14.7 PACKAGING OF RADIOPHARMACEUTICALS

14.7.1 Due to the short half-life of certain radiopharmaceuticals it may be necessary to despatch the products before all the tests are completed. This does not reduce the need for a formal recorded decision to be taken by an authorized person as to whether or not the product should be released based on the production and quality control data available at the time. Specifications should define at which stage of testing a decision on release may be taken.

14.7.2 All containers must be checked by a Health Physicist for radioactive contamination before packaging and the radiation levels emanating from the package monitored by a Health Physicist.

14.7.3 IAEA transport regulations prescribe the maximum acceptable levels of radiation measured at the surface of the package and one metre from the package permitted on road and air transport. The conditions under which the packages may be transported are also prescribed.

14.8 NON-RADIOACTIVE KITS

14.8.1 Non-radioactive chemicals are supplied as kits to be reconstituted with the radioactive eluate from a radionuclide generator such as a Molybdenum-99 / Technetium-99m generator at the hospital. These kits must conform to the requirements of pharmaceuticals as listed in the chapter on guidelines for small volume parenterals.

14.8.2 The preparation of these radiopharmaceuticals at the hospital must be carried out using aseptic technique. It may be acceptable to carry out this work under environmental conditions of a lower grade than those prescribed for aseptic work when the following situation pertains:

·the preparation is done entirely by transference of materials between closed containers, for example by use of syringe and hypodermic needle penetrating a rubber closure (so-called 'closed procedures')
·manipulations are performed within a contained work station which, whilst giving the required degree of operator protection, also maintains the critical working zone at the standard of Class 1
·the product is administered within a few hours of preparation.

14.9 DISTRIBUTION AND RECALLS

14.9.1 Detailed distribution records should be maintained and there should be procedures which describe the measures to be taken for stopping the use of defective radiopharmaceuticals. Recall procedures should be shown to be operable within a very short time.

CHAPTER 15:

BIOLOGICAL MEDICINES

15.1 PRINCIPLES

15.1.1 Biological medicines comprise those derived or extracted from living organisms or tissues and those which contain living or inactivated organisms in the end product.

15.1.2 There are 4 sub-categories, namely:
ANTIGENS: These include vaccines, toxoids, allergens, venoms, etc.

ANTIBODIES: These include antitoxins, antisera, immunoglobulins, etc.

BLOOD FRACTIONS: These include all preparations and components of human blood, made from donor pools exceeding 12 donors.

OTHER: This includes in-vivo diagnostics, venom, etc.

15.1.3 The methods employed in the manufacture of biological medicinal products are a critical factor in shaping the appropriate regulatory control. Biological medicinal products can be defined therefore largely by reference to their method of manufacture. Biological medicinal products prepared by the following methods of manufacture will fall under this chapter.

(a) Microbial cultures, excluding those resulting from r-DNA techniques.

(b) Microbial and cell cultures, including those resulting from recombinant DNA or hybridoma techniques.

(c) Extraction from biological tissues.

(d) Propagation of live agents in embryos or animals.

(Not all aspects of this chapter may necessarily apply to producers in category (a).

15.1.4 The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and processes. The way in which biological medicinal products are produced, controlled and administered make some particular precautions necessary.

Unlike conventional medicinal products, which are reproduced using chemical and physical techniques capable of a high degree of consistency, the production of biological medicinal products involves biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products are variable. Moreover, the materials used in these cultivation processes provide good substrates for growth of microbial contaminants.

Control of biological medicinal products usually involves biological analytical techniques which have a greater variability than physico-chemical determinations. In-process controls therefore take on a greater importance in the manufacture of biological medicinal products.

15.1.5 The principles of good manufacturing practice still apply, but it is important to be aware of the difficulties posed by the different nature of biological materials. The use of material from living organisms requires increased emphasis on some aspects of manufacturing different from those of other pharmaceuticals.

15.2 PERSONNEL

15.2.1 All personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological medicinal products are manufactured should receive additional training specific to the products manufactured and to their work. Personnel should be given relevant information and training in hygiene and microbiology.

15.2.2 Persons responsible for production and quality control should have an adequate background in relevant scientific disciplines, such as bacteriology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology, immunology and veterinary medicine, together with sufficient practical experience to enable them to exercise their management function for the processes concerned.

15.2.3 The immunological status of personnel may have to be taken into consideration for product safety. All personnel engaged in production, maintenance, testing and animal care (and inspectors) should be vaccinated where necessary with appropriate specific vaccines and have regular health checks. 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 infectious agents. Visitors should generally be excluded from production areas.

15.2.4 Any changes in the immunological status of personnel which could adversely affect the quality of the product should preclude work in the production area. Production of BCG vaccine and tuberculin products should be restricted to staff who are carefully monitored by regular checks of immunological status and chest X-ray.

15.2.5 In the course of a working day, personnel should not pass from areas where exposure to live organisms or animals is possible to areas where other products are handled. If such passage is unavoidable, clearly defined decontamination measures, including changes of clothing and shoes and, where necessary, showering should be followed by staff involved in any such production.

15.3 PREMISES AND EQUIPMENT

15.3.1 The degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the product and the production step bearing in mind the level of contamination of the starting materials and the risk to the finished product.

15.3.2 The risk of cross-contamination between biological medicinal products, especially during those stages of the manufacturing process in which live organisms are used, may require additional precautions with respect to facilities and equipment, such as the use of dedicated equipment, production on a campaign basis and the use of closed systems. The nature of the product as well as the equipment used will determine the level of segregation needed to avoid cross-contamination.

15.3.3 In principle, dedicated facilities should be used for the production of BCG vaccine and for the handling of live organisms used in production of tuberculin products.

15.3.4 Dedicated facilities should be used for the handling of Bacillus anthracis, Clostridium botulinum and Clostridium tetani until the inactivation process is accomplished.

15.3.5 Production on a campaign basis may be acceptable for other spore forming organisms provided that the facilities are dedicated to this group of products and not more than one product is processed at any one time.

15.3.6 Simultaneous production in the same area using closed systems of biofermenters may be acceptable for products such as monoclonal antibodies and products prepared by DNA techniques.

15.3.7 Processing steps after harvesting may be carried out simultaneously in the same production area provided that adequate precautions are taken to prevent cross-contamination. For killed vaccines and toxoids, such parallel processing should only be performed after inactivation of the culture or after detoxification.

15.3.8 Positive pressure areas should be used to process sterile products but negative pressure in specific areas at point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or cabinets are used for aseptic processing of pathogens, they should be surrounded by a positive pressure sterile zone.

15.3.9 All filtration units should be specific to the processing area concerned and recirculation of air should not occur from areas handling live pathogenic organisms.

15.3.10 The layout and design of production areas and equipment should permit effective cleaning and decontamination (e.g. by fumigation). The adequacy of cleaning and decontamination procedures should be validated.

15.3.11 Equipment used during handling of live organisms should be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.

15.3.12 Pipework systems, valves and vent filters should be properly designed to facilitate cleaning and sterilization. The use of 'clean of place' and 'sterilize in place' systems should be encouraged. Valves on fermentation vessels should be completely steam sterilizable. Air vent filters should be hydrophobic and validated for their scheduled life span.

15.3.13 Effluents which may contain pathogenic microorganisms should be effectively decontaminated.

15.3.14 Due to the variability of biological products or processes, some additives or ingredients have to be measured or weighed during the production processes (e.g. buffers). In these cases, small stocks of these substances may be kept in the production area.

15.4. ANIMAL QUARTERS AND CARE

15.4.1 Animals are used for the manufacture of a number of biological products, for example polio vaccine (monkeys), snake antivenoms (horses and goats), rabies vaccine (rabbits, mice and hamsters) and serum gonadotrophin (horses). In addition, animals may also be used in the quality control of most sera and vaccines e.g. pertussis vaccine (mice), pyrogenicity (rabbits), BCG vaccine (guinea-pigs).

15.4.2 Quarters for animals used in production and control of biological products should be separated from production and control areas. The health status of animals from which some starting materials are derived and of those used for quality control and safety testing should be monitored and recorded. Staff employed in such areas must be provided with special clothing and changing facilities.

15.5 DOCUMENTATION

15.5.1 Specifications for biological starting materials may need additional documentation on the sources, origin, method of manufacture and controls applied, particularly microbiological controls.

15.5.2 Specifications are routinely required for intermediate and bulk biological medicinal products.

15.6 PRODUCTION

15.5.1 THE POSSIBILITY OF CONTAMINATION

15.5.1.1 Due to the inherent characteristics of biological material special care should be taken during collection and processing to avoid microbial growth and contamination, which could lead to sub-standard or hazardous products or substantial losses.

15.6.2 THE POSSIBILITY OF INFECTION

15.6.2.1 A particular hazard associated with biological materials is that an element of a pool of starting material may contain an infectious agent. This is a hazard to staff who will have to process the material and appropriate precautions must be taken. Processing steps must be designed to inactivate and eliminate both the known and the potential infectious agents which may be present in the material. No completely reliable test exists for the presence of any pathogenic bacteria or virus so that good manufacturing practices are essential to reduce the chances of this hazard.

15.6.3 WHERE THE PRODUCT ITSELF IS AN INFECTIOUS AGENT

15.6.3.1 Many highly effective vaccines consist of living organisms which have been selected for minimal pathogenicity and maximal immunogenicity (attenuated). Facilities and staff for propagating, processing and filling each product must be physically separated from those used for other products.

15.6.3.2 Similarly, as these products do not undergo a terminal sterilization procedure and do not usually contain preservative materials, it is extremely important that premises and staff are isolated from facilities handling or testing infectious virulent materials (e.g. challenge strains or diagnostic facilities). The checks on the health of staff in these production areas must also be more stringent than those for other production staff.

15.6.3.3 For products containing living organisms, tests for the absence of contaminants are more complex and must include tests to demonstrate the maintenance of attenuation.

15.6.3.4 Where an inactivated infectious agent is included in a product, it is impossible to reliably detect extremely low levels of infectivity, thus it is necessary to estimate the infectivity of the preparation at various times during inactivation, and to use this data to calculate a time when the theoretical infectivity of the preparation reaches an acceptable level.

15.6.4 STARTING MATERIALS

15.6.4.1 The source, origin and suitability of starting materials should be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available. In such cases, release of a finished product is conditional on satisfactory results of these tests.

15.6.4.2 Where sterilization of starting materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be sued for inactivation of biological materials (e.g. irradiation).

15.6.4.3 Where a biological medicine is derived or extracted from living organisms or tissues, there is always the probability of batch to batch variation of the starting material. Genetic variation in a pool of material from a number of individuals or organisms, can occur. This may be prevented through strict controls over each seed lot. It may be necessary to ensure purity of the seed lot prior to each production sequence through finger-printing methods such as DNA sequencing.

15.6.4.4 The yield and / or quality may also be affected by e.g. minor differences in growth conditions of a cultivated starting material.

15.6.4.5 Due to deterioration of material during collection, storage or processing, aberrant forms of the products can result and the yield can vary from batch to batch.

15.6.5 SEED LOT AND CELL BANK SYSTEM

15.6.5.1 In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal products obtained by microbiological culture, cell culture or propagation in embryos and animals should be based on a system of master and working seed lots and/or cell banks.

15.6.5.2 The number of generations (doublings, passages) between the seed lot and the cell bank and the finished product should be consistent with the registration dossier. Scaling up of the process should not change this fundamental relationship.

15.6.5.3 Seed lots and cell banks should be adequately characterized and tested for contaminants. Their suitability for use should be further demonstrated by the consistency of the characteristics and the quality of the successive batches of the product. Seed lots and cell banks should be established, stored and used in such a way as to minimize the risks of contamination or alteration.

15.6.5.4 Establishment of the seed lot and cell bank should be performed in a suitably controlled environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons.

15.6.5.5 Evidence of the stability and recovery of the seeds and the banks should be documented. Storage containers should be hermetically sealed, clearly labelled and kept at an appropriate temperature. An inventory should be meticulously kept. Storage temperature should be recorded continuously for freezers and properly monitored for liquid nitrogen. Any deviation from set limits and any corrective action taken should be recorded.

15.6.5.6 Only authorized personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Access to stored material should be controlled. Different seed lots or cell banks should be stored in such a way to avoid confusion or cross-contamination. It is desirable to split the seed lots and cell banks and to store the parts at difference locations so as to minimize the risks of total loss.

15.6.5.7 All containers of master or working cell banks and seed lots should be treated identically during storage. Once removed from storage, the containers should not be returned to stock.

15.6.6 OPERATING PRINCIPLES

15.6.6.1 The growth promoting properties of culture media should be demonstrated.

15.6.6.2 Addition of materials or cultures to fermenters and other vessels and the taking of samples should be carried out under carefully controlled conditions to ensure that absence of contamination is maintained. Care should be taken to ensure that vessels are correctly connected when addition or sampling takes place.

15.6.6.3 Centrifugation and blending of products can lead to aerosol formation and containment of such activities to prevent transfer of live microorganisms is necessary.

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

15.6.6.5 Careful consideration should be given to the validation of the necessary virus removal or inactivation undertaken.

15.6.6.6 In cases where the virus inactivation or removal process is performed during the manufacture, measures should be taken to avoid the risk of recontamination of treated products by non-treated products.

15.6.6.7 A wide variety of equipment is used for chromatography, and in general such equipment should be dedicated to the purification of one product and should be sterilized or sanitized between batches. The use of the same equipment at difference stages of processing should be discouraged. Acceptance criteria, life span and sanitization or sterilization method of columns should be defined.

15.7 QUALITY CONTROL

15.7.1 In-process controls play an especially important role in ensuring the consistency of the quality of biological medicinal products. Those controls which are crucial for quality (e.g. virus removal) but which cannot be carried out on the finished product, should be performed at an appropriate stage of production.

15.7.2 It may be necessary to retain samples of the intermediate products in sufficient quantities and under appropriate storage conditions to allow the repetition or confirmation of batch control.

15.7.3 Continuous monitoring of certain production processes is necessary, for example fermentation. Such data should form part of the batch record.

15.7.4 Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.

15.7.5 SPECIAL REQUIREMENTS FOR FINAL TESTING

15.7.5.1 Biological medicines require biological tests to ensure efficacy and safety. In-vitro tests are not sufficient and in-vivo animal testing is required. Animal testing should be conducted in accordance with regulations.

15.7.6 WASTE DISPOSAL

15.7.6.1 Infectious material and toxins must be adequately inactivated before disposal. The inactivation system used must be validated.

CHAPTER 16

MANUFACTURE OF HERBAL MEDICINAL PRODUCTS INCLUDING HOMEOPATHIC PRODUCTS

16.1 PRINCIPLE

Because of their often complex and variable nature, and the number and small quantity of defined active ingredients, control of starting materials, storage and processing assume particular importance in the manufacture of herbal medicinal products.

16.2 PREMISES

16.2.1 STORAGE AREAS

16.2.1 Crude (i.e. unprocessed) plants should be stored in separate areas. The storage areas should be well ventilated and be equipped in such a way as to give protection against the entry of insects or other animals, especially rodents. Effective measures should be taken to prevent the spread of any such animals and microorganisms brought in with the crude plant and to prevent cross-contamination. Containers should be located in such a way as to allow free air circulation.

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

16.2.1.3 Storage of plants, extracts, tinctures and other preparations may require special conditions of humidity, temperature or light protection: these conditions should be provided and monitored.

16.2.2 PRODUCTION AREAS

16.2.2.1 Specific provisions should be taken during sampling, weighing, mixing and processing operations of crude plants whenever dust is generated, to facilitate cleaning and to avoid cross-contamination, as for example, dust extraction, dedicated premises, etc.

16.3 DOCUMENTATION

16.3.1 SPECIFICATIONS FOR STARTING MATERIALS

16.3.1.1 Apart from the data described in General Guide, specifications for medicinal crude plants should include, as far as possible:

- the botanical name (with, if appropriate, the name of the originator of the classification, e.g. Linnaeus;
- the details of the source of the plant (country of region, and where applicable, cultivation, time of harvesting, collection procedures, possible pesticides used, etc.);
- whether the whole plant or only a part is used;
- when a dried plant is purchased, the drying system should be specified;
- the description of the plant and its macro and microscopical examination;
- the suitable identification tests including, where appropriate, identification tests for known active ingredients, or markers. A reference authentic specimen should be available for identification purposes;
- the assay, where appropriate of constituents of know therapeutic activity or of markers;
- the methods suitable to determine possible pesticide contamination and limits accepted;
- the tests to determine fungal and/or microbial contamination, including aflatoxins and pest-infestations, and limits accepted;
- the tests for toxic metals and for likely contaminants and adulterants;
- the tests for foreign materials.

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

16.3.2 PROCESSING INSTRUCTIONS

16.3.2.1 The processing instructions should describe the different operations carried out upon the crude plant such as drying, crushing and sifting, and include drying time and temperatures, and methods used to control fragment or particle size. It should also describe security sieving or other methods of removing foreign materials.

16.3.2.2 For the production of a vegetable drug preparation, instructions should include details of base or solvent, time and temperatures of extraction, details of any concentration stages and methods used.

16.3.3 SAMPLING

16.3.3.1 Due to the fact that crude drugs are an aggregate of individual plants and contain an element of heterogeneity, their sampling has to be carried out with special care by personnel with particular expertise. Each batch should be identified by its own documentation.

16.3.4 QUALITY CONTROL

16.3.4.1 Quality Control personnel should have particular expertise in herbal medicinal products in order to be able to carry out identification tests and recognize adulteration, the presence of fungal growth, infestations, non-uniformity within a delivery of crude plants, etc.

16.3.4.2 The identity and quality of vegetable drug preparations and of finished product should be tested as described in the note for guidance "Quality of herbal remedies".

CHAPTER 17:

MEDICAL GASES

17.1 PRINCIPLE

17.1.1 Gases, either in compressed or liquefied form, intended for medical use should be manufactured, filled, stored, distributed and documented in accordance with the general principles outlined in this Guide, appropriately interpreted to suit the special context of gaseous products.

17.2 GENERAL REQUIREMENTS

17.2.1 Although order, tidiness, cleanliness and security sufficient to avoid the risk of error, mix-up or contamination are required, certain recommendations given elsewhere in the Guide (for example on premises and equipment) may not always be applicable to a product which is never in direct contact with the factory environment. Nevertheless, particularly to encourage desirable attitudes towards medicinal products, areas where medical gases are filled should be maintained at an appropriate standard of cleanliness and order.

17.2.2 The gas production plant should be continually monitored for the quality and impurity levels of the gas produced, and similar tests should be carried out on bulk storage vessels at specified regular intervals.

17.2.3 The gas production, treatment and filling plant should be designed, installed and maintained so as to avoid contamination of the gas. Filters are necessary after driers to prevent contamination with particles of desiccant.

17.2.4 The areas used for filling of medical gases should be segregated from areas used for filling gases for other (e.g. industrial) purposes. The "medical" nature of such areas should be emphasized.

17.2.5 Staff employed in the production, filling and testing of medical gases should be made aware of the special importance of their work and the potential hazards to patients.

17.3 PIPELINES

17.3.1 Gas pipelines should be colour coded to BS 1710 (Identification of Pipelines) and HTM 22 (Piped Medical Gases, etc.). All gas outlets should be conspicuously marked to indicate the name of the gas supplied to the outlet. Cleaning and purging of pipelines should follow written procedures, and checks for the absence of cleaning agents or other contaminants should be carried out before the line is released for use.

17.4 FILLING AREAS

17.4.1 Filling areas should be of sufficient size, and have an orderly lay-out which will permit:

- allocation of separate marked areas for different gases and different cylinder sizes
- clearly identifiable segregation of empty cylinders from full cylinders
- clear distinguishing of the stage reached by given cylinders (e.g. "awaiting filling", "filled", "awaiting test and/or inspection", "released").

17.4.2 The method used to achieve these various levels of segregation will depend on the nature, extent or complexity of the over-all operation, but marked-out floor areas, partitions, barriers, labels and signs should be used, as appropriate.

17.5 PREPARATION OF RETURNED CYLINDERS

17.5.1 New cylinders and cylinders returned for re-filling should be checked as clean and suitable before re-use. Cylinders returned from customers should be prepared for re-filling as follows:
·cylinders due for statutory hydraulic testing, or which require repainting, or which are damaged in any way must receive the appropriate treatment before filling. If a cylinder is to be re-painted in a different colour, for use with a different gas, the old paint must be completely removed before re-painting

·old date / batch labels, and any markings applied by the customer, must be removed

·any water or debris in the valve outlets must be removed by an airjet or other suitable means before the cylinder valve is opened.

17.6 FILLING

17.6.1 Before a cylinder is filled, steps should be taken to avoid the risk of contamination of the new gas with any possibly contaminated gas remaining in the cylinder, by employing appropriate blow-down, purging and evacuation procedures. Checks should be made to ensure compliance with points under 17.5.1 above, and in particular to ensure that the cylinder is colour-coded (ref. BS 1319 1976), labelled, stenciled or otherwise marked in accordance with the nature of the gas to be filled.

17.7 LOT IDENTIFICATION

17.7.1 In addition to identification labelling or marking, all filled cylinders should have attached a lot identifying label. If, because of the continuous nature of gas production, it is not possible to relate this directly to a bulk batch of gas, it should at least be indicative of date, time and place of filling, and permit access to a relevant test record.

17.8 RELEASE

17.8.1 Following filling, all cylinders should be leak-tested by an appropriate method, and held in quarantine until released by Quality Control, after checks have been made to ensure:

·that all necessary tests have been carried out, and that the recorded results are within specification
·that the cylinders have not exceeded the hydraulic test date, are in good condition and correctly painted and are properly identity- and batch-labelled and stenciled
·that the cylinder valve is in good condition and the protective cap or sleeve over the outlet has been properly applied.

17.8.2 It is not normally necessary or appropriate to retain finished product samples.

17.9 STORAGE

17.9.1 Gas cylinders should be stored under cover, and not subjected to extremes of temperature. Areas where they are stored should be clean, dry, well ventilated and free from combustible materials.

17.9.2 Storage arrangements should permit segregation of different gases and of full / empty cylinders and permit rotation of stock.

17.9.3 Cylinders should be stored so that they remain clean, dry and with their markings unobscured.

17.9.4 Storage arrangements for gas-mixtures should be such so as to avoid separation of the mixture into its component gases.

CHAPTER 18:

GOOD PHARMACEUTICAL WHOLESALING PRACTICE

18.1 PRINCIPLES

18.1.1 Good wholesaling practices should be seen as an extension of the manufacturer's endeavors to assure the maintenance of product quality by having adequate storage conditions, record keeping and compliance with legal requirements. The recommendations of relevant sections of this Guide in relation to buildings, pest control, stock records and stock rotation should be followed.

18.2 GENERAL REQUIREMENTS

18.2.1 Key personnel involved in the warehousing of medicinal products should have the ability and experience appropriate to the responsibility of ensuring that the products or materials are properly handled.

18.2.2 The area should be protected against unauthorized entry.

During operating hours, the business must at all times be conducted under the continuous personal supervision of a pharmacist.

Proper training relating to quality, handling, quantity relations, storage requirements, distribution and safety must be provided for all personnel.

Sufficient security must be provided to prevent pilferage and/or unauthorided entry.

18.3 STORAGE

18.3.1 The warehouse, storage areas and surroundings should be maintained in a clean and tidy condition, free from accumulated waste. Spilled substance should be promptly cleaned up and rendered safe.

All waste material should be removed on a regular basis.

Programmes for regular cleaning must be drawn up and followed.

18.3.2 Stocks should be received in a separate reception area, and examined for correctness against order and for absence of damaged containers.

18.3.3 Medicinal products should be stored apart from other goods which could cause harmful cross-contamination.

Sufficient lighting should be provided to enable all operations to be carried out accurately and safely.

All products should be stored off the floor.

18.3.4 All products should be protected from excessive local heating, and from undue exposure to direct sunlight, and (unless they are known to be unaffected) from freezing. Minimum and maximum temperatures should be monitored.

18.3.5 Special storage facilities should be provided as necessary to protect products from deterioration and to comply with the manufacturer's directions and with legal requirements.

18.3.6 Refrigerated storage areas should be equipped with temperature recorders or other temperature monitoring devices. Control should be adequate to maintain all parts of the storage area within the specified temperature range.

Temperature should be monitored and recorded periodically. Records of temperature should be reviewed regularly.

Written procedures must be available detailing the action to be taken in the event of a temperature violation occurring.

All thermoliable products must be distributed under temperature-controlled conditions to maintain the cold chain.

18.3.7 There should be a system to ensure stock rotation, with regular and frequent checks that the system is operating correctly. Products beyond their expiry date or shelf-life should be removed from usable stock and neither sold nor supplied.

18.3.8 Stock which is damaged or withheld from supply, and which is not immediately destroyed, should be kept apart from saleable stock, so that it cannot be sold in error, and so that leakage from any broken package cannot contaminate other goods.

18.3.9 Stocks of sterile products with broken seals, damaged packaging, or suspected of possible contamination must not be sold or supplied.

18.4 TRANSPORT

The sale of medicine shall only take place to persons legally entitled thereto. Deliveries should be made only to other authorised wholesalers or to persons authorised to supply medicinal products.

18.4.1 Products should be transported in such a way that:

·the identification of the product is not lost
·the product does not contaminate, and is not contaminated by, other products or materials
·adequate precautions are taken against spillage or breakage
·the cold chain, if required, is preserved
·the specific storage conditions of the product are not grossly exceeded or exceeded for an unacceptable length of time
·medicinal products requiring controlled temperature storage should also be transported by appropriate specialized means.

18.5 DOCUMENTATION AND CONTROL

18.5.1 Goods which have been rejected, recalled or returned should be placed in adequately segregated storage to avoid confusion with other materials and products and prevent redistribution, until a decision has been reached as to their disposition. Records of all goods returned should be kept.

18.5.2 There should be a written procedure for implementing a manufacturer's product recall, and records of any recalled products received into the warehouse should be kept. It is useful to have a record keeping system by batch which would assist with effective recall from the retailer. A person should be designated as responsible for execution and co-ordination of recalls.

18.5.3 There should be a written procedure for the handling of spillages of harmful Products (e.g. cytotoxics, hormones, penicillins).

18.5.4 There should be a written procedure for the handling of product complaints.

18.5.5 Legal requirements regarding the documentation and control of scheduled medicines should be adhered to.

There must a system for the recognition of and prompt and correct handling by the pharmacist of Schedule 6 or 7 substances and for those products requiring storage at specific temperature ranges.

Schedule substances should only be purchased from manufacturers or distributors registered as such with the South African Pharmacy Council.

All applicable documentation and receipts for Scheduled substances should be retained on the premises for the statutory period of time.

Records should be kept of each purchase and sale. Records should ensure the traceability of the origin and destination of products.

All documentation should be made available on request to the authorities.

Accurate and accessible records of all sales of Scheduled substances must be made, indicating the date oft supply, customer, customer address, product name and quantity.

A valid written order must be obtained prior to sale and/or despatch of Schedule 6 or Schedule 7 substances. The order must comply with statutory regulations.

All records must be kept for the statutory period of time.

The sale of medicines should only take place to persons legally entitled thereto. Proof of registration of the purchaser with the relevant statutory body must be in possession of the wholesaler before medicines are sold.

Stock that can no longer be used must be destroyed in an appropriate manner, such as not to cause a harmful or potentially harmful hazard, and to prevent accidental usage.

18.5.6 Goods which have left the care of the wholesaler should only be returned to saleable stock if:

·the goods are in their original unopened containers and in good condition and bear the valid registration numbers
·it is known that the goods have not been subject to adverse conditions
·they have been examined and assessed by a person authorized to do so. This assessment should take into account the nature of the product, any special storage conditions it requires, and the time elapsed since it was issued. If necessary, advice should be sought from the person responsible for the Quality Control of the manufactured product.

18.5.7 It is useful to employ a batch-tracking system which enables the supply of specific batches to be traced.

CHAPTER 19 :

ELECTRONIC DATA PROCESSING

19.1 PRINCIPLES

19.1.1 The introduction of Electronic Data Processing into systems of manufacturing, storage and distribution does not alter the need to observe the relevant principles, given elsewhere in the Guide. Where Electronic Data Processing replaces a manual operation in a system there should be no adverse impact on product quality or Good Manufacturing Practice.

19.2 RESPONSIBILITIES

19.2.1 The responsibilities of key personnel described in the Guide are not changed by the use of computers, and it is essential that there is the closest co-operation between Production, Quality Control and Electronic Data Processing Departments.

19.2.2 Persons with appropriate expertise should be responsible for the design and introduction of a proposed computer system. These or other expert persons should be retained to review the system at appropriate intervals.

19.2.3 Employees whose duties involve the use of a computer system should be appropriately trained in its correct use. Written operating procedures should be readily available to these employees. On-line help screens could be used for this purpose. Records of operator training should be kept.

19.3 VALIDATION

19.3.1 The development, implementation and operation of a computer system should be carefully documented at all stages and each step proven to achieve its written objective under challenging test conditions.

19.3.2 The extent of validation necessary will depend on a number of factors:

i) the use to which the system is to be put.
ii) whether the validation is to be prospective or retrospective
iii) whether novel elements are incorporated

Validation should be considered as part of the complete life cycle of a computer system. The cycle includes the stages of planning, specification, programming, testing, commissioning, document operation, monitoring and modifying.

19.3.3 A control document (system specification) should be prepared specifying the objectives of a proposed computer system, the data to be entered and stored, the flow of data, how it interacts with other systems and procedures, the information to be produced, the limits of any variable and the operating program(s) and test programs. Examples of each document produced by the program should be included. A functional specification should also be prepared to provide instructions for testing, operating and maintaining the system and the names of the person or persons responsible for its development and operation.

19.3.4 Computers should be protected from disturbances caused by fluctuations in the electrical supply and from loss of memory due to supply failure, electrical / magnetic disturbances or high temperatures.

19.3.5 Before a system using a computer is brought into use it should be tested and confirmed as being capable of achieving desired results. If a manual system is being replaced it is advisable to run the two in parallel for a time, as part of this testing and validation.

1 9.3.6 At installation and after a suitable period of running a new system, it should be independently reviewed and compared with the system specification and functional specification to ascertain whether it is meeting all of its requirements.

1 9.3.7 Alterations to a system or to a computer programme should only be made in accordance with a defined procedure which should including provision for checking, approving and implementing the change. Such an alteration should be implemented with the agreement of the person responsible for the part of the system concerned, and the alteration should be recorded.

1 9.3.8 Data collected directly from manufacturing or monitoring equipment should be checked periodically to confirm that it has been accurately and reliably transferred. Similarly, data or control signals transmitted from a computer to equipment involved in the manufacturing process should be checked periodically to ensure accuracy and reliability.

1 9.4 SECURITY

1 9.4.1 Data should only be entered or amended by persons authorized to do so. Suitable methods of deterring unauthorized entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals. The method of final release by computer of a batch for sale or supply should uniquely identify the person effecting the release. There should be a defined procedure for the issue, cancellation and alteration of authorization to amend data, including the changing of personal codes.

1 9.4.2 The entry of critical data into a computer by an authorized person (e.g. entering a master processing formula) should require independent verification and release of use by a second authorized person.

1 9.4.3 The computer program should create a complete record ("audit trail") of all entries and amendments to the data base.

1 9.4.4 Adequate alternative arrangements should be available, i.e. disaster recovery procedure, for systems which need to be operated in the event of a break-down. The procedures to be followed if the system fails or breaks down, should be defined and tested. Regular backups of all files should be stored in a secure location to prevent wilful or accidental damage. Any failure and remedial action taken should be recorded.

1 9.4.5 It should be possible to obtain printed copies of electronically stored data.

1 9.4.6 Stored data should be checked for accessibility, durability and accuracy, especially after any relevant changes have been made to the computer equipment or its programmes.

1 9.4.7 Care should be taken to ensure that computer systems are not contaminated by computer viruses.

CHAPTER 20 :

SECURITY GUIDELINES

20.1 PRINCIPLE

20.1.1 Adequate security measures are essential to protect pharmaceutical installations against unauthorized entry or deliberate adulteration of products.

20.1.2 Legitimate procedures should be followed for the removal/transportation of stock and materials to prevent pilferage or theft.

20.2 SECURITY PERSONNEL

20.2.1 Sufficient resources should be provided to establish an adequate security force on a 24 hour, 7 days per week basis.

20.2.2 A security manager should be appointed in writing to identify, evaluate and propose corrective measures to reduce risk to acceptable levels. He should be conversant with the Criminal Procedures Act and Labour Legislation.

20.2.3 Security staff should be security vetted and should be adequately trained and knowledgeable about Company procedures and practices as they impact on security operations.

20.3 ENTRY TO SITE

20.3.1 A risk evaluation is recommended to identify potential means of unauthorized entry during daylight as well as after hours.

20.3.2 The following security measures may be appropriate:

·a perimeter fence of good quality
·adequate security lighting
·limited and restricted access to all production and storage areas (especially scheduled) medicines
·adequate gates of sound construction, that are lockable
·security guards patrolling the grounds during the day and night. A telephone for the use of night security staff to use in the event of unlawful entry or fire, or an adequate electronic alarm system
·guard dogs and handlers for night patrol.

20.4 ENTRY TO BUILDINGS

20.4.1 The contents of the building are important in determining the level of protection required. The following security measures may be appropriate:

·robust outside doors
·good quality locks
·inaccessible windows
·installations of burglar alarms which should elicit a response and be regularly tested.

20.4.2 Consideration should be given to restricting and controlling entry to vital areas within buildings where high risk items are kept and the use of high security rooms and alarms.

20.5 INTERNAL SECURITY

20.5.1 There should be established procedures covering a number of security related activities, e.g.

·Locking of areas, control and storage of keys including the use of a key register
·Authorization of personnel who need access to vital or high-risk areas

Listing certain areas as "Restricted area - for authorized personnel only"
·control of all unnecessary staff movement between departments including personnel who are authorized to be in one area from moving freely to other high-risk areas
·control over the movement of customers and visitors
·control of the movement of stock ensuring that there is no opportunity for pilferage in transit. This also applies between the factory and the customer
·random physical checking of inventories
·the checking of waste as it is removed from production areas and the independent checking of cleaning and security staff where outside contractors are used
·checking of batch yields by a responsible person during processing and immediately on completion in case low yields may be the result of pilferage
·the searching of staff on leaving the premises or at any other time. Refer to Criminal Procedures Act
·screening of staff on employment, including careful checking of references
·particular attention should be paid to delivery services and other vehicles entering and leaving the premises.

CHAPTER 21:

SAFETY AND ENVIRONMENTAL PROTECTION

21.1 PRINCIPLES

21.1.1 The purpose of safety guidelines is to provide for the safety of persons at a workplace or in the course of their employment or in connection with the use of machinery.

21.1.2 Good Environmental Practice entails the minimization of waste at source and the disposal of waste in a manner harmless to the environment.

21.1.3 This chapter provides guidelines for practices and procedures which constitute Good Environmental Practice.

21.2 SAFETY

21.2.1 It is important to maintain a high level of safety awareness in pharmaceutical factories. To this end the importance of training cannot be over-emphasized.

21.2.2 Safety in the workplace is controlled by the Occupational Safety and Health Act (85 of 1993).

21.2.3 Factories are inspected on an annual basis by the Occupational Safety Association (NOSA). Regular safety self-inspections should also be undertaken.

21.2.4 The following should always be considered:

·buildings, machinery, vehicles, equipment etc. should be kept in a good state of repair
·fire preventative measures, as well as action steps in case of fire should be in place
·the dangers associated with electricity should be highlighted
·the nature of work/material will determine the level of personal protection necessary (helmets, safety glasses, headcovers, masks, respirators, ear protection, overalls, gloves, safety shoes etc.)
·first aid equipment and medicine should be available and accessible for the treatment of injured persons. Qualified first aid personnel should be available.

21.2.5 Special attention should be given to the manufacture, storage, use and handling of, and the exposure of employees and other persons to, hazardous materials; and the performance of work in hazardous or potentially hazardous conditions or circumstances.

21.3 ENVIRONMENTAL PROCEDURES

21.3.1 In addition to all applicable legal requirements, pharmaceutical companies may institute additional in-house requirements.

21.3.2 Procedures and controls to minimize the discharge to the environment of hazardous substances may include the following:

·procedures and controls regarding the discharge of hazardous substances into sewage and storm water drains where the material could accumulate or interfere with treatment processes
·emission to the atmosphere from process vents, storage vessels, area ventilating systems, incinerator stacks and fugitive emissions
·contamination of soil, water or the atmosphere due to spill, leakage from any source (storage tanks etc.), malfunction of control equipment, fire or explosion or from inadequate or improper treatment, storage or disposal practices.

21.3.3 Where possible, the company should have methods of rendering waste substances harmless to the environment.
21.3.4 There should be procedures to control the generation, transportation, storage, treatment or disposal of hazardous wastes. The most effective control of hazardous waste is the reduction or elimination of the waste. To that end, re-use, recycling, reclamation, inactivation or destruction is more desirable than land disposal or deep well injection. Other techniques should be thoroughly investigated before land disposal is selected.

21.3.5 Emergency procedures to minimize hazards associated with discharges to the environment should be developed. Procedures to co-ordinate internal and external emergency groups should be considered.

21.3.6 The capabilities of vendor suppliers and contract-acceptors should also be evaluated from an environmental point of view.

21.3.7 Monitoring programs should be developed to determine that compliance with legal and/or in-house specifications is maintained.

21.3.8 Procedures should be developed for the operation and maintenance of pollution control and monitoring equipment and should include preventative maintenance and training programmes.

21.3.9 Records should be retained in accordance with legal and/or in-house requirements.

21.3.10 The integrity of underground storage tanks and associated piping and equipment should be routinely verified. Alternatives to underground storage of potentially hazardous substances should be considered.

21.3.11 The preferred strategy for all waste management is reduction of waste at source.

CHAPTER 22:

STERILE PRODUCTS

22.1 INTRODUCTION

These standards do not replace any of the general GMP standards but must be seen as supplementary to them, the focus being on small volume injectable manufacture by aseptic process or terminal sterilization. The manufacture of sterile preparations has special requirements in order to minimise risks of microbiological contamination, and of particulate and pyrogen contamination. Terminal sterilization is generally achieved on one of three ways:

- ethylene oxide fumigation
- gamma irradiation
- steam sterilization (Autoclaving)

while aseptically prepared products are rendered sterile in bulk form through filtration and then processed into pre-sterilized containers under conditions which minimise the potential for change microbial contamination.

The major elements to be considered in aseptic processing include:

1. training of personnel;
2. layout and specifications for buildings and facilities;
3. particulate and microbial environmental monitoring programs;
4. systems for water, steam, air and other process gases;
5. descriptions of and procedures for manufacturing operations include people, materials, material flow, solution preparation and associated acceptance criteria;
6. use and validation of sterilization processes, including sanitization practices;
7. validation methods and data requirements for medial fills and container/closure systems;
8. operating practices for disposition of product, investigation reviews, and release/reject decisions.

22.2 DEFINITIONS

AIRBORNE PARTICULATE CLEANLINESS CLASSES

The airborne particulate 4 classes or grades shown below apply to the manufacture of sterile products.

Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide an homogeneous air speed of 0.30 m/s for vertical flow and 0.45 m/s for horizontal flow.

Grade B: In case of aseptic preparation and filling the background environment for grade A zone.

Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classifications for these grades are given in the following table.

ENVIRONMENTAL GRADES FOR CLEAN ZONES/AREA:

	at rest		in operation(c)	
GRADE	Maximum permitted number of particles/m^3 equal to or above			
	0,5um	5um	0,5um	5um
A	3 500	-	3 500	-
B(a)	3 500	-	350 000	2 000
C(a)	350 000	2 000	3 500 000	20 000
D(a)	3 500 000	20 000	-	-

Notes:

a) In order to reach B, C and D air grades, the number of air changes should generally be higher than 20 per hour in a room with a good air flow pattern and appropriate filters; HEPA for grades A, B and C.

b) Appropriate alert and action limits should be set for the particular operation.

The guidance given for the maximum permitted number of particles in the "at rest" condition corresponds approximately to the US Federal standard 209 E as follows: Class 100 (grades A and B). Class 10000 (grade C) and Class 100000 (grade D).

c) Recommended limits for contamination may be exceeded on isolated occasions and require only an examination of the production conditions and the control system. If frequency is high or shows an upward trend then action should be taken.

ASEPTIC AREA

A room or suite of rooms or special area within a clean area, designed, constructed, serviced and used with the intention of preventing microbial contamination of the product.

ASEPTIC FILLING

That part of aseptic processing whereby the product is sterilised separately, then filled and packaged using sterilised containers and closures in critical processing zones.

ASEPTIC PROCESSING AREA (APA)

Controlled environment, consisting of several zones, in which the air supply, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels.

BATCH

A defined quantity of material, or bulk, intermediate or finished product that is intended or purported to be uniform in character and quality, and which has been produced during a defined cycle of manufacture. To complete certain stages of manufacture it may be necessary to divide a batch into a number of sub-

batches, which are later brought together to form a final uniform batch. A batch is sometimes described as a lot.

For the purpose of a sterility test, a batch is a collection of sealed containers prepared in such a manner that the risk of microbial contamination may be considered the same for each of the units in it. It may be defined as one of the following:

(a) one sterilizer load

(b) the quantity of containers filled aseptically in one working session at one work station. A working session should be deemed to terminate whenever there is a significant change in circumstances which could affect the risk of product contamination (for example, a change of filling equipment, a change in the team of operators or a machine break-down). What in fact constitutes 'a significant change' should be documented and agreed upon in advance by the persons responsible for Production and Quality Control.

(c) in the case of aseptically filled products which are subsequently freeze-dried, a batch should be one freeze-drier load if this is less than in (b) above.

BIOBURDEN

The total number of viable microorganisms on or in health care product prior to sterilization.

BIOLOGICAL INDICATOR MICRO-ORGANISM

Micro-organism of a known sterilization resistance, that is used to develop and/or validate a sterilization process. The micro-organisms are frequently used on a carrier, which is supporting material on which test organisms are deposited.

BLOW/FILL/SEAL TECHNOLOGY

Blow/fill/seal units are specialist purpose built equipment in which, in one continuous operation, containers are formed from thermoplastic granule, filled and then sealed.

BUBBLE POINT PRESSURE TEST

Membrane filters have discrete pores or capillaries penetrating from one side of the membrane to the other. When a membrane has been completely wetted, liquid is held in these capillary pores by surface tension. The Bubble Point of a membrane is defined as the minimum gas pressure required to break this surface tension and force the liquid out of the capillaries. Bubble point is a measure of relative pore size.

CHANGING ROOM

A room or suite of rooms designed for the changing of clothes and from which a clean or aseptic area is entered.

CHEMICAL DISINFECTANT

A chemical or chemical solution capable of destroying micro-organisms through dehydration (alcohols), alkylation (aldehydes), protein denaturation (phenols), oxidation (iodine/chlorine) and wall permeability (quaternary ammonium compounds).

CLEAN ROOM

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

CRITICAL AREAS

Areas where sterilized products or containers/closures are exposed to the environment.

CRITICAL SURFACES

Surfaces which come into contact with sterilized product or containers/closures that may lead to contamination of product contact surfaces if not appropriately controlled.

D VALUE

Sterilization exposure under a defined set of conditions that result in one logarithmic (to the base 10) or 90% reduction in the population of a particular micro-organism.

DECONTAMINATION

The process of removing organisms and rendering the object safe for handling.

DISINFECTION

A process that kills or destroys most disease producing micro-organisms but rarely kills all spores. Disinfectants are used on inanimate objects as opposed to antiseptics which are used on living tissue.

FOGGING

Decontamination process performed by generating an aerosol or vapour of a disinfectant.

INTEGRITY TEST

Test to determine the functional performance of a filter system.

LAMINAR AIRFLOW

Air flowing in a single pass in a single direction, through a clean room or clean room area with uniform velocity along parallel flow-lines. Laminar air flow systems should provide a homogeneous air speed of 0.30m/s for vertical flow and 0.45m/s for horizontal flow.

LARGE VOLUME PARENTERALS

A sterile single dose injectable product intended for administration through the skin with a nominal fill volume of more than 100ml. It may be packed in glass or suitable plastic material.

MEDIA FILLS

Method of evaluating an aseptic process using a microbial growth medium. (Media fills are understood to be synonymous to simulated product fills, simulated filling operations, broth trials, broth fills, etc.)

POSITIVE PRESSURE

Atmospheric pressure which is higher than the immediate surrounding areas usually measured in inches of water or Pa.

QUALIFICATION

INSTALLATION QUALIFICATION (IQ)

Installation qualification (IQ) demonstrates that the unit under test is in compliance with all relevant criteria and safety standards, and is calibrated and regularly scheduled for preventive maintenance.

OPERATIONAL QUALIFICATION (OQ)

Operational qualification (OQ) testing demonstrates that the equipment functions as intended, that procedures exist describing operation of the equipment, and that personnel have been trained to set- up, operate and maintain the equipment.

PERFORMANCE QUALIFICATION (PQ)

Performance qualification (PQ) testing involves actual challenges to the system to substantiate its effectiveness and reproducibility.

SANITIZING

A process which results in a reduction in microbial population on an inanimate object to a relatively safe level.

SMALL VOLUME PARENTERAL

A sterile injectable product intended for administration under or through the skin with a nominal fill volume of 100 ml or less. It may be packaged in glass or suitable plastic material.

STEAM-IN-PLACE

Steam-in-place allows the entire healthcare product processing system to be steam sterilized as a single entity, eliminating or reducing the need for aseptic connections. Examples include tanks, filling lines, transfer lines, filtration systems and water for injection systems.

STERILE PRODUCTS

These may be classified broadly into two categories according to their manner of production, those that must be processed by aseptic means at some or all stages, and those which are sterilized when sealed in their final container (terminally sterilized) which are in a state free of viable micro-organisms.

STERILIZING FILTER

A appropriate sterilizer is to be used from an approved vendor who has the necessary supporting data on file.

STERILITY

The complete absence of living organisms.

NOTE:- The state of sterility is an absolute. There are no degrees of sterility. However the judging of sterility is probabilistic. While the probability may be reduced to a very low number, it can never be reduced to zero.

VALIDATION

The action of proving that any material, process, procedure, activity, system, equipment or mechanism used in manufacture or control can, will and does achieve the desired and intended result(s).

22.3 **FACILITIES**

Layout and construction features which shall be considered in the design of an APA include:

a) wall and floor surfaces which can be cleaned and which resist disinfectants;
b) avoidance of ledges and other horizontal surfaces which could collect particulates or disturb air flow;
c) installation of pipes, ducts and other utilities in a manner to avoid recesses and other surfaces difficult to clean;
d) adequate space for gowning areas, garment storage, soiled garment disposal, and hand washing;
e) separation of gowning and preparation areas from the APA by means of airlocks, pass-through windows for components, supplies and equipment;
f) maintain appropriate pressure differentials required for the given product and process;

22.3.1 The following minimum specification is described for facility design and controls. Additional requirements may be necessary for specific processes. Production of sterile preparations should be carried out in a clean area whose entry should be through airlocks for personnel or for goods. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has all been passed through filters of an appropriate efficiency.

22.3.2 There should be separate or defined areas of operation to prevent contamination. For aseptic processing there should be, as appropriate, an air supply filtered through high efficiency particulate air (HEPA) filters under positive pressure and systems for monitoring the environment and maintaining equipment used to control aseptic conditions. Monitoring results should be considered when reviewing batch documentation for finished product release.

22.3.3 In addition equipment for adequate control over air pressure, micro-organisms, dust, humidity and temperature should be provided where appropriate. Air filtration systems, including prefilters and particulate matter air filters, should be used where appropriate on air supplied to production areas.

22.3.4 Processing should be conducted in a cleanroom suite, constructed and operated in accordance with the air cleanliness standards. In order to control the microbiological and particulate cleanliness of the various grades/classes of operation, the areas should be monitored using various methods, eg. volumetric air sampling, settle plates, surface sampling (swabs, contact plates).

22.3.5 The filling of products to be terminally sterilized should be carried out in an appropriate environment for control of viable and non-viable airborne particulate matter. Extra precautions in the form of contained work stations and/or laminar air flow protection may be necessary when solutions intended for intravenous use are filled into wide-necked containers.

22.3.6 Equipment should be designed and installed so that it may be easily cleaned, disinfected or sterilized as required. Exposed surfaces should be smooth, impervious and unbroken in order to minimise shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents/disinfectants.

22.3.7 Non-sterile products should not be processed in the same area at the same time as sterile products.

22.3.8 Vaccines of dead organisms, or of bacterial extracts, may be filled (after inactivation) in the same premises as other sterile medicinal products. Spore forming organisms should be processed in separate premises or well isolated suites at least until any inactivation stage is completed. Live or attenuated vaccines should be processed and filled in premises separate from other processing or filling operations. Different live vaccines should be processed and filled separately from each other. Separation may be achieved in space or, given adequate cleaning and disinfection, in time. Special isolation facilities may be needed for highly contagious micro-organisms.

22.3.9 The processing of animal tissue materials and of micro-organisms (not required for the current manufacturing process), the performance of test procedures involving animals or micro-organisms, and any animal houses, must be well separated from premises for manufacturing sterile medicinal products, with completely separate ventilation systems, and separate staff.

22.3.10 Where equipment, such as filling equipment, connecting lines, and filter holders, is steam sterilized in autoclaves, it is important that established loading patterns of heat distribution be determined and the ability to achieve sterilization be monitored. One way of ensuring replication of the validated conditions is to follow established loading configuration diagrams and include them as part of the processing record.

22.3.11 Where equipment, such as large tanks and immobile piping is sterilized in place by the passage of pressurized steam, it is important that validation consider temperature and pressure at various locations. This will identify potential "cold spots" where there may be insufficient heat to attain sterility. Some in-line filters in piping systems cause a significant pressure differential across the filter, resulting in a temperature drop on the downstream side. One method of determining if such a drop in temperature will adversely affect the sterilization procedure involves the placement of suitable biological indicators at appropriate downstream locations. Validation could also include measurements of temperature and pressure at various points.

22.3.12 As far as possible, equipment fittings and services should be designed and installed so that maintenance and repairs may be carried out without additional personnel having to enter the clean aseptic rooms. If maintenance must be carried out within these areas, personnel concerned should receive appropriate training in the elements of microbiology and sterile area procedures. When within the areas they should be appropriately dressed, and use tools and equipment which have been sterilized or disinfected. Areas entered for maintenance should be cleaned and disinfected before processing recommences if the required standards of cleanliness and asepsis have not been maintained during the work.

22.3.13 Recording apparatuses should be accurately calibrated on installation and thereafter checked at scheduled intervals.

22.3.14 Validation of equipment performance on installation, is essential. Planned maintenance and frequent checks on performance are also important for critical items of equipment such as sterilizes, air filtration systems, and skills. Checks on steam and hot air sterilizes should include heat distribution and heat penetration studies. Filter efficiency tests should be conducted on air supply systems. Details of maintenance operations and performance checks should be recorded.

22.3.15 When blow/fill/seal units are used, particular attention should be paid to at least the following: equipment design and qualification, validation and reproducibility of cleaning and sterilization, background cleanroom environment in which equipment is located, operator training and clothing, interventions in the critical zone of the equipment, including any aseptic assembly prior to the commencement of filling.

22.3.16 Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimizing microbial and particle contamination of protective clothing. They should be effectively flushed with filtered air. Hand washing facilities should be provided only in the first stage change.

22.3.17 Airlocked doors should not be opened simultaneously. Airlocks should be equipped with interlocks to avoid simultaneous opening of doors.

22.3.18 Control of temperature and relative humidity, if necessary, within defined tolerances and, if possible, monitored continuously.

Aseptic processing facilities shall be designed to promote flow of components and materials in order to:

a) maintain the microbiological integrity of critical processing zones;
b) minimize the entry of contamination from outside the APA, and contain any such contamination so it does not reach critical processing zones; and
c) prevent mingling of clean and dirty items.

22.3.20 **Aseptic Processing Area (APA)**

Access to the aseptic processing area shall be restricted to qualified personnel with sufficient airflow and a positive differential air pressure existing relative to areas outside the APA to prevent contamination of the APA by adjacent areas.

22.3.21 **Processing Zones**

22.3.21.1 **Critical Processing Zones**
Critical processing zones shall be identified, and microbial and total particulate specifications shall be documented. These zones shall contain less than 3 500 particles of $\geq$ 0.5 um per cubic metre of air.

NOTE: This quality of air is commonly referred to as Class 100, Class M 3.5 or Class A/B in existing, commonly used national and international air quality standards.

All product contact and component sampling sites in the critical processing zone shall be monitored for environmental control during each operational shift.

22.3.21.2 **Other Processing Zones**

Other processing areas shall contain less than 350,000 particles of $\geq$ 0.5 um per cubic metre of air.

NOTE: This quality of air is commonly referred to as Class 10,000 Class M 5.5 or Class C in existing, commonly used national and international air quality standards.

22.3.21.3 **Non-sterile Support Areas**

Support areas shall contain less than 3,500,000 particles of $\geq$ 0.5 um per cubic metre of air.

NOTE: This quality of air is commonly referred to as Class 100,000, Class M 6.5 or Class D in existing, commonly used national and international air quality standards.

Personnel in support areas shall wear garments designed to minimize particulate generate, but these garments normally need not be sterile prior to use.

The disinfection and environmental monitoring of this area is less frequent than that utilized for the processing zones.

22.3.22 Temperature and humidity levels shall be specified, controlled and maintained to assure employee comfort while maintaining product attributes as this has a direct impact on aseptic techniques and the potential level of contamination.

These requirements should be met with a full complement of operational personnel and all equipment in operation.

22.4 AIR HANDLING SYSTEMS

The basic elements of environmental air systems and control programmes require proper design and control of the aseptic processing facilities including: relative humidity, room temperature, air velocity, HEPA filtration, laminar airflow, and room to room air balance.

22.4.1 Air quality and the monitoring of particulate matter (viable and non-viable) as a means to control physical and biological contamination in the manufacture of injectable products, is one part of the total system of control which should be designed to ensure compliance with the class limits as it applies to areas of manufacture and preparation of product and components. These include filtration though HEPA filters into clean rooms and suitable filtration into critical areas.

22.4.2 In the table below and at the end of this chapter are the basic environmental standards for various operations. These are arranged in classes.

ENVIRONMENTAL REQUIREMENTS FOR SPECIFIC OPERATIONS

OPERATIONS	WORK ZONE (CLASS)	CLEAN ROOM (CLASS)
Compounding and non-sterile filtration of bulk	-----	3
Preparation of containers and closures	-----	3
Washing, drying and depyrogenation of components	-----	3
Filling and sealing of products to be terminally sterilized.	2	3
Aseptic Fill	1/A	1/B
Aseptic Fill in form fill seal machine.	1/A	3
Aseptic addition to sterile manufactured product.	1/A	3

A filtered air supply should maintain a positive pressure relative to the surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent areas of different grades should have a pressure difference of 15 pascals (guidance value).

22.4.3
It should be demonstrated that air-flow patterns do not present a contamination risk eg. that particles are distributed from a particle-generating person, operation, machine, etc. to a zone of higher product risk.

22.4.4 A warning system should be provided to indicate failure in the air supply. Indicators pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly.

22.4.5 A determination of airflow patterns shall demonstrate that the airflow is appropriate to the process being performed and shall include investigations with the effects of turbulence which may interfere with the sweeping action of the air. These determinations shall be documented.

Airflow patterns, appropriate to the actual process being performed, should be tested for turbulence that would interfere with the sweeping action of the air.

22.4.6 **HEPA Filter Integrity**

Receipt of HEPA filters shall be accompanied by a supplier's certification that indicates the filter has an efficiency of 99.997% for the retention of 0.3 um or larger particles.

Upon installation, HEPA filters shall be integrity tested by a suitable method, e.g. cold DOP test.

Filters shall be velocity tested periodically, and airflow patterns shall be reassured whenever an airflow configuration change has been introduced. Tests shall be performed in the event of a change in the situation that might affect the integrity of the filter.

22.5 **SANITIZATION AND MONITORING**

22.5.1 Microbiological contamination should be controlled and monitored by appropriate procedures approved by Quality Control.

22.5.2 Cleanrooms and related areas should be cleaned frequently and thoroughly. Non-disposable "sticky mats" should be washed daily. Cleaning activities should be documented as per an approved procedure.

22.5.3 For Aseptic Processing where disinfection is employed to further reduce the surface contamination level, the choice of disinfectants and the way that they are used should be described in a procedure. In addition, detergents, disinfectants and antiseptics should be supplied sterile, or be sterile-filtered or otherwise sterilized at the use-dilution, or be sterilized as a concentrate and diluted only with sterile water. Diluted disinfectants or antiseptics should not be stored. Containers should not be topped up. Disinfectants/detergents used should be validated and approved. When disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly to detect the development of resistant strains. Disinfectants and detergents used in Class 1 and 2 areas should be sterilised prior to use.

22.5.4 Fogging should not be used as air contaminants are readily dissipated by natural or mechanical ventilation. Fumigation with humidified formaldehyde vapour may be employed to reduce microbiological contamination in places inaccessible to surface disinfection, however if fogging or fumigation is used, the process should be validated.

22.5.5 Cleanrooms and related areas should be monitored at planned intervals for airborne particulate contamination.

22.5.6 Cleanrooms and related areas should also be monitored at planned intervals for microbiological contamination using a combination of "settling plates", surface sampling and air sampling and the results obtained should be used to determine "warning", "action" and "shut-down" levels.

22.5.7 Gowning procedures should be proceduralized and monitored where aseptic filling procedures are practiced.

22.5.7.1 Written gowning procedures, training programmes, monitoring programmes and follow-up procedures shall be established.

At the time of entry into the gowning area, staff shall wear dedicated clothing (eg. plant uniform) and shoes.

Staff should enter the gowning area by way of an airlock.

NOTE: Generally, a mesh hair-net and beard cover, if required, are donned at the airlock. Disposable shoe covers may be used in addition to, or in place of, dedicated shoes.

Employees shall restrict movement in the APA in order to:

a) Avoid unnecessary movements which can generate particles or create turbulence;

b) Avoid reaching across open containers and exposed product and components;

c) Avoid blocking airflow over critical surfaces.

Employees shall regularly check gloves and gowns for proper fit and integrity. Gowned personnel should avoid unnecessary contact with walls, floors and cleaned surfaces with talking among personnel minimized.

Personnel conducting filling operations should not be exchanged during a shift with employees performing other functions within the APA. Operators working in non-sterile support areas shall not have access to the critical processing zone.

22.5.8 Monitoring should be frequent and should take place whilst normal production operations are in progress. In the case of aseptic filling it should provide the basis for the assessment of aseptic hygiene throughout the filling process. Results should be tabulated or graphed and assessed and prompt remedial action taken according to the monitoring standards established. Additional monitoring should be conducted after particular events such as spillages, cleaning, maintenance or fumigation.

22.5.9 Micro-organisms recovered from cleanrooms should be routinely identified, at least to genus level.

22.5.10 In a new unit, with a new process or with new operators, microbial monitoring should be sufficiently intensive to determine patterns and levels of contamination. Once suitable conditions have been established, monitoring may be reduced to a level which will demonstrate maintenance of those conditions.

22.5.11 There should be specific written procedures and documentation for:

- all cleaning and disinfecting of the APA
- Procedures shall include utilization of approved agents, the cleaning schedule, disinfectant application, post-disinfection cleaning if required, and employee safety precautions, including care and storage of cleaning aids. Only cleaning agents and disinfecting agents which have been tested, validated and approved, shall be used.
- the dismantling, cleaning and decontamination of all equipment.
- the cleaning of bulk containers and their subsequent inspection for release for use in processing.
- the control of external contamination of bulk containers during use.
- the assembly of filters and the connecting of hoses and pipelines.

22.5.12 Items brought into cleanrooms, including means of transport, should be of a standard of cleanliness compatible with the environmental standard for the room.
22.5.13 For Aseptic Processing when equipment maintenance or testing has been carried out within a Class 2 or cleaner area, and where the required standards of cleanliness and/or asepsis have not been maintained during this work, the area should be cleaned, and, where appropriate, disinfected and fumigated before processing recommences. This also applies to broth filling procedures which may contaminate the filling area.

22.5.14 The absence of disinfectant and cleaning agent residuals on product contact surfaces shall be confirmed. The manufacturers' instructions should be followed with respect to storage and use. Disinfectants shall be batched with a stated expiration date, and containers should not be refilled. Interchanging or rotating disinfectants should be reconsidered due to potential changes in environmental flora (isolates). A sporicidal agent may be necessary when environmental monitoring indicates the presence of sporeforming organisms, molds and fungi.

The effectiveness and frequency of the disinfection procedure shall be determined as part of the process validation. Evaluation of the efficacy of disinfectants should be related to the reduction of types and numbers of micro-organisms recovered from surfaces during routine environmental monitoring.

22.6 PERSONNEL TRAINING

22.6.1 Responsibility for monitoring the processing of sterile products should be delegated by management to a person competent through training and experience in the relevant aspects of microbiology, hygiene and the correct manufacture of sterile products. Only the minimum number of personnel required should be present in the clean area. Personnel involved with maintenance and cleaning should be trained prior to employment and supervised.

22.6.2 Personnel required to work in clean aseptic areas should be selected with care to ensure that they may be relied upon to observe the appropriate discipline and are not subject to any chronic disease or condition which would present an abnormal microbiological hazard to the product. The same principles should be applied to visitors to cleanrooms. Inspections and controls should be conducted from outside the area as far as possible.

22.6.3 All personnel (including those concerned with cleaning, testing and maintenance) should receive regular training in cleanroom procedures and in disciplines relevant to the correct manufacture of sterile products, including hygiene and the basic elements of microbiology.

22.6.4 When external staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their supervision.

22.6.5 Training should be carried out upon recruitment of staff and at regular, planned intervals in accordance with a formal training programme. Records, specific for each member of staff, should be maintained.

22.6.6 Personnel involved in the manufacture of sterile preparations should maintain high standards of personal hygiene and cleanliness and be instructed to report any condition (e.g. diarrhoea, coughs, colds, infected skin or hair, wounds) which may cause the shedding of abnormal numbers or types of contaminants. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by designated competent person.

22.6.7 Clothing should be appropriate to the work zone environment in which the personnel will be working. In addition, the following requirements should be adhered to:

·bulky or fluffy personal clothing should be removed before aseptic or cleanroom garments are donned
·wristwatches and jewellery, other than a simple wedding ring should not be worn. Cosmetics which can shed particles should not be used
·beards and moustaches should be covered during the compounding of products
·persons engaged in aseptic processing should wear sterilized or disinfected footwear and should change garments at least every working session

·persons working in Class 2 rooms should wear a single- or two-piece trouser suit gathered at the wrists and with high neck. Headgear must totally enclose hair and beard and be of the helmet/cowl type, tucked into the neck of the suit. Footwear should totally enclose the feet, and trouser-bottoms should be tucked inside the footwear

·sterilize non powdered rubber or plastic gloves, when worn, should be disinfected regularly during operations using a suitable spray and changed at regular intervals or when damaged.

22.6.8 Outdoor clothing should not be brought into the changing rooms associated with clean or aseptic areas, and personnel entering these changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a clearly displayed written procedure.

22.6.9 Clean and aseptic area clothing should be laundered or cleaned and thereafter handled in such a way that it does not gather contaminants which can later be shed. Separate laundry facilities for such clothing are desirable. It should be noted that some methods of sterilization may damage fibres and reduce effective garments. Washing and sterilization operations should follow a clearly displayed written procedure.

22.6.10 For each worker in a class 2 room, clean, sterile, protective garments should be provided at each work session.

22.7 **MANUFACTURING REQUIREMENTS AND CONTROLS**

22.7.1 Starting materials should be selected so as to contain only minimal quantities of micro-organisms or pyrogenic material. The material specification should include requirements for microbial monitoring, with limits as necessary.

22.7.2 Precautions should be taken during all processing stages, before and after sterilization to avoid contamination of the product with micro-organisms.

22.7.3 Activities and conversation in clean and aseptic areas should be kept to a minimum. Movements of personnel should be controlled and methodical, so as to avoid excessive shedding of particles and organisms due to over-vigorous activity and to avoid disruption of air flow patterns.

22.7.4 Containers and other materials liable to generate particles or fibres should not be taken into areas of Class 1 or Class 2.

22.7.5 The intervals between the washing and drying and the sterilization of components and equipment should be as short as possible and subject to a time limit appropriate to the storage conditions. The interval between sterilization and use of these materials should also be subject to a time limit.

22.7.6 Articles required in an aseptic area should be sterilized and passed into the area in such a way which will avoid contamination of the area.

22.7.7 The time between the start of the preparation of a solution and its sterilization (or sterile filtration) should be as short as possible and subject to a limit for each product that takes into account its composition and the prescribed method of storage.

22.7.8 Unless special storage precautions are taken, bulk solutions should have no greater volume than can be filled in one working day and should be filled into final containers and sterilized within one working day.

22.7.9 The microbiological load of products should be as low as practicable prior to sterilization eg. all solutions should be passed through a bacteria-retaining filter immediately before filling.

22.7.10 Each procedure used for the sterilization of a particular quantity or volume of a material, component, or product should have been demonstrated to be effective and reliable by suitable validation studies.

22.7.11 Batch processing records for sterile products should include details of the sterilization of the components and equipment used.

22.7.12 Water treatment plants should be designed, constructed, and maintained to ensure the reliable production of water of the required quality. They should not be operated beyond their designed capacity. The water should be produced, stored and distributed in such a manner as to discourage microbial growth (eg. by constant circulation at temperatures above 70°C, and avoidance of places where water may remain stagnant such as U-bends, 'dead ends' and ill-designed valves).

22.7.13 Water sources, water treatment equipment and treated water should be monitored regularly for chemical, microbial and pyrogen contamination as relevant. Records should be maintained of the results of the monitoring, and of any remedial action.

22.7.14 Unsterilized distilled water intended for further processing or sterilization should not stand for more than a short time unless special precautions are taken, such as storage above 65°C, to prevent both the growth of bacteria and the consequent development of pyrogens.

22.7.15 Where water or solutions are held in sealed vessels, any pressure relief outlets should be protected by hydrophobic microbial air filters.

22.7.16 Components and containers should be handled after the final cleaning process in such a way that they are not subject to recontamination. The final rinse should be with purified water of appropriate quality.

22.8 VALIDATION OF ASEPTIC PROCESS

22.8.1 Aseptic processing and filling equipment, used in aseptic work procedures and environments should be validated for their overall performance at the time of qualification and at regular intervals thereafter by test runs in which suitable sterilized agents which will not inhibit microbial growth are passed through the routine procedures up to the sealing of filled final containers. In the case of liquid processing the test agent should be soybean-casein digest medium and the filled sealed containers should be incubated for at least 14 days at 3$\pm$2 °C. When appropriate to the product, other media or temperatures may also be used. In the case of solid or semisolid processing, a process should be developed to imitate the filling operation as closely as possible. Full microbiological test controls should be carried out.

22.8.2 For each container type, at least 3 000 typical containers should be filled to the labelled quantity and sealed in an undivided test run. The test run should be carried out immediately after a regular production run and in "worse case" conditions. No growth should be observed in the incubated containers, but production may continue if not more than three containers show evidence of microbial growth after incubation (i.e. contamination rate of not more than 0,1 %).

22.8.3 Initial validation should employ at least three runs, which should not be continuous, but consideration should also be given to employing more than 3 000 units in subsequent runs in order to reach statistical significance in estimating the contamination rate.

22.8.4 Continuing validation should occur at least twice per year for each shift for each filling/sealing line. All personnel should take part in a media fill at least once per year. The duration of the run should be sufficient to cover all manipulations that are normally performed in actual processing at filling rates comparable to standard Production.

22.8.5 Medium should be made to contact the entire inside surface of the containers being filled at intervals during the incubation period, e.g. by swirling or tumbling. Media fertility and stasis tests should be carried out.

22.8.6 Consideration should be given to validating the ability of the medium used to grow micro-organisms recovered from environmental monitoring or from sterility testing.

22.8.7 When a new aseptic process is introduced, when any significant change is made in such a process or in the equipment, when staff are being trained and at regular intervals thereafter, the efficacy of

aseptic procedures should be validated, eg. by filling a sterile liquid nutrient medium or powder and testing for the incidence of contamination. Such fillings should be carried out under normal operating conditions.

22.8.8 Procedures shall be in place describing the operations of all critical equipment. The qualification of equipment generally includes calibration, installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ).

22.8.9 Processing equipment such as sterilizers, component washers, filters, fillers, closure placement equipment, sealing machinery, and lyophilizers shall be qualified as part of the overall programme. Product contact surfaces shall be sterilized and process validated.

22.8.10 Process related utilities such as purified water, water-for-injection, pharmaceutical compressed air (and/or other gases), clean or water-for-injection steam, and clean-in-place/steam-in/place systems shall be validated.

22.8.11 The following measures should be addressed for steam-in-place systems:

a) displacement and elimination of entrapped air;
b) constant bleeds or steam traps at all low points to eliminate condensate buildup;
c) strict adherence to the steam-in-place procedures;
d) proper maintenance of the integrity of the system after the process;
e) strict adherence to the maximum filter specifications for temperature, pressure, and flow, and
f) avoidance of back pressure on filters during steam-in-place.

22.9 STERILIZATION PROCESSES

22.9.1 General

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

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

22.9.1.3 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 confirmed. Such validation should be repeated at suitable scheduled intervals and whenever significant modifications have been made to the equipment. Records should be kept of the results.

22.9.1.4 Products which are intended to be sterile, should be preferably heat sterilized in final sealed containers. Each cycle of heat sterilization should be monitored by means of temperature probes to determine if the heat distribution in the sterilization vessel is uniform.

22.9.1.5 The charts of automatic recorders of cycle parameters should constitute part of the batch processing records of sterile products and should be marked to identify the batch or batches to which each applies.

22.9.1.6 Each separate sterilizing basket, package, pallet etc., of products or components undergoing sterilization should be fastened to ensure its integrity and should bear in a conspicuous position a visual indicator to demonstrate whether or not it has passed through a sterilization cycle.

22.9.1.7 To verify the continuing effectiveness of dry heat sterilizing cycles, suitable microbiological indicators of known high resistance to the dry heat sterilization process should be included in sterilizing cycles and placed at representative locations in typical loads. The indicators should be located in the most difficult-to-sterilize site within the sterilizer and, where appropriate, within the product.

22.9.2 **Moist Heat**

22.9.2.1 This method is suitable only for water-wettable materials and aqueous solutions. Other materials must be sterilized by other methods.
22.9.2.2 Moist heat sterilization is achieved by exposure to saturated steam under pressure in a suitably designed chamber. Under these conditions there is an exact relationship between steam temperature and pressure, but the pressure is used solely to obtain the temperature required and otherwise contributes nothing to the sterilization process. The temperature and not the pressure must be used to control and monitor the process.

22.9.2.3 Whilst temperatures and periods of treatment are recommended in official compendia, (eg.121 °C for 15 minutes), other combinations of temperature and time can be used provided they have been validated. It is important to recognize that the temperature-time relationship is complex, that at temperatures below 115 °C disproportionately long periods of time are required, and that as temperature is reduced, the process may become progressively less reliable.

22.9.2.4 Items to be sterilized (other than aqueous medicinal products in sealed containers) should be wrapped in a material which allows removal of air and prevents penetration by micro-organisms after sterilization. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

22.9.2.5 Unless special precautions are taken, air must be displaced from the chamber, and from materials within the chamber, either by a period of free steaming before the sterilization cycle begins or by use of a vacuum pump.

22.9.2.6 Mixtures of steam with air may be used for sterilizing sealed containers of aqueous fluids provided that steps are taken to ensure homogeneity of the steam-air mixture throughout the chamber, and the process has been validated.

22.9.2.7 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time-period is commenced. This time must be determined for each type of load to be processed before the method is adopted.

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

22.9.3 **Dry Heat**

22.9.3.1 Dry heat is suitable for sterilizing equipment, non-aqueous liquids and other materials which can withstand the temperatures required. Various combinations of temperature and time are recommended in official compendia but other combinations of temperature and time can be used provided they have been validated.

22.9.3.2 Heating should be carried out in an oven or other equipment which will achieve sterilizing conditions throughout the load. The method of loading used should not be such as to lead to an uneven temperature distribution.

22.9.3.3 Before the timed sterilization period begins, sufficient time must be allowed for the temperature of the whole load to reach the requisite level. This time should be determined for each type of load to be processed, and the timed sterilization period should not start until the entire load is known to have reached that level .

22.9.4 **Filtration Sterilization**

22.9.4.1 Sterilization by filtration should only be employed when heat sterilization cannot be applied because of its detrimental effect on the active ingredients.

22.9.4.2 Solutions or liquids can be sterilized by filtration through a sterile filter of nominal pore size of 0,22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds but not all viruses or mycoplasmas.

22.9.4.3 The integrity of the filter assembly should be checked by an appropriate method, such as a bubble-point pressure test or forward-flow pressure test immediately before and after use. Abnormal filtration flow-rates should be noted and investigated. Results of these filter-integrity checks should be recorded in the batch record.

22.9.4.4 Any potentially fibre or particle releasing filter should be followed by a downstream non-fibre releasing filter that will retain such particles.

22.9.4.5 If it is intended to use a filter for an extended period, the effectiveness of the process should be validated, taking into account such aspects as the microbial content of the solution, the capacity and efficacy of the filter and its housing, and the potential for growth of organisms on or through the filter. It is preferable not to use the filter for longer than one working day.

22.9.4.6 Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilized micro-organism retaining filter, immediately prior to filling, may be advisable.

22.9.4.7 The time interval between sterilizing a bulk solution by filtration and filling it into final containers should be kept to a defined minimum, appropriate to the conditions under which the filtered bulk is stored.

22.9.4.8 Filters should not adversely affect the quality or content of solutions by removal of ingredients from them or by release of substances into them. Asbestos filter pads should not be used for filtration of parenteral products. Filters should be treated as starting materials and subjected to quality control. Filters must be sterilized when aseptic filling is carried out.

22.9.4.9 Any new or modified filtration system for sterilization should be validated for integrity before it is placed in service and a record of such validation kept. Only positive pressure filtration should be employed.

22.9.4.10 Where the bulk batch is divided into lots for different sterilization or lyophilisation cycles, all such lots should be distinguishable from one another, by label and in the records.

22.9.5 **Biological Indicators**

22.9.5.1 Biological and chemical indicators used alone are not acceptable as proof of sterility.

22.9.5.2 Biological indicators (i.e. preparations of bacterial cultures, usually spores of selected resistant strains) are much less reliable than physical monitoring methods (except in ethylene oxide sterilization).

22.9.5.3 Strict precautions must be taken when handling biological indicators due to the hazard of introducing potential contaminants into an otherwise microbiologically clear area.

22.9.5.4 Microbiological indicators should be treated as starting materials and subjected to quality control.

22.9.6 **Chemical Indicators**

22.9.6.1 Chemical indicators are available for heat, ethylene oxide and radiation sterilization, usually in the form of adhesive tapes or patches, colour spot cards, small tubes or sachets. They change colour as a result of chemical reaction brought about by the sterilization process, but it is possible for the change to take place before the sterilizing time has been completed, and hence, with the exception of plastic dosimeters used in radiation sterilization, they are unsuitable as proof of sterilization.

22.9.6.2 Certain other substances with melting points which coincide with the sterilization temperature may be used as indicators in heat sterilization. They indicate that the temperature has been reached, but not that it has been maintained, or for how long.

22.9.6.3 Radiation-sensitive colour discs, not to be confused with plastic dosimeters, are used to differentiate between packages which have been subjected to irradiation and those which have not. They are not indicators of successful sterilization, and the monitoring of radiation sterilization by calibrated plastic dosimeters is the only way of ensuring that the sterilizing dose has been given.

22.9.7 **Ethylene oxide**

22.9.7.1 This method should only be used when no other method is practicable. During process validation it should be shown that there is 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.

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

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

22.9.7.4 Each sterilization cycle should be monitored with suitable biological indicators appropriately distributed through the load. The information so obtained should form part of the batch record.

22.9.7.5 Records should be obtained of the time taken to complete the cycle, the pressure, temperature and humidity within the chamber during the process, the gas concentration and total amount of gas used. The pressure and temperature recorded during the cycle should form part of the batch record.

22.9.7.6 After sterilization, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to be reduced to defined validated levels.

22.9.8 **Radiation**

22.9.8.1 Radiation sterilization is used mainly for sterilization of heat sensitive materials and products.

22.9.8.2 During the sterilization procedure the radiation dose should be measured. For this purpose dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeter absorbance should be read within a short period after exposure to radiation.

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

22.9.9 **Air Removal**

The removal of air from a steam- n-place system may be accomplished by one of two methods:

a) by gravity
b) through the use of vacuum

22.9.10 **Condensate Removal**

Condensate should be continuously removed from all low points to maintain sterilization conditions in the system.

22.9.11 **Post-sterilization system integrity**

System integrity shall be maintained after sterilization. The system should then be purged of steam and condensate and maintained under positive pressure until ready for use.

NOTE 15: The introduction of gas can dry the system prior to use, which is very important if the product to be processed is non-aqueous.

22.9.12 **Depyrogenation**

Data should be available that demonstrates a knowledge of the (or endotoxin) loading on components prior to treatment in a depyrogenation process. When a depyrogenation process is used, the data shall demonstrate that the process will remove a greater quantity of endotoxin than may have been originally present in the component or product.

NOTE: Plastic medical devices and/or containers may be depyrogenated by rinse processes, and/or high temperature moulding, and/or extrusion processes prior to filling. Rubber compound stoppers may be rendered pyrogen-free by multiple cycles of washing and rinsing prior to final steam sterilization. The final rinse should be water-for-injection quality.

22.9.13 **Gases**

Compressed air shall be dry and oil-free. All compressed gases that contact products, container/closures or product contact surfaces shall be filter sterilized.

22.9.14 **Processing Time**

The total time for the product filtration and filling operations, and holding time after filtration and prior to filling, shall be limited to a defined maximum. Elapsed time between component washing and sterilizing should be minimized.

22.9.15 **Sampling**

All product contact and component sampling sites in the critical processing zone shall be monitored for environmental control during each operational shift. If the environmental control programme indicates that specified limits are exceeded, corrective action shall be taken in accordance with written procedures.

Other processing zones shall be monitored frequently, with sampling frequency based on classification of the zones and testing data.

Sampling in critical processing zones shall be performed in a manner which presents a minimal contamination risk to the product.

Support areas shall be routinely monitored, but may be monitored on a less frequent basis than processing zones

22.9.15.1 **Sampling Sites**

Sampling sites should be derived from and consistent with those used during validation activities. The individual sampling sites for each programme should be at the discretion of the manufacturer reflecting differences in facility/equipment design and processing parameters.

22.10 **QUALITY CONTROL**

22.10.1 **Sterility Testing**

22.10.1.1 A test for sterility must be carried out on samples from each batch of sterile products except for products for which approval to omit the test for sterility has been specifically granted by the inspecting authority.

22.10.1.2 Where a batch of product is sterilized as a series of lots, each of which is subjected to a separate sterilizing cycle or is subjected in processing to different treatment which may affect its sterility, eg. different lyophilisation cycles, each lot should be tested for sterility.

22.10.1.3 Samples for the test of sterility should be taken:

- in the case of aseptically prepared products, at regular intervals during the filling operation so as to be representative of the whole of the batch or filling session. In particular the samples should include containers filled at the beginning and end of the batch and after any significant interruption of work. Resampling for retesting must follow the same principle. Where possible, the first and last units filled should be part of the initial sample from all prescribed locations and at all prescribed times . These should be divided between test samples and retention samples.

- records should be kept of the results of all sterility tests and control tests. Contamination rates for different products and for different sterility test techniques should be calculated periodically and compared. and their significance assessed.

- for products which have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

22.10.2 **Pyrogen Testing**

22.10.2.1 The water used in the preparation of sterile products should be tested for pyrogens at least once per week and after any repair or disturbance to the system, using, for example the limulus amoebocyte lysate test. Sampling should include "worst case" situations, including start-up. Water for injection stored below 65 °C should be tested at least twice weekly for microbial and pyrogen contamination.

22.10.2.2 Appropriate samples for pyrogen testing should include those taken from the first units filled, the last units filled, the first units filled immediately following a break in the filling line (eg. a filter change) and the first units filled following prolonged downtime periods, i.e. one hour or more.

22.10.3 **Media Fills**

Media filling in conjunction with comprehensive environmental monitoring of the aseptic area can be particularly valuable in evaluating the aseptic processing of sterile products. The media fill should simulate the aseptic process as far as reasonably practical.

Scheduled media fill requalifications shall occur at least every six months for each aseptic process and filling line. The media fill run shall be of sufficient duration to cover all manipulations normally performed in actual processing. Media fill evaluations shall be incubated for at least 14 days at temperature ranges of 20-25 and 30-35. Requalification acceptance criteria shall meet the number of runs and total filled units which is summarized as follows:

a) For production batch sizes of less than 500 units, 3 media fill runs of the maximum batch size shall be conducted.

b) Alternatively, for small production batch sizes where infrequent batches (less than 4 per year) are filled, or for clinical batches, it shall be acceptable to requalify the process of line by performing a single media fill run, containing a quantity of units at least equal to the production batch, immediately after the production batch is filled.

c) For production batch sizes between 500 and 2,999 units 1 media fill run of at least the maximum batch size shall be conducted.

d) For production batch sizes greater than 3 000 units, 1 media fill run of at least 3 000 units shall be conducted.

Guidance values for microbiological monitoring of clean rooms in operation

	Maximum number of viable organisms (a)			
GRADE	air sample cfu/m^3	settle place (90mm) cfu/4 hour	contact place (55mm) cfu	glove print 5 fingers cfu
A	< 1 (b)	< 1 (b)	< 1 (b)	<1 (b)
B	10	5	5	5
C	100	50 (c)	25	-
D	200	100 (c)	50	-

Notes:

(a) Recommended limits for contamination may be exceeded on isolated occasion and require only an examination of the production conditions and the control system. If the frequency is high or shows an upward trend then action should be taken.

(b) Low values involved here are only reliable when a large number of samples is taken.

(c) For Grades C and D settle plates may be exposed for less than 4 hours.

Grade	Examples of operations
A	Aseptic preparation and filling. Filling of products to be terminally sterilized when products are unusually at risk.
B	Transfer and storage of containers of freeze-dried products and components for aseptic filling.
C	Preparation of solutions and components for subsequent sterile filtration and aseptic filling. Preparation of solutions and components for subsequent filling and terminal sterilization when products or components are considerably exposed or unusually at risk. Filling of products to be terminally sterilized.
D	Preparation of solutions and components for subsequent filling and terminal sterilization.

22.11 FINISHING OF STERILE PRODUCTS

22.11.1 Ampoules should be sealed by a "drawing-off" technique rather than by tip-sealing.

22.11.2 Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined delay.

22.11.3 Filled containers of parenteral products for administration to humans should be inspected individually. When this inspection is visual it should be done under suitable controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed adequate breaks from inspection.

22.11.4 Where automatic/electronic/photo-electric methods of inspection are used, the effectiveness of the equipment should be validated and its sensitivity monitored.
22.11.5 Tests to demonstrate the integrity of seals of closures on product containers should be carried out during the production of each batch. These results should form part of the batch processing records.

22.11.6 Wherever the nature of the product makes it possible, every filled and sealed container of parenteral product should be tested for physical defects and for particulate contamination.

22.11.7 It is appropriate to monitor and control the microbiological content of the water and other materials used in the leak test procedure.

22.12 BATCH RELEASE

22.12.1 The decision to release a batch of sterile product for use should take account of not only the specific production records and results of tests performed on that batch, but also the cumulative test records and information gathered from the monitoring of the environment, personnel, intermediate products, equipment and processes, both before and during the manufacturing of the batch.

CHAPTER 23

ISOLATOR TECHNOLOGY

23.1 PRINCIPLES

23.1.1 Isolator technology is now widely used and accepted for the aseptic processing of pharmaceuticals. The use of barrier systems offers improvements in the handling of pharmaceutical products in circumstances where product protection and the maintenance of asepsis, and/or operator protection and the control of hazardous substances are critical requirements. Isolators have several advantages over conventional clean rooms and laminar flow cabinets for aseptic preparation and dispensing of injections. Isolators provide an acceptable level of sterility assurance for aseptic operations. Isolators cannot be regarded as totally sealed units since access to the controlled workspace must be open when materials are transferred into and out of this area and the workspace is continuously supplied with HEPA filtered air. Other than this air supply, the controlled workspace of the isolator will, when in use, be sealed from its background environment.

23.1.2 Critical SOP's include those detailing sanitisation, introduction of material, withdrawal of material, and training of personnel.

23.2 DEFINITION OF TERMS

23.2.1 Isolator

A containment device which utilises barrier technology for the enclosure of a controlled workspace.

23.2.2 Type 1 Isolator

An isolator primarily designed to protect the product from process-generated and external factors that would compromise its quality.

23.2.3 Type 2 Isolator

An isolator designed to protect the product from process-generated and external factors that would compromise its quality and to protect the operator from[n hazards associated with the product during operation and in the event of failure.

23.2.4 Air lock

An enclosed space with two or more doors and which is interposed between the controlled workspace and the background environment of the isolator, for the purpose of controlling air flow between them and to facilitate the transfer of materials between them.

23.2.5 Alarm

An audible and/or visible signaling system which warns of a fault condition. It must incorporate a device to ensure that it cannot be cancelled until corrective action is taken.

23.2.6 Background Environment

The environment in which the isolator is sited. Background environments are categorised in table 3.

23.2.7 Controlled Work Space

An enclosed space constructed and operated in such a manner and equipped with appropriate air handling and filtration systems to reduce to a pre-defined level the introduction, generation and retention of contaminants within it.

23.2.8 Critical Zone

That part of the controlled workspace where containers are opened and product is exposed. Particulate and microbiological contamination should be reduced to levels appropriate to the intended use.

23.2.9 Decontamination

A process which reduces contaminating substances to a de-defined acceptance level.

23.2.9.1 Sanitisation

That part of decontamination which reduces viable micro-organisms.

23.2.9.2 Particulate Decontamination

That part of decontamination which reduces visible and sub-visible levels to a defined acceptable level.

23.2.9.3 Chemical Decontamination

That part of decontamination which reduces chemical contamination to a defined acceptance level.

23.2.10 Docking Device

A sealable chamber which can be (completely removed from or locked onto an isolator and then opened without contamination passing into, or out of, the controlled workspace or the chamber.

23.2.11 Exhaust Filter

A filter through which the exit stream of air from an isolator

23.2.12 HEPA (High Efficiency Particulate Air) Filter

Filters with no greater than 0,003 % penetration of 0,5 um particles when tested according to BS 3928.

23.2.13 Laminar Flow

Airflow in which the entire body of air within a confined area moves with uniform velocity along parallel flow lines.

Note: May also be referred to as 'unidirectional flow'.

23.2.14 Sterilisation

The process applied to a specified field which inactivates viable micro-organisms and thereby transforms the non-sterile field into a sterile one.

23.2.15 Transfer Chamber
A device which facilitates the transfer of goods into or out of the controlled workspace whilst minimising the transfer of contaminants.

23.2.16 Transfer Hatch

See Transfer Chamber.

23.2.17 Transfer Isolator

A separate isolator which can be fixed or removable and which is attached to the main operational unit, acting as a complete transfer device.

23.2.18 Transfer Device

A device, which can be fixed or removable, which allows materials to be transferred into or out of the controlled

23.2.19 Transfer Port

See transfer chamber.

23.2.20 Transfer System

The process of transfer of materials into and out of the isolator through a transfer device.

23.2.21 Turbulent Flow

A flow of air which is non-laminar.

23.3 ISOLATOR DESIGN PRINCIPLES

Altnough the specifications should not be restrictive, there are basic design parameters to which isolators should conform.

23.3.1 Air input may be laminar flow, turbulent flow, or a combination of the two.

23.3.2 The critical zone of the controlled workspace should be equivalent to the EC Grade A, but the airflow in the critical zone need not be laminar flow (see 23.3.3).

23.3.3 If the isolator is not supplied with a laminar air flow system, tests should be performed so as to confirm that only air complying with the requirements of EC Grade A is applied to the critical zone. Air should be effectively swept from the controlled workspace and startling vortices. Stagnant areas should not exist.

23.3.4 Type 2 isolators should operate under negative pressure.

23.3.5 Type 2 isolators for use with radiopharmaceuticals should incorporate an appropriate radiation protective system against ionising radiations.

23.3.6 For operator protection, in the event of a breach in type 2 isolators a minimum breach velocity of O,7m sec- should be maintained.

23.3.7 The transfer of materials into and out of the controlled workspace is a critical factor of the isolator's operation. The transfer device separates the background environment from the Grade A controlled workspace. It should be designed such that it does not compromise the Grade A controlled environment. To this end an interlocked device will provide greater security. The size of the transfer device should be sufficient to allow all necessary materials and equipment to be passed through

Note: Commissioning studies should include tests to confirm that contaminants will not pass from the transfer device into the controlled work area. A fully validated transfer procedure should be in place.

23.3.8 All internal surfaces (including seals, holes, screws) should be accessible to the operator for cleaning and disinfection purposes without compromising the isolator's integrity. They should be resistance to corrosion by cleansing and disinfecting agents and should be capable of withstanding gaseous disinfection or sterilisation.

23.3.9 The pressure differential between the Grade A controlled workspace and the background environment should be continuously monitored.

23.3.10 All filters in isolators in which hazardous substances are handled must have a safe change facility. Both the manufacturer and the user should be made aware of the risks associated with changing filters.

23.3.11 All exhaust (or re-circulated) air should pass through one or more HEPA filters. Extract air from type 2 isolators should normally be ducted to the outside through one or more HEPA filters and another necessary absorption media (eg. carbon). Where isolators are used infrequently or low levels of hazardous materials are handled, then the exhaust air may be re-circulated into the background environment through two HEPA filters in series provided the risk has been assessed and has been shown to be low risk. (For further details of exhaust filters see also appendix 5.)

23.3.12 When designing isolators, consideration should be given to optical clarity, lighting, noise levels, humidity, electrical safety, temperature, vibration, ergonomics and the comfort of the operator (s),

23.3.13 Pressure differentials and the direction of air flow should be such that when the access between the transfer system and the controlled workspace is open, contaminants will not pass into the controlled workspace and, additionally in type 2 isolators, operator protection is also maintained.

23.3.14 If a fixed transfer device has its own air supply it should be HEPA filtered.

23.3.15 The air change rates in all parts of the isolator system should be sufficient to maintain the defined grade of environment

Note: The air change rate will be such that any unfiltered air that enters the isolator or transfer device will be purged from the system within 5 minutes.

23.3.16 The fan should not be capable of damaging the filters in their maximum loaded state.

23.3.17 Isolators should have the facility to enable routine leak testing and particle counts to be carried out in the isolator itself and in its transfer devices. Where access points are provided for test equipment they should be labelled.

23.3.18 The isolator should be designed so that the HEPA filters can be integrity tested in situ.

23.4 THE SITING OF ISOLATORS

23.4.1 Isolator(s) should be sited in a dedicated rooms(s) used only for the isolator and its ancillary equipment and related activities. The interior surfaces of the rooms (walls, floors, ceiling) should be smooth, free from cracks and open joints. They should not shed particulate matter and should allow easy and effective cleaning and sanitisation.

23.4.2 The classification of the background environment in which the isolator is located will depend upon the design and, operational characteristics of the isolator, but should be at least grade D. When deciding on the siting of isolators, consideration should be given to the following:
The type of isolator - type I/type 2.
The transfer system - see appendix 1.
The level and frequency of use i.e. dispensing/ preparation/manufacture.

In order to address these variables, isolators have been classified according to the transfer system. Details of the different transfer systems and the corresponding transfer devices are shown in appendix 1. The background environment for the isolator can then be categorised as I, II, III, IV, V or EC Grade A-D depending upon the transfer system and the use to which the isolator will be put (tables 1 and 2).

23.4.3 The definitions of air quality categories I-V are given in table 3. The categories have been defined according to their permitted levels of viable and non viable particles. For comparative purposes, the requirements of the different environmental classifications from commonly quoted standards documents are also included in the table.

it should be noted that the levels of viable micro-organisms for categories II-IV of the background environment are more stringent than then nearest grade of air quality specified in the EC GMP.

23.4.4 For pharmaceutical applications the major criterion upon which the background environment is categorised should be the risk of microbiological contamination of the product. For this reason the environment has been classified in this document according to the number of viable organisms that can be detected.

It is recognised however that environmental testing is not a guarantee that environmental quality is maintained.
Procedures and quality systems should be used to provide the necessary level of quality assurance.

23.5 FACTORY ACCEPTANCE TEST (FAT)

23.5.1 A factory acceptance test (FAT) should be performed. The report should cover at least a check against Customer Order for completeness, visual check for appearance and identification, the record of serial numbers of filters, dimensional check, electrical installation and safety check, functional check, including operation of interlocks and alarms and documentation dossier.

23.6 INSTALLATION QUALIFICATION (IQ)

23.6.1 Qualification data (records) of the isolator should at least cover installation qualification (IQ), i.e. integrity and leakage test, filter integrity test, filter mounting integrity test, instrument check and calibration as well as functional check of all operating systems.

23.7 OPERATIONAL QUALIFICATION (OQ)

23.7.1 Operational qualification (OQ) should be performed.

23.7.2 Records should cover checks on air flow rates, pressures controlled within specified limits, air flow patterns, temperature and humidity patterns, particle counts as well as noise and light levels.

23.7.3 Testing of filters and filter housings should be done at regular intervals.

23.7.4 The vibration effects of HVAC fans and filling equipment on joints and particularly on hepa filter clamping systems should be tested. Maximum limits for vibration should be set, monitored and controlled.

23.7.5 The ventilation/filtration system should be appropriate for functions performed in the isolator and should be validated.

23.7.6 Leak tests of the Isolator should be performed on a regular basis, including the glove/sleeve system.

23.8 PERFORMANCE QUALIFICATION (PQ)

23.8.1 Performance qualification (PQ) should be performed.

23.8.2 Sterilisation cycles with standard loadings should be developed and validated.

23.8.3 There should be relevant SOP's with respect to operations being performed.

2 3.9 MICROBIOLOGICAL MONITORING

23.9.1 General

Viable particle monitoring for micro-organisms and non-visible particle monitors should be performed at regular intervals.

A plan of the isolator should be prepared with coded positions for settle plate, swabbing and air sampling sites. The following methods may be employed:

23.9.2 Settle Plates
Coded and dated, sterile, tryptone soya agar plates should be exposed for two hours at all test sites within the isolator. These should be incubated in accordance with a written SOP at the appropriate temperature for up to five days, or as otherwise chosen by the microbiologist.

23.9.3 Surface Samples
Surface samples at coded sites using sterile contact plates or sterile moistened swabs should be taken

Note: Each sample site should be sanitized to remove any material transferred to it during the sampling process.

23.9.4 Active Air Sampling

Samples should be taken at the coded sites.

Where the test utilises standard plates or strips, these should be incubated at the appropriate temperature for up to five days.

The point during the production process that finger dabs should be carried out should be defined eg. at a break time or end of a day's work, in accordance with a written SOP

23.9.6 Broth, or Media Fills (Media Process Simulation)

The broth fill is a validation procedure that challenges both operator and facilities. The purpose of broth fills is to simulate routine aseptic operations in such a way as to produce broth filled units that can be tested for microbiological contamination.

The number of units filled should represent a normal batch size.

Incubate at the designated temperature for up to 14 days. If the final container is part filled to ensure all surfaces are in contact with broth at some stage during incubation.

A procedure should define actions following positive results and should focus initially on whether the facility/equipment or operator practices are failing.

Note: The type of broth used is often sterile tryptone soya broth that may be presented in double strength to allow for dilution with buffer, saline, or water to simulate the process. Any suitable liquid

culture medium may however be used but the ability of the broth to support growth should be demonstrated.

23.10 SANITISATION OF MATERIALS

This section addresses disinfection procedures using chemical agents during which fluids are applied to surfaces with the intention of reducing the count of micro-organisms inside the controlled workspace of an isolator.

23.10.1 Introduction

Most isolator systems will require two different procedures:

- A procedure for treatment of the impervious internal surfaces of the isolator and external surfaces of the resident equipment.

- A second procedure for treating surfaces of transient components which will be present in the isolator for a particular procedure.

The cleaning down of equipment and related treatments can employ a wide range of agents. Components and other aids to production should usually be treated with alcohol-based preparations, which enable rapid evaporation of the solvent of such disinfectant agents and therefore facilitates a smooth, responsive work flow during production.

23.10.2 Methods for Treating Resident Surfaces

Transient material should be removed from the controlled workspace. Internal surfaces should be cleaned with a non-corrosive and low residue detergent. There should be no evidence of corrosion due to incompatibility with disinfection regimes.

23.10.3 Methods for Treating Transient Surfaces

The surfaces of components and aids to preparation (syringes etc.) should be treated by using rapid drying agents, such as aspectically filtered alcohol (70% w/v ethanol or isopropanol).

23.10.4 Disinfectants should not penetrate outer packaging and thus contaminate the contents.

23.11 GAS STERILISATION OF ISOLATOR SYSTEMS

23.11.1 Introduction

Alcohol-based solutions are routinely used to sanitise equipment and component surfaces during aseptic processing. The major disadvantage of this technique is that alcoholic agents process negligible activity against bacterial endospores. Control measures can minimise the incidence of spores on the surfaces of vials, syringe wraps etc; but their absence is not assured. A properly designed and validated gas treatment of isolator systems can reduce the probability of spores surviving and increase the sterility assurance of the product.

Gaseous agents may be introduced into the controlled workspace of the isolator system to sterilise the entire space, integral surfaces and transient or resident components inside. It reduces the numbers of viable micro-organisms to a predetermined and acceptable level.

23.11.2 Objectives of Gas Sterilization

Various gaseous agents can be used within suitably-designed isolators to achieve sterilisation of working and component surfaces, thereby significantly reducing the overall probability of sterility failure in the final product.

Note: This process does not guarantee product sterility, but merely eliminates one of the factors which can result in product contamination during aseptic processing.

23.11.3 Choice of Agent

The ideal sterilant would have the following properties:

rapidly lethal against all micro-organisms, highly penetrative, non-aggressive to metals or polymers, rapid elimination of residues and harmless to humans.

A sterility assurance level of 10^6 of better should be achieveable. A variety of methods are available and include the use of ethylene oxide, formaldehyde, paracetic acid, hydrogen peroxide or chlorine dioxide.

The agent of choice will be determined by a number of and equipment-related factors. For pharmaceutical applications in isolators the sterilants in most general use are peracetic acid and hydrogen peroxide.

23.11.4 Gas Contact

To ensure their effectiveness, the sterilant vapours must be in contact with all contaminated surfaces. The following points should be considered:

* Equipment should be raised appreciably above worktops, and efforts made to provide point contact of supports.

* Components should not be laid on worktops or other solid surfaces. Wire baskets or racking can be utilised to approximate point contact support. Wherever possible, containers and components should be suspended farce point contacts (eg. wire hooks), to allow free circulation of sterilant around all items. If necessary components should be rotated or repositioned during processing to ensure all surfaces are exposed to the gaseous sterilant.

* Glove/gauntlet fingers should be fully extended, and supported well clear of the worktop in such a way that the glove/sleeve materials are not unduly folded.

Critical validation issues associated with the sterilisation process should include the concentration of the sterilent, uniform distribution of sterilent, contact times, temperature aeration post sterilisation, condensate removals and residue as well as the frequency of sterilisation.

23.11.5 Microbiological Validation

Biological indicators (BI) can be used to confirm the effectiveness of the selected conditions and standard patterns. The test organisms should be selected to represent a known challenge to the process. In practice Bacillus subtilis (var niger) is frequently used, at a concentration of 10^6 - 10^7 spores per strip.

Initial tests should concentrate on establishing approximate death curves for the test organism, and/or progressively increasing sterilant contact time until the target lethality is achieved. The process contact time and sterilant vapour concentration should then be selected to include an acceptable safety margin, which makes allowance also for the compatibility of equipment and with the sterilant. Once process conditions have been established, the cycle/loading pattern should be validated by performing replicate cycles, again using BI's in worst case positions. Positive controls should be performed and the recovery conditions verified. When some degree of occlusion is unavoidable such that the diffusion path of gas is greater than 1 or 2 ram, the actual lethality delivered can be investigated by direct inoculation of the surfaces and estimation of survivors. Positive controls should be used for other techniques and recovery conditions verified as being effective.

23.11.6 Routine Cycle Monitoring

The correct loading of the isolator prior to gassing should be the subject of properly documented control, and it is good practice for isolator access doors to be locked once correct loading has been checked. The gas generator's airflow and sterilant dispenser flow are often pre-set by the manufacturer, but if this is not the case their correct adjustment should also be formally documented. The generator should ideally allow these parameters, as well as sterilant injection time, to be recorded for each cycle, as happens with steam sterilisers. If the generator does not feature computer or chart recording of data, the parameters should be manually recorded at regular intervals, and documented for each cycle.

TABLE 3

DEFINITION OF AIR QUALITY CATEGORIES 1-V.
COMPARISON WITH EQUIVALENT INTERNATIONAL STANDARDS

CATEGORIES OF BACKGROUND ENVIRONMENT OF ISOLATOR	STANDARDS OF BACKGROUND ENVIRONMENT						NEAREST INTERNATIONAL STANDARDS			
	Particle Count (Particles M^{-3})				Viable Micro-organisms		European GMP	Current British Standard BS5295:1989	Previous British Standard BS5295:1976	US Federal Standard 209E
	0,5uM	5 uM	10 uM	25 uM	Airborne viable count (colonies M^{-3})	Settle plate (colonies per plate)	GRADE	CLASS	CLASS	CLASS
	35	0						C		1
	350	0						D		10
I	3,500	0			5	1 per 2 plates	B	F	1	100
	35,000	200						H		1,000
	350,000	2,000	450				C	J	2	10,000
II	3,500,000	20,000	4,500	500	50	5	D	K	3	100,000
III	NS	200,000	45,000	5,000	100	10		L	4	
IV	NS	NS			500	50				
V		NS			NS	NS				

CHAPTER 24

AEROSOLS & METERED DOSE INHALERS

24.1 PRINCIPLE

The manufacture of pressurized aerosol products for inhalation with metering valves requires special consideration because of the particular nature of this form of product. It should be done under conditions which minimise microbial and particulate contamination. Assurance of the quality of the valve components and, in the case of suspensions, of uniformity is also of particular importance.

24.2 GENERAL

24.2.1 There are presently two common manufacturing and filling methods as follows:

24.2.1.1 Two-shot system (pressure filling). The active ingredient is suspended in a high boiling point propellant, the dose is put into the container, the valve crimped on and the lower boiling point propellant is injected through the valve stem to make up the finished product. The suspension of active ingredient in propellant is kept cool to reduce evaporation loss.

24.2.1.2 One-shot process (cold filling). The active ingredient is suspended in a mixture of propellants and held either under high pressure or at a low temperature, or both. The suspension is then filled directly into the container in one shot.

24.3 PREMISES AND EQUIPMENT

24.3.1 Manufacture and filling should be carried out as far as possible in a closed system.

24.3.2 Where products or clean components are exposed, the area should be fed with treated filtered air, and should be entered through airlocks.

24.3.3 Suitable systems should exist to determine required environment conditions and to monitor and control these conditions, e.g. temperature controls and propellant loss.

24.4 PRODUCTION AND QUALITY CONTROL

24.4.1 Metering valves for aerosols are more complex pieces of engineering than most items used in pharmaceutical production. Their specifications, sampling and testing should recognise this. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.

24.4.2 All fluids (e.g. liquid or gaseous propellants) should be filtered to remove particles greater than 0,2 micron. An additional filtration where possible immediately before filling is desirable.

24.4.3 Containers and valves should be cleaned using a validated procedure appropriate to the use of the product to ensure the absence of any contaminants such as fabrication aids (e.g. lubricants) or undue microbiological contaminants. Containers should be fed to the filling line in a clean condition or cleaned on line immediately before filling.

24.4.4 Precautions should be taken to ensure uniformity of suspensions at the point of fill throughout the filling process.

24.4.5 When a two-shot filling process is used, it is necessary to ensure that both shots are of the correct weight in order to achieve the correct composition.

24.4.6 Controls after filling should ensure the absence of undue leakage. Any leakage test should be performed in a way which avoids microbial contamination or residual moisture.

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MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

ADDENDUM 6

DISSOLUTION TESTING

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

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DISSOLUTION TESTING

1. INTRODUCTION

This guideline describes the setting of dissolution specifications as a quality control requirement and also describes how to conduct dissolution testing in support of a request for a waiver for bioequivalence testing.

Although intrinsic dissolution of the active pharmaceutical ingredient (API) is an important consideration when formulating solid oral dosage forms, the dissolution behaviour of solid oral dosage forms provides important information to ensure drug product quality. Hence, dissolution testing has been established as an extremely valuable tool to monitor batch-to-batch consistency and the primary utility of a dissolution test is therefore to establish dissolution specifications for relevant drug products for the purposes of quality assurance.

Dissolution testing can also be useful in providing information on drug product quality following certain post-approval changes made to the product, such as changes in formulation, manufacturing process, site of manufacture and the scale-up of the manufacturing process. The various classes of changes where dissolution can be used in support of a bio-waiver are described in the MCC's document on major and minor changes.

In addition, where solid oral dosage forms have been proportionally formulated in different strengths and the drug follows linear kinetics, dissolution data can be used in support of a bio-waiver for lower strengths of such dosage forms provided an acceptable bioequivalence study has been carried out on one strength, usually the highest strength.

Drug absorption from oral dosage forms depends on adequate release of the active pharmaceutical ingredient (API) from the product. Physico-chemical factors such as dissolution or solubility of the drug under physiologic conditions and its permeability through the membranes of the gastrointestinal tract play pivotal roles in this respect. Due to the critical nature of these factors, dissolution of a drug product *in vitro* can, in certain instances, be relevant to anticipate the *in vivo* performance.

2. SETTING DISSOLUTION SPECIFICATIONS FOR IMMEDIATE RELEASE SOLID ORAL DOSAGE FORMS

2.1 Objectives

i. To provide general recommendations for dissolution testing and setting dissolution specifications for quality control.

ii. To obtain information on test batches used in bioavailability/ bioequivalence studies and pivotal clinical studies to support specifications for quality control.

iii. To be used as a tool in quality control to demonstrate batch-to-batch and lot-to-lot consistency during manufacture.

2.2 Dissolution Specifications

Primarily, *in vitro* dissolution specifications are used to ensure batch-to-batch consistency and to indicate potential problems of bioavailability.

i. For new drug products, dissolution specifications must be based on data obtained from acceptable clinical, pivotal bioavailability, and/or bioequivalence batches.

ii. In the case of multi-source pharmaceutical products the dissolution specifications are generally the same as the reference product.

These specifications should be confirmed by comparison of the dissolution performance of the multi-source pharmaceutical product and reference product from an acceptable bioequivalence study.

If the dissolution performance of the multi-source pharmaceutical product is substantially different from that of the reference product and the *in vivo* data remain acceptable, a different dissolution specification for the multi-source pharmaceutical product may be set.

iii. Once dissolution specifications are set, the drug product should comply with those specifications throughout its shelf life.

Setting dissolution specifications for multi-source pharmaceutical products may be classified in three categories as described below.

2.2.1 Drug Product Dissolution Test Available in an Acceptable Pharmacopoeia

In this instance the quality control dissolution test should be the test described in the BP, USP or EP. Use of any other pharmacopoeia must be justified and acceptable to the MCC.

It is recommended that a dissolution profile be generated by taking samples at 15-minute intervals or less using the specified pharmacopoeial method for test and reference products (12 units each).

Additional dissolution data may also be required when scientifically justified e.g. when the pharmacopoeia does not specify a dissolution test for all API's in a combination product.

2.2.2 Pharmacopoeial Drug Dissolution Test Not Available

Comparative dissolution testing using test and reference products under a variety of test conditions is recommended.

The test conditions may include different dissolution media (pH 1 to 6.8), addition of surfactant, or use of an official basket or paddle apparatus with varying agitation.

In all cases, profiles should be generated as previously recommended.

The dissolution specifications should be set based on available bioequivalence and other data. In addition, the method used must be justified and validated.

2.2.3 Special Cases.

For poorly water soluble drug products (e.g. glyburide), dissolution testing at more than one time point, and preferably a dissolution profile, is recommended for quality control purposes. Alternatively, the use of the USP apparatus 4 (Flow-Through Method) should be considered for the development of dissolution specifications for such products.

3 *IN VITRO* DISSOLUTION TESTING IN SUPPORT OF A BIO-WAIVER (Bioequivalence Surrogate Inference)

3.1 Immediate Release Drug Products with Class 1 API's

3.1.1 Objectives

To provide recommendations for requesting a waiver of *in vivo* bioequivalence studies for immediate release (IR) solid oral dosage forms where the API is classified as Class 1 according to the Biopharmaceutics Classification System (Reference 1).

3.1.2 Classification Criteria

In the Biopharmaceutics Classification System (BCS) an API is classified as having high or low solubility and high or low permeability.

i. An API is considered to be *highly soluble* when the highest dose strength is soluble in ≤250mL of aqueous buffer over the pH range of 1.0 to 8.0.

ii. An API is considered to be *highly permeable* when the extent of absorption in humans is determined to be greater than 90% of an administered dose in the absence of documented instability in the gastrointestinal tract, or whose high permeability has been determined experimentally (Reference 1) and reported in the literature.

According to the BCS, a Class 1 API is both *highly soluble* and *highly permeable*.

An immediate release (IR) dosage form can be classified as either rapidly or slowly dissolving and is considered *rapidly dissolving* when not less than 85% of the label amount of the API dissolves within 30 minutes using USP Apparatus 1 at 100rpm (or Apparatus 2 at 50rpm) in a volume of 900mL, or less, in each of the following three media:

- acidic media such as 0.1N HCl
- pH 4.5 buffer
- pH 6.8 buffer

3.1.3 Requirements for Bio-Waivers for Immediate Release Drug Products

When an immediate release drug product is *rapidly dissolving* and contains a Class 1 API i.e. the API is both *highly soluble* and *highly permeable*, a bio-waiver for the multi-source product may be granted on the basis of acceptable dissolution data.

Dissolution should be greater than 85% in 30 minutes in each of the following three media:

- acidic media such as 0.1N HCl
- pH 4.5 buffer
- pH 6.8 buffer

DISSOLUTION TESTING

3.2 Proportionally Similar Dosage Forms

When a bio-waiver is requested for lower strengths of drug products which are proportionally formulated (see Guideline for Bioavailability and Bioequivalence....), the following dissolution testing is required:

i. Dissolution of test and reference products should be conducted in each of the following three media:
   - acidic media such as 0.1N HCl
   - pH 4.5 buffer
   - pH 6.8 buffer

ii. Dissolution profiles of test and reference products should be compared as described below for each of the three media.

   Similarity in dissolution profiles must be assessed using f_1 and f_2 but only f_2 data will be used as the acceptance criterion.

   An f_2 value $\geq$ 50 indicates sufficiently similar dissolution profiles such that further *in vivo* studies are not necessary.

iii. When both the test and reference products dissolve to the extent of 85% or more of the label amount in □15 minutes in all three dissolution media recommended above, comparison of test and reference dissolution profiles are not necessary.

iv. Dissolution data in support of bio-waivers for higher strength proportionally similar dosage forms will not normally be considered. However, is a successful biostudy was carried out on a lower strength for reasons of safety (see Guideline for Bioavailability and Bioequivalence....), then dissolution testing on higher strengths will be considered.

3.3 Comparison of a Foreign Reference Product with a Reference Product Registered and Marketed in South Africa

As an interim measure, bioequivalence studies submitted where a foreign reference product has been used will require comparative dissolution profiles between the foreign product and the innovator product marketed in South Africa.

i. Dissolution of test and reference products should be conducted in each of the following three media:
   - acidic media such as 0.1N HCl
   - pH 4.5 buffer

- pH 6.8 buffer

ii. Dissolution profiles of test and reference products should be compared as described in section 3.4 for each of the three media.

Similarity in dissolution profiles must be assessed using f_1 and f_2 but only f_2 data will be used as the acceptance criterion.

An f_2 value ≥50 indicates sufficiently similar dissolution profiles such that further *in vivo* studies are not necessary.

iii. When both the test and reference products dissolve to the extent of 85% or more of the label amount in ≤15 minutes in all three dissolution media recommended above, comparison of test and reference dissolution profiles are not necessary.

3.4 Comparison of Dissolution Profiles

A dissolution profile comparison may be carried out using a simple model independent approach to assess overall profile similarity as well as similarity or differences at each dissolution sample time point.

This approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles (Reference 2). The difference factor (f_1) calculates the (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves:

$$f_1 = \{[\sum_{t=1}^{n} |R_t - T_t|] / [\sum_{t=1}^{n} R_t]\}. 100$$

Where n is the number of time points, R_t is the dissolution value of the reference batch at time t, and T_t is the dissolution value of the test batch at time t.
The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_2 = 50. \log\{[1 + (1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5}.100\}$$

A specific procedure to determine difference and similarity factor is as follows:

1. Determine the dissolution profile of two products (12 units each) of the test and reference products.

DISSOLUTION TESTING

2. Using the mean dissolution values from both curves at each time interval, calculate the difference factor (f_1) and similarity factor (f_2) using the above equations.

3. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, the f_1 values up to 15 (0 – 15) and f_2 values greater than 50 (50 – 100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products.

This model independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available. The following recommendations should also be considered:

1. The dissolution measurements of the test and reference batches should be made under exactly the same conditions. The dissolution time points for both profiles should be the same (e.g., 15, 30, 45, 60 minutes).

2. Only one measurement should be considered after 85% dissolution of both the products.

3. To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%.

4 Dissolution Testing Requirements For Minor And Major Amendments To The Formulation Of Pharmaceutical Products And Related Manufacturing Procedures Including Their Site Of Manufacture.

When amendments are made to pharmaceutical products, manufacturing procedures and other associated processes including change of site their impact on quality must be demonstrated. The following describes the use of dissolution testing as an indicator of quality which may be applicable as describe below.

The following dissolution tests are recommended:

DISSOLUTION TESTING

4.1 Types of Dissolution Test

4.1.1 Case A Dissolution Testing

Dissolution testing should be conducted as a release test according to the original submission or in accordance with compendial requirements for that product.

4.1.2 Case B Dissolution Testing

Dissolution testing should be conducted as a multi-point test in the application/ compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached for the proposed and currently registered formulation.

4.1.3 Case C Dissolution Testing

Dissolution testing should be conducted as a multi-point test in water, 0.1N HCl and buffer at pH=4.5 and 6.8 for the proposed and currently registered formulations at 15, 30, 45, 60 and 120 minutes or until either 90% of drug from the drug product is dissolved or an asymptote is reached. In the case of poorly soluble drugs, comparisons can be made using alternative compendial methods and media that have been appropriately justified.

4.2 Types of Changes

4.2.1 Minor Changes

In the event that the minor change made is such that there is unlikely to be an effect on the quality and performance of a dosage form then Case A dissolution testing is appropriate.

4.2.2 Intermediate Changes

In the event that the changes made may have a significant impact on the quality and performance of a dosage form then Case B dissolution testing is appropriate. However if the change is made to a product containing a BCS class 1 compound then 85% must be dissolved in 15 minutes in the media used in the application or compendial requirements.

For low permeability, high solubility drugs, dissolution profiles should be generated in the application/compendial medium as previously described for Case B dissolution testing. For high permeability, low solubility compounds, multi-point dissolution profiles should be carried out according to Case C dissolution testing.

Profiles of the currently used product and the proposed product should be proven similar according to the f_2 requirements as describe in this Guideline.

4.2.3 **Major Changes**

In the case of changes that are highly likely to have a significant impact on formulation quality and performance, *in vivo* bioequivalence testing must be conducted. Case B or Case C dissolution testing may also be required. Biowavers may be considered if a proven *in vitro-in vivo* correlation (IVIVC) has been shown.

5. REFERENCES

1. Guidance for Industry. Waiver of In-Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000.

2. Mathematical Comparison of Dissolution Profiles. Pharm. Technol. 20:6 (1996) 64-74, J.W. Moore and H.H.Flanner.

MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

ADDENDUM 5

BIOAVAILABILITY AND BIOEQUIVALENCE DATA REQUIRED AS PROOF OF EFFICACY

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

BIOAVAILABILITY/BIOEQUIVALENCE

ABLE OF CONTENTS

1. INTRODUCTION

Adequate evidence/proof of efficacy and safety for all multisource products in the form of appropriate *in vivo* bioequivalence studies must be submitted with each application for the registration of a medicine.

To exert an optimal therapeutic action an active moiety should be delivered to its site of action in an effective concentration for the desired period. To allow reliable prediction of the therapeutic effect the performance of the dosage form containing the active substance should be well characterised.

Comparison of therapeutic performances of two pharmaceutical products containing the same active substance is a critical means of assessing the possibility of using either the innovator or a multi-source (generic) pharmaceutical product. Assuming that in the same subject a similar plasma drug concentration time course will result in similar drug concentrations at the site of action and thus in a similar effect, pharmacokinetic data instead of therapeutic results may be used to establish bioequivalence.

The objectives of this guideline are to:

i. Define when bioavailability or bioequivalence data will be required in order to prove safety and efficacy.

ii. Provide guidance on the design and conduct of studies and the evaluation of data.

iii. Provide guidance when *in vitro* instead of *in vivo* data may be used.

iv. Provide guidance when suitably validated pharmacodynamic methods can be used to demonstrate bioequivalence.

For pharmaceutical products where the active ingredient is not intended to be delivered into the general circulation, the common systemic bioavailability approach cannot be applied. Under these conditions availability (local) may be assessed by quantitative measurements which appropriately reflect the presence of the active ingredient at the site of action.

2 DEFINITIONS

2.1 Active Pharmaceutical Ingredient (API)

A substance or compound used or intended to be used in the manufacture of a pharmaceutical product and which is expected to have a medicinal or pharmacological effect when administered.

2.2 Pharmaceutical Product

Any preparation for human or veterinary use containing one or more active pharmaceutical ingredients with or without pharmaceutical excipients or additives that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

2.3 Pharmaceutical Equivalence

Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same active pharmaceutical ingredient(s) in the same dosage form, if they meet the same or comparable standards and if they are intended to be administered by the same route.

Pharmaceutical equivalence does not necessarily imply bioequivalence as differences in the excipients and/or the manufacturing process can lead to differences in the product performance.

2.4 Therapeutic Equivalence

Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

2.5 Bioavailability

Bioavailability refers to the rate and extent to which the active pharmaceutical ingredient, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action.

It may be useful to distinguish between the "absolute bioavailability" of a given dosage form as compared with that (100%) following intravenous administration (e.g. oral solution *vs.* iv.), and the "relative bioavailability" as compared with another form administered by the same or another non-intravenous route (e.g. tablets vs. oral solution).

2.6 Bioequivalence

Bioequivalence is defined as the absence of a significant difference in the bioavailability between two pharmaceutically equivalent products under similar conditions in an appropriately designed study.

Comparative studies using clinical or pharmacodynamic end points may be used to demonstrate bioequivalence.

2.7 Pharmaceutical Dosage Form

A pharmaceutical dosage form is a pharmaceutical product formulated to produce a specific physical form (e.g. tablet, capsule, solution etc.) suitable for administration to human and animal subjects.

2.8 Multi-Source (Generic) Pharmaceutical Product

Multi-source pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent.

2.9 Proportionally Similar Dosage Forms/Products

Pharmaceutical products are considered proportionally similar in the following cases:

i. When all active pharmaceutical ingredients and inactive components are in exactly the same proportion between different strengths (e.g. a 100mg strength tablet has all active and inactive pharmaceutical ingredients exactly half of a 200mg strength tablet and twice that of a 50mg strength tablet).

ii. When the active and inactive ingredients are not in exactly the same proportion but the ratios of inactive pharmaceutical ingredients to the total weight of the dosage form are within the limits defined by the Guideline for Major and Minor Amendments.

iii. When the pharmaceutical products contain high potency active pharmaceutical ingredients and these products are of different strengths but are of similar weight.

The difference in API content between strengths may be compensated for by weight changes in one or more of the inactive pharmaceutical excipients provided that the total weight of the pharmaceutical product remains within 10% of the weight of the pharmaceutical product on which the bioequivalence study was performed. In addition, the same inactive pharmaceutical excipients must be used for all strengths, provided that the changes remain within the limits defined by the Guideline for Major and Minor Amendments.

Exceptions to the above definitions may be considered provided justification is submitted.

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3. DESIGN AND CONDUCT OF STUDIES FOR ORALLY ADMINISTERED PHARMACEUTICAL PRODUCTS

A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products. In the following sections, requirements for the design and conduct of bioavailability or bioequivalence studies are formulated.

3.1 Design

The study should be designed in such a way that the formulation effect can be distinguished from other effects. If the number of formulations to be compared is two, a balanced two-period, two-sequence crossover design is considered to be the design of choice.

However, under certain circumstances and provided the study design and the statistical analyses are scientifically sound, alternatively well-established designs such as parallel designs for very long half-life substances could be considered.

In general, single dose studies will suffice, but there are situations in which steady-state studies may be required and must be justified.

To avoid carry-over effects, treatments should be separated by adequate wash-out periods.

The sampling schedule should be planned to provide an adequate estimation of Cmax and to cover the plasma drug concentration time curve long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity.

If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples during the terminal log linear phase.

For long half-life drugs (> 24 hours) the study should cover a minimum of 72 hours unless 80% is covered before 72 hours.

For immediate release dosage forms, studies must be done under fasting conditions, unless food effects influence bioavailability. If the dosage directions specifically state administration with food, both fed and fasted studies are required. For modified release dosage forms the influence of food must be demonstrated to exclude any possibility of dose dumping, hence both fed and fasted studies are required.

3.2 Subjects

3.2.1 Number of Subjects

It is recommended that the number of subjects should be justified on the basis of providing at least 80% power of meeting the acceptance criteria.

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The minimum number of subjects should not be less than 12. If 12 subjects do not provide 80% power more subjects should be included.

A minimum of 20 subjects is required for modified release oral dosage forms.

The number of subjects required to provide an 80% power of meeting and passing the acceptance criteria for the 0,8 - 1,25 acceptable interval can be determined from Table 1 below (Reference 1).

Table 1 Sample sizes to attain a power of 70%, 80% and 90% in the case of the multiplicative model: á = 5 %, θ_1=0.8, θ_2=1.25 and various CVs.

CV	Power	μ_T/μ_R							
(%)	(%)	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
5.0	70	10	6	4	4	4	4	6	16
7.5		16	6	6	4	6	6	10	34
10.0		28	10	6	6	8	8	16	58
12.5		42	14	8	8	8	12	24	90
15.0		60	18	10	10	10	16	32	128
17.5		80	22	12	12	12	20	44	172
20.0		102	30	16	14	16	26	56	224
22.5		128	36	20	16	20	30	70	282
25.0		158	44	24	20	22	38	84	344
27.5		190	52	28	24	26	44	102	414
30.0		224	60	32	28	32	52	120	490
5.0	80	12	6	4	4	4	6	8	22
7.5		22	8	6	6	6	8	12	44
10.0		36	12	8	6	8	10	20	76
12.5		54	16	10	8	10	14	30	118
15.0		78	22	12	10	12	20	42	168
17.5		104	30	16	14	16	26	56	226
20.0		134	38	20	16	18	32	72	294
22.5		168	46	24	20	24	40	90	368
25.0		206	56	28	24	28	48	110	452
27.5		248	68	34	28	34	58	132	544
30.0		292	80	40	32	38	68	156	642
5.0	90	14	6	4	4	4	6	8	28
7.5		28	10	6	6	6	8	16	60
10.0		48	14	8	8	8	14	26	104
12.5		74	22	12	10	12	18	40	162
15.0		106	30	16	12	16	26	58	232
17.5		142	40	20	16	20	34	76	312
20.0		186	50	26	20	24	44	100	406
22.5		232	64	32	24	30	54	124	510
25.0		284	78	38	28	36	66	152	626
27.5		342	92	44	34	44	78	182	752
30.0		404	108	52	40	52	92	214	888

Note: Less than 12 subjects should not be used even if the above table indicates that a power of 80% can be attained with less than 12 subjects.

To determine the number of subjects required, proceed as follows:

i. Determine the CV% of the appropriate BA/BE parameter for the drug under investigation from published literature or an appropriate pilot study.

ii. Choose an appropriate mean test/ reference ratio that is envisaged for the BA/BE parameter (μ_T / μ_R). Ideally this value will be 1.00, however, in practice this is seldom the case so the choice of this ratio is at the discretion of the Sponsor/Applicant.

iii. Determine from the table the number of subjects required for the appropriate CV%, Power and μ_T / μ_R.

For example, if the drug under investigation has an AUC CV of 20% and if a μ_T/μ_R of 0.95 or 1.05 is selected, then a minimum of 20 and 18 subjects respectively will be required for a power of 80%.

Alternatively, the sample size can be calculated using appropriate power equations, which must be presented in the protocol.

Add-ons will be permitted but the number of subjects in the add-on should not exceed the initial number of subjects in the study, unless fully justified. The applicant must show that the data are homogeneous using appropriate statistical tests. The provision for add-ons must be made in the protocol *a priori*.

3.2.2 Selection of Subjects

The subject population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. Therefore, the studies should normally be performed with healthy volunteers.

The inclusion/exclusion criteria should be clearly stated in the protocol.

In general, subjects should exhibit the following characteristics:

i. **Sex:** Subjects may be selected from either sex, however, the risk to women of childbearing potential should be considered on an individual basis.

ii. **Age**: Between 18 and 55 years of age.

iii. **Mass**: Have a body mass within the normal range according to accepted normal values for the Body Mass Index (BMI=weight in Kg divided by height in meters squared i.e. Kg /m^2) or within 15% of ideal body mass e.g. Metropolitan Height and Weight Tables which can be found in the following reference: Statistical Bulletin (Metropolitan Life Foundation) Vol 64, No 1, Jan-Jun 1983, or any other such recognised reference.

iv. **Informed Consent**: All subjects participating in the study must be capable of giving informed consent.

v. **Medical Screening**: Subjects should be screened for suitability by means of clinical laboratory tests, an extensive review of medical history, and a comprehensive medical examination. Depending on the drug's therapeutic class and safety profile special medical investigations may have to be carried out before, during and after the completion of the study.

vi. **Smoking/Drug and Alcohol Abuse**: Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. If moderate smokers are included (less than 10 cigarettes per day) they should be identified as such and the possible influences of their inclusion on the study results should be discussed in the protocol.

3.2.3 Inclusion of Patients

If the active substance under investigation is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers it may be necessary, under suitable precautions and supervision, to use patients instead. In this case the applicant should justify the use of patients instead of healthy volunteers.

3.2.4 Genetic Phenotyping

Phenotyping and/or genotyping of subjects can be considered for exploratory bioavailability studies. It may also be considered in crossover studies (e.g. bioequivalence, dose proportionality, food interaction studies etc.) for safety or pharmacokinetic reasons.

If a drug is known to be subject to major genetic polymorphism, studies could be performed in cohorts of subjects of known phenotype or genotype for the polymorphism in question.

3.3 Standardisation of the Study Conditions

The test conditions should be standardised in order to minimise the variability of all factors involved, except that of the products being tested. Therefore standardisation of the diet, fluid intake and exercise is recommended.

i. **Dosing**: The time of day for ingestion of doses should be specified.

ii. **Fluid Intake at Dosing**: As fluid intake may profoundly influence the gastric transit of orally administered dosage forms, the volume of fluid administered at the time of dosing should be constant (e.g. 200 ml).

iii. **Food and Fluid Intake**: In fasted studies the period of fasting prior to dosing should be standardised and supervised. All meals and fluids taken after dosing should also be standardised in regard to composition and time of administration and in accordance with any specific requirements for each study.

iv. **Concommitant Medication**: Subjects should not take other medicines during a suitable period before and during the study and should abstain from food and drinks, which may interact with circulatory, gastrointestinal, liver or renal function (e.g. alcoholic or xanthine-containing beverages or certain fruit juices).

v. **Posture and Physical Activity**: As the bioavailability of an active moiety from a dosage form can be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardised.

3.4 Sample Collection and Sampling Times

Under normal circumstances, blood should be the biological fluid sampled to measure the concentrations of the drug. In most cases the drug may be measured in serum or plasma, however, in some cases, whole blood may be more appropriate for analysis.

When blood is collected:

i. The duration of blood sampling in a study should be sufficient to account for at least 80% of the known AUC to infinity (AUC_∞). This period is approximately three terminal half-lives of the drug.

ii. For most drugs 12 to 18 samples including a pre-dose sample should be collected per subject per dose.

iii. Sample collection should be spaced such that the maximum concentration of drug in blood (C_{max}) and the terminal elimination rate constant (K_{el}) can be estimated.

iv. At least three to four samples should be obtained during the terminal log-linear phase to estimate K_{el} by linear regression analysis.

v. The actual clock time when samples are collected as well as the elapsed time relative to drug administration should be recorded.

If drug concentrations in blood are too low to be detected and a substantial amount (> 40%) of the drug is eliminated unchanged in the urine, then urine may serve as the biological fluid to be sampled.

When urine is collected:

i. The volume of each sample must be measured immediately after collection and included in the report.

ii. Urine should be collected over an extended period and generally no less than seven times the terminal elimination half-life so that the amount excreted to infinity (Ae_∞) can be estimated.

iii. Sufficient samples must be obtained to permit an estimate of the rate and extent of renal excretion. For a 24-hour study, sampling times of 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 hours are usually appropriate.

3.5 Characteristics to be Investigated

3.5.1 Blood/Plasma/Serum Concentration *versus* Time Profiles

In most cases evaluation of bioavailability and bioequivalence will be based upon measured concentrations of the parent compound (i.e. the API) where the shape of and the area under the plasma concentration *versus* time curves are generally used to assess the rate and extent of absorption.

In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound.

i. If the concentration of the active substance is too low to be accurately measured in the biological matrix.

ii. If there is a major difficulty with the analytical method.

iii. If the parent compound is unstable in the biological matrix.

iv. If the half-life of the parent compound is too short thus giving rise to significant variability.

Justification for not measuring the parent compound must be submitted by the applicant and bicequivalence determinations based on metabolites should be justified in each case.

Sampling points should be chosen so that the plasma concentration *versus* time profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

i. AUC_t, AUC_∞, C_{max}, t_{max} for plasma concentration *versus* time profiles.

ii. AUC_τ, C_{max}, C_{min}, fluctuation (%PTF) and swing (%Swing) for studies conducted at steady state.

iii. Any other justifiable characteristics (cf. Appendix I).

iv. The method of estimating AUC-values should be specified.

3.5.2 Urinary Excretion Profiles

In the case of API's predominantly excreted renally, the use of urine excretion data may be advantageous in determining the extent of drug input. However, justification must also be given when this data is used to estimate the rate of absorption.

Sampling points should be chosen so that the cumulative urinary excretion profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

i. Ae_t, Ae_∞ as appropriate for urinary excretion studies.

ii. Any other justifiable characteristics (cf. Appendix I).

iii. The method of estimating AUC-values should be specified.

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3.5.3 Pharmacodynamic Studies

If pharmacodynamic parameters/effects are used as bioequivalence criteria, justification for their use must be submitted by the applicant. Bioequivalence determinations based on these measurements should be justified in each case. In addition:

i. A dose response relationship should be demonstrated.

ii. Sufficient measurements should be taken to provide an appropriate pharmacodynamic response profile.

iii. The complete effect curve should remain below the maximum physiological response.

iv. All pharmacodynamic measurements/methods must be validated with respect to specificity, accuracy and reproducibility.

3.6 Chemical Analysis

The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and cGMP.

Bioanalytical methods used to determine the active moiety and/or its metabolic product(s) in plasma, serum, blood or urine or any other suitable matrix must be well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted.

The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) in a specific biological matrix. Validation should therefore address the following characteristics of the assay (Reference 2):

i. Stability of stock solutions.

ii. Stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage.

iii. Specificity.

iv. Accuracy.

v. Precision.

vi. Limits of detection and quantitation.

vii. Response function.

viii. Robustness and ruggedness.

A calibration curve should be generated for each analyte in each analytical run and it should be used to calculate the concentration of the analyte in the unknown samples in the run.

A number of separately prepared Quality Control samples should be analysed with processed test samples at intervals based on the total number of samples.

All procedures should be performed according to pre-established Standard Operating Procedures (SOPs).

All relevant procedures and formulae used to validate the bioanalytical method should be submitted and discussed.

Any modification of the bioanalytical method before and during analysis of study specimens may require adequate revalidation and all modifications should be reported and the scope of revalidation justified.

3.7 Reference Product

N.B. Products that are not registered in South Africa cannot be used as reference products in bioequivalence studies submitted in support of an application e.g. a product approved for marketing in another country(s) but not approved for marketing in South Africa cannot be used as a reference product.

3.7.1 Reference Products Registered and Marketed in South Africa

The reference product must be an innovator product registered with the Medicines Control Council (MCC) and must be procured in South Africa except that an "OLD MEDICINE" may be used as a reference product when no other such product has been registered and provided that it is available on the South African market. If more than one such product is available, then the product that is the market leader in South Africa should be used as the reference (e.g. IMS database).

3.7.2 Reference Products Registered but not Procured inside South Africa.

1. A foreign reference product can be used provided that the following evidence is submitted:

   i. The reference product has an identical formulation (the same in all respects) as the innovator product marketed in South Africa.

   ii. The reference product is manufactured by the same method as the innovator product marketed in South Africa.

   iii. The reference product is manufactured at the same site as the innovator product marketed in South Africa.

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The intention of the above clause is to provide for the use of a reference product where that innovator product has been imported for use in South Africa.

2. As an interim measure, bioequivalence studies submitted where a foreign reference product has been used will require comparative dissolution profiles between the foreign product and the innovator product marketed in SA and must meet the f_2 requirements when tested in dissolution media of pH 1.2, 4.5 and 6.8, using an appropriate dissolution apparatus (see Guideline for Dissolution Testing).

The intention of the above clause is to make provision for dossiers submitted prior to the implementation of this guideline.

3.7.3 Reference Products Registered in South Africa but not Marketed (Available) in South Africa

If a reference product is registered in SA but cannot be procured (i.e. is not available) in South Africa, then the reference product used can be obtained from outside South Africa provided that the product meets the following criteria:

i. The reference product must be a conventional, immediate-release oral dosage form.

ii. There is no documented evidence of bioavailability problems related to the active pharmaceutical ingredient(s) or the pharmaceutical product, or ingredients or products of similar chemical structure or formulations.

iii. It must be documented that the pharmaceutical product is authorised for marketing by the health authority of a country with drug registration requirements acceptable to the MCC. In such instances the registration requirements of the country where the reference product was approved must be submitted.

iv. It must be documented that the pharmaceutical product is marketed in the country of origin by the same innovator company or corporate entity which currently markets the same active pharmaceutical ingredient in the same dosage form in South Africa; or, that it is marketed in the country of origin through a licensing arrangement with the innovator company or corporate entity which currently markets the product in South Africa. The country of manufacture must be stated.

v. Copies of the labelling for the reference as well as the innovator product marketed in South Africa, together with Certificates of Analysis for both products, analysed using the specifications for description, assay, content uniformity and dissolution proposed in the submission for the multi-source product, must be provided.

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vi. The active pharmaceutical ingredient is uncomplicated i.e. it does not exhibit any of the following:

- A narrow therapeutic range or safety margin, e.g. it does not require careful dosage titration or patient monitoring.
- A steep dose / response relationship.
- A risk of serious undesired effects.
- Complicated or variable pharmacokinetics e.g.:
  - non linear pharmacokinetics
  - variable or incomplete absorption
  - an absorption window, i.e. site specific absorption
  - substantial first-pass metabolism (>40%)
  - an elimination half life of 24 hours or more

vii. The active pharmaceutical ingredient must not be a pro-drug.

viii. The dosage form:

- Contains a single API.
- Contains the same quantity of medicinal ingredient as the innovator product registered in South Africa.
- Is the same as the dosage form registered in South Africa with respect to colour, shape, size, weight, type of coating and other relevant attributes.

3.7.4 Reference Products for Combination Products

Combination products should in general, be assessed with respect to bioavailability and bioequivalence of individual active substances:

i. Either individually (in the case of a new combinations), or

ii. Using an existing combination as the reference.

iii. In the former instance, immediate release oral dosage forms containing a single API can be used as the reference. These reference products may include "OLD MEDICINES".

Bioequivalence testing of such products will be permitted only for those products approved by the MCC.

BIOAVAILABILITY/BIOEQUIVALENCE

3.8 Study Products and Batch Size

3.8.1 Study Products

The following information on test and reference products must be submitted:

i. Assay of test and reference product.

ii. Comparative dissolution profiles of the test and the reference product.

iii. A CoA of the API used in the test product bio-batch as well as quality control data demonstrating compliance with the specifications.

In addition, the test and reference products must conform to the following:

i. Test and the reference product should not differ by more than 5% in assay.

ii. A sufficient number of retention samples of both test and reference products used in the bioequivalence study must be kept by the study sponsor for one year in excess of the accepted shelf life or two years after completion of the trial or until approval, whichever is longer, in order to allow re-testing if required by the MCC.

iii. A complete audit trail of procurement, storage, transport and other use of both the test and reference products must be recorded.

3.8.2 Batch Size

The bio-batch used in the bioequivalence study must satisfy the following requirements:

i. The bio-batch must be a minimum of 100 000 units or atleast 10% of the production batch which ever is greater.

   If the bio-batch is less than 100 000 the applicant must motivate and justify the use of a smaller batch.

ii. If the production batch is smaller than 100 000 units, a full production batch will be required.

iii. A high level of assurance must be provided that the product and process used in the production of the product will be feasible on an industrial scale. If the product is subjected to further scale-up, this should be validated appropriately.

3.9 Data Analysis

The primary concern of bioequivalence assessment is to quantify the difference in bioavailability between the test and reference products and to demonstrate that any clinically important difference is unlikely.

3.9.1 Statistical Analysis

The statistical method for testing relative bioavailability (i.e average bioequivalence) is based upon the 90% confidence interval for the ratio of the population means (Test/Reference) on the log-transformed scale, for the parameters under consideration.

Pharmacokinetic parameters derived from measures of concentration, e.g. AUC_t, AUC_∞, C_{max} should be analysed using ANOVA. Data for these parameters should be transformed prior to analysis using a logarithmic transformation.

If appropriate to the evaluation, the analysis technique for t_{max} should be non-parametric and should be applied to untransformed data.

In addition to the appropriate 90% confidence intervals, summary statistics such as geometric and arithmetic means, SD and %RSD as well as ranges for pharmacokinetic parameters (minimum and maximum) should be provided.

3.9.2 Acceptance Range for Pharmacokinetic Parameters

The pharmacokinetic parameters to be tested, the procedure for testing and the acceptance ranges should be stated beforehand in the protocol.

3.9.2.1 Single-Dose Studies

In single-dose studies designed to determine average bioequivalence, acceptance criteria for the main bioequivalence parameters are as follows:

i. AUC_t - ratio

The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

In certain cases an alternative approach may be acceptable.

Justification for the use of alternative methods e.g. scaled average bioequivalence (ABE) based on sound scientific principles for the evaluation of the bioequivalence of highly variable drugs has been described in the literature (Reference 2 and 3). Use of alternative methods MUST be stated *a priori* in the protocol and cannot be added retrospectively.

ii. C_{max} - ratio

The 90% confidence interval for the test/reference ratio should lie within an acceptance interval of 75 – 133% calculated using log transformed data, except for narrow therapeutic range API's when an acceptance interval of 80 – 125% will apply.

In certain cases e.g. in the case of highly variable API's, a wider interval or other appropriate measures may be acceptable but must be stated *a priori* and justified in the protocol (See references 3 and 4).

3.9.2.2 Steady-State Studies

i. Immediate Release Dosage Forms

The acceptance criteria are the same as for single dose studies but using AUC_τ instead of AUC_t

ii. Controlled/Modified Release Dosage Forms

The acceptance criteria are as follows:

- AUC_τ - ratio

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

- $C_{max\,(ss)}$ and $C_{min\,(ss)}$

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.75-1.33 (75 – 133%) calculated using log transformed data.

- %Swing and %PTF

  The 90% confidence interval for the test/reference ratio should lie within the acceptance interval of 0.80-1.25 (80 – 125%) calculated using log transformed data.

3.10 Reporting of Results

The report of a bioavailability or a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation complying with GCP, GLP and cGMP.

3.10.1 Clinical Report

In addition to the protocol etc., the clinical section of the bioequivalence study report should include the following:

i. A statement indicating the independence of the ethics committee.

ii. Documented proof of ethical approval of the study.

iii. A complete list of the members of the ethics committee, their qualifications and affiliations.

iv. An independent monitor's report on the study.

v. Names and affiliations of the all investigator(s), the site of the study and the period of its execution.

vi. The names and batch numbers of the products being tested.

vii. The manufacturing sites (address of the manufacturer of both the reference and the test product).

viii. Expiry date of the reference product and the date of manufacture of the test product used in the study.

ix. Assay and comparative dissolution profiles for test and reference products.

x. CofA of the API used in the test product bio-batch.

xi. A signed statement confirming that the test product used in the bio-study is the same as the one that is submitted for registration.

xii. A summary of adverse events which must be accompanied by a discussion on the influence of these events on the outcome of the study.

xiii. A summary of protocol deviations (sampling and non-sampling) which must be accompanied by a discussion on the influence of these adverse events on the outcome of the study.

xiv. Subjects who drop out or are withdrawn from the study should be identified and their withdrawal fully documented and accounted for.

3.10.2 Analytical Report

The analytical section of the bioequivalence report should include the following which must be clearly presented:

i. The full analytical validation report.

ii. All individual subject concentration data.

iii. All individual plasma concentration *versus* time profiles presented on a linear/linear as well as log/linear scale (or, if appropriate, cumulative urinary excretion data presented on a linear/linear scale).

iv. Calibration data i.e. raw data and back-calculated concentrations for standards, as well as calibration curve parameters for the entire study.

v. Quality control samples for the entire study.

vi. Chromatograms from analytical runs for 20% of all subjects (or a minimum of 4 subjects) including chromatograms for the associated standards and quality control samples.

vii. Analytical data from subjects who dropped out of the study due to an adverse drug event should also be presented.

viii. A summary of protocol deviations which must be accompanied by a discussion on the influence of these deviations on the outcome of the study. Protocol deviations must be justified.

3.10.3 Pharmacokinetic and Statistical Report

The pharmacokinetic and statistical section of the bioequivalence report should include the following, which must be clearly presented:

i. All drug concentration *versus* time data from the bio-study. This data must be submitted in hard copy and also formatted on a diskette in a format compatible for processing by SAS software. Individual subject data should be in rows and arranged in columns which reflect the subject number, phase number, sequence, formulation and sample concentration *versus* time data (Appendix 2).

ii. The method(s) and programs used to derive the pharmacokinetic parameters from the raw data.

iii. A detailed ANOVA and/or non-parametric analysis, the point estimates and corresponding confidence intervals for each parameter of interest.

iv. Tabulated summaries of pharmacokinetic and statistical data.

v. The statistical report should contain sufficient detail to enable the statistical analysis to be repeated, e.g. individual demographic data, randomisation scheme, individual subject concentration vs. time data, values of pharmacokinetic parameters for each subject, descriptive statistics of pharmacokinetic parameters for each formulation and period.

vi. Drug concentration data of any subject withdrawn from the study due to an adverse drug event should also be submitted, but should not be included in the statistical analysis.

3.10.4 Quality Assurance

i. The study report should be accompanied by a signed QA statement confirming release of the document.

ii. A declaration must be made by the applicant to indicate whether the site(s) (clinical and analytical) where the study was performed was subjected to a pre-study audit to ascertain the status of GCP and GLP &/or cGMP conditions at the site(s). All audit certificates should clearly indicate the date of audit and the name(s), address(es) and qualifications of the auditor(s).

iii. The applicant should submit an independent monitor's report on the clinical portion of the study. This report should clearly indicate the date of monitoring and the name, address and qualifications of the monitor and should be included in the study report.

3.11 Expiry Dates of Biostudies

The bioavailability/ bioequivalence study must have been completed not longer than three years prior to the date of submission.

4 BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

4.1 Orally Administered Drug Products Intended for Systemic Action

4.1.1 Solutions

A bioequivalence waiver may be granted for oral solutions, elixirs, syrups or other solubilized forms containing the same active pharmaceutical ingredient(s) in the same concentration(s) as the South African reference product and containing no ingredient known to significantly affect absorption of the medicinal ingredient(s).

4.1.2 Suspensions

Bioequivalence for a suspension should be treated in the same way as for immediate release solid oral dosage forms.

4.1.3 Immediate Release Products – Tablets and Capsules

In general bioequivalence studies are required. *In vivo* BE studies should be accompanied by *in vivo* dissolution profiles on all strengths of each product. Waivers for *in vivo* bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on comparative dissolution studies may be acceptable (see Guideline for Dissolution Testing).

BIOAVAILABILITY/BIOEQUIVALENCE

4.1.4 Modified Release Products

Modified release products include delayed release products and extended (controlled) release products. In general bioequivalence studies are required. In addition to the studies required for immediate release products, a food-effect study is necessary. Multiple dose studies are generally not recommended.

4.1.5 Miscellaneous Oral Dosage Forms

Rapidly dissolving drug products, such as buccal and sublingual dosage forms, should be tested for *in vitro* dissolution and *in vivo* BA and/or BE. Chewable tablets should also be evaluated for *in vivo* BA and/or BE. Chewable tablets (as a whole) should be subject to *in vitro* dissolution because they might be swallowed by a patient without proper chewing. In general, *in vitro* dissolution test conditions for chewable tablets should be the same as for non-chewable tablets of the same active ingredient/moiety.

4.2 Orally Administered Drugs Intended for Local Action

Generally BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated *in vitro* studies are required.

4.3 Parenteral Solutions

The applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently approved product.

In the case of other parenteral routes other than i/v., e.g. intramuscular or subcutaneous, if the test product is of the same type of solution (aqueous) as the reference product, contains the same concentration of the same active substance and the same or comparable excipients as the medicinal product currently approved, then bioequivalence testing is not required provided that the formulation does not contain an excipient(s) known to significantly affect absorption of the active ingredient(s).

For all other parenterals bioequivalence studies are required.

For intramuscular dosage forms monitoring is required until at least 80% of the AUC_∞ has been covered.

4.4 Topically Administered Products

4.4.1 Locally Acting

Topical preparations containing corticosteroids intended for application to the skin and scalp, the human vasoconstrictor test (blanching test) is recommended

to prove bioequivalence. Validated visual and/or chromometer data will be necessary.

Topical formulations, other than a simple solution, with bacteriostatic, bactericidal, antiseptic and/or antifungal claims, clinical data (comparative clinical efficacy) will be required. Microbial growth inhibition zones will not be acceptable as proof of efficacy. Simple solutions however, may qualify for a waiver based on appropriate *in vitro* test methods.

Proof of release by membrane diffusion will not be accepted as proof of efficacy unless there has been data to show the correlation between release through a membrane and clinical efficacy data.

Whenever systemic exposure resulting from locally applied, locally acting medicinal products entails a risk of systemic adverse reactions, systemic exposure should be measured.

4.4.2 Systemically Acting

For locally applied products with systemic action e.g. transdermal products, a bioequivalence study is always required.

4.5 Products Intended for Other Routes of Administration

Products for local use (oral, nasal, inhalation, ocular, dermal, rectal, vaginal etc. administration.) intended to act without systemic absorption the approach to determine bioequivalence based on systemic measurements is not applicable and pharmacodynamic or comparative clinical studies are required. However, pharmacokinetic studies may be required as measures of safety.

4.6 Variations or Post Registration Amendments

For all post registration changes that require proof of efficacy the requirements of this guideline will be applicable.

5. WAIVERS OF *IN VIVO* BIOEQUIVALENCE STUDIES

Bio-waivers will be considered under the circumstances detailed below.

5.1 Immediate Release Products

5.1.1 Class 1 Drug Substances

When the drug product contains a Class 1 drug substance(s) (based on the Biopharmaceutics Classification System, BCS), and the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients

a bio-waiver may be acceptable.

The drug substances must be highly soluble, highly permeable and the dosage form rapidly dissolving (see Guideline for Dissolution Testing).

The applicant must provide relevant information to prove that the drug substance falls within the Class 1 classification (Reference 5).

5.1.2 Different Strength Dosage Forms

When the drug product is the same dosage form but of a different strength and is proportionally similar (See Section 2.9) in its active and inactive ingredients, a bio-waiver may be acceptable.

In such cases the demonstration of bioequivalence *in vivo* of one or more of the lower strength/s may be waived based on dissolution tests (see Guideline for Dissolution Testing) and an *in vivo* study on the highest strength.

1. **For Multi-source pharmaceutical products**, conducting an *in vivo* study on a strength that is not the highest may be appropriate for reasons of safety. In this case a waiver may be considered for the higher strength when an *in vivo* BE study was performed on a lower strength of the same drug product provided that:

   i. Linear elimination kinetics has been shown over the therapeutic dose range.

   ii. The higher strength is proportionally similar to the lower strength.

2. **For New Chemical Entities** with questions on toxicity, bio-wavers for a higher strength will be determined to be appropriate based on:

   i. Clinical safety and/or efficacy studies including dose desirability of the higher strength, and

   ii. Linear elimination kinetics over the therapeutic dose range, and

   iii. The higher strength being proportionally similar to the lower strength, and

   iv. The same dissolution procedures being used for both strengths and similar dissolution results obtained.

Dissolution profiles are required for all strengths. The f_2 similarity factor should be used to compare dissolution profiles from different strengths of a product. An f_2 value ≥50 indicates a sufficiently similar dissolution profile such that further *in vivo* studies are not necessary. For an f_2 value <50, it may be necessary to conduct an *in vivo* study. The difference factor, f_1, must also be submitted but will not be used as an acceptance criterion (Reference 6).

Note: Details on the performance of dissolution studies are described in the Guideline for Dissolution Testing and not in the BA-BE guideline.

5.2 Modified Release Products

5.2.1 Beaded Capsules - Lower Strength

For extended release beaded capsules where the strength differs only in the number of beads containing the active ingredient, a single-dose, fasting BE study should be carried out on the highest strength. A bio-waiver for the lower strength based on dissolution studies can be requested.

Dissolution profiles in support of a bio-waiver should be generated for each strength using the recommended dissolution test methods described in the Guideline for Dissolution Testing.

5.2.2 Tablets – Lower strength

For extended release tablets when the drug product is:

i. In the same dosage form but in a different strength, and

ii. Is proportionally similar in its active and inactive ingredients, and

iii. Has the same drug release mechanism,

an *in vivo* BE determination of one or more lower strengths may be waived based on dissolution testing as previously described. Dissolution profiles should be generated on all the strengths of the test and the reference products.

For Section 5.2.1 and 5.2.2 above, the f_2 factor should be used to compare profiles from the different strengths of the product. An f_2 value of ≥50 can be used to confirm that further *in vivo* studies are not needed (see Guideline for Dissolution Testing).

6 References

1. Sample size determination for bioequivalence assessment by means of confidence intervals. International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 29 No. 1 (1991) 1-8, E. Diletti, D. Hauschke and V.W. Steinijans.

2. Workshop Report: Shah, V.P. et al., *Pharmaceutical Research*: 2000; 17:1551-1557.

3. Evaluation of the Bioequivalence of Highly-Variable Drugs and Drug Products. Pharm. Res. 18:6 (2001) 728-733, L. Tothfalusi, L. Endrenyi, K.K. Midha, M. J. Rawson and J.W. Hubbard.

4. Limits for the Scaled Average Bioequivalence of Highly-Variable Drugs and Drug Products. Pharm. Res. 20:3 (2003) 382-389, L. Tothfalusi and L. Endrenyi.

5. Guidance for Industry. Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000.

6. Mathematical Comparison of Dissolution Profiles. Pharm. Technol. 20:6 (1996) 64-74, J.W. Moore and H.H.Flanner.

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APPENDIX 1 - Abbreviations and Symbols.

C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
$C_{max\ (ss)}$	maximum plasma concentration at steady-state
$C_{min\ (ss)}$	minimum plasma concentration at steady-state
C_{av}	average plasma concentration
t_{max}	time to C_{max}
AUC_t	area under the plasma/serum/blood concentration-time curve from time zero to time t where t is the last time point with measurable concentration.
AUC_∞	area under the plasma/serum/blood concentration-time curve from time zero to time infinity
AUC_τ	AUC during a dosage interval at steady state
MRT	mean residence time
Ae_t	cumulative urinary excretion from drug administration until time t
Ae_∞	Amount of unchanged drug excreted in the urine at infinite time (7-10 half lives).
$t_{1/2}$	elimination half-life
%PTF	$(C_{max\ (ss)} - C_{min\ (ss)}) / C_{av}.100$
%Swing	$(C_{max\ (ss)} - C_{min\ (ss)}) / C_{min}.100$

APPENDIX 2 - Example of Bio-Study Data Formatted for SAS.
Note: Data should preferably be saved in .sas files but can also be saved in free-format ASCII DOS TEXT files.

```
Subj. #     Seq.      Period  Form  t1       t2       t3       t4       t5       t6       t7       t8       t9       t10
t11      t12      t13      t14      t15      t16      t17      t18      t18      t20      t21

   01        AB        1        A      0.000    n.nnn    nn.nnn   nn.nnn   nn.nnn   nnn.nnn nnn.nnn nn.nnn   nn.nnn   nn.nnn
nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   n.nnn    n.nnn    n.nnn    n.nnn
   01        AB        2        B      0.000    n.nnn    nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn
nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   n.nnn    n.nnn    n.nnn    n.nnn    n.nnn    n.nnn
   02        BA        1        B      0.000    n.nnn    nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn
nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   n.nnn    n.nnn    n.nnn    n.nnn
   02        BA        2        A      0.000    n.nnn    nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn
nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   nn.nnn   n.nnn    n.nnn    n.nnn    n.nnn
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MEDICINES CONTROL COUNCIL

DEPARTMENT OF HEALTH

MEDICINES CONTROL COUNCIL

ADDENDUM 4

STABILITY STUDIES

This document has been prepared to serve as a recommendation to applicants wishing to submit applications for registration of medicines. It represents the Medicines Control Council's current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy. It is important for applicants to adhere to the administrative requirements to avoid delays in the processing of applications.
This guideline will come into effect from 1 October 2004.
Guidelines and application forms are available from the office of the Registrar of Medicines.

REGISTRAR OF MEDICINES
MS M.P. MATSOSO
DATE: 29/4/2003

STABILITY STUDIES

The Tripartite guideline, which has been developed within the Expert Working Group (Quality) of the International Conference on Harmonization (ICH), provides a general indication on the requirements for stability testing. It primarily addresses the information required in applications for registration for new chemical entities and associated medicinal products. This guideline is adopted with only minor modifications. It contains aspects relating to testing conditions, numbers of batches to be tested and the requirements regarding follow-up stability data and applicants are advised to study this guideline carefully.

Applicants are reminded that the Tripartite guideline has now been included in the USP23 (<1196>) and latest updates appear on the ICH website.

Applicants are also referred to the following guidelines on the ICH website:
1. Stability Data Package for Registration in Climatic Zones III and IV (Q1F)
2. Photostability Testing (Q1B)

Appendices 1 and 2 attached to this guideline comprise -
APPENDIX 1 - GLOSSARY AND INFORMATION
APPENDIX 2 - APPROPRIATE TESTS

Index to Guideline contents

STABILITY

1 STABILITY TRIAL DESIGN

There shall be a written testing program designed to assess stability characteristics of dosage forms. The results of such stability testing shall be used in determining appropriate storage conditions and retest or expiry dates.

The design of the study should consider the methodology for determining the stability of the active substance and dosage forms. The following factors must be considered in designing a stability trial:

1.1 ACTIVE PHARMACEUTICAL INGREDIENT

1.1.1 New Chemical Entity

1.1.1.i General

Information on the stability of the active substance is an integral part of the systematic approach to stability evaluation.

The actual studies to be carried out will depend on the nature of the active substance, but may include the effect of elevated temperatures or low temperatures, susceptibility to moisture, oxidation and the effect of light. The effect of pH and high oxygen atmosphere may be important for aqueous solutions or suspensions of the active substance.

1.1.1.ii Stress Testing

Stress testing helps to determine the intrinsic stability of the molecule by establishing degradation pathways in order to identify the likely degradation products and to validate the stability indicating power of the analytical procedures used.

1.1.1.iii Formal Studies