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.

1 7.6 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 willful 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).