2.2.7 Consultants

Only in exceptional circumstances should persons engaged part time or in a consultative capacity be appointed to key positions. Consultants advising on the manufacture, processing, packing, or storage of medicines shall have sufficient education, training and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address and qualifications of any consultants and the type of service they provide.

2.2.8 Head of Production
The Production Manager, in addition to his responsibilities for production areas, equipment, operations and records; for the management of production personnel; and for the manufacture of products in accordance with the appropriate Master Formulation and Manufacturing instructions, will have other responsibilities bearing on quality which he should share, or exercise jointly, with the person responsible for Quality Control.

2.2.9 Head of Quality Control

The person responsible for Quality Control should have the authority to establish, verify and implement all quality control procedures. He should have the authority, independent of Production, to approve materials and products, and to reject, as he sees fit, starting materials, packaging materials and intermediate, bulk and finished products which do not comply with the relevant specification, or which were not manufactured in accordance with the approved methods and under the prescribed conditions, and to evaluate batch records. (His authority in relation to packaging materials may be limited to those which may influence product quality, identity, and safety in use).

2.2.10 The shared or joint responsibilities of the Head of Production and Head of Quality Control may include authorising written procedures; master documentation, monitoring and control of the manufacturing environment; plant cleanliness; process validation; training of personnel; approval of suppliers of materials and of contract acceptors; protection of products and material against spoilage and deterioration; retention of records; the monitoring of compliance with the requirements of GMP; the inspection, investigation and taking of samples in order to monitor factors which may affect product quality. It is important that both direct and shared responsibilities are understood by those concerned.

2.2.11 In some companies there is appointed a Quality Assurance Manager who oversees all the quality assurance arrangements and reports to senior management. The person responsible for Quality Control may report to the Quality Assurance Manager and share some of the responsibilities with him.

The person responsible for Quality Assurance should be part of the decision-making process in all matters that affect the quality of products including development, production, laboratory, storage, distribution, vendors and third party contractors

2.3 LEGAL ASPECTS

2.3.1 Pharmaceutical Companies

2.3.1.1 South African law lays down certain requirements for pharmaceutical companies, the managing director and pharmacists e.g.:
·the company and the managing director (who must be a pharmacist residing in the Republic) must be registered with the Pharmacy Council

·all directors must confirm that they will abide by the Pharmacy Council's ethical rules

·pharmaceutical operations must be conducted under the constant personal supervision of a pharmacist whose name is displayed over the main entrance

·certain duties and responsibilities must be performed by pharmacists e.g. manipulation, preparation or compounding of medicines, manufacturing, furnishing of advice with regard to medicines, distribution and sale of medicines.

2.3.2 Further Legal Requirements

2.3.2.1 South African law further lays down requirements for the following activities:

·labelling of medicines, including package inserts

·records and registers for scheduled medicines

·sale of medicines only to registered and approved customers

·registration of medicines with the Medicines Control Council

·adherence to standards

·reporting of adverse reactions and technical errors

·advertising of medicines

·carrying and supply of professional samples.

2.3.3 Narcotics/Psychotropics

2.3.3.1 The Medicines and Related Substances Control Act No 101 of 1965 requires returns to be submitted in respect of Schedule 6, Schedule 7, and specified Schedule 5 Substances before 28 February of each year. The Act further requires that wholesalers and manufacturers keep registers of sales and receipts of both Schedule 6 and Schedule 7 Substances, and records of Schedule 5 Substances.

2.3.3.2 The International Narcotics Control Board (I.N.C.B.) has requested the co-operation of the Government of the Republic of South Africa with regard to expanding the requirement of obtaining permits for the importation and exportation of Schedule 6 and Schedule 7 Substances, for all substances under international control. Companies importing or exporting Schedule 5 substances or medicines, which are internationally controlled, are expected to obtain import and/or export permits, although it is not required by law. After the importation or exportation of narcotic drugs or psychotropic substances had been affected, reporting by means of returning the triplicate copy of the permit to the Department of Health, should be done without delay.

2.3.3.3 Any unusual loss or theft of narcotic or psychotropic drugs, should immediately be reported to the South African Police Services and to the Registrar of Medicines.

2.3.3.4 The Department of Health prescribes the procedure to be followed for the destruction of large quantities of Schedule 6 or Schedule 7 drugs, and requires a written statement of quantities of drugs to be destroyed.

2.4 QUALIFICATIONS

2.4.1 Each person engaged in the manufacture, processing, packing or storage of a medicine shall have the education, training and experience or combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in general and specific GMP and written procedures as they relate to the employee's functions. Training in GMP shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to ensure that employees remain familiar with GMP requirements applicable to them.

2.4.2 Each person responsible for supervising the manufacture, processing, packing or storage of a medicine shall have the education, training and experience or combination thereof, to perform assigned functions in such a manner as to provide assurance that the medicine has the quality, safety, efficacy and availability that it purports or is represented to possess.

2.4.3 There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing or storage of each medicine.

2.5 TRAINING

2.5.1 All Production, Quality Assurance and Stores personnel and all other personnel (eg. maintenance, service and cleaning staff) whose duties take them into manufacturing areas, or which bear upon manufacturing activities, should be trained in the principles of GMP and in the practice (and the relevant theory) of the tasks assigned to them.

2.5.2 Besides the basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given and its practical effectiveness should be periodically assessed. Written training programs should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.

2.5.3 Personnel working in areas where contamination is a hazard e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

2.5.4 To assess the effectiveness of training, checks should be carried out to confirm that designated procedures are being followed by staff at all levels.

2.5.5 Visitors or untrained personnel should not be taken into the manufacturing areas. However, if deemed necessary, they should be given information in advance, particularly about personal hygiene and prescribed protective clothing which may be required. They should be closely supervised.

2.5.6 The concept of Quality Assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

2.5.7 Pharmacist Intern (Industry)

After formal university education, the Pharmacist Intern must undergo one year internship in Industry, being trained as prescribed by the South African Pharmacy Council.

2.5.8 Pharmacist's Assistant (Industry)

After formal education by the PMA, the Pharmacist's Assistant in Industry is required to pass the Pharmacy Council's examination which enables the assistant to perform certain functions of a Pharmacist as defined by the Pharmacy Council.

2.6 HYGIENE

2.6.1 Personal Hygiene

2.6.1.1 High standards of personal cleanliness should be observed by all those concerned with production processes. (The special requirements for Sterile Products are covered in Chapter 22).

2.6.1.2 Personnel should be instructed to use the handwashing facilities.

2.6.1.3 Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include instructions relating to the health, hygiene practices and clothing of personnel. These instructions should be understood and followed in a very strict way by every person whose duties take him into the manufacturing and control areas. They should be promoted by management and widely discussed during training sessions.

2.6.1.4 Eating, drinking, chewing and smoking, or the storage of food, drink, smoking materials and personal medication should not be permitted within manufacturing areas or in any other area where they might adversely influence product quality.

2.6.1.5 Direct contact should be avoided between the operators' hands and starting materials, intermediates and products (other than when they are in closed containers), as well as with any part of the equipment that comes into contact with the products.

2.6.2 Area Control

2.6.2.1 Requirements regarding personal hygiene and protective clothing apply to all persons (including visitors, maintenance personnel, senior management and inspectors) entering production areas.

2.6.2.2 All persons entering production areas should wear protective garments appropriate to the processes being carried out. The garments should be regularly and frequently cleaned and not worn outside the factory premises. Changing Rooms should be provided.

2.6.2.3 Only personnel authorised by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

2.6.3 Medical Checks

2.6.3.1 There should be pre-employment medical checks and at regular intervals thereafter, and steps should be taken to see that no person with a disease in a communicable form, or with open lesions on the exposed surface of the body, is engaged in the manufacture of medicinal products. Visual inspection staff should pass an annual eye examination.

2.6.3.2 Staff should be required to report infections and skin lesions and a defined procedure followed when they are reported. Supervisory staff should look for the signs and symptoms of these conditions.

CHAPTER 3:

PREMISES AND EQUIPMENT

3.1 PRINCIPLES

3.1.1 Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products and safety of personnel.

3.2 PREMISES

3.2.1 General Requirements

3.2.1.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2.1.2 Construction should ensure that it prevents the entry of insects, animals (especially rodents) or birds and that the premises can be easily cleaned and disinfected. A Pest and Insect Control programme should be in place at all times. Toxic baits should be carefully controlled and used in such a way that they cannot present a hazard to products or materials.

3.2.1.3 The building must at all times be maintained in good order with repairs being carried out in such a way that they do not present a hazard to the quality of the products.

3.2.1.4 Waste materials should be continually removed from the premises and written sanitation procedures should be available detailing schedules, methods, materials and equipment available. Responsibility should be assigned in writing. Cleaning and disinfection should be on-going on a regular basis and must include change rooms, wash rooms, toilets and refreshment areas.

3.2.1.5 Adequate lighting and ventilation should be provided in all areas and equipment for controlling dust, humidity, pressure and temperatures should be appropriate for the processes taking place in any particular area. Environmental conditions should be monitored regularly and recorded.

3.2.2 Production Areas

3.2.2.1 Production areas should have a logical layout in order to prevent mix-ups and should have sufficient space to carry out the production in an orderly manner.

3.2.2.2 Production areas should be separated in such a way as to suit the operations taking place and should not be used as a right of way for personnel who do not work in them

3.2.2.3 Production of potent products should be in separate facilities which have been purposely designed to accommodate them and which protect the personnel from the product and vice versa.

3.2.2.4 Production of penicillins, biologicals, certain antibiotics, certain hormones and certain cytotoxics should take place in dedicated facilities designed specially for their manufacture. The principle of campaign working in the same facilities can be accepted provided specific precautions are taken and the process and its effect have been validated. Refer to appendices covering Penicillins, Cephalosporins and Sex Hormones. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

3.2.2.5 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

3.2.2.6 Production areas should be ventilated with air control facilities appropriate to the products handled, to the operations undertaken and to the external environment. Particular attention should be paid to dust-generating operations e.g. dispensary.

3.2.2.7 Filtration of outside air and air returned to the atmosphere should be the minimum requirement. Air can be blown into the factory and extracted but product must not migrate into passages or other areas. This can be achieved by e.g. blowing air into the passages and extracting it from each department through suitable filters which prevent contamination of the airducts.

3.2.2.8 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

3.2.2.9 Dust extraction and collection should be in place where dust is generated. All drains should have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

3.2.2.10 All pipes, fittings and other services should be designed and sited in such a way that they do not create places that are difficult to clean. Floors, walls and ceilings should be of materials that facilitate cleaning.

3.2.2.11 In-process controls may be done within the production area provided they do not carry any risk for the production.

3.2.3 Storage Areas

3.2.3.1 Storage areas should be designed or adapted to ensure good storage conditions. They must be clean and dry and maintain acceptable temperature limits.

3.2.3.2 Special storage areas such as flammable stores, cold rooms or low humidity rooms should be provided for materials that require these conditions. The environment should be continuously monitored and equipped with alarms to alert personnel in case of failure, so that alternative arrangements can be made.

3.2.3.3 There should be sufficient space for proper segregation of the various categories of materials and products. Acceptance and despatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow incoming material containers to be cleaned prior to storage.

3.2.3.4 Warehouses that are not computer controlled should provide separate areas clearly demarcated and preferably physically separated for the following categories of material - sampling, quarantined, raw, packaging, intermediate, finished products, rejected, recalled and returned materials or products. Areas must be restricted to authorized personnel.

3.2.3.5 Computer controlled warehouses must have a system which gives equivalent security.

3.2.3.6 Printed packaging materials and highly potent substances should be controlled and kept under safe and secure conditions.

3.2.3.7 Warehouses should be secured against theft and the higher scheduled medicines and raw materials should be locked in separate secured areas.

3.2.4 Quality Control Laboratories

3.2.4.1 Quality Control Laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radio-isotopes, which should also be separated from each other.

3.2.4.2 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

3.2.4.3 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

3.2.4.4 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

3.2.5 Ancillary Areas

3.2.5.1 Rest rooms, smoking areas and refreshment rooms should be separate from other areas.

3.2.5.2 Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas and should be well ventilated.

3.2.5.3 Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

3.2.5.4 Animal houses should be well isolated from other areas with a separate entrance for animal access and separate air handling facilities.

3.3 EQUIPMENT

3.3.1 Manufacturing equipment should be designed, located and maintained to suit its intended purpose.

3.3.2 Equipment should be installed and located in such a way as to prevent any risk of error or of contamination.

3.3.3 Repair and maintenance operations should not have any effect on the quality of the Products. Adequate records should be kept.

3.3.4 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

3.3.5 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition. Adequate cleaning records indicating previous product made, should be kept.

3.3.6 Equipment for the purpose of washing and cleaning should be chosen and used in such a way so as not to be a source of contamination itself.

3.3.7 Inasmuch as water is used more copiously and widely than any other substance in pharmaceutical manufacturing, its quality is of the utmost importance. The two most important attributes over which control must be exercised are the content of solids and the number of micro-organisms.

3.3.8 Water used for the manufacture of medicines should be purified by ion exchange treatment, reverse osmosis or distillation. Ion-exchange columns and reverse osmosis units require special attention in that they afford sites for micro-organisms to lodge, to multiply and to enter the water. Frequent monitoring and regeneration of these units is called for.

3.3.9 Distilled, deionized and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.
3.3.10 Production equipment should not adversely affect the quality of the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product. The product should not come into contact with other materials such as coolants and lubricants.

3.3.11 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

3.3.12 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. More frequent verification of some weighing equipment may be advisable. Adequate records of such tests should be maintained.

3.3.13 Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a medicinal product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written programme designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

3.3.14 Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to, and output from the computer or related system, of formulae or other records or data shall be checked for accuracy. A backup file of data entered into the computer or related system shall be maintained, except where certain data such as calculations are eliminated by computerization or other automated processes. In such instances either a written record of the programme (source code) shall be maintained or the system should be validated. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasure or loss, shall be maintained.

3.3.15 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

3.3.16 Where applicable, liquid products should pass through suitable filtration equipment before being filled. The type of filter will vary from product to product but no asbestos filters should be used. For instance, syrups may be passed through in-line strainers while solutions are generally pumped through a filterpress. Filtration can be fine enough to exclude bacteria, if this is necessary. Filters should not shed fibres or adversely affect the product.

CHAPTER 4:

MATERIALS MANAGEMENT

4.1 PRINCIPLES

4.1.1 There should be written procedures for the control, purchasing, receipt, storage, handling and issuing of raw materials, packaging material components, intermediate and finished products. All materials should be handled and stored in a manner to prevent contamination. deterioration and intermixing.

4.2 PURCHASING

4.2.1 All materials should be purchased against an approved and adequate specification which defines not only the grade and quality of the material, but also the nature of the packaging and container to be used.

4.2.2 Materials should be purchased and sourced only from approved suppliers and manufacturers. Choice of vendor should be based mainly on quality considerations.

4.2.3 Raw materials and packaging components should only be purchased by buyers who are adequately trained and who possess sufficient technical knowledge.

4.3 RECEIVING

4.3.1 Upon receipt and before acceptance, each container or grouping of containers should be examined visually for appropriate labelling, (including name, batch number, expiry date, supplier) damage and contamination, and quality control informed as necessary. The number of containers should be compared with the order document and invoice. Containers should be dusted or cleaned if required, and protected from contamination during storage.

Materials should only be taken into stock if all the relevant documentation (eg. delivery note and COA) is accompanied.

4.3.2 All materials subject to quality control should be stored under quarantine and withheld from use, until the lot has been tested or examined, as appropriate, and released by quality control.

4.3.3 Each container or grouping of containers should be identified with standard nomenclature and a distinctive code for each lot in each shipment received, which should be used in recording the disposition of each lot. Each lot should be appropriately labelled and identified as to its status (i.e. quarantined, approved or rejected). This may be done manually or the status may be controlled by appropriate and validated computer systems.

4.4 STORAGE

4.4.1 Materials which are in quarantine, approved or rejected should be segregated from each other. Such segregation may be accomplished by one or more of the following means:

·storage in physically separated areas
·clear and easily distinguishable status labelling
·a system of control, e.g. by computers, bar-codes or other means, which reliably prevents the inadvertent use of unapproved material.

4.4.2 Materials should be stored under suitable conditions, taking into account the following requirements:

·storage temperature
·humidity
·direct light
·exposure to air

4.4.3 Containers should be stored off the floor and suitably spaced from other materials, walls and from other batches of the same material.

4.4.4 Materials approved for use should be rotated so that the stock with the earliest expiry date is used first.

4.4.5 Materials should be resettled or re-examined, as appropriate, and approved or rejected by quality control if necessary e.g. after storage for long periods or after exposure to adverse conditions. An adequate system for monitoring the storage period should be maintained.

4.4.6 Storage of printed packaging materials requires strict and careful control, e.g.:

·storage in separate locked areas with each component stored separately with suitable identification
·under supervision of a suitably trained and responsible person
·obsolete components should be immediately destroyed.

4.4.7 Access to all storage and holding areas should be limited to authorized personnel.

4.5 ISSUING

4.5.1 Issuing of materials should be performed by suitably trained and responsible persons.

4.5.2 Records should be maintained for quantities received, approved, issued and returned, to enable clear reconciliations to be performed. Discrepancies require thorough investigation.

4.5.3 Rejected materials should be identified and controlled under a system which prevents their use in operations for which they are unsuitable. A separate area should be used. Only materials approved by quality control should be used.

4.5.4 Issuing of printed packaging materials requires strict and careful control, eg.:

·transport in sealed containers
·excess components should be destroyed if intermixing could have occurred
·returned components should be identified and stored in such a way so as to prevent mix-ups.

CHAPTER 5:

MANUFACTURING

5.1 PRINCIPLE

5.1.1 Manufacturing operations must follow clearly defined written procedures in order to produce products of the requisite quality and must comply with their authorized manufacturing documents as well as all legal requirements.

5.2 VALIDATION (SEE CHAPTER 9)

5.2.1 Before any manufacturing operation can be considered as routine it should be validated.

5.2.2 Validation studies of manufacturing methods should be conducted in accordance with defined procedures. Results and conclusions must be recorded.

5.2.3 New manufacturing procedures should be subject to methods to demonstrate the suitability of such procedures for routine processing. The defined process must be shown to yield a product consistently of the required quality.

5.2.4 Significant amendment to the manufacturing process which may affect product quality and/or the reproductivity of the process should be validated. This includes changes to materials and equipment.

5.2.5 Periodic re-validation should become a routine procedure to ensure that processess and procedures remain capable of achieving the intended results.

5.3 DISPENSING

5.3.1 Starting material should only be purchased from approved suppliers and in accordance with the registration dossier.

5.3.2 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

(a) The designated name of the product and the internal code reference, where applicable

(b) a batch number given at receipt

(c) where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected)

(d) where appropriate, an expiry date or a date beyond which retesting is necessary.

5.3.3 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

5.3.4 Only starting materials which have been released by the Quality Control Department and which are within their shelf-life should be used.

5.3.5 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

5.3.6 Each dispensed material and its mass or volume should be independently checked and signed for by a pharmacist or other legally authorized person.

5.3.7 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

5.3.8 The addition of each material to the mix should be checked and signed for by a pharmacist or other legally authorized person.

5.4 MANUFACTURING OPERATIONS

5.4.1 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination. Materials for a particular batch should, as far as possible, be kept together.

5.4.2 All manufacturing areas and equipment should be checked for cleanliness prior to starting production.

5.4.3 At every stage of processing, products and materials should be protected from microbial and other contamination.

5.4.4 At all times during processing, all materials, bulk containers, major items of equipment and, where appropriate, rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

5.4.5 Labels applied to containers, equipment or premises should adhere well and be clear, unambiguous and in the company's agreed format. It is often helpful, in addition to the wording on the labels, to use colours to indicate status (for example: green for released, red for rejected).

5.4.6 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

5.4.7 Normally, non-medicinal products should not be produced in areas and with the equipment destined for the production of medicinal products.

5.4.8 Access to production premises should be restricted to authorized personnel.

5.4.9 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be approved in writing by an authorized person(s), with the involvement of the Quality Control Department, when appropriate.

5.4.10 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits. Any such discrepancies should be investigated and explained.

5.5 IN-PROCESS CONTROL

5.5.1 Production staff should follow defined and authorized procedures for each stage of each manufacturing process.

5.5.2 At all key steps of manufacture there should be some form of control to ensure compliance with the authorized procedure. Critical steps should be signed for.

5.5.3 In-process laboratory tests may need to be carried out before moving to the next step in production or as soon as possible after completion of that step. Formal approval of some results may be necessary.

5.5.4 All inappropriate labels must be removed from containers or equipment before these items enter the manufacturing area.

5.5.5 Environmental control should be carried out and recorded, when necessary.

5.6 CONTAMINATION

5.6.1 Contamination of raw material or of a product by another material or product must be avoided. The risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues in equipment, from water and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, some hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or given over an extended period.

5.6.2 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:

(a) production in segregated areas (required for products such as penicillins, some hormones, live vaccines, live bacterial preparations and some other biologicals - see Appendices), or by campaign production (separation in time) followed by appropriate cleaning

(b) providing appropriate air-locks and air extraction

(c) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air

(d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed

(e) using cleaning and decontamination procedures of known effectiveness. (Ineffective cleaning of equipment is a common source of cross- contamination). Vacuum and wet cleaning methods are preferred

(f) using "closed systems" of production

(g) testing for residues and use of cleaning status labels on equipment.

5.6.3 Measures to prevent cross-contamination and the effectiveness of the measures should be checked periodically according to set procedures.

5.6.4 Microbial contamination should be controlled by air filtration, effective cleaning, disinfection and ensuring only the minimum number of personnel required enter the area. The area must at all times be

neat and tidy to prevent accumulation of materials that could promote microbial growth. Insects, animals and birds must be totally excluded.

5.6.5 All personnel (including those concerned with cleaning and maintenance) should receive regular training in the disciplines necessary to prevent microbial and other contamination.

5.6.6 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.

5.6.7 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

5.6.8 Intermediate and bulk products should be kept under appropriate storage conditions and for controlled periods.

5.5.9 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.7 REPROCESSING

5.7.1 Material may be re-worked or recovered by an appropriate and authorized method, provided that the material is suitable for such reprocessing, that the resultant product meets its specification, that there is no significant change in product quality and that Quality Control authorization is obtained. Documentation should accurately record the reworking processes carried out. The reprocessing of rejected products should be exceptional.

5.7.2 Residues and re-worked or recovered material which might adversely affect product quality, efficacy or safety should not be used in subsequent batches.

5.7.3 The treatment of product residues and reworked or recovered material and the means of their inclusion in a subsequent batch should be specifically authorized and documented.

5.7.4 Limits, approved by Quality Control, should be established for the amount of any such material which may be added to a subsequent batch.

5.7.5 Batches incorporating residues should not be released until the batches from which the residues originated have been tested and found suitable for use.

5.7.6 Methods of re-processing should be specifically authorized and fully documented, once any potential risks have been evaluated and found negligible.

5.7.7 The need for additional testing including stability of any Finished Product which has been re-processed (or to which residues have been added) should be considered.

CHAPTER 6

PACKAGING

6.1 PRINCIPLES

6.1.1 Packaging operations must follow clearly defined written procedures in order to produce finished products of the requisite quality and must comply with their authorized packaging documents as well as all legal requirements. Special attention must be paid to labels and labelling throughout the entire packaging cycle.

6.2 COMPONENT ISSUE

6.2.1 The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

6.2.2 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. If the quantity or volume of loose printed packaging material is too large to be placed in separate closed containers eg. several pallets of cartons, adequate alternative control measures must be taken to ensure no mix-ups occur.

Packaging materials should be issued for use only by authorized personnel following an approved and documented procedure.

6.2.3 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

6.2.4 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

6.3 PACKAGING OPERATIONS

6.3.1 When preparing a programme for the packaging operation, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

6.3.2 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list and signed for. Certain checks eg. printed packaging material, printing operations and bulk identity should be performed and signed for by a pharmacist or legally authorized person.

6.3.3 The name and batch number of the product being handled should be displayed at each Packaging station or line.

6.3.4 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

6.3.5 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate security procedures should be applied to ensure that no mix-ups or mislabelling can occur.

6.3.6 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

6.3.7 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

6.3.8 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

6.3.9 Printed and embossed information on packaging materials should be easily legible and resistant to fading or erasing.

6.3.10 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments, metal particles and unwanted moisture.

6.3.11 All pipelines and other equipment for transporting product to the packaging line should be thoroughly cleaned, inspected and labelled according to a specific written procedure.

6.3.12 Hand packing operations require increased vigilance to prevent inadvertent mix-ups.

6.3.13 Products which have been involved in any deviation from standard procedure or other unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorized personnel. Detailed record should be kept of this operation.

6.3.14 On completion of a packaging run, the quantities of finished product should be reconciled with the amount of bulk product issued, the amount of packaging material issued, and the material remaining.

6.3.15 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product or printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for. Reconciliation of printed packaging materials may not be necessary if other suitable means of preventing the introduction of foreign components are in use, e.g. bar-code readers

6.3.16 At the end of the pack-out the packaging line should be inspected to ensure that all material relating to that particular product or run has been removed and that all equipment is cleaned. Special attention should be devoted to ensuring that no tablets, capsules or other small items have fallen into parts of the equipment. Special attention to ensure that no labels remain in the equipment or on the floor should be part of the inspection.

6.3.17 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded.

6.3.18 Special care must be taken to control the return of any unused packaging materials to the packaging materials warehouse.

6.4 IN-PROCESS CONTROL

6.4.1 During the packaging process the packing line should be continually monitored to ensure that the integrity of the finished product is not in any way compromised. Written procedures and tabulated check lists should be signed at regular intervals by competent and suitably trained people.

6.4.2 Automated controls and monitors should be checked regularly during the production run and validated from time to time.

6.4.3 On-line control of the product during packaging should include at least checking the following:

·general appearance of the package
·fill masses/volumes or quantity comply
·whether the packages are complete
·whether the correct products and packaging materials are used
·whether any over-printing is correct
·seal integrity
·correct functioning of line monitors.

6.4.4 Samples taken away from the packaging line should not be returned.

6.5 CONTAMINATION

6.5.1 Every effort should be made to ensure that packaging takes place in an orderly and tidy manner that will ensure there are no mix-ups between one product and another.

6.5.2 Products that are similar in appearance should not be packaged in close proximity to one another at the same time.

6.5.3 Packaging lines should be well separated and, if possible, physical barriers that will prevent the migration of material from one line to another should be in place.

6.5.4 Special precautions should be taken to prevent the inadvertent transfer of components by personnel moving between packing lines, e.g. inspectors and maintenance staff.

6.6 FINISHED PRODUCT RELEASE

6.6.1 Finished products must be placed in quarantine in such a way that they cannot be removed for use until such time as they are released.

6.6.2 Samples of the product taken at intervals during the packaging process must be retained for examination by the quality control laboratory and for retention purposes.

6.6.3 Documentation should be reconciled, completed/and sent for a complete documentation audit by quality assurance.

6.6.4 When all required parameters are satisfied, including the document audit, Quality Control may recommend release of the product from its quarantine status.

6.6.5 The finished product should be released for sale by a pharmacist.

CHAPTER 7:

QUALITY CONTROL

7.1 PRINCIPLES

7.1.1 In order to achieve reliable results, Quality Control laboratories should have sufficient resources and appropriate facilities, with properly trained, managed and motivated staff, and adopt good quality control laboratory practices. Materials and products should not be released for use or supply until their quality has been judged satisfactory. Quality Control should be independent from Production. Quality Control should adopt procedures necessary to ensure that the relevant tests and checks are carried out.

7.2 RESPONSIBILITIES

7.2.1 The Quality Control department is responsible for approving or rejecting raw materials, intermediates, finished products and components for use or supply to the market

7.2.2 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing and packaging documentation, compliance with Finished Product Specification and examination of the final finished pack. Where the local applicant or holder of a registration certificate makes use of a contract laboratory (overseas), the local applicant or holder of a registration certificate or the local laboratory as listed in the registration certificate, should do at least a visual identification of the final product.

7.2.3 Quality Control is not confined to laboratory operations but must be integrated into the Quality Assurance activities. It is involved in all decisions which may concern the quality of the product (i.e. quality planning, co-ordination and control activities). It further includes the review of all plant systems and procedures, audits, organization and documentation.

7.2.4 The Quality Control department will also have the following responsibilities:

·sampling of materials subject to quality control and the keeping of retention samples and records
·monitoring the stability of products
·investigation of complaints related to the quality of the product
·the testing or supervision of the testing of all materials and products
·the control over labeling of containers for materials and Products

All these operations should be carried out in accordance with written procedures, and where necessary, recorded.

7.2.5 The Quality Control department may also have responsibilities in the following areas :
·validation of critical equipment and procedures
·approval of third party contractors and vendors
·approval of all deviations and reworks

7.3 EQUIPMENT

7.3.1 Control laboratories should be designed, equipped, maintained and of sufficient space to suit the operations to be performed in them, and include provision for the storage of documents and samples.

7.3.2 Chemical, biological and microbiological laboratories should be separated from each other and from manufacturing areas. Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

7.3.3 Control laboratory equipment and instrumentation should be appropriate to the testing procedures undertaken.

7.3.4 Equipment and instruments should be serviced and calibrated at suitable specified intervals and readily available records maintained for each instrument or piece of equipment.

7.3.5 Written operating instructions should be readily available for each instrument.

7.3.6 As necessary, analytical methods should include a step to verify that the equipment is functioning satisfactorily.

7.3.7 Control laboratories and equipment should be kept clean, in accordance with written standard operating procedures and schedules. Records/logs should be kept.

7.3.8 Personnel should wear clean protective clothing and personal protective equipment appropriate to the duties being performed.

7.4 PERSONNEL

7.4.1 The Quality Control laboratory should be under the authority of a person with appropriate qualifications and experience and with sufficient responsibility and authority to carry out the required duties adequately.

7.4.2 All relevant quality control staff should be suitably educated, trained and motivated to perform their tasks adequately.

7.5 SAMPLING

7.5.1 Samples should be taken in such a manner that they are representative of the batch of material from which they are taken, in accordance with approved written sampling procedures. These procedures should include:

·the method of sampling
·the equipment to be used
·the amount of sample to be taken
·instructions for any required sub-division of the sample

·the type and condition of sample container to be used
·any special precautions to be observed, especially in regard to sampling of sterile or noxious materials.
·cleaning and storage of sampling equipment.

Any sampling by production personnel should only be done in accordance with these approved procedures.

7.5.2 Each sample container should bear a label indicating its contents, with the batch or lot number reference and the date of sampling. The sampler should initial on the label and there should be an indication from which container the sample was taken. It should also be possible to identify the bulk containers from which samples have been drawn and which containers have been sampled.

7.5.3 Care should be taken to avoid contamination, or deterioration whenever a material or product is sampled. Sampled containers should be resealed in such a way so as to prevent damage to, or contamination of, or by, the contents.

7.5.4 Retention samples from each batch of finished products should be retained until one year after the expiry date. Finished products should be kept in their final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) should be retained until at least the expiry date of the batch in which they are used. Reference samples of materials and products should be of a size sufficient to permit at least one full re-examination.

7.6 TESTING

7.6.1 Analytical methods should be suitably validated. Only methods approved for use should be used. All tests required to be performed should be carried out.

7.6.2 Before the material is released or rejected, the results obtained should be checked to make sure that they are consistent with all other information. Any calculations should be documented and critically examined.

7.6.3 All the in-process controls, even those made in the production area by production personnel, should be done according to methods approved by Quality Control and the results recorded.

7.6.4 Microbiological testing and testing using animals should be performed and controlled in a manner that assures their suitability and reliability.

7.7 STANDARDS, REAGENTS

7.7.1 Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media.

7.7.2 Reagents made up in the laboratory should be prepared by persons competent to do so, following laid-down procedures. As applicable, labelling should indicate the concentration, standardisation factor, shelf-life, and storage conditions. If relevant, a date for re-standardisation should be recorded. The label should be signed, and dated, by the person preparing the reagent.

7.7.3 Reference standards, any secondary standards prepared from them and purchased reagents should be dated where necessary and be stored, handled and used following written procedures, so as not to prejudice their quality. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use. A record of these tests should be maintained.

7.7.4 Both positive and negative controls should be applied to verify the suitability of microbiological culture media. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

7.8 DOCUMENTATION

7.8.1 Quality Control procedures should be established, validated, implemented and recorded so as to assure the adequate and reliable performance of all quality control operations.

7.8.2 The following master documentation should be readily available to the Quality Control Department:

·specifications
·sampling procedures
·testing procedures and records (including analytical worksheets and/or laboratory notebooks)
·analytical reports and/or certificates
·data from environmental monitoring, where required
·validation records of test methods, where applicable
·procedures for and records of the calibration of instruments and maintenance of equipment.

7.8.3 The following test records should be kept:

·name and quantity of product or material and code reference where applicable
·dates of receipt, sampling and testing
·manufacturer and/or supplier of product or material
·supplier's batch or lot number

·tests performed
·reference to the relevant specifications and test methods used and to any certificates of analysis
·test results including observations and calculations
·initials of analyst and the person who verified the testing and calculations where appropriate
·decision statement regarding release, rejection or other status and signature of responsible person taking the decision.

7.8.4 In addition to the above records, analysts' laboratory records should also be retained, with the basic data and calculations from which test results were derived (e.g.. weighings, readings, recorder charts, etc.).

7.8.5 It is useful to record test results in a manner that will facilitate comparative reviews of those results and the detection of trends.

7.8.6 Any Quality Control documentation relating to a batch record should be retained for at least one year after the expiry date of the batch.

7.9 STABILITY

7.9.1 A written programme of on-going, follow-up stability should be designed and implemented so as to monitor the quality of the various marketed products throughout their intended shelf-life.

7.9.2 Tests should be performed that are indicative of stability and if necessary additional tests monitoring possible degradation and deterioration should be included.

7.9.3 Stability samples should be stored in their final, marketed containers and storage conditions should be consistent with those approved for the product in question.

7.9.4 Results from stability trials should be used to confirm or modify the prevailing shelf-life and storage conditions.

CHAPTER 8:

DOCUMENTATION

8.1 PRINCIPLES

8.1.1 Documentation is an essential part of the Quality Assurance System. Its purposes are to define the system of control, to reduce the risk of error inherent in purely oral communication, to ensure that personnel are instructed in the details of, and follow, the procedures concerned, and to permit investigation and tracing of defective products. The system of documentation should be such that the history of each batch of product, including the utilisation and disposal of starting materials, packaging materials and intermediate, bulk and finished products, may be determined.

8.1.2 Every applicant or holder of a registration certificate should be in possession of Master documentation, whether he manufactures the product or makes use of a third party manufacturer.

8.1.3 There should be authorised (signed and dated) specifications for a least raw materials, formula of the product, manufacturing method, printed packaging material, final product specification, in process tests, test methods and packaging material.

8.1.4 Master documents should be authorised, and the name of the applicant or holder of a registration certificate should be visible.

8.1.5 Master documents should be kept at the registered premises of the applicant or holder of the registration certificate.

8.1.6 Master documents should be properly controlled, and access thereto limited.

8.1.7 The registration dossier should be compliant with Master documentation.

8.1.8 There should be a written procedure for updating of master documentation and the system should endure that current, approved master documentation is being used.

8.1.9 A formal system should be in place to control changes to master documentation. Changes to master documents should be communicated to the appropriate departments and written approval prior to implementation of changes should be obtained from the regulatory authority where applicable.

8.1.10 Possession of mater documentation is a pre-requisite of medicines.

8.1.11 All relevant documentation, including the registration dossier and master documentation, should be handed to the new proposed applicant, should the current applicant or holder of a registration certificate apply to the regulatory authority for a change of applicancy.

8.2 PREPARATION, ISSUE AND USE OF DOCUMENTS

8.2.1 To facilitate proper and effective use, documents should be designed and prepared with care, and with particular attention to the following points:

(a) the company's name, the title (which should be unambiguous), nature and purpose of the document should be clearly stated. The document should be laid out in an orderly fashion, and be easy to check. Each page should be sequentially numbered. Where a document has been revised, systems should exist to prevent inadvertent use of superseded documents.

(b) the way the document is to be used, and by whom, should be clearly apparent from the document itself.

(c) where documents bear instructions they should be written in the imperative as numbered steps. They should be clear, precise, unambiguous and in a language the user can understand. Such documents should be readily available to all concerned with carrying out the instructions.

(d) documents which require the entry of data should:

·provide sufficient space for the entry
·allow adequate spacing between entries
·show headings clearly indicating what is to be entered.

(e) persons making entries should do so in clear legible writing, and should confirm the entry by adding their initials or signatures. Ticking should be avoided.

(f) all entries should be made in ink or other indelible medium.

(g) the size and shape of documents and the quality and colour of the paper used should be considered in relation to the typing / printing, reproduction and filing facilities available.

(h) reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process. If working documents are computer generated these should be checked against an authorised master and signed for correctness.

8.2.2 Documents should contain all necessary, but no superfluous data. Any headings, or places for entries, which cease to be used should be removed at the earliest opportunity.

8.2.3 Documents should be approved, signed and dated by appropriate, competent and authorized persons.

8.2.4 Documents (other than records) should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the registration dossier.

8.2.5 Records should be completed at the time each action is taken in such a way that all significant activities concerning the manufacture of medicinal products are traceable.

8.2.6 Data may be recorded by electromagnetic or photographic means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorised persons should be able to enter or modify data in the computer; access should be restricted by passwords or other means and entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that, during the period of retention, the data can be rendered legible within an appropriate period of time.

8.2.7 If an error is made or detected on a document it should be corrected in such a manner that the original entry is not lost and the correction initialed and dated. Where appropriate, the reason for the correction should be recorded. No correction fluid should be used.

8.2.8 Documents should be kept up to date. Any amendments should be formally authorised and signed. In the case of permanent amendments, the amended document should be replaced at the earliest opportunity by a newly prepared document.

8.2.9 The documentation system should include provision for regular review and revision as necessary.

8.2.10 An out-dated or superseded document should be removed from active use. The marked "Superseded" copy should be retained for reference purposes.

8.2.11 When a document has been revised, systems should exist to prevent inadvertent use of superseded documents.

8.2.12 Documents and other records, including original data such as laboratory notebooks should be retained for at least one year after expiry date of the batch. Documents should be easily retrievable.

8.3 MASTER SPECIFICATIONS

8.3.1 Starting Materials

8.3.1.1 There should be an authorised specification for each starting material.

8.3.1.2 Each specification should be dated and include:

(a) a designated name, with reference to monograph specifications where appropriate, and. preferably, a code reference unique to the material

(b) a reference to any alternative proprietary designation of the material

(c) a description of the physical form of the material

(d) sampling instructions

(e) tests and limits for identity, purity, physical and chemical characteristics, microbiological standards (where appropriate) and assay

(f) details of, or reference to, the test methods to be used to assess compliance with the specification

(g) approved supplier(s) of the material

(h) safety precautions to be observed

(i) storage conditions

j) frequency of re-testing the stored material

NOTE - Certain of the requirements may not necessarily appear on the prime specification document. There may be, for example, standard company sampling procedures and lists of approved suppliers to which the specification refers.

8.3.2 Packaging Materials

8.3.2.1 There should be packaging material specifications, approved by the person responsible for Quality Control.

8.3.2.2 Each specification should be dated and include:

(a) a designated name, with preferably a code-reference unique to the material. This reference may also appear on printed materials

(b) a description of the nature, dimensions and material of construction of the component with the quality standards, control limits, mould references, drawings and details of text, as applicable

(c) details of, or reference to the test methods to be used to assess compliance with the specification

(d) approved supplier(s) of the component
(e) sampling instructions

(f) storage conditions

(g) frequency of re-inspection of the stored component.

NOTE - Certain of these requirements may not necessarily appear on the prime specification document. See Note under 'Starting Materials' above.
See definition of 'Packaging Material' in Glossary. The need for detailed specifications may not apply to 'Other Packaging Materials'.

8.3.2.3 A file of reference specimens of current printed packaging materials should be maintained. This should include a colour standard

8.3.3 Intermediates and Bulk Products

8.3.3.1 These specifications should, as appropriate, be similar to specifications for starting materials and Finished Product specifications.

8.3.3.2 These specifications should be available if these products are imported, or if data obtained from these products are used for evaluation of the finished product eg. cores of coated tablets.

8.3.4 Finished Products

8.3.4.1 There should be specifications, approved at least by the person responsible for Quality Assurance, defining the nature and quality of each finished product.

8.3.4.2 Each specification should be dated and include:

(a) the designated name of the product and a code reference where applicable

(b) a description of the physical form of the product and a reference to container and package details

(c) sampling instructions

(d) tests and limits for identity, purity, physical and chemical characteristics, microbiological standards (where appropriate) and assay, with details of (or reference to) the test methods to be used

(e) safety precautions to be observed

(f) storage conditions and the claimed or approved shelf life.

(g) frequency of re-examination of the stored product to confirm the established shelf-life (for stability purposes).

NOTE - Certain of these requirements may not necessarily appear on the prime document. See Note under 'Starting Materials' above.

8.4 MASTER MANUFACTURING INSTRUCTIONS

8.4.1 A formally authorised Master Formula and Method should exist for each product and batch size to be manufactured.

8.4.2 The Master Formula should be dated and include:

(a) the name of the product with a code reference relating it to its specification

(b) a description of the pharmaceutical form and strength of the product and batch size