(c) a list of all starting materials to be used (see 8.4.3) with the amount of each, whether or not they appear in the Finished Product. All quantities should be stated in a uniform system of measurement, with a statement of any calculated overage. Where material of variable potency is to be used the permissible limits of variation and the total potency required for a batch should be stated

(d) a statement of the total expected final yield with the acceptable limits and of relevant intermediate yields where applicable.

8.4.3 Each starting material should be designated in the Master Formula by:

(a) the Approved or Monograph Name, and / or any other descriptive name, by which it can be specifically identified and which is used whenever that material is referred to

(b) a code reference which is unique to that material.

8.4.4 The Method should be dated and, as appropriate, include:

a) a statement of the manufacturing location and the equipment to be used

(b) the methods, or reference to the methods, to be used for preparing the equipment (e.g. cleaning, assembling, calibrating, sterilising)

(c) Detailed stepwise processing instructions, including:
·a check that the materials used are those intended
·any required pre-treatment of materials
·sequences for adding materials
·mixing and other processing times (as appropriate)
·temperatures (as relevant)
·safety precautions to be observed
·critical time limitations.

(d) a statement of the theoretical and/or expected amount of product at pertinent stages of manufacture

(e) details of any in-process controls, with instructions for sampling and with control limits

(f) requirements for bulk storage of the product, including containers, labels, storage time limits and special storage conditions.

8.5 MASTER PACKAGING INSTRUCTIONS

8.5.1 A formally authorised Master Packaging Instruction should exist for each pack size and type. It should be dated and (as appropriate) include, or have a reference to:

(a) the name of the product

(b) a description of its pharmaceutical form and strength where applicable

(c) the pack size expressed as number, mass or volume of the product in the final container

(d) a complete list with quantities, sizes and types of all the packaging materials required for a standard batch size

(e) the code or reference number of each material which relates it to its specification

(f) a specimen or facsimile of relevant printed packaging material, where practicable

(g) a description of the packaging operation with an indication of the equipment to be used

(h) details of any required preparation of packaging materials (e.g. washing, blowing, sterilising)
(i) details of any over-printing necessary

(j) special precautions to be observed

(k) details of any in-process controls to be applied, with instructions for sampling and with control limits.

(l) line clearance checks prior to starting the packaging operation

NOTE - It is useful to be able to refer to superseded Master Packaging Instructions.
Where products may be stored in partially packaged form, requirements for such storage should be laid-down in the master documentation, or for example, in standard procedures.

8.6 BATCH RECORDS (STARTING MATERIALS)

8.6.1 The receipt of the delivery of each starting material should be recorded. The record should include:

(a) date of receipt

(b) name of material

(c) name of material on delivery note and/or containers - if different from (b)

(d) supplier's name

(e) supplier's batch or reference number

(f) total quantity and number of containers received

(g) the batch identifying number assigned on, or after, receipt.

8.6.2 The testing of each starting material should be recorded and should be in accordance with the master specifications. The testing record should include:

(a) date of sampling and date of testing

(b) name and quantity of material

(c) the batch identifying number

(d) results of all tests

(e) identity of person(s) who performed tests

(f) a cross reference to any relevant certificate of analysis

(g) analyst's signature and the signed release or rejection (or other status decision) by Quality Control

(h) a clear statement of the assigned potency where this can vary.

NOTE - It is useful to record analytical data in a manner that will facilitate comparative reviews of past results and the detection of trends.

8.6.3 Stock records should be maintained of starting materials that will permit stock reconciliations to be made.

NOTE - Special requirements for substances scheduled six and higher are controlled by regulations in Act 101 of 1965.
8.6.4 A sample of the starting material sufficient in size to permit analytical re-examination should be retained as part of the starting material record.

8.7 BATCH RECORDS (PACKAGING MATERIALS)

8.7.1 The receipt of the delivery of each packaging material should be recorded. The record should include:

(a) date of receipt

(b) name and quantity of material

(c) supplier's name and any reference or batch number

(d) any batch identifying number assigned on, or after, receipt.

8.7.2 The testing and inspection of packaging materials should be recorded and be in accordance with the master specifications. The testing record should include:

(a) date of sampling and the date of testing (or inspection)
(b) name of material

(c) the batch identifying number

(d) results of testing and inspection

(e) name of person(s) who carried out testing or inspection

(f) analyst's signature and the signed release or rejection (or other status decision) by Quality Control.

NOTE - It is useful to record these data in a manner that will facilitate comparative reviews of past results and the detection of trends.

8.7.3 Stock records should be maintained of packaging materials that will permit stock reconciliations to be made.

NOTE - Lesser standards of control and documentation may be applied to packaging materials which can have limited influence on product quality. See also 'Packaging Materials' in Glossary.

8.8 BATCH RECORDS (MANUFACTURING)

8.8.1 Batch Manufacturing Records should be kept for each batch manufactured and should carry a batch reference number and be based upon the currently approved version of the Master Formula and Method. The method of preparation should be designed to avoid transcription errors. Photocopying or some similar method of preparing the basic document is to be preferred.

8.8.2 If Batch Manufacturing Records do not include complete details of the Method, the operator must have ready access to the currently approved Method.

8.8.3 Before any manufacture proceeds there should be recorded checks that the equipment and work-station are clear of previous products and documents and of materials not required for the process in hand and that equipment is clean and suitable for use.

8.8.4 During manufacturing the following should be entered onto the Batch Manufacturing Records, at the time that each action was taken and, after completion, the record should be dated and signed in agreement by the person responsible for processing operations:

(a) the batch identifying number of each of the starting materials used and the amount used

(b) where the Master Formula permits variation in the quantity of starting material, a record of the amount actually used

(c) dates of commencement and completion of manufacture and of significant intermediate stages

(d) where more than one batch of a given starting material is used, a record of the actual amount of each batch

(e) the batch identifying number and amount of any recovered or re-work material added and at what stage of the manufacturing process it was added to the mix

(f) the initials of the person(s) who weighed or measured each material and the initials of the person(s) who checked each of these operations, this check being not only of the quantity but also of the labelled identity and batch number of the material

NOTE - Critical steps such as weighing, measuring and 'adding to the mix' should be checked and signed for by a pharmacist or other legally authorised person.

(g) the amount of product obtained at pertinent intermediate stages of manufacture

(h) the initials of the person responsible for each critical stage of manufacture

(i) the results of all in-process controls, with the initials of the person(s) carrying them out

NOTE - The in-process control document could be a separate document.

(j) reference to the precise items of major equipment used, where several of the same type are available for use (i.e. where equipment is replicated). This information may be recorded in 'Plant Usage Logs'. A cross-reference to this should be included in the Batch Manufacturing Record [BMW]

(k) details of, and signed authorisation for, any deviation from the Master Formula and Method

(l) the final batch yield and the number of bulk containers

(m) signed agreement by the process supervisor that apart from any deviation noted in (k) above, manufacture has proceeded in accordance with the Master Formula and Method, and that process or yield variations are adequately explained

8.9 BATCH RECORDS (PACKAGING)

8.9.1 Batch Packaging Records should be kept for each batch or part-batch processed and should be based upon the currently approved version of the Master Packaging Instruction and prepared from it by a method designed to avoid transcription errors (photocopying or some similar method is to be preferred). The Record should carry the quantity of bulk product to be packed, the planned quantity of finished product and should bear a batch reference number, which is specific to a particular packaging run. The batch number which appears on the finished product should be this number, or one which may be easily related to it.

NOTE - The bulk product and packaging reference numbering system must make it possible to relate a packaging operation to a bulk batch and the bulk batch to any packaging operation(s).

8.9.2 If the Batch Packaging Records do not include details of the method of packaging, these should be readily available to the operator(s).

8.9.3 Before any packaging is undertaken checks should be made that each packaging line or station is clear of previous product, packaging components records or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded and each packaging line opened and closed by a pharmacist, other legally authorised person or quality control.
8.9.4 During packaging, the following should be entered onto the Batch Packaging Records, at the time that each action is taken:

(a) the batch number and expiry date of the Bulk Product to be packaged

(b) dates and times of commencement and completion of packaging and of significant intermediate stages

(c) the initials of the person(s) who issued the bulk product and printed packaging materials and of the person(s) who confirmed their correct identity and quantity

NOTE - The identity of the bulk product and printed packaging material should be checked and signed for by a pharmacist or other legally authorised person.

(d) the total quantities of the packaging materials used, with a batch identifying reference to primary and printed packaging materials (specimens of printed packaging materials used including specimens of the overprinting should be attached, or alternatively there should be an arrangement which will permit later reference to specimens of the printed packaging materials used)

(e) the results of any in-process controls, together with the initials of the person responsible for carrying them out

(f) the initials of the persons who carried out each significant stage of the packaging operation

(g) a record of the packaging machines, line or area used.

8.9.5 Records should be kept of the amount of bulk product supplied, printed materials issued and finished packs produced and reconciliations performed where required. (Alternative measures to ensure correctness of finished pack may be used).

8.9.6 Notes on any special problems including details of any deviations from the packaging instructions with written authorisation by an appropriate person should be kept.

8.10 OTHER PROCEDURES AND RECORDS

8.10.1 Intermediate Bulk and Finished Product Test Records

8.10.1.1 These records should include:

(a) the date of manufacture

(b) the date of testing

(c) the batch number and expiry date

(d) the name, code reference and quantity of the material and/or product

(e) the tests done and the results

(f) analyst's signature and the signed release or rejection (or other status decision) by Quality Control.

NOTE - The method of recording should facilitate comparative reviews of past results and the detection of trends.

8.10.1.2 A sample of the final packaged product sufficient in size to permit full re-examination as necessary should be retained as part of the record. If this is not practicable or economic (due, for example, to an unusually large pack size) then a smaller sample in a similar type of pack may be retained.

8.10.2 Receipt Records

8.10.2.1 There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material. The records of the receipts should include:

(a) the name of the material on the delivery note and/or the containers

(b) the 'in-house' name of material (if different from (a))

(c) date of receipt

(d) supplier's name and, if possible, manufacturer's name

(e) manufacturer's batch or reference number

(f) total quantity and number of containers received

(g) the batch identifying number assigned after receipt

(h) any relevant comment (e.g. state of the containers).

8.10.2.2 There should be written procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

8.10.3 Distribution Records

8.10.3.1 To facilitate effective recall, records of distribution should be kept showing the date and the name and addresses of all persons to whom the manufacturer supplies each specific batch of product.

8.10.4 Complaints Records

8.10.4.1 A record should be maintained of all complaints relating to product or packaging quality. This record should show the nature of the complaint, results of investigations and action taken. The record should be maintained in such a manner that significant recurrent complaints can be recognised and appropriate action taken eg. tracking of trends.

8.10.5 Other Documents

8.10.5.1 Where relevant to the scale of an operation, the maintenance of departmental and equipment logs (i.e. running, dated records of equipment usage, products manufactured and cleaning of equipment and manufacturing areas) is recommended.

8.10.5.2 Where appropriate, there should be written procedures and the associated records of actions taken or conclusions reached for:
-validation
-maintenance, cleaning, sanitation
-personnel matters including training, clothing, hygiene
-environmental monitoring
-pest control
-recalls

8.10.5.3 Clear operating directions should be available for major items of manufacturing or testing equipment.

8.10.6 Retention of Records

8.10.6.1 Batch Manufacturing and Packaging Records plus the relevant test records, must be retained until at least one year after the expiry date of the batch. Finished product samples should be retained at least until the expiry date of the product, plus one year. Starting material records and samples should be retained until at least the expiry date of the batch in which they are used. Finished product reference samples should be stored under ambient conditions, or as directed on the label.

8.11 ANALYTICAL RECORDS

8.11.1 Sampling and Approval Documentation

8.11 .1.1 There should be documentation systems set up with the object of ensuring that:

(a) starting and packaging materials are in fact sampled and tested in accordance with previously specified procedures

(b) materials are not taken into usable stock until the specified checks and tests have been performed and the material formally approved by Quality Control (alternative arrangements may be made when an acceptable certificate of analysis is available)

(c) intermediate, bulk and finished products and any re-worked or recovered materials are sampled and tested in accordance with previously defined procedures and that products will not be released for sale or supply until all data on the intermediate, bulk and finished product have been reviewed and approval given by Quality Control.

8.11.2 Sampling

8.1 1.2.1 There should be written procedures for sampling, which include details of the person authorized to take samples, the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

8.11.3 Testing

8.11.3.1 There should be written procedures for testing of products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded and the records, together with all supporting documentation should be kept.

8.11.4.1 Written release and rejection procedures should be available for materials and products and in particular for the release for sale of the finished product by a pharmacist. This release should include the completion of a check list which will ensure that all important release criteria have been met.

8.12 OTHER DOCUMENTATION REQUIRED

8.12.1 Site Master File
A description of the manufacturing facility, including a company profile plus a description of the premises, equipment, personnel and standard operating procedures relating to manufacture and the quality system. This must be lodged with the Medicines Control Council.

8.12.2 Validation Master Plan (VMP)
Each applicant should have a VMP (See Chapter 9).

8.12.3 PLANNED PREVENTATIVE MAINTENANCE PROGRAMME
A Planned Preventative Maintenance Programme and Standard Operating Procedure for carrying out the maintenance, should be in place. It should refer to all relevant equipment and apparatus to be included in the programme. Responsible persons, should be listed, carrying out maintenance in

accordance with the specified time schedule. Records should be kept as evidence of maintenance checks and repairs.

8.12.4 Contract Manufacture, Analysis and Services
Technical Agreements outlining who is responsible for specific activities relating to the manufacture, analysis, servicing and quality control at each stage of the process must be compiled and signed by the responsible persons in each company. These may form part of the contract or may be separate agreements. Copies must be available for audit purposes.

CHAPTER 9:

VALIDATION

9.1 PRINCIPLES

9.1.1 One of the axioms of manufacturing is that no two objects are ever made exactly alike. Five factors contribute to these variations, namely variations inherent in process methods; materials; the manufacturing environment; the human element; and inspection methods.

9.1.2 As long as these five sources of variation fluctuate in a normal or expected manner, a stable pattern of **change causes of** variation develops (i.e. the variations lie within the so-called "normal curve"). When only change causes are present in a process, that process is considered to be in control. However, when an **assignable cause of variation** is also present the variation will be excessive, and the process is then classified as being out of control (i.e. beyond the expected or "normal curve" variation).

9.1.3 A process is in a **state of control** when all the assignable causes of variation have been eliminated, any only chance causes of variation are present. Such a process has thus been demonstrated to be capable of consistency delivering specified results, i.e. the process has been **validated.**

9.1.4 Statistical process control methods may be used to demonstrate that a process had been validated (i.e. is in a state of control). The control chart method of analysis and presentation of data may for instance be used to document the variations that occur in the central tendency and dispersion of a set of observations relating to a specific quality characteristic.

9.1.5 A process which is in a state of control contributes to productivity and profitability by reducing waste; increasing the yield of saleable product; and reducing the cost of inspection and test activities. Moreover, appropriate validation studies will facilitate pre-registration audits and expedite product registration. Validation therefore makes good business sense.

9.1.6 Validation is an integral part of current good manufacturing practice; it is, therefore, also an element of the quality assurance programme associated with a particular product or process.

9.1.7 Validation involves the accumulation of documentary evidence relating to a process, item of equipment, or facility. This is achieved by means of **validation protocol** which should exist for every product and which details the tests to be carried out, the frequency of testing, and the results anticipated (acceptance criteria).

9.1.8 A **prospective validation** programme is one that is implemented before the equipment or facility comes on stream, or before the product is manufactured.

9.1.9 A **retrospective validation** programme is based on a review of historical manufacturing and testing data.

9.1.10 A **concurrent validation** programme refers to the ongoing review and evaluation of prospective or retrospective validation data.

9.1.11 A validation programme should be co-ordinated by a multidisciplinary committee comprised of the different functions that are involved in the programme. Typically, the members of this **validation committee** would be drawn from departments such as production, quality assurance, microbiological and analytical quality control, pharmaceutical development, engineering, and maintenance. The committee approves and issues written protocols, and reviews the data obtained in order to approve or reject the programme results.

9.1.12 Validation and qualification should be conducted in accordance with defined written standard operating procedures.

9.2 VALIDATION MASTER PLAN

The validation programme should be co-ordinated by means of a formal policy document, usually referred to as a **validation master plan** (VMP).

9.2.1 Each company should have a Validation Master Plan which describes its overall philosophy, intention and approach to be used for establishing performance adequacy, and which identifies which items are subject to validation and the nature and extent of such testing and the applicable validation and qualification protocols and procedures.

9.2.2 The VMP should be a concise and easy to read document which will serve as a guide to the validation committee, and personnel who are responsible for implementing validation protocols. The VMP should also be viewed as being a source document for use by regulatory auditors.

9.2.3 The VMP should typically include at least the following sections:

* Approval page and table of contents
* Introduction and objectives
* Plant and process description
* Personnel, planning and scheduling
* Responsibilities of committee members
* Process control aspects
* Equipment, apparatus, processes and systems to be validated
* Acceptance criteria
* Documentation required including reference to validation protocols
* SOP's
* Training requirements

9.2.4 The Validation Protocol

9.2.4.1 The Validation protocol should clearly describe the procedure to be followed for performing validation. The protocol should include at least the objectives of validation and qualification study, site of the study, the responsible personnel, description of equipment to be used (including calibration before and after validation). SOP's to be followed, standards and criteria for the relevant products and processes, the type of validation, and time/frequency should be stipulated. The processes and/or parameters to be validated (e.g. mixing times, drying temperatures, particle size, drying times, physical characteristics, content uniformity etc.) should be clearly identified.

9.2.4.2 A written report should be available after completion of the validation. The results should be evaluated, analysed and compared with acceptance criteria. All results should meet the criteria of acceptance and satisfy the stated objective. If necessary, further studies should be performed. If found acceptable, the report should be approved and authorised (signed and dated).

9 2 4 3 The report should include the title and objective of the study, refer to the protocol, details of material, equipment, programmes and cycles used and details of procedures and test methods. The results should be compared with the acceptance criteria.

9.2.4.4 Included in the final report, should be recommendations on the limits and criteria to be applied to all future production batches and could form part of the basis of a batch manufacturing document.

9.2.4.5 There should be levels where validation and qualification should be performed, and the level should determine the intensity of these products. It should be least for liquid preparations (solutions) and most for patenteral medicines, and for solid dosage forms it should depend on the criticality of the product as far as the patient is concerned.

9.3 QUALIFICATION

Before a process can be validated the equipment, facilities, and services used in that process must themselves be validated. Such an operation is referred to as **qualification.** Qualification is, therefore, an integral part of process validation which, in turn, is part of good manufacturing practice.
9.3.1 An **installation qualification** (IQ) protocol is used to document the specific (static) attributes of a facility or item of equipment, in order to prove that the installation of the unit has been correctly performed and that the installation specifications of the manufacturer have been met. The IQ protocol should be numbered, dated, and approved for issue by appropriately authorised personnel. The document may comprise the following:

- introduction and objectives
- plant inventory number
- standard operating procedure number
- purpose of the facility or equipment
- design and construction details
- details of services required and provided
- addenda such as chart recorder traces, technical drawings, etc acceptance criteria

The IQ data should be reviewed and approved before operational qualification commences.

9.3 2 An **opperational qualification** (OQ) protocol is used to document specific (dynamic) attributes of a facility or item of equipment to prove that it operates as expected throughout its operating range. As with the IQ protocol, to OQ protocol should be numbered, dated and formally approved. The tests should be designed to demonstrate that the unit performs properly at the limits of its operating conditions, as well ad within its normal operating range. If measurements are made on a statistical basis, then this must be fully described in the protocol. In addition to the operational tests, an OQ protocol may typically include:

- introduction and objectives
- brief identification information
- visual inspection parameters
- functioning of switches and indicator lights
- check and calibration of sensors, probes, gauges, recorders, air flow rates, direction, pressures, temperatures, etc.
- filter integrity and efficiency tests
- cleaning procedures
- details of qualification instrumentation used
- acceptance criteria
- actions resulting from the OQ (what to do when out of spec. results are obtained)
- requalification timescales and triggering factors

The OQ data should be formally reviewed and approved before process validation can commence.

9.3.3 A **performance qualification** (PQ) protocol may be used in cases where performance data are gathered over a long period of time. Under these circumstances, it is difficult to "sign off" the operational qualification (OQ) as complete. One solution is to define and approve the OQ at a single point in time, and to create a PQ protocol which is then used as a the vehicle for amassing the ongoing data.

9.4 PROCESS VALIDATION

When qualification is complete, process validation (PV) can begin. In some cases, PV may be conducted concurrently with IQ, for example, where an item of equipment is dedicated to one process producing one product. Process validation is organised and administered in the same way as qualification, by the writing and issuing of process validation protocols and the accumulation and review of data against agreed acceptance criteria.

Validation should be considered in the following situations:

Validation should be considered in the following situations:

* totally new processes
* new equipment
* processes and equipment which have been altered to suit changing priorities
* processes where the end product test if poor and an unreliable indicator of product quality

9.4.1 Validation In Development (Prospective Validation)

9.4.1.1 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

In this phase the extent to which deviations from the chosen processing parameters can influence product quality should also be evaluated.

9.4.1.2 In general the final batch size should not be more than ten times the batch size of the representative development batches.

9.4.2 Validation In Production (Concurrent validation)

The validation in the production unit mainly comprises the determination and evaluation of the process parameters of the facilities applied for the scale-up to final batch size. The control of all critical process parameters, the results of the in-process controls, final controls and stability tests should prove the suitability of the important individual steps of a procedure.

At least three batches (including at least two production batches in the final batch size) should be validated, to show consistency. Worst case situations should be considered.

9.4.2.1 When certain processes or products have been validated during the development stage, it is not always necessary to re-validate the whole process or product if similar equipment is used or similar products have been produced, provided that the final product conforms to the in-process control and final product specifications.

9.4.2.2 There should be a clear distinction between in-process controls and validation. In-process tests are performed each time on a batch-to-batch basis using specifications and methods devised during the development phase. The objective is to monitor the process continuously.

9.4.2.3 Validation of the process can, however, be partly based on the processing and evaluation of in-process data provided it is evident that the reliability of the process can be unequivocally and accurately judged in terms of the results from these in-process control tests and final end product tests.

9.4.2.4 Validation is a once-off procedure that should only be repeated if major changes to equipment or processes have taken place. The objective is to establish a valid process. In-process control and validation co-exist in Good Manufacturing Practice or Quality Assurance systems. In-process data can be used (after processing of the data) during the validation study, or it may form the basis of a retrospective validation exercise. (See below). Thus, the results of in-process controls can be used to provide some of the evidence required for validation but are no substitute for validation.

9.4.2.5 Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

9.4.2.6 As a rule re-validation is required under the following circumstances:

- change of formulae, procedures or quality of raw materials
- change of equipment, installation of new equipment, major revisions to machinery or apparatus and breakdowns
- major changes to process parameters
- changes to facilities and installations which influence the process
- on appearance of negative quality trends
- on appearance of new findings based on current knowledge, e.g. sterilisation where the frequency of checking is dependent on sophistication of in-process methodology

NOTE: The extent of re-validation will depend on the nature and significance of the changes.

9.4.3 Retrospective Validation

9.4.3.1 The analysis of in-process and end product testing has been widely used retrospectively in process validation. Usually statistical packages as well as manual reviews (including the monitoring of trend analysis) are used. In some cases retrospective validation is sufficient to establish a process as valid.

9.4.3.2 Retrospective validation may be allowed, when the formulation procedure and equipment have not been altered. A critical examination of the in-process control data and of the analytical results should be performed. Where existing data is not adequate, additional tests should be performed.

9.5 VALIDATION OF FACILITIES AND EQUIPMENT

9.5.1 New facilities and equipment which are components of a production process or are used for in-process control must be qualified before being put into operation. This is to ensure that they fulfill the relevant requirements and that no negative influence on product quality or measured values arises.

9.5.2 Specification qualification, design qualification, installation qualification, operational qualification and performance qualification should be considered when new equipment is acquired. Equipment and apparatus should be capable of meeting the original design specifications.

9.5.3 All instrumentation attached to equipment should be checked for accuracy, reliability and reproducibility. Such qualification studies could be carried out on-site or off-site, either by the user of the supplier.

9.5.4 Qualified and validated equipment should be monitored from time to time, to ensure that the fixed processing parameters are being maintained. This could be achieved by suitable instrumentation of different types, measuring temperatures, pressures, humidity, fill volumes etc. International standards should be used as reference point and all calibration data should be accurately documented.

9.5.5 Retrospective validation of old facilities and validation arising from changes should be evaluated in terms of criticality and the processes that are ultimately affected in the production of quality product.

9.6 VALIDATION OF ANALYTICAL METHODS

9.6.1 Analytical testing procedures including stability testing methods must be validated to demonstrate their reliability. This should be done during product design.

9.6.2 Revalidation may be necessary in the following circumstances:

* changes in the synthesis of a drug substance;
* changes in the composition of a finished product;
* changes in the analytical procedure
* changes in the manufacturing process that will effect the method

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well.

9.6.3 Method validation should not be confused with system suitability tests. System suitability testing verified the suitability if an analytical system at the time the test is performed.

9.6.4 Methods, (other than pharmacopoeal methods), should be validated. Typical validation characteristics which should be considered, include accuracy, precision, (repeatability and intermediate precision), specificity, detection limit, quantitation limit, linearity and range. Robustness should be considered at an appropriate stage in the development of an analytical procedure.

9.7 CLEANING VALIDATION

9.7.1 There should be written Standard Operating Procedures, detailing cleaning processes for different sections in the manufacturing facility, with appropriately documented and completed cleaning logs.

9.7.2 There should be written a SOP's detailing the cleaning process for equipment and apparatus.

9.7.3 There should be a written SOP detailing how cleaning processes will be validated, referring to accountabilities, acceptance criteria and revalidation requirements. Acceptance limits should be scientifically justifiable. The complexity and design of the equipment, training or operators, size of the system, and time delay between end of processing and cleaning should be kept in mind when designing the cleaning SOP. Microbiological aspects of cleaning (bioburden control), should further be considered. Written protocols to be followed during validation should detail sampling procedures (direct sampling, rinse samples, in-process control monitoring), analytical methods (specificity and sensitivity) of analytical methods to be used.

9.7.4 Evidence should be provided to ensure that equipment is consistently cleaned from product, detergent and microbial residues to an acceptable level.

9.7.5 Cleaning validation is particularly relevant in the case of highly active substances.

9.8 COMPUTER SYSTEM VALIDATION

See Chapter 19.

9.9 GENERAL

The following aspects could be considered during the validation of specific dosage forms.

9.9.1 **Validation of tabletting:** In the case of an oral tablet manufactured by granulation and compression, the critical process parameters may include (but not be limited to):

- particle size distribution of the active
- blending time for the powder
- granulating time and speed
- amount of granulating fluid-binder concentration
- drying time - final moisture content
- granule particle size distribution
- granule active content and homogeneity
- blending time of external phase
- tablet hardness with respect to water content, friability, disintegration, and dissolution
- lubrication level with respect tablet hardness, disintegration, dissolution and die-ejection force

- tablet weight and thickness control uniformity of content

If the tablet is film coated, the following additional parameters may require validation:

- spray rate of coating solution
- inlet and outlet air temperatures
- coating weight of polymer with respect to table appearance, friability, disintegration, and dissolution

9.9.2 **Validation of sterile products:** The general pattern of process validation is the same as for non-sterile, and similar critical process parameters need to be defined and controlled. The key additional requirement is the absence of microbial contamination. This necessitates validation of the sterilisation process for terminally sterilised products, or of the sterilisation, filling and sealing processes for aseptically prepared products. Attention should also be given to water systems and air handling systems.
In the case of steam sterilised products:

- bioburden before sterilisation
- heat distribution
- influence of container size (minimum of three batches of each size)
  influence of chamber loading patterns (minimum of three batches of each loading pattern)

In the case of aseptically filled products:

- assurance that the product and packaging materials are sterile
- assurance that product sterility is maintained during the filling and sealing process
- filter bubble point tests (at least on three product batches)
- determination of pressure drop, stability time, pressure hold time, and pressure decay before and after a production run.

CHAPTER 10:

RETURNED GOODS

10.1 PRINCIPLE

10.1.1 A clearly defined policy must be followed to ensure that returned goods are of an acceptable quality and have not expired before they are taken back into stock; otherwise they must be destroyed.

10.2 PROCEDURES

10.2.1 Goods which have been rejected, recalled or returned should be placed in adequately segregated storage to avoid confusion with other materials and products and to prevent redistribution, until a decision has been reached as to their disposition. Any action taken should be appropriately recorded.

10.2.2 A Finished Product returned from the Manufacturer's own stores or warehouse (because, for example, of soiled or damaged labels or outer packaging) may be relabelled or bulked for inclusion in subsequent batches, provided that there is no risk to product quality and the operation is specifically authorised and documented. If such products are re-labelled, extra care is necessary to avoid mix-up or mis-labelling.

10.2.3 Finished Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for resale, relabelling or bulking with a subsequent batch only after they have been critically assessed by the person responsible for Quality Control. The nature of the product, any special storage conditions it requires, its condition and history and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical re-processing to recover the active ingredient may be possible.

CHAPTER 11 :

COMPLAINTS, ADVERSE EVENTS, RECALLS AND WITHDRAWALS

11.1 PRINCIPLES

11.1.1 The full significance of a complaint may only be appreciated by certain responsible persons and then possibly only with the knowledge of other related complaints. A procedure must therefore exist to channel complaint reports appropriately.

11.1.2 A complaint, [or otherwise] reported product defect, or adverse event* may lead to the need for a recall. Any action taken to recall a product suspected or known to be defective or hazardous, should be prompt and in accordance with a pre-determined plan. The procedures to be followed should be specified in writing and made known to all who may be concerned.

11.1.3 Definitions
Adverse event* or experience:
Any untoward medical occurrence in a patient treated with a pharmaceutical product/device, reported from any source. This does not imply that a causal relationship exists with this treatment.

Adverse Drug Reaction:
A response to a drug which is noxious or unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function i.e. an adverse event for which a causal relationship is suspected between drug and event.

Unexpected Adverse Drug Reaction
An adverse reaction, the nature or severity of which is not consistent with applicable product information or labelling i.e. those recorded on the Package Insert [PI]

11.2 COMPLAINTS

11.2.1 A system should be established for dealing with complaints which should include written procedures indicating the responsible person(s) (e.g.pharmacist and/or deputy pharmacist) through whom the complaints are to be channeled. The responsible person must have appropriate knowledge and experience and the necessary authority to decide the action to be taken.

11.2.2 All complaints concerning a product defect should be recorded with all the original details and thoroughly investigated. The responsible person should decide whether, and what, subsequent action is necessary.

11.2.3 Complaint records should be regularly reviewed for any indication of specific recurring problems requiring attention and possibly the recall of marketed products.

11.2.4 Written records involving a medicine shall be maintained until at least one year after the expiration date of the medicine, or one year after the date that the complaint was received, whichever is longer.

11.2.5 The written record shall include the following information, where known:

·date of receiving complaint
·the name and strength of the medicine and lot number
·name of complainant, nature of complaint
·detailed record of the investigation
·details of the action taken to prevent recurrence of the problem that led to the negative effect on the product
·reply to complainant.

11.2.6 If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.

11.2.7 All the decisions and measures taken as a result of a complaint should be recorded and referenced in the corresponding batch records.

11.2.8 Where an investigation is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

11.2.9 Trend analysis should be performed in an event to identify possible recurrent causes leading to a negative effect on a product.

11.3 ADVERSE EVENTS

11.3.1 A system should be established for dealing with adverse events which should include written procedures indicating the responsible person(s) (pharmacist and/or deputy pharmacist) through whom the reports and activities are to be channeled. The responsible person must have appropriate knowledge and experience and the necessary authority to decide the action to be taken.

11.3.2 All adverse events concerning product quality must be thoroughly investigated. The responsible person should decide whether, and what, subsequent action is necessary. This action should be recorded and the record filed with the details of the original adverse event report.

11.3.3 Adverse event records should be regularly reviewed for any indication of a trend that may warrant a recall or withdrawal.

11.4 RECALLS

11.4.1 WITHDRAWAL implies the total withdrawal of the product from the market.

11.4.2 RECALL refers to the removal from the market of a specific batch or batches of the product.

11.4.3 The recall of a particular batch or batches of a product from the market may be occasioned by the manufacturer or distributor, either following reports of adverse reactions to a particular batch of a product, or as the result of on-going stability studies, or by the authorities (Department of Health/Medicines Control Council) as a result of adverse reaction reports or for other reasons such as formulation, labeling or other errors.

11.4.4 The managing director or nominated deputy should initiate and co-ordinate all recall activities which should involve the head of Quality Management. In the event of an adverse event a Crisis Committee involving key personnel should be set up and involved.

11.4.5 There should be a written recall procedure which is capable of being initiated promptly and put into operation at any time, inside or outside normal working hours. It should include emergency and 'out of hours' contacts and telephone numbers.

11.4.6 The recall procedure should be shown to be practicable and operable within reasonable time (e.g. by conducting internal 'dummy runs'). It should be revised as necessary to take account of changes in procedures or responsible person(s).

11.4.7 The notification of recall should include:

(a) the name of the product, including the INN and Trade Names, its strength and pack size, and main therapeutic class
(b) the product batch number(s)
(c) the nature of the defect and the reason for the recall or withdrawal decision [including the discovery of counterfeit medicines*]

(d) the action to be taken
(e) the urgency of the action (with reasons, indication of health risk, as appropriate)
(f) the date of the recall or withdrawal

11.4.8 Account should be taken of any goods which may be in transit when the recall is initiated.

11.4.9 The distribution records should be readily available to the person(s) responsible for recalls and contain sufficient information on wholesalers and customers (e.g. addresses, telephone numbers inside or outside working hours, batches and amounts delivered) including exported products and medical samples.

*In the case of counterfeit medicines the MCC should be informed immediately as well as the appropriate Industry Action Committee.

11.4.10 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.

11.4.11 All Regulatory Authorities of all countries to which products may have been distributed should be promptly informed if products are intended to be recalled because they are, or are suspected of being defective.

11.4.12 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.

Enclosure:
Manufacturer's Post-Withdrawal Decision Checklist

CHAPTER 12:

CONTRACT MANUFACTURE ANALYSIS AND SERVICING

12.1 PRINCIPLES

12.1.1 The relative responsibilities of the Contract Giver and the Contract Acceptor relating to specific activities in manufacture, analysis and the provision of services should be clearly understood and agreed, with the object of avoiding misunderstandings which could result in a product or work of unsatisfactory quality. The Contract Giver (the Applicant) bears the ultimate responsibility for ensuring that the product specification complies with relevant legal requirements, that the product as manufactured meets its specification, and that the specified quality is maintained during storage, transport and distribution.

12.2 MANUFACTURE AND/OR PACKAGING

12.2.1 A Contract Giver should assure himself that the Contract Acceptor has adequate premises, equipment, and staff with sufficient knowledge and experience, to carry out satisfactorily the work placed with him. In order to do this the Contract Giver should audit the Contractor Acceptor's premises, equipment and systems both before the contract is given and at regular intervals thereafter. Audit reports should be issued and kept on record. A contract Giver may only use the contract manufacturer or packer as approved in the registration dossier. A Contract Giver shall not authorise a Contract Acceptor to commence manufacture/packaging/testing of a medicine, until he has assured himself, and authorised in his own handwriting, that all the necessary master documents and/or specifications, generated by the Contract Acceptor for use in his own facility, are in accordance with the particulars contained in the Contract Giver's (applicant or holder of a registration certificate) master documentation and registration dossier. The specification/master documents should be in compliance with the requirements as stipulated in Chapter 8. The Contract Acceptor shall not commence manufacture/packaging/testing of a medicine until he is in possession of specification/master documents that have been authorised by the Contract Giver.

12.2.2 The Contract Acceptor should refrain from any activity which may adversely affect products manufactured for a Contract Giver. A Contract Acceptor must ensure that all legal requirements of the relative Acts are met, prior to accepting contract work (e.g. registerability of medicines).

12.2.3 The technical arrangements made in connection with a contract should be in writing. The limits of the responsibilities accepted by each of the parties should be clearly laid down in a Technical Agreement which can be included in the body of the contract or as an Addendum to the contract. The technical agreement should cover all aspects relating to responsibilities w.r.t setting of specifications, acquisition of material (e.g. raw or starting material, packaging components, printed packaging material), as well as the lines of reporting and communication.

This should be in compliance with the organogram, job descriptions and standard operating procedures.

The technical agreement should address all aspects relating to change control. The Technical agreement may refer to standard operating procedures agreed to by both parties, agreeing to the process to be followed should any changes take place during the manufacturing process. These changes should be controlled in accordance with the minor/major change policy of the Medicines Control Council, as communicated to the industry. The applicant or holder of a registration certificate must be informed of any change that took place, as well as the Registrar of Medicines. Where relevant, permission must be obtained from the Medicines Control Council, prior to implementation of the change. Where necessary, master documentation and registration dossiers should be updated in accordance with standard operating procedures and policy.

Where changes took place during manufacture/packaging/testing, a detailed deviation report should be written, describing the change, the reasons for the change, who was responsible or managed the

change, the implication of the change and the effect the change will have on the product, approval of the change etc. and be discussed with the applicant or holder of a registration certificate.

12.2.4 Any change in technical arrangements should be agreed upon by both parties and should be laid down in writing.

12.2.5 The parties to a manufacturing contract should each appoint competent persons to:

·draw up the Technical Agreement for manufacture
·agree upon arrangements for in-process control tests, for testing of raw materials, components and Finished Products and for reworking if necessary
·define the mechanism by which a batch is released for sale after review of the manufacturing, packaging and analytical records.

12.2.6 A Contract Acceptor should not pass to a third party any of the work entrusted to him by a Contract Giver without the latter having evaluated the arrangements and given his consent.

12.2.7 Arrangements made with a third party should ensure that the exchange of information is on the same basis as between the Contract Giver and the original Contract Acceptor.

12.2.8 If a Contract Giver supplies materials, the Contract Acceptor should be given a signed statement from the Contract Giver that the Vendor has been audited and is approved, as well as a copy of the Certificate of Analysis of the raw/starting material (at least the active raw/starting material). The Contract Giver should supply the Contract Acceptor with specifications/master documentation for all materials handled by the Contract Acceptor. If this is not possible for reasons of commercial or research confidentiality, he should be given sufficient information to enable him to process the material correctly, and details of:
·any potential hazard to premises, plant, personnel, or to other materials or products
·the legal status of the materials and resultant products.

12.2.9 If a Contract Acceptor supplies materials, the Contract Giver should specify the quality required in the specification/master document.

12.2.10 A Contract Acceptor should check that all products or materials delivered to him are suitable for the purpose intended.

12.2.11 A Contract Giver should ensure that all products or materials delivered to him by the Contract Acceptor comply with the specifications. If products are delivered directly from a Contract Acceptor to the market, the Contract Giver should provide for this check to be made before they are released for sale. Note: The Contract Giver is legally responsible for the final release of each batch for sale.

12.2.12 Manufacturing and analytical records and reference samples should be kept by, or be readily available to the Contract Giver. The documents kept should facilitate recall from sale of any batch of the product. The responsibility for arranging and managing a recall or withdrawal of any batch of a product must be clearly specified in the Technical Agreement as well as the management of adverse event reporting.

12.2.13 The above guidelines should also be used for sale/distribution contracts where applicable. A Contract Acceptor, should on receipt of materials, take all material into his own system of receival of goods in accordance with the requirements of GMP.

12.2.14 Contract Givers must ensure that all the necessary documentation accompanies all material delivered to Contract Acceptors, as stock should not be received without the relevant and/or necessary documentation, e.g. invoices, delivery notes, instructions etc. Contract Acceptors may return goods delivered, should the necessary documentation not be included.

12.2.15 All containers delivered to Contract Acceptors, should be properly labelled in accordance with GMP requirements.

12.2.16 The guidelines under 12.2 should also be used for sale/distribution contracts where applicable, as well as the requirements in Chapter 18.

12.3 CONTRACT ANALYSIS

12.3.1 As appropriate, the above provisions may apply also to contract analysis.

12.3.2 Although analysis and testing may be undertaken by a Contract Analyst, the responsibility for Quality Control cannot be delegated to him.

12.3.3 The nature and extent of any contract analysis to be undertaken should be agreed upon and clearly defined in writing, and procedures for taking samples should be as set out.

12.3.4 The Contract Analyst should be supplied with full specifications/master documents of the materials to be tested as well as full details of the test methods relevant to the material under examination. These will need to be confirmed as suitable for use in the context of the contract laboratory.

12.3.5 Formal written arrangements should be made for the retention of samples and of records of test results.

12.3.6 Periodic audits should be carried out on the work performed by the contract laboratory. Audit reports should be kept on record.

12.3.7 The requirements of Chapter 7 applies.

12.4 SERVICE CONTRACTS

12.4.1 Where service or maintenance work is performed (e.g. on manufacturing or test equipment, sterilisers, controlled air supply systems) the Contract Giver should assure himself that the Contract Acceptor has sufficient equipment, staff, knowledge and experience to carry out the work correctly.

12.4.2 There should be a written contract which should clearly specify the work to be carried out and the form and detail of the report or certification required. The report or certificate should state clearly what work was done and the result achieved, and declare whether or not the equipment performs in compliance with specification.

12.4.3 A Standard Operating Procedure should specify the acceptable limits between services or maintenance of equipment, systems etc.

CHAPTER 13:

VETERINARY MEDICINES

13.1 PRINCIPLE

13.1.1 Medicinal products for veterinary use should be manufactured in accordance with the principles outlined in this Guide.

13.2 GENERAL REQUIREMENTS

13.2.1 Some veterinary medicines such as those used for mass external treatment of animals (e.g. sheep dips), have no direct equivalent amongst products for human use and the recommendations on manufacturing premises and equipment given elsewhere in the Guide may not be appropriate. Sufficient order, tidiness, cleanliness and product security is however always required in order to minimise the risk of formulation error, mix-up and contamination. In addition, the general systems and procedures in this guide still apply to veterinary medicines.

13.2.2 In the manufacture and filling of terminally sterilised parenteral veterinary medicines, particular attention should be given to the need to minimise microbiological contamination of the product before sterilisation. Pyrogen contamination (endotoxin level) should be controlled to the same limits as for human medicines.

13.3 SPECIAL REQUIREMENT

13.3.1 Manufacture of premixes for medicated feedingstuffs

- a medicated feeding stuff is any mixture of a veterinary product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties as a medicinal product.

- a premix for medicated feedingstuffs is any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs.

13.3.1.1 The manufacture of premixes for medicated feedingstuffs requires the use of large quantities of vegetable matter which is likely to attract insects and rodents. Premises should be designed, equipped and operated to minimize this risk and should also be subject to a regular pest control programme.

13.3.1.2 Because of the large volume of dust generated during the production of bulk material for premixes, specific attention should be given to the need to avoid cross contamination and facilitate cleaning, for example the installation of sealed transport systems and dust extraction, whenever possible. The installation of such systems does not, however, eliminate the need for regular cleaning of production areas.

13.3.1.3 Parts of the process likely to have significant adverse influence on the stability of the active ingredients(s) (e.g. use of steam in pellet manufacture) should be carried out in a uniform manner from batch to batch.

13.3.1.4 Consideration should be given to undertake the manufacture of premixes in dedicated areas which, if at all possible, do not form part of a main manufacturing plant. Alternatively, such dedicated areas should be surrounded by a buffer zone in order to minimize the risk of contamination of other manufacturing areas.

13.3.2 The manufacture of ectoparasiticides

13.3.2.1 Ectoparasiticides for external application to animals which are veterinary medicinal products, and subject to registration, may be produced and filled on campaign basis in pesticide specific areas. However, other categories of veterinary medicinal products should not be produced in such areas.

13.3.2.2 Adequate validated cleaning procedures should be employed to prevent cross contamination, and steps should be taken to ensure the secure storage of the veterinary medicinal product in accordance with the guide.

13.3.3 The manufacture of veterinary medicinal products containing penicillins

13.3.3.1 The use of penicillins in veterinary medicine does not present the same risks of hypersensitivity in animals as in humans. Although incidents of hypersensitivity have been recorded in horses and dogs, there are other materials which are toxic in certain species e.g. the ionophore antibiotics in horses. Although desirable, the requirements that such products be manufactured in dedicated, self-contained facilities may be dispensed with in the case of facilities dedicated to the manufacture of veterinary medicinal products only. However, all necessary measures should be taken to avoid cross-contamination and any risk to operator safety in accordance with the guide. In such circumstances, penicillin-containing products should be manufactured on a campaign basis and should be followed by appropriate, validated decontamination and cleaning procedures.

13.3.4 Retention of samples

13.3.4.1 It is recognized that because of the large volume of certain veterinary medicinal products in their final packaging, in particular premixes, it may not be feasible for manufacturers to retain samples from each batch in its final packaging. However, manufacturers should ensure that sufficient representative samples of each batch are retained and stored in accordance with the guide.

13.3.4.2 In all cases, the container used for storage should be composed of the same material as the market primary container in which the product is marketed.

13.3.5 Sterile veterinary medicinal products

13.3.5.1 Where this has been accepted by the competent authorities, terminally sterilised veterinary medicinal products may be manufactured in a clean area of a lower grade than specified for "Sterile preparations", but at least in a grade D environment.

CHAPTER 14:

RADIOPHARMACEUTICALS

Radiompharmaceutical products should be manufactured in accordance with the principles outlined in this guide.

14.1 PRINCIPLES

14.1.1 Radiopharmaceutical preparations are preparations containing one or more radionuclides. They may be formulated in any of the pharmaceutical formulations covered in this guide and the general and specific guidance should be followed at all times, but considerations must be given to the special requirements of radiation work.

14.1.2 The manufacturing and handling of radiopharmaceuticals is potentially hazardous. The level of risk depends in particular on the types of radiation emitted and the half-lives of the radioactive isotopes. Particular attention must be paid to the prevention of cross-contamination, to the retention of radionuclide contaminants and to waste disposal. Special consideration may be necessary with reference to small batch sizes made frequently for many radiopharmaceuticals. Due to their short half-life, some radiopharmaceuticals are released before completion of certain Quality Control tests. In this case, the continuous assessment of the effectiveness of the Quality Assurance system becomes very important.

14.2 REGISTRATION REQUIREMENTS

14.2.1 Care should be taken to comply with national and local regulations concerning production, supply, storage, use and disposal of radioactive products.

14.2.2 Premises in which radioactive work is conducted must be licensed by the Department of Health.

14.2.3 Radiopharmaceuticals, produced by a nuclear reactor or cyclotron, may only be used by physicians who are qualified by specific training in the safe use and handling of radioisotopes, and whose experience and training have been approved by an appropriate governmental agency authorised to licence the use of radionuclides.

14.2.4 All people engaged in radioactive work are required by law to be registered as radiation workers. Maximum permitted radiation doses for radiation workers are prescribed by the International Atomic Energy Agency and are monitored by film badges and pocket dosimeters or TLD. At all times the ALARA principle (i.e. as low as reasonably attainable dose) applies to any person working with radioactivity.

14.3 PERSONNEL

14.3.1 All personnel (including those concerned with cleaning and maintenance) employed in areas where radioactive products are manufactured should receive additional training specific to this class of products. In particular, they should be given detailed information and appropriate training on radiation protection.

14.4 PREMISES AND EQUIPMENT

14.4.1 Radioactive products should be stored, processed, packaged and controlled in dedicated and self-contained facilities. The equipment used for manufacturing operations should be reserved exclusively for radiopharmaceuticals.

14.4.2 In order to contain the radioactive particles, it may be necessary for the air pressure to be lower where products are exposed than in the surrounding areas. However, it is still necessary to protect the product from environmental contamination.

14.4.3 For sterile products, the working zone where products or containers may be exposed should comply with the environmental requirements described for Sterile Products. This may be achieved by the provision within the work station of a laminar flow of HEPA-filtered air and by fitting air-locks to entry ports. Total containment work stations may provide these requirements. They should be in an environment conforming to at least a grade D.

14.4.4 Air extracted from areas where radioactive products are handled should not be recirculated; air outlets should be designed to avoid possible environmental contamination by radioactive particles and gases.

14.4.5 There should be a system to prevent air entering the clean area through extraction ducts e.g. when the extraction fan is operating.

14.5 PRODUCTION AND HANDLING OF RADIOACTIVE PREPARATIONS

14.5.1 Each isotope should be worked in a separate specially shielded, contained work station to prevent cross-contamination of the radionuclide. Production of different radioactive producers in the same workstations and at the same should be avoided in order to minimize the risk of cross-contamination or mix-up. The operator must be shielded from the radiation which must be contained in the work station.

14.5.2 Radioactive materials should be handled in a contained work station operated at an air-pressure below that of the room in which it is sited. Air admitted to the work station should still have passed through terminal filters of appropriate porosity so that the required class conditions are maintained at the point of greatest risk, where products are exposed.

14.5.3 All operations should be carried out in such a manner as to minimize the risk of microbial or particulate contamination.

14.5.4 All sterile products are terminally sterilised before despatch either by autoclave or filtration.

NOTE: The radiation in the radiopharmaceutical is not sufficient to effect sterilisation.

14.5.5 Process validation, in-process controls and monitoring or process parameters and environment assume particular importance in cases where it is necessary to take the decision to release or reject a batch or a product before all the tests are completed.

14.6 QUALITY CONTROL

14.6.1 When products have to be dispatched before all the tests are completed, this does not obviate the need for a formal recorded decision to be taken by the Qualified Person on the conformity of the batch. In this case there should be a written procedure detailing all production and Quality Control data which would be considered before the batch is dispatched. A procedure should also describe the measures to be taken by the Qualified Person if unsatisfactory test results are obtained after dispatch.

14.6.2 Unless otherwise specified in the marketing authorization, reference samples of each batch should be retained.