanation

These guidelines do not replace any of the sections in Parts One and Two but stress specific points for the manufacture of sterile preparations to minimize the risks of microbiological, particulate, and pyrogen contamination.

General

17.1 The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for goods. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of an appropriate efficiency.
Table 1. Air classification system for manufacture of sterile products

<table>
<thead>
<tr>
<th>Grade</th>
<th>Maximum number of particles permitted per m³</th>
<th>Maximum number of viable microorganisms permitted per m³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5–5 mm</td>
<td>&gt;5 mm</td>
</tr>
<tr>
<td>A (Laminar-airflow workstation)</td>
<td>3 500</td>
<td>none</td>
</tr>
<tr>
<td>B</td>
<td>3 500</td>
<td>none</td>
</tr>
<tr>
<td>C</td>
<td>350 000</td>
<td>2 000</td>
</tr>
<tr>
<td>D</td>
<td>3 500 000</td>
<td>20 000</td>
</tr>
</tbody>
</table>

17.2 The various operations of component preparation (such as containers and closures), product preparation, filling, and sterilization should be carried out in separate areas within the clean area.

17.3 Clean areas for the production of sterile products are classified according to the required characteristics of the air, in grades A, B, C, and D (see Table 1).

To obtain air of the required characteristics, methods specified by the national authorities should be used. It should be noted that:

- Laminar-airflow systems should provide a homogeneous air speed of about 0.30 m/s for vertical flow and about 0.45 m/s for horizontal flow but precise air speeds will depend on the type of equipment.

- In order to reach the B, C, and D air grades, the number of air changes should generally be higher than 20 per hour in a room with a good airflow pattern and appropriate HEPA (high-efficiency particulate air) filters.

- Low values for contaminants are reliable only when a large number of air samples are taken.

- The guidance given for the maximum permitted number of particles corresponds approximately to the United States Federal Standard 209E (1992) as follows: Class 100 (grades A and B), Class 10 000 (grade C), and Class 100 000 (grade D).

It may not always be possible to demonstrate conformity with particular air standards at the point of fill when filling is in progress, owing to the generation of particles or droplets from the product itself.

17.4 Each manufacturing operation requires an appropriate air cleanliness level in order to minimize the risks of particulate or microbial contamination of the product or materials being handled. Section 17.5 gives the minimum air grades required for different manufacturing operations. The particulate and microbiological conditions given in Table 1 should be maintained in the zone immediately surrounding the product whenever the product is exposed to the environment. These conditions should also be achieved throughout the background environment if no personnel are present in the processing area, and if the standards fall for any reason it should be possible to recover the conditions after a short "clean-up" period. The utilization of absolute-barrier technology and automated systems to minimize human interventions in processing areas can produce significant advantages in ensuring the sterility of manufactured products. When such techniques are used, the recommendations in these supplementary guidelines, particularly those relating to air quality and monitoring, still apply, with appropriate interpretations of the terms "workstation" and "environment".

Manufacture of sterile preparations

17.5 Manufacturing operations are here divided into three categories: first, those in which the preparation is sealed in its final container and terminally sterilized; second, those in which the preparation is sterilized by filtration; and third, those in which the preparation can be sterilized neither by filtration nor terminally and consequently must be produced
from sterile starting materials in an aseptic way. Area grades as specified in sections 17.5.1–17.5.3, must be selected by the manufacturer on the basis of validation runs (e.g., sterile media fills).

Terminally sterilized products

17.5.1 Solutions should generally be prepared in a grade C environment in order to give low microbial and particulate counts, suitable for immediate filtration and sterilization. Solution preparation could be allowed in a grade D environment if additional measures were taken to minimize contamination, such as the use of closed vessels. For parenterals, filling should be done in a laminar-airflow workstation (grade A) in a grade C environment. The preparation of other sterile products, e.g., ointments, creams, suspensions, and emulsions, and filling of containers should generally be done in a grade C environment before terminal sterilization.

Sterile filtered products

17.5.2 The handling of starting materials and the preparation of solutions should be done in a grade C environment. These activities could be allowed in a grade D environment if additional measures were taken to minimize contamination, such as the use of closed vessels prior to filtration. After sterile filtration, the product must be handled and dispensed into containers under aseptic conditions in a grade A or B area with a grade B or C background respectively.

Other sterile products prepared from sterile starting materials in an aseptic way

17.5.3 The handling of starting materials and all further processing should be done in a grade A or B area with a grade B or C background respectively.

Personnel

17.6 Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. Inspections and controls should be conducted from outside the areas as far as possible.

17.7 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, including 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 supervision.

17.8 Staff who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

17.9 High standards of personal hygiene and cleanliness are essential, and personnel involved in the manufacture of sterile preparations should be instructed to report any condition that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person.

17.10 Outdoor clothing should not be brought into the clean areas, and personnel entering the changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a written procedure.

17.11 The clothing and its quality has to be adapted to the process and the workplace, and worn in such a way as to protect the product from contamination.

17.12 Wrist-watches and jewellery should not be worn in clean areas, and cosmetics that can shed particles should not be used.
17.13 Clothing should be appropriate to the air grade of the area where the personnel will be working. The description of clothing required for each grade is given below.

**Grade D:** The hair and, where appropriate, beard should be covered. Protective clothing 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:** The hair and, where appropriate, beard should be covered. A single or two-piece trouser suit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes should be worn. The clothing should shed virtually no fibres or particulate matter.

**Grade B:** Headgear should totally enclose the hair and, where appropriate, beard; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets; sterilized non-powdered rubber or plastic gloves and sterilized or disinfected footwear should be worn; trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and should retain particles shed by the body.

17.14 For every worker in a grade B room, clean sterilized protective garments should be provided at each work session, or at least once a day if monitoring results justify it. Gloves should be regularly disinfected during operations, and masks and gloves should be changed at least at every working session. The use of disposable clothing may be necessary.

17.15 Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization there may be an increased risk of shedding particles. Washing and sterilization operations should follow standard operating procedures.

**Premises**

17.16 All premises should as far as possible be designed to avoid the unnecessary entry of supervisory or control personnel. Grade B areas should be designed so that all operations can be observed from outside.

17.17 In clean areas, all exposed surfaces should be smooth, impervious, and unbroken in order to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.

17.18 To reduce the 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 carefully designed to avoid uncleanable recesses; sliding doors are undesirable for this reason.

17.19 False ceilings should be sealed to prevent contamination from the space above them.

17.20 Pipes and ducts should be installed so that they do not create recesses that are difficult to clean.

17.21 Sinks and drains should be avoided wherever possible and should be excluded from areas where aseptic operations are carried out. Where installed they should be designed, located, and maintained so as to minimize the risks of microbial contamination; they should be fitted with effective, easily cleanable traps with air breaks to prevent back-flow. Any floor channel should be open and easily cleanable and be connected to drains outside the area in a manner that prevents ingress of microbial contaminants.

17.22 Changing rooms should be designed as airlocks and used to provide separation of the different stages of changing, so minimizing microbial and particulate contamination of protective clothing. They should be effectively flushed with filtered air. The use of separate changing rooms for entering and leaving clean areas is sometimes
desirable. Hand-washing facilities should be provided only in the changing rooms, not in areas where aseptic work is done.

17.23 Airlock doors should not be opened simultaneously. An interlocking system and a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

Equipment

17.24 A filtered air supply should maintain a positive pressure relative to surrounding areas under all operational conditions and flush the area effectively. Moreover, particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which the product and the cleaned components in contact with it are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified if it becomes necessary to contain materials such as pathogenic, highly toxic, radioactive, or live viral or bacterial materials. Decontamination facilities and the treatment of air leaving a clean area may be necessary for some operations.

17.25 It should be demonstrated that airflow patterns do not present a contamination risk, for example care should be taken to ensure that airflows do not distribute particles from a particle-generating person, operation, or machine to a zone of higher product risk.

17.26 A warning system should be included to indicate failure in the air supply. An indicator of pressure difference should be fitted between areas where this difference is important and the pressure difference should be regularly recorded.

17.27 Consideration should be given to restricting unnecessary access to critical filling areas, e.g., grade A filling zones, by the use of a physical barrier.

17.28 A conveyor belt should not pass through a partition between a clean area B and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized (e.g., in a sterilizing tunnel).

17.29 Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods.

17.30 As far as possible, equipment fittings and services should be designed and installed so that operations, maintenance, and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance should be resteriled after complete reassembly wherever possible.

17.31 When equipment maintenance is carried out within the clean area, clean instruments and tools should be used, and the area should be cleaned and disinfected where appropriate before processing recommences, if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.

17.32 All equipment, including sterilizers, air-filtration systems, and water-treatment systems including stills, should be subject to planned maintenance, validation, and monitoring; its approved use following maintenance work should be documented.

17.33 Water-treatment plants should be designed, constructed, and maintained so as to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water should be produced, stored, and distributed in a manner that prevents microbial growth—for example, by constant circulation at 80°C or not more than 4°C.

Sanitation
17.34 The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with a written programme approved by the quality control department. Where disinfectants are used, more than one type should be employed, with periodic alterations. Monitoring should be regularly undertaken in order to detect the emergence of resistant strains of microorganisms. In view of its limited effectiveness, ultraviolet light should not be used as a substitute for chemical disinfection.

17.35 Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should not be stored for long periods unless sterilized. Partly emptied containers should not be topped up.

17.36 Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

17.37 Clean areas should be monitored at planned intervals during operations by means of microbial counts of air and surfaces; where aseptic operations are performed, monitoring should be frequent to ensure that the environment is within specifications. The results of monitoring should be considered when batches are assessed for approval. Air particulate quality should also be evaluated on a regular basis. Additional monitoring is sometimes desirable even when there are no production operations, e.g., after validation of systems, cleaning, and fumigation.

Processing

17.38 Precautions to minimize contamination should be taken during all processing stages, including the stages before sterilization.

17.39 Preparations containing live microbiological organisms should not be made or containers filled in areas used for the processing of other pharmaceutical products; however, vaccines of dead organisms or of bacterial extracts may be dispensed into containers, after validated inactivation and validated cleaning procedures, in the same premises as other sterile pharmaceutical products.

17.40 The use of nutrient media that support microbial growth in trials to simulate aseptic operations (sterile media fills, "broth fills") is a valuable part of overall validation of an aseptic process. Such trials should have the following characteristics:

(a) They should simulate as closely as possible actual operations, taking into account such factors as complexity of operations, number of personnel working, and length of time.

(b) The medium or media selected should be capable of growing a wide spectrum of microorganisms, including those that would be expected to be found in the filling environment.

(c) They should include a sufficient number of units of production to give a high degree of assurance that low levels of contamination, if present, would be detected.

It is recommended that at least 3000 units of production be included in each broth-fill trial. The target should be zero growth and anything above 0.1% of units contaminated should be considered unacceptable. Any contamination should be investigated. Broth fills should be repeated at regular intervals, and whenever a significant alteration in the product, premises, equipment, or process warrants revalidation.

17.41 Care should be taken that validations do not harm the processes.

17.42 Water sources, water-treatment equipment, and treated water should be monitored regularly for chemicals, biological contamination, and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use. Records should be maintained of the results of the monitoring and of any action taken.
17.43 Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum, and the movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.

17.44 Microbiological contamination of starting materials should be minimal, and the "bioburden" should be monitored before sterilization. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.

17.45 The presence of containers and materials liable to generate fibres should be minimized in clean areas and avoided completely when aseptic work is in progress.

17.46 Components, bulk-product containers, and equipment should be handled after the final cleaning process in such a way that they are not recontaminated. The stage of processing of components, bulk-product containers, and equipment should be properly identified.

17.47 The interval between the washing and drying and the sterilization of components, bulk-product containers, and equipment, as well as between sterilization and use, should be as short as possible and subject to a time-limit appropriate to the validated storage conditions.

17.48 The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retaining filter should be as short as possible. A maximum permissible time should be set for each product that takes into account its composition and the prescribed method of storage.

17.49 Any gas that is used to purge a solution or blanket a product should pass through a sterilizing filter.

17.50 The microbiological contamination of products ("bioburden") should be minimal prior to sterilization. There should be a working limit on contamination immediately before sterilization that is related to the efficiency of the method to be used and the risk of pyrogens. All solutions, in particular large-volume parenterals, should be passed through a microorganism-retaining filter, if possible immediately before the filling process. Where aqueous solutions are held in sealed vessels, any pressure-release outlets should be protected, e.g., by hydrophobic microbial air filters.

17.51 Components, bulk-product containers, equipment, and any other articles required in a clean area where aseptic work is in progress should be sterilized and, wherever possible, passed into the area through double-ended sterilizers sealed into the wall. Other procedures that achieve the same end of not introducing contamination (e.g., triple wrapping) may be acceptable in some circumstances.

17.52 The efficacy of any new processing procedure should be validated, and the validation should be repeated at regular intervals thereafter or when any significant change is made in the process or equipment.

Sterilization

17.53 Sterilization can be achieved by moist or dry heat, by ethylene oxide (or other suitable gaseous sterilizing agent), by filtration with subsequent aseptic filling of sterile final containers, or by irradiation with ionizing radiation (but not with ultraviolet radiation unless the process is thoroughly validated). Each method has its particular applications and limitations. Where possible and practicable, heat sterilization is the method of choice.

17.54 All sterilization processes must be validated. Particular attention should be given when the adopted sterilization method is not in accordance with pharmacopoeial or other national standards or when it is used for a preparation that is not a simple aqueous or oily solution. In any case, the sterilization process must be in accordance with the marketing and manufacturing authorizations.
17.55 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. This work should be repeated at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

17.56 Biological indicators should be considered only as an additional method for monitoring the sterilization. If they are used, strict precautions should be taken to avoid transferring microbial contamination from them.

17.57 There should be a clear means of differentiating products that have not been sterilized from those that have. Each basket, tray, or other carrier of products or components should be clearly labelled with the name of the material, its batch number, and an indication of whether or not it has been sterilized. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the lot is, in fact, sterile.

Sterilization by heat

17.58 Each heat sterilization cycle should be recorded by appropriate equipment with suitable accuracy and precision, e.g., on a time/temperature chart with a suitably large scale. The temperature should be recorded from a probe at the coolest part of the load or loaded chamber, this point having been determined during the validation; the temperature should preferably be checked against a second independent temperature probe located at the same position. The chart, or a photocopy of it, should form part of the batch record. Chemical or biological indicators may also be used but should not take the place of physical controls.

17.59 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time is started. This time must be determined for each type of load to be processed.

17.60 After the high-temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized, unless it can be shown that any leaking container would not be approved for use.

Sterilization by moist heat

17.61 Sterilization by moist heat is suitable only for water-wettable materials and aqueous solutions. Both temperature and pressure should be used to monitor the process. The temperature recorder should normally be independent of the controller, and there should be an independent temperature indicator, the reading from which is routinely checked against the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilization period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.

17.62 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows removal of air and penetration of steam but prevents recontamination after sterilization. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

17.63 Care should be taken to ensure that steam used for sterilization is of suitable quality and does not contain additives at a level that could cause contamination of the product or equipment.

Sterilization by dry heat

17.64 The process used for sterilization by dry heat should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is supplied, it should be passed through a microorganism-retaining filter. Where this process of sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins would be required as part of the validation.

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Sterilization by radiation

17.65 Radiation sterilization is used mainly for the sterilization of heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.

17.66 If radiation sterilization is carried out by an outside contractor, the manufacturer has the responsibility of ensuring that the requirements of section 17.65 are met, and that the sterilization process is validated. The responsibilities of the radiation plant operator (e.g., for the right dose) should also be specified.

17.67 During the sterilization procedure the radiation dose should be measured. For this purpose, dosimeters that are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number, and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are used, they should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation. Biological indicators may be used only as an additional control. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilization. The information obtained should constitute part of the batch record.

17.68 Validation procedures should ensure that consideration is given to the effect of variations in the density of the packages.

17.69 Handling procedures should prevent any mix-up between irradiated and non-irradiated materials. Each package should carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.

17.70 The total radiation dose should be administered within a predetermined time span.

Sterilization by ethylene oxide

17.71 Various gases and fumigants may be used for sterilization. Ethylene oxide should be used only when no other method is practicable. During process validation it should be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material. These limits should be incorporated into the specifications.

17.72 Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

17.73 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilization.

17.74 Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

17.75 Biological indicators should be stored and used according to the manufacturer's instructions, and their performance checked by positive controls.

17.76 For each sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature, and humidity within the chamber during the process, and of the gas concentration. The pressure and temperature should be recorded throughout the cycle on a chart. The records should form part of the batch record.
17.77 After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to fall to the defined level. This process should be validated.

Filtration of pharmaceutical products that cannot be sterilized in their final container

17.78 Whenever possible, products should be sterilized in the final container, preferably by heat sterilization. Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22 mm (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.

17.79 Owing to the potential additional risks of the filtration method as compared with other sterilization processes, a double filter layer or second filtration via a further sterilized microorganism-retaining filter immediately prior to filling may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

17.80 Filters that shed fibres should not be used. The use of asbestos-containing filters should be absolutely excluded.

17.81 The integrity of the filter should be checked by an appropriate method such as a bubble point test immediately after each use (it may also be useful to test the filter in this way before use). The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this should be noted and investigated. Results of these checks should be recorded in the batch record.

17.82 The same filter should not be used for more than one working day unless such use has been validated.

17.83 The filter should not affect the product by removal of ingredients from it or by release of substances into it.

Finishing of sterile products

17.84 Containers should be closed by appropriately validated methods. Samples should be checked for integrity according to appropriate procedures.

17.85 Containers sealed under vacuum should be sampled and the samples tested for maintenance of that vacuum after an appropriate predetermined period.

17.86 Filled containers of parenteral products should be inspected individually. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eyesight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals.

Quality control

17.87 Samples taken for sterility testing should be representative of the whole of the batch but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example:

(a) for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;

(b) for products that have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.
17.88 The sterility test applied to the finished product should be regarded only as the last in a series of control measures by which sterility is assured and can be interpreted only in conjunction with the environmental and batch processing records.

17.89 Batches failing an initial sterility test should not be released on the basis of a second test unless an investigation into the type of organism found, and into the environmental and batch processing records involved, show that the original test was invalid.

17.90 For injectable products, consideration should be given to monitoring the water and the intermediate and finished product for endotoxins, using an established pharmacopoeial method that has been validated for each type of product. For large-volume infusion solutions, such monitoring of water or intermediates should always be done, in addition to any tests required by the marketing authorization on the finished product. When a sample fails a test, the cause of failure should be investigated and remedial action taken where necessary.

**Biological products**

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Authors
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1. Scope of these guidelines

These guidelines are intended to complement those provided in "Good manufacturing practices for pharmaceutical products" (1).

The regulatory procedures necessary to control biological products are in large part determined by the sources of products and methods of manufacture. Manufacturing procedures within the scope of these guidelines include:

— growth of strains of microorganisms and eukaryotic cells,

— extraction of substances from biological tissues, including human, animal and plant tissues (allergens),

— recombinant DNA (rDNA) techniques,

— hybridoma techniques,

— propagation of microorganisms in embryos or animals.
Biological products manufactured by these methods include allergens, antigens, vaccines, hormones, cytokines, enzymes, human whole blood and plasma derivatives, immune sera, immunoglobulins (including monoclonal antibodies), products of fermentation (including products derived from rDNA) and diagnostic agents for *in vitro* use.

2. Principles

The manufacture of biological products shall be undertaken in accordance with the basic principles of good manufacturing practices (GMP). The points covered by these guidelines should therefore be considered supplementary to the general requirements set out in "Good manufacturing practices for pharmaceutical products" (1), and relate specifically to the production and control of biological products. In drawing up these guidelines, due consideration was given to the draft "Guidelines for national authorities on quality assurance for biological products", the final version of which appears as Annex 2 to the forty-second report of the WHO Expert Committee on Biological Standardization (2).

The way in which biological products are produced, controlled and administered makes some particular precautions necessary. Unlike conventional pharmaceutical products, which are normally produced and controlled using reproducible chemical and physical techniques, biological products are manufactured by methods involving biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These processes display inherent variability, so that the range and nature of by-products are variable. For this reason, in the manufacture of biological products full adherence to GMP is necessary for all production steps, beginning with those from which the active ingredients are produced.

Control of biological products nearly always involves biological techniques that have a greater variability than physicochemical determinations. In-process controls take on a great importance in the manufacture of biological products because certain deficiencies may not be revealed by testing the finished product.

The present guidelines do not lay down detailed requirements for specific classes of biological products, and attention is therefore directed to other guidance issued by WHO, and in particular to the Requirements for Biological Substances, which include requirements for vaccines (2, Annex 7).

3. Personnel

3.1 The manufacturing establishment and its personnel shall be under the authority of a person who has been trained in the techniques used in manufacturing biological substances and who possesses the scientific knowledge upon which the manufacture of these products is based. The personnel shall include specialists with training appropriate to the products made in the establishment.

3.2 Personnel required to work in clean and aseptic areas should be selected with care, to ensure that they may be relied upon to observe the appropriate codes of practice and are not subject to any disease or condition that could compromise the integrity of the product microbiologically or otherwise. High standards of personal hygiene and cleanliness are essential. Staff should be instructed to report any conditions (e.g. diarrhoea, coughs, colds, infected skin or hair, wounds, fever of unknown origin) that may cause the shedding of abnormal numbers or types of organisms into the working environment. Health checks on personnel for such conditions should be required before employment and periodically thereafter. Any changes in health status that could adversely affect the quality of the product shall preclude the person concerned from working in the production area.

3.3 Only the minimum number of personnel required should be present in clean and aseptic areas when work is in progress. Inspection and control procedures should be conducted from outside these areas as far as possible.

3.4 During the working day, personnel shall not pass from areas where live microorganisms or animals are handled to premises where other products or organisms are handled unless clearly defined decontamination measures, including a

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change of clothing and shoes, are followed. Persons not concerned with the production process should not enter the production area except for essential purposes, and in that case they shall be supplied with sterile protective clothing.

3.5 The staff engaged in the manufacturing process should be separate from the staff responsible for animal care.

3.6 The names and qualifications of those responsible for approving lot processing records (protocols) should be registered with the national control authority.

3.7 To ensure the manufacture of high-quality products, personnel should be trained in good manufacturing and laboratory practices in appropriate fields such as bacteriology, virology, biometry, chemistry, medicine, immunology and veterinary medicine.

3.8 Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

3.9 All personnel engaged in production, maintenance, testing and animal care (and inspectors) should be vaccinated with appropriate vaccines and, where appropriate, be submitted to regular testing for evidence of active tuberculosis. Apart from the obvious problem of exposure of staff to infectious agents, potent toxins or allergens, it is necessary to avoid the risk of contamination of a production batch with these agents.

3.10 Where BCG vaccines are being manufactured, access to production areas shall be restricted to staff who are carefully monitored by regular health checks. In the case of manufacture of products derived from human blood or plasma, vaccination of workers against hepatitis B is recommended.

4. Premises and equipment

4.1 As a general principle, buildings must be located, designed, constructed, adapted and maintained to suit the operations to be carried out within them. Laboratories, operating rooms and all other rooms and buildings (including those for animals) that are used for the manufacture of biological products shall be designed and constructed of materials of the highest standard so that cleanliness, especially freedom from dust, insects and vermin, can be maintained.

4.2 Interior surfaces (walls, floors and ceilings) shall be smooth and free from cracks; they shall not shed matter and shall permit easy cleaning and disinfection. Drains should be avoided wherever possible and, unless essential, should be excluded from aseptic areas. Where installed they should be fitted with effective, easily cleanable traps and with breaks to prevent back-flow. The traps may contain electrically operated heating devices or other means for disinfection. Any floor channels should be open, shallow and easily cleanable and be connected to drains outside the area in a manner that prevents ingress of microbial contaminants.

4.3 Sinks shall be excluded from aseptic areas. Any sink installed in other clean areas shall be of suitable material such as stainless steel, without an overflow, and be supplied with water of potable quality. Adequate precautions shall be taken to avoid contamination of the drainage system with dangerous effluents. Airborne dissemination of pathogenic microorganisms and viruses used for production and the possibility of contamination by other types of viruses or substances during the production process, including those from personnel, shall be avoided.

4.4 Lighting, heating, ventilation and, if necessary, air-conditioning should be designed to maintain a satisfactory temperature and relative humidity, to minimize contamination and to take account of the comfort of personnel working in protective clothing. Buildings shall be in a good state of repair. The condition of the buildings should be reviewed regularly and repairs carried out when and where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not compromise products. Premises should provide sufficient space to suit the operations to be carried out, allowing an efficient flow of work and effective communication and supervision. All buildings and rooms shall be clean and sanitary at all times. If rooms intended for the manufacture of biological substances are used for other purposes, they shall be cleaned thoroughly and, if necessary, sanitized before the
manufacture of biological substances is resumed. Areas used for processing animal tissue materials and microorganisms not required for the current manufacturing process and for performing tests involving animals or microorganisms must be separated from premises used for manufacturing sterile biological products and have completely separate ventilation systems and separate staff.

4.5 If certain products are to be produced on a campaign basis, the layout and design of the premises and equipment shall permit effective decontamination by fumigation, where necessary, as well as cleaning and sanitizing after the production campaign.

4.6 Seed lots and cell banks used for the production of biological products should be stored separately from other material. Access should be restricted to authorized personnel.

4.7 Live organisms shall be handled in equipment that ensures that cultures are maintained in a pure state and are not contaminated during processing.

4.8 Products such as killed vaccines, including those made by rDNA techniques, toxoids and bacterial extracts may after inactivation be dispensed into containers on the same premises as other sterile biological products, providing that adequate decontamination measures are taken after filling, including, if appropriate, sterilization and washing.

4.9 Spore-forming organisms shall be handled in facilities dedicated to this group of products until the inactivation process is accomplished. For *Bacillus anthracis*, *Clostridium botulinum* and *Clostridium tetani*, strictly dedicated facilities should be utilized for each individual product. Where campaign manufacture of spore-forming organisms occurs in a facility or suite of facilities, only one product should be processed at any one time.

4.10 Dedicated facilities and equipment shall be used for the manufacture of medicinal products derived from human blood or plasma.

4.11 All containers of biological substances, regardless of the stage of manufacture, shall be identified by securely attached labels. Cross-contamination should be prevented by adoption of some or all of the following measures:

— processing and filling in segregated areas;

— avoiding manufacture of different products at the same time, unless they are effectively segregated;

— containing material transfer by means of airlocks, air extraction, clothing change and careful washing and decontamination of equipment;

— protecting against the risks of contamination caused by recirculation of untreated air, or by accidental re-entry of extracted air;

— using "closed systems" of manufacture;

— taking care to prevent aerosol formation (especially by centrifugation and blending);

— excluding pathological specimens sent in for diagnosis from areas used for manufacturing biological substances;

— using containers that are sterilized or are of documented low "bioburden".

4.12 Positive-pressure areas should be used to process sterile products, but negative pressure is acceptable in specific areas where pathogens are processed. In general, any organisms considered to be pathogenic should be handled within specifically designed areas under negative pressures, in accordance with containment requirements for the product concerned.
4.13 Air-handling units should be dedicated to the processing area concerned. Air from operations involving pathogens shall not be recirculated and, in the cases of organisms in a group above Risk Group 2 (3), shall be exhausted through sterilizing filters that are regularly checked for performance.

4.14 Specific decontamination systems should be considered for effluent when infectious and potentially infectious materials are used for production.

4.15 Pipework, valves and vent filters shall be properly designed to facilitate cleaning and sterilization. Valves on fermentation vessels shall be completely steam-sterilizable. Air-vent filters shall be hydrophobic and shall be validated for their designated use.

4.16 Small stocks of substances that have to be measured or weighed during the production process (e.g. buffers) may be kept in the production area, provided that they are not returned to the general stocks. Otherwise, dry materials used to formulate buffers, culture media, etc. should be weighed and put into solution in a contained area outside the purification and aseptic areas in order to minimize particulate contamination of the product.

5. Animal quarters and care
(General requirements for animal quarters, care and quarantine are given in reference 4.)

5.1 Animals are used for the manufacture and control of a number of biological products. Animals shall be accommodated in separate buildings with self-contained ventilation systems. The buildings' design and construction materials shall permit maintenance in a clean and sanitary condition free from insects and vermin. Facilities for animal care shall include isolation units for quarantine of incoming animals and provision for vermin-free food storage. Provision shall also be made for animal inoculation rooms, which shall be separate from the postmortem rooms. There shall be facilities for the disinfection of cages, if possible by steam, and an incinerator for disposing of waste and of dead animals.

5.2 The health status of animals from which starting materials are derived and of those used for quality control and safety testing should be monitored and recorded. Staff employed in animal quarters must be provided with special clothing, changing facilities and showers. Where monkeys are used for the production or quality control of biological products, special consideration is required, as laid down in the revised Requirements for Biological Substances No. 7 (Requirements for Poliomyelitis Vaccine (Oral)) (5).

6. Production

6.1 Standard operating procedures shall be available and maintained up to date for all manufacturing operations.

6.2 Specifications for starting materials should include details of their source, origin and method of manufacture and of the controls applied, in particular microbiological controls, to ensure their suitability for use. Release of a finished product is conditional on satisfactory results being obtained in the tests on starting materials.

6.3 Media and cultures shall be added to fermenters and other vessels under carefully controlled conditions to avoid contamination. Care shall be taken to ensure that vessels are correctly connected when cultures are added.

6.4 If possible, media should be sterilized \textit{in situ}. In-line sterilizing filters for routine addition of gases, media, acids, alkalis, defoaming agents, etc. to fermenters should be used where possible.

6.5 Careful consideration should be given to the validation of sterilization methods.

6.6 When an inactivation process is performed during manufacture, measures should be taken to avoid the risk of cross-contamination between treated and untreated products.
6.7 A wide variety of equipment is used for chromatography; in general such equipment should be dedicated to the purification of one product and should be sterilized or sanitized between batches. Problems of decontamination and purification may arise through repeated use of the same equipment at the same or different stages of processing. The life span of columns and the sterilization method shall be defined. Particular care should be given to monitoring microbial loads and endotoxins.

7. Labelling

7.1 All products shall be clearly identified by labels. The labels used must remain permanently attached to the containers under all storage conditions and an area of the container should be left uncovered to allow inspection of the contents. If the final container is not suitable for labelling (for example a capillary tube), it should be in a labelled package.

7.2 The information given on the label on the container and the label on the package shall be approved by the national control authority.

7.3 The label on the container shall show:

— the name of the drug product;
— a list of the active ingredients and the amount of each present, with a statement of the net contents, e.g. number of dosage units, weight or volume;
— the batch or final lot number assigned by the manufacturer;
— the expiry date;
— recommended storage conditions or handling precautions that may be necessary;
— directions for use, and warnings and precautions that may be necessary;
— the nature and amount of any substance used in the preparation of the biological product that is likely to give rise to an adverse reaction in some recipients;
— the name and address of the manufacturer or the company and/or the person responsible for placing the drug on the market.

7.4 The label on the package shall, in addition to the information shown on the label on the container, show at least the nature and amount of any preservative or additive in the product.

7.5 The leaflet in the package should provide instructions for the use of the product, and mention any contraindications or potential adverse reactions.

8. Lot processing records (protocols) and distribution records

8.1 Processing records of regular production lots must provide a complete account of the manufacturing history of each lot of a biological preparation, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the licensed procedures.

8.2 A separate processing record should be prepared for each lot of biological product, and should include the following information:
8.3 The records shall be of a type approved by the national control authority. They shall be retained for at least two years after the expiry date of a lot or batch of a biological product and be available at all times for inspection by the national control authority.

8.4 Records must make it possible to trace all steps in the manufacture and testing of a lot, and should include records of sterilization of all apparatus and materials used in its manufacture. Distribution records must be kept in a manner that permits rapid recall of any particular lot, if necessary.

9. Quality assurance and quality control

9.1 The quality assurance and/or quality control department should have the following principal duties:

— to prepare detailed instructions for each test and analysis;

— to ensure adequate identification and segregation of test samples to avoid mix-up and cross-contamination;

— to ensure that environmental monitoring and equipment validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;

— to release or reject raw materials and intermediate products, if necessary;

— to release or reject packaging and labelling materials and the final containers in which drugs are to be placed;
— to release or reject each lot of finished preparation;

— to evaluate the adequacy of the conditions under which raw materials, intermediate products, and finished biological preparations are stored;

— to evaluate the quality and stability of finished products and, when necessary, of raw materials and intermediate products;

— to establish expiry dates on the basis of the validity period related to specified storage conditions;

— to establish and, when necessary, revise control procedures and specifications; and

— to be responsible for the examination of returned preparations to determine whether such preparations should be released, reprocessed or destroyed; adequate records of the distribution of such preparations should be maintained.

9.2 A manufacturer's quality control laboratory shall be separated from the production area and ideally should be in a separate building. The control laboratory should be designed and equipped and of such a size as to be a self-contained entity, with adequate provision for the storage of documents and samples, preparation of records and performance of the necessary tests.

9.3 In-process controls play a specially important role in ensuring the consistent quality of biological products. Tests that are crucial for quality control but that cannot be carried out on the finished product shall be performed at an appropriate stage of production.

9.4 Performance of all qualitative and quantitative tests mentioned in the specifications for starting materials may be replaced by a system of certificates issued by the producer of the starting material, provided that:

— there is a history of reliable production,

— the producer is regularly audited, and

— at least one specific identity test is conducted by the manufacturer of the final product.

9.5 Samples of intermediate and final products shall be retained in sufficient amount and under appropriate storage conditions to allow the repetition or confirmation of a batch control. However, reference samples of certain starting materials, e.g. components of culture media, need not necessarily be retained.

9.6 Certain operations require the continuous monitoring of data during a production process, for example monitoring and recording of physical parameters during fermentation.

9.7 Special consideration needs to be given to the quality control requirements arising from production of biological products by continuous culture.

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Investigational pharmaceutical products for clinical trials in humans

1. Introductory note

The legal status of investigational pharmaceutical products for human use varies from country to country; in some of them (e.g. Germany, the United States and others), these products are manufactured and inspected like "normal" licensed pharmaceutical products. In most other countries, however, they are not covered by legal and regulatory provisions in the areas of good manufacturing practice (GMP) inspection, etc.

However, the EC guide on GMP (1) recommends that the principles of GMP should be applied, as appropriate, to the preparation of these products, and the WHO guide on GMP, according to the statement in the general considerations, is applicable to "the preparation of clinical trials supplies" (2, page 18).

2. General considerations

The present guidelines supplement both the WHO guide on GMP and the guidelines on good clinical practice (GCP) for trials on pharmaceutical products (3). The application of the principles of GMP to the preparation of investigational products is necessary for several reasons:

• To assure consistency between and within batches of the investigational product and thus assure the reliability of clinical trials.
To assure consistency between the investigational product and the future commercial product and therefore the relevance of the clinical trial to the efficacy and safety of the marketed product.

To protect subjects of clinical trials from poor-quality products resulting from manufacturing errors (omission of critical steps such as sterilization, contamination and cross-contamination, mix-ups, wrong labelling, etc.), or from starting materials and components of inadequate quality.

To document all changes in the manufacturing process.

In this context, the selection of an appropriate dosage for clinical trials is important. While it is accepted that in early trials the dosage form may be very different from the anticipated final formulation (e.g. a capsule instead of a tablet), in the pivotal Phase III studies it should be similar to the projected commercial presentation; otherwise these trials will not necessarily prove that the marketed product is both efficacious and safe.

If there are significant differences between the clinical and commercial dosage forms, data should be submitted to the registration authorities to demonstrate that the final dosage form is equivalent, in terms of bioavailability and stability, to that used in the clinical trials. Final manufacturing methods must be revalidated following changes in processes, scaling-up, transfer to other manufacturing sites, etc.

This Annex specifically addresses those practices that may be different for investigational products, which are usually not manufactured in accordance with a set routine, and which may possibly be incompletely characterized during the initial stages of clinical development.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

clinical trial
Any systematic study on pharmaceutical products in human subjects, whether in patients or other volunteers, in order to discover or verify the effects of, and/or identify any adverse reaction to, investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

Clinical trials are generally divided into Phases I–IV. It is not possible to draw clear distinctions between these phases, and different opinions about details and methodology do exist. However, the individual phases, based on their purposes as related to the clinical development of pharmaceutical products, can be briefly defined as follows:

**Phase I.** These are the first trials of a new active ingredient or new formulations in humans, often carried out in healthy volunteers. Their purpose is to make a preliminary evaluation of safety, and an initial pharmacokinetic/pharmacodynamic profile of the active ingredient.

**Phase II.** The purpose of these therapeutic pilot studies is to determine activity and to assess the short-term safety of the active ingredient in patients suffering from a disease or condition for which it is intended. The trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. This phase is also concerned with the determination of appropriate dose ranges/regimens and (if possible) the clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

**Phase III:** This phase involves trials in large (and possibly varied) patient groups for the purpose of determining the short- and long-term safety-efficacy balance of formulation(s) of the active ingredient, and assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated, and special
features of the product must be explored (e.g. clinically relevant drug interactions, factors leading to differences in effect, such as age). The trials should preferably be randomized double-blind, but other designs may be acceptable, e.g. long-term safety studies. In general, the conditions under which the trials are conducted should be as close as possible to the normal conditions of use.

Phase IV. In this phase studies are performed after the pharmaceutical product has been marketed. They are based on the product characteristics on which the marketing authorization was granted and normally take the form of post-marketing surveillance, and assessment of therapeutic value or treatment strategies. Although methods may differ, the same scientific and ethical standards should apply to Phase IV studies as are applied in premarketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc., are normally regarded as trials of new pharmaceutical products.

investigational product
Any pharmaceutical product (new product or reference product) or placebo being tested or used as a reference in a clinical trial.

investigator
The person responsible for the trial and for protecting the rights, health and welfare of the subjects in the trial. The investigator must be an appropriately qualified person legally allowed to practise medicine/dentistry.

monitor
A person appointed by, and responsible to, the sponsor for monitoring and reporting the progress of the trial and for the verification of data.

order
An instruction to process, package and/or ship a certain number of units of an investigational product.

pharmaceutical product
For the purpose of this Annex, this term is defined in the same way as in the WHO guidelines on GCP (3), i.e. as any substance or combination of substances which has a therapeutic, prophylactic or diagnostic purpose, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

product specification file(s)
Reference file(s) containing all the information necessary to draft the detailed written instructions on processing, packaging, labelling, quality control testing, batch release, storage conditions and shipping.

protocol
A document which gives the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. It should be dated and signed by the investigator/institution involved and the sponsor, and can, in addition, function as a contract.

shipping/dispatch
The assembly, packing for shipment, and sending of ordered medicinal products for clinical trials.

sponsor
An individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator independently initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

4. Quality assurance
Quality assurance of pharmaceutical products has been defined and discussed in detail in the guide on GMP (2, pages 25–26).

The quality of dosage forms in Phase III clinical studies should be characterized and assured at the same level as for routinely manufactured products. The quality assurance system, designed, established and verified by the manufacturer, should be described in writing, taking into account the GMP principles to the extent that they are applicable to the operations in question. This system should also cover the interface between the manufacture and the trial site (e.g. shipment, storage, occasional additional labelling).

5. Validation

(For additional advice on validation, see Validation of manufacturing processes, pp. 53–71.)

Some of the production processes for investigational products that have not received marketing authorization may not be validated to the extent necessary for a routine production operation. The product specifications and manufacturing instructions may vary during development. This increased complexity in the manufacturing operations requires a highly effective quality assurance system.

For sterile products, there should be no reduction in the degree of validation of sterilizing equipment required. Validation of aseptic processes presents special problems when the batch size is small, since the number of units filled may be not adequate for a validation exercise. Filling and sealing, which is often done by hand, can compromise the maintenance of sterility. Greater attention should therefore be given to environmental monitoring.

6. Complaints

The conclusions of any investigation carried out in response to a complaint should be discussed between the manufacturer and the sponsor (if different) or between the persons responsible for manufacture and those responsible for the relevant clinical trial in order to assess any potential impact on the trial and on the product development, to determine the cause, and to take any necessary corrective action.

7. Recalls

Recall procedures should be understood by the sponsor, investigator and monitor in addition to the person(s) responsible for recalls, as described in the guide on GMP (2, pages 28–29).

8. Personnel

Although it is likely that the number of staff involved will be small, people should be separately designated as responsible for production and quality control. All production operations should be carried out under the control of a clearly identified responsible person. Personnel concerned with development, involved in production and quality control, need to be instructed in the principles of GMP.

9. Premises and equipment

During the manufacture of investigational products, different products may be handled in the same premises and at the same time, and this reinforces the need to eliminate all risks of contamination, including cross-contamination. Special attention should be paid to line clearance in order to avoid mix-ups. Validated cleaning procedures should be followed to prevent cross-contamination.

For the production of the particular products referred to in section 11.20 of the guide on GMP (2, page 38), campaign working may be acceptable in place of dedicated and self-contained facilities. Because the toxicity of the materials may not be fully known, cleaning is of particular importance; account should be taken of the solubility of the product and excipients in various cleaning agents.

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10. Materials

Starting materials

The consistency of production may be influenced by the quality of the starting materials. Their physical, chemical and, when appropriate, microbiological properties should therefore be defined, documented in their specifications, and controlled. Existing compendial standards, when available, should be taken into consideration. Specifications for active ingredients should be as comprehensive as possible, given the current state of knowledge. Specifications for both active and non-active ingredients should be periodically reassessed.

Detailed information on the quality of active and non-active ingredients, as well as of packaging materials, should be available so as to make it possible to recognize and, as necessary, allow for any variation in production.

Chemical and biological reference standards for analytical purposes

Reference standards from reputable sources (WHO or national standards) should be used, if available; otherwise the reference substance(s) for the active ingredient(s) should be prepared, tested and released as reference material(s) by the producer of the investigational pharmaceutical product, or by the producer of the active ingredient(s) used in the manufacture of that product.

Principles applicable to reference products for clinical trials

In studies in which an investigational product is compared with a marketed product, steps should be taken to ensure the integrity and quality of the reference products (final dosage form, packaging materials, storage conditions, etc.). If significant changes are to be made in the product, data should be available (e.g. on stability, comparative dissolution) that demonstrate that these changes do not influence the original quality characteristics of the product.

11. Documentation

Specifications (for starting materials, primary packaging materials, intermediate and bulk products and finished products), master formulae, and processing and packaging instructions may be changed frequently as a result of new experience in the development of an investigational product. Each new version should take into account the latest data and include a reference to the previous version so that traceability is ensured. Rationales for changes should be stated and recorded.

Batch processing and packaging records should be retained for at least 2 years after the termination or discontinuance of the clinical trial, or after the approval of the investigational product.

Order

The order may request the processing and/or packaging of a certain number of units and/or their shipping. It may only be given by the sponsor to the manufacturer of an investigational product. It should be in writing (though it may be transmitted by electronic means), precise enough to avoid any ambiguity and formally authorized, and refer to the approved product specification file (see below).

Product specification file(s)

A product specification file (or files) should contain the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release, storage conditions and/or shipping. It should indicate who has been designated or trained as the authorized person responsible for the release of batches (see reference 2, page 18). It should be continuously updated while at the same time ensuring appropriate traceability to the previous versions.
Specifications

In developing specifications, special attention should be paid to characteristics which affect the efficacy and safety of pharmaceutical products, namely:

- The accuracy of the therapeutic or unitary dose: homogeneity, content uniformity.
- The release of active ingredients from the dosage form: dissolution time, etc.

In addition, the package size should be suitable for the requirements of the trial.

Specifications may be subject to change as the development of the product progresses. Changes should, however, be made in accordance with a written procedure authorized by a responsible person and clearly recorded. Specifications should be based on all available scientific data, current state-of-the-art technology, and the regulatory and pharmacopoeial requirements.

Master formulae and processing instructions

These may be changed in the light of experience, but allowance must be made for any possible repercussions on stability and, above all, on bioequivalence between batches of finished products. Changes should be made in accordance with a written procedure, authorized by a responsible person and clearly recorded.

It may sometimes not be necessary to produce master formulae and processing instructions, but for every manufacturing operation or supply there should be clear and adequate written instructions and written records. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture.

Packaging instructions

The number of units to be packaged should be specified before the start of the packaging operations. Account should be taken of the number of units necessary for carrying out quality controls and of the number of samples from each batch used in the clinical trial to be kept as a reference for further rechecking and control. A reconciliation should be carried out at the end of the packaging and labelling process.

Labelling instructions

The information presented on labels should include:

- The name of the sponsor.
- A statement: “for clinical research use only”.
- A trial reference number.
- A batch number.
- The patient identification number.

(This is not necessarily inserted at the manufacturing facility but may be added at a later stage.)
• The storage conditions.

• The expiry date (month/year) or a retest date.

Additional information may be displayed in accordance with the order (e.g. dosing instructions, treatment period, standard warnings). When necessary for blinding purposes, the batch number may be provided separately (see also "Blinding operations" on p. 137). A copy of each type of label should be kept in the batch packaging record.

Processing and packaging batch records

Processing and packaging batch records should be kept in sufficient detail for the sequence of operations to be accurately traced. They should contain any relevant remarks which increase existing knowledge of the product, allow improvements in the manufacturing operations, and justify the procedures used.

Coding (or randomization) systems

Procedures should be established for the generation, distribution, handling and retention of any randomization code used in packaging investigational products.

A coding system should be introduced to permit the proper identification of "blinded" products. The code, together with the randomization list, must permit proper identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation. The coding system must permit determination without delay in an emergency situation of the identity of the actual treatment product received by individual subjects.

12. Production

Products intended for use in clinical trials (late Phase II and Phase III studies) should as far as possible be manufactured at a licensed facility, e.g.:

• A pilot plant, primarily designed and used for process development.

• A small-scale facility (sometimes called a "pharmacy") separate both from the company's pilot plant and from routine production.

(Note: Some manufacturers use the term "pharmacy" to designate other types of premises, e.g. areas where starting materials are dispensed and batches compounded.)

• A larger-scale production line assembled to manufacture materials in larger batches, e.g. for late Phase III trials and first commercial batches.

• The normal production line used for licensed commercial batches, and sometimes for the production of investigational pharmaceutical products if the number, e.g. of ordered ampoules, tablets or other dosage forms, is large enough.

The relation between the batch size for investigational pharmaceutical products manufactured in a pilot plant or small-scale facility to the planned full-size batches may vary widely depending on the pilot plant or "pharmacy" batch size demanded and the capacity available in full-size production.

The present guidelines are applicable to licensed facilities of the first and second types. It is easier to assure compliance with GMP in facilities of the second type, since processes are kept constant in the course of production and are not normally changed for the purpose of process development. Facilities of the remaining types should be subject to all GMP rules for pharmaceutical products.
Administratively, the manufacturer has yet another possibility, namely to contract out the preparation of investigational products. Technically, however, the licensed facility will be of one of the above-mentioned types. The contract must then clearly state, inter alia, the use of the pharmaceutical product(s) in clinical trials. Close cooperation between the contracting parties is essential.

Manufacturing operations

Validated procedures may not always be available during the development phase, which makes it difficult to know in advance what critical parameters and in-process controls would help to control these parameters. Provisional production parameters and in-process controls may then usually be deduced from experience with analogous products. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continuously to the experience gained in production.

For sterile investigational products, assurance of sterility should be no less than for licensed products. Cleaning procedures should be appropriately validated and designed in the light of the incomplete knowledge of the toxicity of the investigational product. Where processes such as mixing have not been validated, additional quality control testing may be necessary.

Packaging and labelling

The packaging and labelling of investigational products are likely to be more complex and more liable to errors (which are also harder to detect) when "blinded" labels are used than for licensed products. Supervisory procedures such as label reconciliation, line clearance, etc., and the independent checks by quality control staff should accordingly be intensified.

The packaging must ensure that the investigational product remains in good condition during transport and storage at intermediate destinations. Any opening of, or tampering with, the outer packaging during transport should be readily discernible.

Blinding operations

In the preparation of "blinded" products, in-process control should include a check on the similarity in appearance and any other required characteristics of the different products being compared.

13. Quality control

As processes may not be standardized or fully validated, end-product testing is more important in ensuring that each batch meets its specification.

Product release is often carried out in two stages, before and after final packaging:

1. Bulk product assessment: this should cover all relevant factors, including production conditions, the results of in-process testing, a review of manufacturing documentation and compliance with the product specification file and the order.

2. Finished product assessment: this should cover, in addition to the bulk product assessment, all relevant factors, including packaging conditions, the results of in-process testing, a review of packaging documentation and compliance with the product specification file and the order.

(Note: This practice also exists at certain large companies with regard to licensed products.)
When necessary, quality control should also be used to verify the similarity in appearance and other physical characteristics, odour, and taste of "blinded" investigational products.

Samples of each batch of product should be retained in the primary container used for the study or in a suitable bulk container for at least 2 years after the termination or completion of the relevant clinical trial. If the sample is not stored in the pack used for the study, stability data should be available to justify the shelf-life in the pack used.

14. Shipping, returns, and destruction

The shipping, return and destruction of unused products should be carried out in accordance with the written procedures laid down in the protocol. All unused products sent outside the manufacturing plant should, as far as possible, either be returned to the manufacturer or destroyed in accordance with clearly defined instructions.

Shipping

Investigational products should be shipped in accordance with the orders given by the sponsor.

A shipment is sent to an investigator only after the following two-step release procedure: (i) the release of the product after quality control ("technical green light"); and (ii) the authorization to use the product, given by the sponsor ("regulatory green light"). Both releases should be recorded.

The sponsor should ensure that the shipment will be received and acknowledged by the correct addressee as stated in the protocol.

A detailed inventory of the shipments made by the manufacturer should be maintained, and should make particular mention of the addressee's identification.

Returns

Investigational products should be returned under agreed conditions defined by the sponsor, specified in written procedures, and approved by authorized staff members.

Returned investigational products should be clearly identified and stored in a dedicated area. Inventory records of returned medicinal products should be kept. The responsibilities of the investigator and the sponsor are dealt with in greater detail in the WHO guidelines on GCP (3).

Destruction

The sponsor is responsible for the destruction of unused investigational products, which should therefore not be destroyed by the manufacturer without prior authorization by the sponsor. Destruction operations should be carried out in accordance with environmental safety requirements.

Destruction operations should be recorded in such a manner that all operations are documented. The records should be kept by the sponsor.

If requested to destroy products, the manufacturer should deliver a certificate of destruction or a receipt for destruction to the sponsor. These documents should permit the batches involved to be clearly identified.

References

Herbal medicinal products

1. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

constituents with known therapeutic activity
Substances or groups of substances which are chemically defined and known to contribute to the therapeutic activity of a plant material or of a preparation.

herbal medicinal product
Medicinal product containing, as active ingredients, exclusively plant material and/or preparations. This term is generally applied to a finished product. If it refers to an unfinished product, this should be indicated.

markers
Constituents of a medicinal plant material which are chemically defined and of interest for control purposes. Markers are generally employed when constituents of known therapeutic activity are not found or are uncertain, and may be used to calculate the quantity of plant material or preparation in the finished product. When starting materials are tested, markers in the plant material or preparation must be determined quantitatively.

medicinal plant
A plant (wild or cultivated) used for medicinal purposes.

medicinal plant material (crude plant material, vegetable drug)
Medicinal plants or parts thereof collected for medicinal purposes.

plant preparations
Comminuted or powdered plant material, extracts, tinctures, fatty or essential oils, resins, gums, balsams, expressed juices, etc., prepared from plant material, and preparations whose production involves a fractionation, purification or concentration process, but excluding chemically defined isolated constituents. A plant preparation can be regarded as the active ingredient whether or not the constituents having therapeutic activities are known.

2. General

Unlike conventional pharmaceutical products, which are usually prepared from synthetic materials by means of reproducible manufacturing techniques and procedures, herbal medicinal products are prepared from material of plant origin which may be subject to contamination and deterioration, and may vary in composition and properties. Furthermore, in the manufacture and quality control of herbal medicinal products, procedures and techniques are often used which are substantially different from those employed for conventional pharmaceutical products.
The control of the starting materials, storage and processing assumes particular importance because of the often complex and variable nature of many herbal medicinal products and the number and the small quantity of defined active ingredients present in them.

3. Premises

Storage areas

Medicinal plant materials should be stored in separate areas. The storage area should be well ventilated and equipped in such a way as to protect against the entry of insects or other animals, especially rodents. Effective measures should be taken to limit the spread of animals and microorganisms introduced with the plant material and to prevent cross-contamination. Containers should be located in such a way as to allow free air circulation.

Special attention should be paid to the cleanliness and good maintenance of the storage areas, particularly when dust is generated.

The storage of plants, extracts, tinctures and other preparations may require special conditions of humidity and temperature or protection from light; steps should be taken to ensure that these conditions are provided and monitored.

Production area

To facilitate cleaning and to avoid cross-contamination whenever dust is generated, special precautions should be taken during the sampling, weighing, mixing and processing of medicinal plants, e.g. by the use of dust extraction or dedicated premises.

4. Documentation

Specifications for starting materials

In addition to the data called for in sections 14 and 18 of “Good manufacturing practices for pharmaceutical products”(1), the specifications for medicinal plant materials should as far as possible include the following:

- The botanical name, with reference to the authors.
- Details of the source of the plant (country or region of origin, and where applicable, method of cultivation, time of harvesting, collection procedures, possible pesticides used, etc.).
- Whether the whole plant or only a part is used.
- When dried plant is purchased, the drying system.
- A description of the plant material based on visual and/or microscopical inspection.
- Suitable identification tests including, where appropriate, identification tests for known active ingredients or markers.
- The assay, where appropriate, of constituents of known therapeutic activity or markers.
- Suitable methods for the determination of possible pesticide contamination and the acceptable limits for such contamination.
• The results of tests for toxic metals and for likely contaminants, foreign materials, and adulterants.

• The results of tests for microbial contamination and aflatoxins.

Any treatment used to reduce fungal/microbial contamination or other infestation should be documented. Instructions on the conduct of such procedures should be available and should include details of the process, tests and limits for residues.

Qualitative and quantitative requirements

These should be expressed in the following ways:

1. Medicinal plant material: (a) the quantity of plant material must be stated; or (b) the quantity of plant material may be given as a range, corresponding to a defined quantity of constituents of known therapeutic activity.

Example:

Name of active ingredient
Sennae folium

Quantity
(a) 900 mg or (b) 830–1000 mg, corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B

2. Plant preparation:
(a) the equivalent quantity or the ratio of plant material to plant preparation must be stated (this does not apply to fatty or essential oils); or
(b) the quantity of the plant preparation may be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity (see example).

The composition of any solvent or solvent mixture used and the physical state of the extract must be indicated.

If any other substance is added during the manufacture of the plant preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substance(s) must be described as "other ingredients" and the genuine extract as the "active ingredient".

Example:

Name of active ingredient
Sennae folium

Quantity
(a) 125 mg ethanolic extract (8:1) or 125 mg ethanolic extract, equivalent to 1000 mg of Sennae folium or (b) 100–130 mg ethanolic extract (8:1), corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B

Other ingredient
Dextrin 20–50 mg

Specifications for the finished product

The control tests for the finished product must be such as to allow the qualitative and quantitative determination of the active ingredients. If the therapeutic activity of constituents is known, this must be specified and determined quantitatively. When this is not feasible, specifications must be based on the determination of markers.
If either the final product or the preparation contains several plant materials and a quantitative determination of each active ingredient is not feasible, the combined content of several active ingredients may be determined. The need for such a procedure must be justified.

Processing instructions

The processing instructions should list the different operations to be performed on the plant material, such as drying, crushing and sifting, and also include the temperatures required in the drying process, and the methods to be used to control fragments or particle size. Instructions on sieving or other methods of removing foreign materials should also be given. Details of any process, such as fumigation, used to reduce microbial contamination, together with methods of determining the extent of such contamination, should also be given.

For the production of plant preparations, the instructions should specify any vehicle or solvent that may be used, the times and temperatures to be observed during extraction, and any concentration methods that may be required.

5. Quality control

The personnel of quality control units should have particular expertise in herbal medicinal products to be able to carry out identification tests, and check for adulteration, the presence of fungal growth or infestations, lack of uniformity in a consignment of medicinal plant materials, etc.

Reference samples of plant materials must be available for use in comparative tests, e.g. visual and microscopic examination and chromatography.

Sampling

Sampling must be carried out with special care by personnel with the necessary expertise since medicinal plant materials are composed of individual plants or parts of plants and are therefore heterogeneous to some extent.

Further advice on sampling, visual inspection, analytical methods, etc., is given in *Quality control methods for medicinal plant materials* (2).

6. Stability tests

It will not be sufficient to determine the stability only of the constituents with known therapeutic activity, since plant materials or plant preparations in their entirety are regarded as the active ingredient. It must also be shown, as far as possible, e.g. by comparisons of chromatograms, that the other substances present are stable and that their content as a proportion of the whole remains constant.

If a herbal medicinal product contains several plant materials or preparations of several plant materials, and it is not feasible to determine the stability of each active ingredient, the stability of the product should be determined by methods such as chromatography, widely used assay methods, and physical and sensory or other appropriate tests.

References


Footnotes


2 Parts One and Two, Part Three, section 18, and the Introductory note, General considerations and Glossary of Good manufacturing practices for pharmaceutical products are reproduced elsewhere in this volume (see pp. 6–13, 13–45, 46–53, 75–83).


