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WHO good manufacturing practices: specific pharmaceutical products

Sterile pharmaceutical products¹

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Introductory note

This document is a revision of section 17 of Part Three of “Good manufacturing practices for pharmaceutical products” (1), which emphasizes specific points for the manufacture of sterile preparations to minimize the risks of microbiological, particulate and pyrogen contamination. It is not exhaustive in character, and some technical requirements may change in line with developments in the field of good manufacturing practices (GMP) or advances in engineering design.

1. General considerations

1.1 The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency.

¹ Good manufacturing practices for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 6 (WHO Technical Report Series, No. 902).

1.2 The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within a clean area. These areas are classified into four grades (see section 4.1).

1.3 Manufacturing operations are divided here into two categories: first, those where the product is terminally sterilized, and second, those which are conducted aseptically at some or all stages.

2. Quality control

2.1 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 that part of the load that is potentially the coolest.

2.2 The sterility of the finished product is ensured by validation of the sterilization cycle in the case of terminally sterilized products, and by “media-fills” runs for aseptically processed products. Batch processing records and, in the case of aseptic processing, environmental quality records, should be examined in conjunction with the results of the sterility tests. The sterility test procedure should be validated for a given product. Pharmacopoeial methods must be used for the validation and performance of the sterility test.

2.3 For injectable products, the water for injection and the intermediate and finished products should be monitored 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 an approved monograph for the finished product. When a sample fails a test, the cause of such failure should be investigated and remedial action taken where necessary.

3. Sanitation

3.1 The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with an approved written programme. 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.

Table 1. Limits for microbiological contamination^a

Grade ^b	Air sample (CFU/m ³)	Settle plates (diameter 90 mm) (CFU/4 hours) ^c	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	<3	<3	<3	<3
B	10	5	5	5
C	100	50	25	—
D	200	100	50	—

^aThese are average values. The grades are defined in section 4.1.

^bThe airborne particulate classification for the four grades is given in Table 2.

^cIndividual settle plates may be exposed for less than 4 hours.

3.2 Disinfectants and detergents should be monitored for microbiological contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized. Disinfectants and detergents used in grade A and B areas (see section 4.1) should be sterilized before use.

3.3 In order to control the microbiological cleanliness of the various grades in operation, the clean areas should be monitored. Where aseptic operations are performed, monitoring should be frequent and methods such as settle plates, and volumetric air and surface sampling (e.g. swabs and contact plates) should be used. The zones should not be contaminated through the sampling methods used in the operations. The results of monitoring should be considered when batch documentation for release of the finished product is reviewed. Both surfaces and personnel should be monitored after critical operations.

3.4 Levels (limits) of detection of microbiological contamination should be established for alert and action purposes, and for monitoring the trends in air quality in the facility. Limits expressed in colony-forming units (CFU) for the microbiological monitoring of clean areas in operation are given in Table 1. The sampling methods and numerical values included in the table are not intended to represent specifications, but are for information only.

4. Manufacture of sterile preparations

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

In order to meet “in operation” conditions, these areas should be designed to reach certain specified air-cleanliness levels in the “at rest” occupancy state. This latter state is the condition where the installation is complete, and production equipment has been installed and is operating, but no operating personnel

Table 2. Airborne particulate classification for manufacture of sterile pharmaceutical preparations

Grade	At rest		In operation	
	Maximum number of particles permitted/m ³		Maximum number of particles permitted/m ³	
	0.5–5.0µm	>5.0µm	0.5–5.0µm	>5.0µm
A	3 500	0	3 500	0
B	3 500	0	350 000	2 000
C	350 000	2 000	3 500 000	20 000
D	3 500 000	20 000	Not defined	Not defined

are present. The “in operation” state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel are present.

For the manufacture of sterile pharmaceutical preparations, four grades are distinguished here, as follows:

- *Grade A*: The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are provided by a laminar-airflow workstation. Laminar-airflow systems should provide a homogeneous air speed of approximately 0.45 m/s \pm 20% (guidance value) at the working position.
- *Grade B*: In aseptic preparation and filling, the background environment for the grade A zone.
- *Grades C and D*: Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classification for the four grades is given in Table 2.

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

- In order to reach the B, C and D air grades, the number of air changes should be appropriate for the size of the room and the equipment and personnel present in it. At least 20 air changes per hour are usually required for a room with a good airflow pattern and appropriate high-efficiency particulate air (HEPA) filters.
- Detailed information on methods for determining the microbiological and particulate cleanliness of air, surfaces, etc. is not given here. Reference should be made to other guidelines published in compendia such as the European, Japanese or United States pharmacopoeias, or in documents issued by the European Committee for Standardization and the International Organization for Standardization (ISO).

Table 3. Comparison of different airborne particulate classification systems for clean areas^a

WHO (GMP)	United States (209E)	United States (customary)	ISO/TC (209)	EEC (GMP)
Grade A	M 3.5	Class 100	ISO 5	Grade A
Grade B	M 3.5	Class 100	ISO 5	Grade B
Grade C	M 5.5	Class 10 000	ISO 7	Grade C
Grade D	M 6.5	Class 100 000	ISO 8	Grade D

EEC: European Commission; ISO/TC: International Organization for Standardization Technical Committee.

^aSource: references 1–4.

The different airborne particulate classification systems for clean areas are shown in Table 3.

4.2 The particulate conditions given in Table 2 for the “at rest” state should be achieved in the absence of the operating personnel after a short “clean-up” period of about 15–20 minutes (guidance value), after completion of the operations. The particulate conditions given in Table 2 for grade A “in operation” should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, owing to the generation of particles or droplets from the product itself.

4.3 In order to control the particulate cleanliness of the various clean areas during operation, they should be monitored.

4.4 Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, the appropriate corrective actions should be taken, as prescribed in the operating procedures.

4.5 The area grades as specified in sections 4.6–4.14 must be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g. sterile media fills). The determination of an appropriate process area environment and a time limit should be based on the microbiological contamination (bioburden) found.

Terminally sterilized products

4.6 Components and most products should be prepared in at least a grade D environment in order to give low microbial and particulate counts, suitable for filtration and sterilization. Where the product is at unusual risk of microbial contamination (e.g. because it actively supports microbial growth, must be held

for a long period before sterilization, or is necessarily not processed mainly in closed vessels), the preparation should generally be done in a grade C environment.

4.7 The filling of products for terminal sterilization should generally be done in at least a grade C environment.

4.8 Where the product is at unusual risk of contamination from the environment (e.g. because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing), the filling should be done in a grade A zone with at least a grade C background.

4.9 The preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilization.

Aseptic preparation

4.10 Components after washing should be handled in at least a grade D environment. The handling of sterile starting materials and components, unless subjected to sterilization or filtration through a microorganism-retaining filter later in the process, should be done in a grade A environment with a grade B background.

4.11 The preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not sterile filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.

4.12 The handling and filling of aseptically prepared products, as well as the handling of exposed sterile equipment, should be done in a grade A environment with a grade B background.

4.13 The transfer of partially closed containers, as used in freeze-drying, should, before stoppering is completed, be done either in a grade A environment with a grade B background or in sealed transfer trays in a grade B environment.

4.14 The preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment with a grade B background when the product is exposed and is subsequently filtered.

Processing

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

4.16 Preparations containing live microorganisms should not be made or containers filled in areas used for the processing of other pharmaceutical products; however, vaccines consisting 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.

4.17 The validation of aseptic processing should include simulating the process using a nutrient medium. The form of the nutrient medium used should generally be equivalent to the dosage form of the product. The process-simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. Consideration should be given to simulation of the worst expected condition. The process-simulation test should be repeated at defined intervals and after any significant modification to the equipment and process. The number of containers used for a medium fill should be sufficient to ensure a valid evaluation. For small batches, the number of containers for the medium fill should be at least equal to the size of the product batch.

4.18 Care should be taken to ensure that any validation does not compromise the processes.

4.19 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.

4.20 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, so as 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.

4.21 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.

4.22 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.

4.23 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.

4.24 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.

4.25 Any gas that is used to purge a solution or blanket a product should be passed through a sterilizing filter.

4.26 The bioburden of products should be monitored before sterilization. There should be a working limit on the contamination of products 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 microbiological air filters.

4.27 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 prevent the introduction of contamination (e.g. triple wrapping) may be acceptable in some circumstances.

4.28 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.

5. Sterilization

5.1 Whenever possible, products intended to be sterile should preferably be terminally sterilized by heat in their final container. Where it is not possible to carry out terminal sterilization by heating due to the instability of a formulation, a decision should be taken to use an alternative method of terminal sterilization following filtration and/or aseptic processing.

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

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

5.4 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.

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

5.6 For effective sterilization, the whole of the material should be subjected to the required treatment and the process should be designed to ensure that this is achieved.

5.7 Biological indicators should be considered only as an additional method of monitoring the sterilization process. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If they are used, strict precautions should be taken to avoid any transfer of microbiological contamination from them.

5.8 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 batch is, in fact, sterile.

5.9 Sterilization records should be available for each sterilization run. They should be approved as part of the batch-release procedure.

6. Terminal sterilization

Sterilization by heat

6.1 Each heat-sterilization cycle should be recorded by means of appropriate equipment of suitable accuracy and precision, e.g. on a time/temperature chart with a suitably large scale. The temperature should be recorded by 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.

6.2 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.

6.3 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.

Sterilization by moist heat

6.4 Sterilization by moist heat (heating in an autoclave) is suitable only for water-wettable materials and aqueous formulations. 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 should be 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.

6.5 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows the removal of air and the 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.

6.6 Care should be taken to ensure that the 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

6.7 Sterilization by dry heat may be suitable for non-aqueous liquids or dry powder products. The process used 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 (e.g. an HEPA filter). Where sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins will be required as part of the validation.

Sterilization by radiation

6.8 Sterilization by radiation 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.

6.9 If sterilization by radiation is carried out by an outside contractor, the manufacturer is responsible for ensuring that the requirements of section 6.8 are met, and that the sterilization process is validated. The responsibilities of the radiation plant operator (e.g. for using the correct dose) should also be specified.

6.10 During the sterilization procedure, the radiation dose should be measured. For this purpose, the dosimeters used must be independent of the dose rate and must provide 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 employed, they should be used within the time-limit of their calibration. Dosimeter absorbances should be read shortly 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.

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

6.12 Handling procedures should prevent any misidentification of 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.

6.13 The total radiation dose should be administered within a predetermined period of time.

Sterilization by gases and fumigants

6.14 This method of sterilization should only be used for products where there is no suitable alternative.

6.15 Various gases and fumigants may be used for sterilization (e.g. ethylene oxide, hydrogen peroxide vapour). 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 concerned. These limits should be incorporated in the specifications.

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

6.17 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. This requirement should be balanced against the need to minimize the waiting time before sterilization.

6.18 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.

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

6.20 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 on a chart throughout the cycle. The records should form part of the batch record.

6.21 After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow concentrations of residual gas and reaction products to fall to their prescribed levels. This process should be validated.

7. Aseptic processing and sterilization by filtration

7.1 The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which has been sterilized by one of the above methods (see sections 5 and 6).

7.2 The operating conditions should be such as to prevent microbial contamination.

7.3 In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to: (a) the environment; (b) the personnel; (c) the critical surfaces; (d) the container/closure sterilization and transfer procedures; (e) the maximum holding period of the product before filling into the final container; and (f) the sterilizing filter.

7.4 Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size $0.22\mu\text{m}$ (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.

7.5 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.

7.6 The fibre-shedding characteristics of filters should be minimal (virtually zero). Asbestos-containing filters must not be used under any circumstances.

7.7 The integrity of the filter should be checked by an appropriate method such as a bubble-point, diffusive-flow or pressure-hold test, immediately after 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 these values should be noted and investigated. The results of these checks should be recorded in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals. Consideration should be given to increased monitoring of filter integrity in processes that involve harsh conditions, e.g. the circulation of high-temperature air.

7.8 The same filter should not be used for more than 1 working day unless such use has been validated.

7.9 The filter should not affect the product either by removing ingredients from it or by releasing substances into it.

8. Personnel

8.1 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 such areas as far as possible.

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

8.3 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.

8.4 High standards of personal hygiene and cleanliness are essential, and personnel involved in the manufacture of sterile preparations should be instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. The action to be taken in respect of personnel who might be introduc-

ing undue microbiological hazards should be decided by a designated competent person.

8.5 Outdoor clothing should not be brought into clean areas, and personnel entering changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a written procedure designed to minimize the contamination of clean area clothing or the carry-through of contaminants to clean areas.

8.6 Wrist-watches and jewellery should not be worn in clean areas, and cosmetics that can shed particles should not be used.

8.7 The clothing worn and its quality should be appropriate for the process and the grade of the working area (workplace). It should be worn in such a way as to protect the product from contamination. The clothing required for each grade is as follows:

- *Grade D.* The hair and, where relevant, beard and moustache should be covered. Protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination from outside the clean area.
- *Grade C.* The hair and, where relevant, beard and moustache 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.
- *Grades A/B.* Headgear should totally enclose the hair and, where relevant, beard and moustache. A single or two-piece trouser suit, gathered at the wrists and with a high neck, should be worn. The headgear should be tucked into the neck of the suit. A face mask should be worn to prevent the shedding of droplets. Appropriate, sterilized, non-powdered rubber or plastic gloves and sterilized or disinfected footwear should be worn. Trouser-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.

8.8 Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B room, clean sterilized or adequately sanitized protective garments should be provided at each work session, or at least once a day if monitoring results justify this. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session. The use of disposable clothing may be necessary.

8.9 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.

9. Premises

9.1 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.

9.2 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.

9.3 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.

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

9.5 Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean.

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

9.7 Changing rooms should be designed as airlocks and used to separate the different stages of changing, thus minimizing particulate and microbiological 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 necessary. Hand-washing facilities should be provided only in the changing rooms, not in areas where aseptic work is done.

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

9.9 A filtered air supply should be used to maintain a positive pressure and an airflow relative to surrounding areas of a lower grade under all operational conditions; it should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of approximately 10–15 pascals (guidance

value). Particular attention should be paid to the protection of the zone of greatest risk, i.e. 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 where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. The decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations.

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

9.11 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.

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

10. Equipment

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

10.2 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.

10.3 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 resterilized after complete reassembly, wherever possible.

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

10.5 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.

10.6 Water-treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Consideration should be given to including a testing programme in the maintenance of a water system. Water for injection should be produced, stored and distributed in a manner which prevents the growth of microorganisms, e.g. by constant circulation at a temperature above 70°C or not more than 4°C.

11. Finishing of sterile products

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

11.2 Containers sealed under vacuum should be sampled and the samples tested, after an appropriate predetermined period, to ensure that the vacuum has been maintained.

11.3 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. The results should be recorded.

References

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Biological products¹

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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

¹ Good manufacturing practices for biological products. In: *WHO Expert Committee on Biological Standardization. Forty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 822) and *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1993, Annex 3 (WHO Technical Report Series, No. 834).

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 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 care¹

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.

¹ General requirements for animal quarters, care and quarantine are given in reference 4.

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 *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:

- the name and dosage of the product;
- the date of manufacture;
- the lot identification number;
- the complete formulation of the lot, including identification of seed or starting materials;
- the batch number of each component used in the formulation;
- the yield obtained at different stages of manufacture of the lot;
- a duly signed record of each step followed, precautions taken and special observations made throughout the manufacture of the lot;
- a record of all in-process control tests and of the results obtained;
- a specimen of the label;
- identification of packaging materials, containers and closures used;
- a dated signature of the expert responsible for approving the manufacturing operations;
- an analytical report, dated and signed by the responsible expert, showing whether the lot complies with the specifications described in the standard operating procedure registered with the national control authority;
- a record of the decision regarding the release or rejection of the lot by the quality control department and, if the lot is rejected, a record of its disposal or utilization.

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.

Authors

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Investigational pharmaceutical products for clinical trials in humans¹

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:

¹ Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report Series, No. 863).

- 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. Validation¹

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 not be 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

¹ For additional advice on validation, see *Validation of manufacturing processes*, pp. 53–71.

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.

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.
- The estimated stability, if necessary, under accelerated conditions, the preliminary storage conditions and the shelf-life of the product.¹

¹ See *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 1.* Geneva, World Health Organization, 1997:46–61.

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.¹
- The storage conditions.
- The expiry date (month/year) or a retest date.

¹ This is not necessarily inserted at the manufacturing facility but may be added at a later stage.

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. 123). 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”)¹ separate both from the company’s pilot plant and from routine production.
- 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 and the planned full-size

¹ Some manufacturers use the term “pharmacy” to designate other types of premises, e.g. areas where starting materials are dispensed and batches compounded.

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 are the critical parameters and what 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

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.

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.

¹ This practice also exists at certain large companies with regard to licensed products.

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

1. *Good manufacturing practice for medicinal products in the European Community*. Brussels, Commission of the European Communities, 1992.
2. Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992:14–79 (WHO Technical Report Series, No. 823).
3. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. In: *The use of essential drugs. Model List of Essential Drugs (Eighth List). Sixth report of the WHO Expert Committee*. Geneva, World Health Organization, 1995:97–137 (WHO Technical Report Series, No. 850).

Herbal medicinal products^{1,2}

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.

¹ Guidelines for the assessment of herbal medicines are provided in *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 1*. Geneva, World Health Organization, 1997:31–37.

² Good manufacturing practices: supplementary guidelines for the manufacture of herbal medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 8 (WHO Technical Report Series, No. 863).

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:

<i>Name of active ingredient</i>	<i>Quantity</i>
Sennae folium	(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:

<i>Name of active ingredient</i>	<i>Quantity</i>
Sennae folium	(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
<i>Other ingredient</i>	
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

1. WHO Expert Committee on Specifications for Pharmaceutical Preparations. *Thirty-second report*. Geneva, World Health Organization, 1992:44–52; 75–76 (WHO Technical Report Series, No. 823).
2. *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1992 (unpublished document WHO/PHARM/92.559/rev. 1; available on request from Health Technology and Pharmaceuticals, World Health Organization, 1211 Geneva 27, Switzerland).

Radiopharmaceutical products¹

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1. Scope of these guidelines

These guidelines are intended to complement those already available for pharmaceutical products (1,2) as well as those for sterile pharmaceutical products (3).

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

- The preparation of radiopharmaceuticals in hospital radiopharmacies.
- The preparation of radiopharmaceuticals in centralized radiopharmacies.
- The production of radiopharmaceuticals in nuclear centres and institutes or by industrial manufacturers.
- The preparation and production of radiopharmaceuticals in positron emission tomography (PET) centres.

Radiopharmaceuticals can be classified into four categories:

1. Ready-for-use radioactive products.
2. Radionuclide generators.
3. Non-radioactive components (“kits”) for the preparation of labelled compounds with a radioactive component (usually the eluate from a radionuclide generator).
4. Precursors used for radiolabelling other substances before administration (e.g. samples from patients).

Radiopharmaceutical products include inorganic compounds, organic compounds, peptides, proteins, monoclonal antibodies and fragments, and oligonucleotides labelled with radionuclides with half-lives from a few seconds to several days.

¹ Guidelines on good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 3 (WHO Technical Report Series, No. 908).

2. Principles

Radiopharmaceuticals must be manufactured in accordance with the basic principles of good manufacturing practices (GMP). The matters covered by these guidelines should therefore be considered as supplementary to the general requirements for GMP previously published (1,2) and relate specifically to the production and control of radiopharmaceuticals. In the preparation of these guidelines, due consideration was given to national or international radiation safety guidelines (4).

Because of their short half-lives, many radiopharmaceuticals are released and administered to patients shortly after their production, so that quality control may sometimes be retrospective. Strict adherence to GMP is therefore mandatory.

3. Personnel

3.1 The manufacturing establishment, whether a hospital radiopharmacy, centralized radiopharmacy, nuclear centre or institution, industrial manufacturer or PET centre, and its personnel should be under the control of a person who has a proven record of academic achievement together with a demonstrated level of practical expertise and experience in radiopharmacy and radiation hygiene. Supporting academic and technical personnel should have the necessary postgraduate or technical training and experience appropriate to their function.

3.2 Personnel required to work in radioactive, clean and aseptic areas should be selected with care, to ensure that they can be relied on to observe the appropriate codes of practice and are not subject to any disease or condition that could compromise the integrity of the product. Health checks on personnel should be requested before employment and periodically thereafter. Any changes in personal health status (e.g. in haematology) may require the temporary exclusion of the person from further radiation exposure.

3.3 Only the minimum number of personnel required should be present in clean and aseptic areas when work is in progress. Access to these areas should be restricted during the preparation of radiopharmaceuticals, kits or sterile set-ups. Inspection and control procedures should be conducted from outside these areas as far as possible.

3.4 During the working day, personnel may pass between radioactive and non-radioactive areas only if the safety rules of radiation control (health physics control) are respected.

3.5 The release of a batch may be approved only by a pharmacist or a person with academic qualifications officially registered as a suitably qualified person, and with appropriate experience in the manufacture of radiopharmaceuticals.

3.6 To ensure the safe manufacture of radiopharmaceuticals, personnel should be trained in GMP, the safe handling of radioactive materials and radiation safety

procedures. They should also be required to take periodic courses and receive training to keep abreast of the latest developments in their fields.

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

3.8 All personnel engaged in production, maintenance and testing should follow the relevant guidelines for handling radioactive products and be monitored for possible contamination and/or irradiation exposure.

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 for the handling of radioactive materials must be specially designed to take into consideration aspects of radiation protection in addition to cleanliness and sterility. Interior surfaces (walls, floors and ceilings) should be smooth, impervious and free from cracks; they should not shed matter and should permit easy cleaning and decontamination. Drains should be avoided wherever possible and, unless essential, should be excluded from aseptic areas.

4.2 Specific disposal systems should be mandatory for radioactive effluents. These systems should be effectively and carefully maintained to prevent contamination and exposure of personnel to the radioactive waste both within and outside the facility.

4.3 Sinks should be excluded from aseptic areas. Any sink installed in other clean areas should be of suitable material and be regularly sanitized. Adequate precautions should be taken to avoid contamination of the drainage system with radioactive effluents.

4.4 Lighting, heating, ventilation and, if necessary, air-conditioning should be designed to maintain a satisfactory temperature and relative humidity to ensure the comfort of personnel working in protective clothing. Buildings should 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 for the operations to be carried out, allowing an efficient flow of work and effective communication and supervision. All buildings and rooms should be clean, sanitary and free from radioactive contamination.

4.5 Ventilation of radiopharmaceutical production facilities should meet the requirement to prevent the contamination of products and the exposure of working personnel to radioactivity. Suitable pressure and airflow patterns should be maintained by appropriate isolation/enveloping methods. Air-handling systems for both radioactive and non-radioactive areas should be fitted with

alarms so that the working personnel in the laboratory are warned of any failure of these systems.

4.6 Dedicated facilities and equipment should be used for the manufacture of any radiopharmaceutical product derived from human blood or plasma. Autoclaves used in production areas for radiopharmaceuticals may be placed behind a lead shield to minimize the radiation exposure of the operators. Such autoclaves should be checked for contamination immediately after use to minimize the possibility of cross-contamination by radioactivity of the products in the next autoclave cycles.

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

- processing and filling in segregated areas;
- avoiding the manufacture of different products at the same time, unless they are effectively segregated;
- containing material transfer by means of airlocks, air extraction, changing clothes 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;
- using sterilized containers.

4.8 Positive pressure areas should be used to process sterile products. In general, any radioactivity should be handled within specifically designed areas maintained under negative pressures. The production of sterile radioactive products should therefore be carried out under negative pressure surrounded by a positive pressure zone ensuring that appropriate air quality requirements are met.

4.9 Separate air-handling units should be used for radioactive and non-radioactive areas. Air from operations involving radioactivity should be exhausted through appropriate filters that are regularly checked for performance.

4.10 Pipework, valves and vent filters should be properly designed to facilitate validated cleaning and decontamination.

5. Production

5.1 Standard operating procedures (SOPs) must be available for all operating procedures and should be regularly reviewed and kept up to date for all manufacturing operations. All entries on batch records should be initiated by the operator and independently checked by another operator or supervisor.

5.2 Specifications for starting materials should include details of their source, origin and (where applicable) method of manufacture and of the controls used to ensure their suitability for use. Release of a finished product should be conditional on satisfactory results being obtained in the tests on starting materials.

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

5.4 A wide variety of equipment is used in the preparation of radiopharmaceuticals. Equipment for chromatography should, in general, be dedicated to the preparation and purification of one or several products labelled with the same radionuclide to avoid radioactive cross-contamination. The life span of columns should be defined. Great care should be taken in cleaning, sterilizing and operating freeze-drying equipment used for the preparation of kits.

5.5 A list of critical equipment should be drawn up, including any equipment such as a balance, pyrogen oven, dose calibrator, sterilizing filter, etc., where an error in the reading or function could potentially cause harm to the patient being given the final product. These devices should be calibrated or tested at regular intervals and should be checked daily or before production is started. The results of these tests should be included in the daily production records.

5.6 Specific equipment for radioactive measurements may be required as well as radioactive reference standards. For the measurement of very short half-lives, national central laboratories should be contacted to calibrate the apparatus. Where this is not possible, alternative approaches, such as documented procedures, may be used.

5.7 In the case of labelling kits, freeze drying should be carried out as an aseptic procedure. If an inert gas such as nitrogen is used to fill vials, it must be filtered to remove possible microbial contamination.

5.8 The dispensing, packaging and transportation of radiopharmaceuticals should comply with the relevant national regulations and international guidelines (5).

6. Labelling

6.1 All products should be clearly identified by labels, which must remain permanently attached to the containers under all storage conditions. An area of the container should be left uncovered to allow inspection of the contents. If the final container is not suitable for labelling, the label should appear on its package. Information on batch coding must be provided to the national and/or regional authorities.

6.2 The labels of radiopharmaceuticals must comply with the relevant national regulations and international agreements. For registered radiopharmaceuticals, the national control authority should approve the labels.

6.3 The label on the container should show:

- (a) the name of the drug product and/or the product identification code;
- (b) the name of the radionuclide;
- (c) the name of the manufacturer or the company and/or the person responsible for placing the drug on the market;
- (d) the radioactivity per unit dose:
 - for liquid preparations, the total radioactivity in the container, or the radioactive concentration per millilitre, at a stated date and, if necessary, hour, and the volume of liquid in the container;
 - for solid preparations, such as freeze-dried preparations, the total radioactivity at a stated date and, if necessary, hour;
 - for capsules, the radioactivity of each capsule at a stated date and, if necessary, hour, and the number of capsules in the container;
 - where relevant, the international symbol for radioactivity.

6.4 The label on the package should state:

- (a) the qualitative and quantitative composition;
- (b) the radioactive isotopes and the amount of radioactivity at the time of dispatch;
- (c) the route of administration;
- (d) the expiry date;
- (e) any special storage conditions;
- (f) mandatory information related to transport regulations for radioactive materials.

6.5 The leaflet in the package should contain the specific product information and indications for use. This information is especially important for preparation kits (cold kits), and should include:

- (a) the name of the product and a description of its use;
- (b) the contents of the kit;
- (c) the identification and quality requirements concerning the radiolabelling materials that can be used to prepare the radiopharmaceutical, namely:
 - the directions for preparing the radiopharmaceutical, including the range of activity and the volume, together with a statement of the storage requirements for the prepared radiopharmaceutical;
 - a statement of the shelf-life of the prepared radiopharmaceutical;
 - the indications and contraindications (pregnancy, children, drug reactions, etc.) in respect of the prepared radiopharmaceutical;
 - warnings and precautions in respect of the components and the prepared radiopharmaceutical, including radiation safety aspects;

- where applicable, the pharmacology and toxicology of the prepared radiopharmaceutical, including the route of elimination and the effective half-life;
- the radiation dose that a patient will receive from the prepared radiopharmaceutical;
- the precautions to be taken by users and patients during the preparation and administration of the product and the special precautions for the disposal of the container and any unconsumed portions;
- a statement of the recommended use of the prepared radiopharmaceutical and the recommended dosage;
- a statement of the route of administration of the prepared radiopharmaceutical;
- if appropriate for particular kits (i.e. those subject to variability beyond the recommended limits), the methods and specifications needed to check radiochemical purity.

7. Production and distribution records

7.1 The processing records of regular production batches must provide a complete account of the manufacturing history of each batch of a radiopharmaceutical, showing that it has been manufactured, tested, dispensed into containers and distributed in accordance with the written procedures.

7.2 Separate records for the receipt, storage, use and disposal of radioactive materials should be maintained in accordance with radiation protection regulations.

7.3 Distribution records should be kept. Since the return of radioactive products is not practical, the purpose of recall procedures for such products is to prevent their use rather than an actual return. If necessary, the return of radioactive products should be carried out in accordance with international and national transport regulations.

8. Quality assurance and quality control

8.1 Radiopharmaceuticals are nearly always used before all quality control testing (e.g. tests for sterility, endotoxin, radionuclidic purity, etc.) has been completed. The implementation of and compliance with the quality assurance programme are therefore essential.

8.2 Quality assurance and/or quality control should have the following principal responsibilities:

- (a) the preparation of detailed instructions for each test and analysis;
- (b) ensuring the adequate identification and segregation of test samples to avoid mix-ups and cross-contamination;

- (c) ensuring that environmental monitoring and equipment and process validation are conducted as appropriate for evaluating the adequacy of the manufacturing conditions;
- (d) the release or rejection of starting materials and intermediate products;
- (e) the release or rejection of packaging and labelling materials;
- (f) the release or rejection of each batch of finished preparation;
- (g) the evaluation of the adequacy of the conditions under which the starting materials, intermediate products and finished radiopharmaceutical preparations are stored;
- (h) the evaluation of the quality and stability of the finished products and, when necessary, of the starting materials and intermediate products;
- (i) the establishment of expiry dates on the basis of the validity period related to specified storage conditions;
- (j) the establishment and revision of the control procedures and specifications;
- (k) assuming the responsibility for retaining samples of radiopharmaceutical products;
- (l) assuming the responsibility for keeping adequate records of the distribution of the radiopharmaceutical products.

8.3 Whenever the size of the establishment permits, quality assurance and quality control duties should be organized in separate groups. Quality assurance should also include the monitoring and validation of the production process.

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

8.5 The performance of all qualitative and quantitative tests mentioned in the specifications for the starting materials may be replaced by a system of certificates issued by the supplier of these materials, provided that:

- (a) there is a history of reliable production;
- (b) the producer or supplier is regularly audited;
- (c) at least one specific identity test is conducted by the manufacturer of the finished radiopharmaceutical.

8.6 Samples of the intermediate and final products should be retained in sufficient amounts and under appropriate storage conditions to allow repeated testing or verification of a batch control. These samples should be kept for an appropriate period in accordance with the shelf-lives of the radioactive components concerned. However, this may sometimes not be applicable, e.g. for radiopharmaceuticals with a short half-life.

8.7 Sampling procedures may be adapted to the purpose of the sampling, the type of controls being applied, and the nature of the material being sampled (e.g.

a small batch size and/or its radioactive content). The procedure should be described in a written protocol.

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