






# REQUIREMENTS OF GOOD MANUFACTURING PRACTICE

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## REQUIREMENTS OF GOOD MANUFACTURING PRACTICES

### CHAPTER 1

# PREMISES

**NOTE :** (The number mentioned against each point is clause no. as per respective guidelines)

## **1. BUILDINGS AND GROUNDS**

### **TGA:**

#### **a. General**

101. Buildings should be located, designed, constructed, adapted and maintained to suit the operations carried out in them.  
Except where special precautions are taken to isolate an interior manufacturing space, buildings should be sited away from incompatible activities such as those that generate chemical or biological emissions.
102. Buildings, including receiving and despatch areas, should be designed, constructed and maintained so as to protect against the effects of weather or ground seepage and the entry and harboring of vermin, birds, pests and pets. Cavities and voids should not be present unless sealed or provided with access for pest control.
103. Animal houses should be isolated from production areas, with separate entrances and air handling facilities, and should comply with the current edition of the NH& MRC/CSIRO/AAC Code of practise for the care and use of animals for experimental purposes.
104. Grounds should be established and maintained so as to minimize ingress into the buildings of dust, soil or other contaminants and should be maintained in an orderly condition.

#### **b. Pipes, ducts and service area**

105. Pipelines carrying services or products between rooms or areas should be identified by colour or by standard markings at suitable intervals and the direction of flow shown.  
Particular care should be taken that product pipelines are not inter-connected or connectable in a manner that invites cross-contamination or product mix-up.  
“Dead legs” (in which circulation cannot occur) should be minimized.
106. In production areas –
  - \* Extraction ducts should be designed to be cleanable and to prevent condensate or accumulated dust from falling back into product or equipment.
  - \* There should be no recesses that cannot be cleaned and a minimum of projecting ledges, shelves, cupboards, pipes, fixtures and fittings
  - \* Exposed overhead roof joists, pipes and ducts should be avoided. Where they are unavoidable, special cleaning procedures and schedules should be written and followed.
  - \* Exposed pipes should not touch walls, but be suspended from or supported by brackets, sufficiently separated to allow thorough cleaning.
  - \* Opening in walls, floors or ceilings through which piping, ducting or other non-structural items pass should be sealed or have removable covers that permit cleaning.
  - \* Light fittings should be located and/or sealed so as not to collect and deposit contamination.
107. Production areas should not normally contain service machinery, or its associated ductwork or pipe-work, except where the ducting or pipes connect directly to equipment. Rooms or areas

containing service machinery should be readily cleanable.

c. Space, layout, Compatibility

108. Sufficient space should be provided for orderly receipt, warehousing and processing so as to minimize clutter and the risk of material or product cross-contamination or mix-up.
109. The lay out of rooms and the manufacturing instructions and procedures used in existing plants should together minimize the tracking of dust, soil or other contaminants into areas where materials are dispensed or product is exposed. In new or refurbished plants, the layout of rooms, corridors and spaces should provide for logical movement of materials and personnel with minimal traffic and for operations to be carried out in defined areas.
110. Access to environmentally controlled areas should be only from corridors or other manufacturing areas.  
Processing and packaging areas should not be used as thoroughfares or, except for work in progress, for storage.
111. Doors that lead from manufacturing areas directly to the outside, e.g. fire exits, should be sealed against contamination. They should be secured in such a way that they may be used only as emergency exits.  
Where internal doors are a barrier to cross-contamination, they should be kept closed when not in use.
112. The operations carried out in any particular area of the premises, whether storage, processing or packaging or whether therapeutic goods or non-therapeutic goods, should be compatible. Special arrangements may be required for pencillins, cephalosporins, anti-neoplastic drugs and other products such as certain steroids – see also contamination control.
113. Except where alternative arrangements are acceptable, a dispensary should be provided for weighing and measuring out starting materials.

d. Air Control

114. Air intakes and exhausts, and associated pipe-work and trunking should be located so as to avoid any hazard to product and to avoid overloading air filters. In particular, intakes should not be sited near wet drains, air exhausts or sources of dust. Provision should be made to clean dust filters and air conditioning filters away from the air handling systems or production areas.
115. The air supplied to work zones in which starting materials (other than packaging materials) are sampled or dispensed, where product is made or filled, or where equipment is dried should be supplied through filters certified to have average arrestance of at least 80% when tested by AS1132-1973 – Methods of test of air filters for use in air conditioning and general ventilation, using test duct no. 1.  
Storage or processing in sealed systems may be excepted from this provision. (See also clause no. 131)
- Notes :**
1. The air so supplied is likely to be equal to or better than the equivalent of a “Class 7000” (approximately 300 particles of 2 micrometers particle size per litre) as extrapolated from AS1386-1989: Cleanrooms and clean Workstations.
  2. Consideration should be given to temperature and relative humidity control : once a significant volume of filtered air is delivered across operators, comfort conditioning is usually found necessary.
116. In all rooms, air supply and extraction points should not be so close or so disposed as to restrict or negate the supply of clean air to worksites and/or the sweep of dust or other contaminants away from worksites.
117. The air flow pattern, throughput rate and proportion of re-circulated air should be selected to afford adequate protection to the product as well as operator safety.
118. The selection of pressure differentials should take into account the relative hazards of incoming and outgoing contamination in each work zone.
119. Air ducts should not be insulated internally except for non-fibrous, non-porous insulation used to avoid or reduce condensation near cooling units or used to reduce the risk of fire near heating units. They should be verified as clean by inspection or testing.

e. Floors, Walls, Ceilings and Associated fittings

120. Floors, walls and ceilings in manufacturing areas should be designed so as not to shed more than a minimum of particles and be free from cracks and open joints. Floors and walls should be non-porous, non-slip and resistant to cleaning agents and to any disinfecting agent use. Floors should be smooth, except for washbays housed in manufacturing areas or mezzanine or platform floor structures.
121. As far as practicable, processing should occur in a dry environment. Where it is essential to provide for spillage or a high volume of floor rinsing, floor should be adequately sloped for drainage. Drains should be of adequate size and have trapped gullies. Close channels should be avoided where possible but if used should be shallow to facilitate cleaning and disinfection.
122. Joins between walls and floors should be easy to clean, adequately sealed and, where appropriate,

coved.

123. Doors (including door edges) and window frames should have a hard, smooth, impervious finish and should close tightly. It is desirable that door and window frames are fitted flush with surrounding walls. The conduct of operations carried out in production rooms should be visible from the outside where necessary for supervision or management.
124. In processing areas the use of wood should be avoided, especially where it may be wetted. Where present, it should be sealed with a coating resistant to chipping, including downward-facing surfaces.
125. Lighting should be adequate for particular tasks. Flush mounting is preferred for new installations.

f. Special facilities and provisions

126. The building design should include adequate provision for dismantling, cleaning, washing and where necessary, sanitizing and drying equipment.  
This should usually be a separate room or area.  
Adequate facilities should be provided for the storage of equipment used by cleaning staff.
127. Suitable provision should be made for the safe storage of waste materials awaiting disposal (See also section 4).
128. Where processing involves the production of live genetically-manipulated organisms which fall under the GMAC guidelines, GMAC review should be sought and documentation of GMAC approval filed.
129. Laboratories should be designed, equipped and maintained and of sufficient space to suit the operations to be performed in them, and should include provision for writing and recording and for the storage of documents and samples. Access to staff amenities should not require movement through contaminated areas.

The overall design and construction of new laboratories should be in accordance with Australian Standard 2982-1987 : Laboratory construction. Additional guidance for the design and construction of microbiological laboratories (excluding sterility testing laboratories) is contained in the NATA publication "Microbiological testing : Laboratory accommodation guidelines".

Chemical, biological and microbiological laboratories should be separated from each other and from production areas. Laboratory air should be conditioned and be handled separately from factory air. Air leaving biological or microbiological laboratories should not contaminate other laboratories.

130. Adequate facilities should be provided for GMP training.
131. A plan of the building(s) showing air handling facilities including key air handling equipment and showing air quality standards, flow rates, proportions re-circulated and relative pressures should be available for inspection.
132. Noise should be minimized.
133. Buildings should be secure against entry of unauthorized personnel. Special precautions should be

taken to check the bona fides and activities of visitors, external maintenance people and contractors such as pest controllers.

**MCA :**

**Premises  
General**

- 3.1 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 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.
- 3.3 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.
- 3.4 Premises should be designed and equipped so as to avoid maximum protection against the entry of insects or other animals.
- 3.5 Steps should be taken in order to prevent the entry of unauthorized people. Production, storage and QC areas should not be used as a right of way by personnel who do not work in them.

**Schedule M :**

**1. General requirements :-**

- 1.1 **Location and surroundings** : The factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any factory which produces disagreeable or obnoxious, odor, fumes, excessive soot, dust, smoke, chemical or biological emissions.
- 1.2 **Building and premises** : The building(s) used for the factory shall be designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of drugs under hygienic conditions. They shall conform to the conditions laid down in the Factories Act, 1948 (63 of 1948)

The premises used for manufacturing, processing, warehousing, packaging, labeling and testing purposes shall be –

- (i) Compatible with other drug manufacturing operations that may be carried out in the same or adjacent area / section;
- (ii) Adequately provided with working space to allow orderly and logical placement of equipment, materials and movement of personnel so as to :
  - (a) avoid the risk of mix-up between different categories of drugs or with raw materials,

intermediates and in-process material;

- (b) avoid the possibilities of contamination and cross-contamination by providing suitable mechanism.
- (iii) Designed / constructed / maintained to prevent entry of insects, pests, birds, vermins, and rodents. Interior surface (walls, floors and ceilings) shall be smooth and free from cracks, and permit easy cleaning, painting and disinfection;
- (iv) Air conditioned, where prescribed for the operations and dosage forms under production. The production and dispensing areas shall be well lighted, effectively ventilated, with air control facilities and may have proper Air Handling units (wherever applicable) to maintain conditions including temperature and, wherever necessary, humidity, as defined for the relevant product. These conditions shall be appropriate to the category of drugs and nature of the operation. These shall also be suitable to the comforts of the personnel working with protective clothing, products handled, operations undertaken within them in relation to the external environment. These areas shall be regularly monitored for compliance with required specifications;
- (v) Provided with drainage system, as specified for the various categories of products, which shall be of adequate size and so designed as to prevent back flow and/or to prevent insects and rodents entering the premises. Open channels shall be avoided in manufacturing areas, and where provided, these shall be shallow to facilitate cleaning and disinfection.
- (vi) The walls and floors of the areas where manufacture of drugs is carried out shall be free from cracks and open joints to avoid accumulation of dust. These shall be smooth, washable, coved and shall permit easy and effective cleaning and disinfection. The interior surfaces shall not shed particles. A periodical record of cleaning and painting of premises shall be maintained.

MCC :

## 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 program 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 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.

**WHO :**

Premises

General :

11.2 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

11.3 Premises used for the manufacture of drug products should be suitably designed and constructed to facilitate good sanitation.

11.4 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products. Premises should be cleaned and, where applicable, disinfected according to detailed written procedures.

11.5 Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

11.6 Premises should be designed and equipped so as to afford maximum protection against the entry of insects and other animals.

**II. GOODS RECEIVAL AND STORAGE AREAS**

**TGA :**

134. Materials should not be stored unprotected outside buildings except where their quality, labeling and containers cannot be affected adversely by the weather.

135. Security arrangements should prevent the coupling of bulk tankers to receival points except by or under the supervision of an authorized person.

136. The goods received at receiving bays, docks, platforms or areas should be protected from dust, dirt and rain.

The arrangement of receival areas and stores should prevent continuous access of external air to the stores.

Space should be provided in or adjacent to receival areas for the temporary storage of received goods whilst they are recorded, examined and, where necessary, externally cleaned.

137. There should normally be a separate sampling area for starting materials. If sampling is carried out in the storage area, it should be conducted in such a way as to prevent contamination or cross- contamination.

138. Storage areas should be adequate and organized to permit suitable and effective separation and



identification of the various materials and products stored.

139. Except where an acceptable alternative system is installed, there should be separate storage areas, designated as “Quarantine” areas, for each of the categories of goods shown in Tablets 139.1. Any system replacing physical quarantine should give equivalent security.
140. Labels and other pre-printed packaging materials, including “APPROVED” status labels, should be stored in a secure manner that will permit access by and issue only to authorized persons in accordance with documented procedures. Storage arrangements should permit clear separation of different labels and of each kind of pre-printed packaging material, so as to minimize the risk of mix-ups.

**Table 139.1 – Quarantine areas**

Material	Quarantine (Q) or Reject (R) area	Security
Starting materials on receipt	Q	
Pre-printed packaging materials	Q	Locked or otherwise secured
Partially finished goods	Q	
Finished goods awaiting transfer to the warehouse	Q	
Finished goods quarantined within the warehouse awaiting release	Q	Locked or otherwise secured
Returned finished goods	Q	Locked or otherwise secured
Rejected starting materials	R	Locked
Rejected or recalled products	R	Locked

141. Stored goods should be maintained in a clean, dry and orderly condition. They should be stored off the floor, and away from walls in a manner that will permit easy cleaning and the use of pest control agents without risk of contamination.
142. Starting and intermediate materials and finished products should be stored in environments compatible with the specifications or labeling instructions for such goods. The conditions of storage for final packaged goods should be compatible with the storage conditions if any specified on the labels of the goods.
143. Controlled storage environments, e.g. deep freeze, refrigerated, air-conditioned, should be monitored using suitable temperature – recording devices and the records reviewed and filed. Temperatures in other storage areas should be monitored & the results tabulated and analyzed so as to demonstrate the suitability of these areas for their purposes. Refrigerated and freezing storage environments should be fitted with an alarm to indicate when refrigeration has failed.
144. Except in special circumstances, stock rotation should be practiced in storage areas for both starting materials and finished products. That is, the oldest approved stock should be used first.

**MCA :**

**Storage areas**

- 3.18 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of the materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.
- 3.19 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required, (e.g. temperature, humidity) these should be provided, checked and monitored.
- 3.20 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.
- 3.21 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.
- 3.22 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.
- 3.23 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.
- 3.24 Highly active materials or products should be stored in safe and secure areas.
- 3.25 Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

**Schedule M :**

**Warehousing area :**

- 2.1 Adequate areas shall be designed to allow sufficient and orderly warehousing of various categories of materials and products like starting and packaging materials, intermediates, bulk and finished products, products in quarantine, released, rejected, returned or recalled, machine and equipment spare parts and change items.
- 2.2 Warehousing areas shall be designed and adapted to ensure good storage conditions. They shall be clean, dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity), these shall be provided, monitored and recorded. Storage areas shall have appropriate house-keeping and rodent, pests and vermin control procedures and records maintained. Proper racks, bins and platforms shall be provided for the storage of materials.
- 2.3 Receiving and dispatch bays shall protect materials and products from adverse weather conditions.
- 2.4 Where quarantine status is ensured by warehousing in separate earmarked areas in the same warehouse or store, these areas shall be clearly demarcated. Any system replacing the physical

quarantine, shall give equivalent assurance of segregation. Access to these areas shall be restricted to authorized persons.

- 2.5 The shall be separate sampling area in the warehousing area for active raw materials and excipients. If sampling is performed in any other area, it shall be conducted in such a way as to prevent contamination, cross-contamination and mix-up.
- 2.6 Segregation shall be provided for the storage of rejected, recalled or returned materials or products. Such areas, materials or products shall be suitably marked and secured. Access to these areas and materials shall be restricted.
- 2.7 Highly hazardous, poisonous and explosive materials such as narcotics, psychotropic drugs and substances presenting potential risks of abuse, fire or explosion shall be stored in safe and secure areas. Adequate fire protection measures shall be provided in conformity with the rules of the concerned civic authority.
- 2.8 Printed packaging materials shall be stored in a safe, separate and secure area.
- 2.9 Separate dispensing areas for Beta lactum, Sex hormones and cytotoxic substances or any such special categories of products shall be provided with proper supply of filtered air and suitable measures for dust control to avoid contamination. Such areas shall be under differential pressure.
- 2.10 Sampling and dispensing of sterile materials shall be conducted under aseptic conditions conforming to Grade A, which can also be performed in a dedicated area within the manufacturing facility.
- 2.11 Regular checks shall be made to ensure adequate steps are taken against spillage, breakage and leakage of containers.
- 2.12 Rodent treatments (pest control) should be done regularly and at least once in a year and record maintained.

#### MCC :

##### 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 dispatch 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 persons.

3.2.3.5 Computer controlled ware houses 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 secure areas.

#### WHO : STORAGE AREAS

11.11 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products : starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.

11.12 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

11.13 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

11.14 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

11.15 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

11.16 Segregation should be provided for the storage of rejected, recalled or returned materials or products.

11.17 Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire, or explosion should be stored in safe and secure areas.

11.18 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labeling and special attention should be paid to the safe and secure storage of these materials.

Weighing areas (may belong to either storage or production areas)

11.19 The weighing of starting materials and the estimation of yield by weighing should usually be carried out in separate weighing areas designed for that use, for eg. with provisions for dust control.

### III. PRODUCTION AREAS

#### MCA :

- 3.6 In order to minimize the risk of a serious medical hazard due to cross contamination dedicated and self contained facilities must be available for the production of particular medicinal products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. from live microorganisms). The production of certain additional products such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non – medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principal of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made . The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.
- 3.7 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- 3.8 The adequacy of the working and in - process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize 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.
- 3.9 Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls , floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.
- 3.10 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.
- 3.11 Drains should be of adequate size, and have stopped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.
- 3.12 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration ) appropriate both to the product handled, to the operations under taken within them and to the external environment.
- 3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.
- 3.14 In case where dust is generated (e.g. during sampling, weighing, mixing and processing

operations, packaging of dry products).specific provisions should be taken to avoid cross-contamination and facilitate cleaning .

- 3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.
- 3.16. Production areas should be well lit, particularly where visual on-line controls are carried out.
- 3.17. In-process controls may be carried out within the production area provided they do not carry any risk for the production.

#### Schedule M :

- 3.1 The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations.
- 3.2 In order to avoid the risk of cross-contamination, separate dedicated and self contained facilities shall be made available for the production of sensitive pharmaceutical products like penicillin or biological preparations with live micro-organisms. Separate dedicated facilities shall be provided for the manufacture of contamination causing and potent products such as beta lactum, Sex hormones and Cyto-toxic substances.
- 3.3 Working and in-process space shall be adequate to permit orderly and logical positioning of equipment and materials and movement of personnel to avoid cross-contamination and to minimize risk of omission or wrong application of any of manufacturing and control measures.
- 3.4 Pipe-work, electrical fittings, ventilation openings and similar service lines shall be designed, fixed and constructed to avoid creation of recesses. Service lines shall preferably be identified by colors and the nature of the supply and direction of the flow shall be marked / indicated.

#### MCC :

- 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. 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 minimize 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 and 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 air ducts.
- 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 operators 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.

**WHO :**

- 11.20 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. live micro-organisms). The production of certain other products, such as some antibiotics, hormones, cytotoxic substances, highly active pharmaceutical products and non-pharmaceutical products, should not be conducted in the same facilities. The manufacture of technical poisons, such as pesticides and herbicides, should not normally be allowed in premises used for the manufacture of pharmaceutical products. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made.
- 11.21 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- 11.22 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical 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.



- 11.23 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.
- 11.24 Pipe-work, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.
- 11.25 Drains should be of adequate size and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.
- 11.26 Production areas should be effectively ventilated, with air-control facilities (including control of temperature and, where necessary, humidity and filtration) appropriate to the products handled, to the operations undertaken, and to the external environment. These areas should be regularly monitored during production and non-production periods to ensure compliance with their design specifications.
- 11.27 Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.
- 11.28 Production areas should be well lit, particularly where visual on-line controls are carried out.

#### IV. QUALITY CONTROL AREAS

##### MCA:

- 3.26 Normally QC laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radioisotopes, which should also be separated from each other.
- 3.27 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.
- 3.28 Separate rooms may be necessary to protect sensitive instruments from vibrations, electrical interference, humidity etc,
- 3.29. Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

##### Schedule M :

- 5.1 QC laboratories shall be independent of the production areas. Separate areas shall be provided each for physico-chemical, biological, microbiological or radio-isotope analysis. Separate instrument room with adequate area shall be provided for sensitive and sophisticated instruments employed for analysis.



5.2 QC laboratories shall be designed appropriately for the operations to be carried out in them. Adequate space shall be provided to avoid mix-ups and cross-contamination. Sufficient and suitable storage space shall be provided for test samples, retained samples, reference standards, reagents and records.

5.3 The design of the laboratory shall take into account the suitability of construction materials and ventilation. Separate air handling units and other requirements shall be provided for biological, microbiological or radio-isotope testing areas. The laboratory shall be provided with regular supply of water of appropriate quality for cleaning and testing purposes.

5.4 QC laboratories shall be divided into separate sections i.e. for chemical, microbiological and wherever required, biological testing. These shall have adequate area for basic installation and for ancillary purposes. The microbiology section shall have arrangements such as airlocks and laminar airflow work station, wherever considered necessary.

**MCC :**

3.2.4.1 QC 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.

**WHO :**

11.29 QC laboratories should be separated from production areas. Areas where biological, microbiological, or radioisotope test methods are employed should be separated from each other.

11.30 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, reference standards (if necessary, with cooling), and records.

11.31 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes and ventilation. Separate air-handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.

11.32 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors, or where it is necessary to isolate the instruments.

**V. ANCILLARY AREAS**

**MCA :**

- 3.30 Rest and refreshment rooms should be separate from other areas.
- 3.31 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.
- 3.32 Maintenance workshops should as far as possible be separate from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for the same.
- 3.33 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

**Schedule M :**

- 4.1 Rest and refreshment rooms shall be separate from other areas. These areas shall not lead directly to the manufacturing and storage areas.
- 4.2 Facilities for changing, storing clothes and for washing and toilet purposes shall be easily accessible and adequate for the number of users. Toilets, separate for males and females, shall not be directly connected with production or storage areas. There shall be written instructions for cleaning and disinfection for such areas.
- 4.3 Maintenance workshops shall be separate and away from production areas. Whenever spares, changed parts and tools are stored in the production area, these shall be kept in dedicated rooms or lockers. Tools and spare parts for use in sterile areas shall be disinfected before these are carried inside the production areas.
- 4.4 Areas housing animals shall be isolated from other areas. The other requirements regarding animal houses shall be those as prescribed in rule 150-C(3) of the Drugs and Cosmetics Rules, 1945 which shall be adopted for production purposes.

**MCC :**

- 3.2.5.1 Rest rooms, smoking areas and refreshment rooms shall be separate from other areas.
- 3.2.5.2 Facilities for changing clothes and for washing and toilet purposes shall 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.

WHO :

- 11.7 Rest and refreshment rooms should be separate from other areas.
- 11.8 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.
- 11.9 Maintenance workshops should if possible separated from production areas. Whenever parts and tools are stored in production area, they should be kept in rooms or lockers provided for the same.
- 11.10 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

VI. WATER SYSTEM

Schedule M :

- 1.3 There shall be validated system for treatment of water drawn from own or any other source to render it potable in accordance with standards specified by the Bureau of Indian Standards or Local Municipality, as the case may be, so as to produce Purified water conforming to Pharmacoeplial specification. Purified water so produced shall only be used for all the operations except washing and cleaning operations where potable water may be used. Water shall be stored in tanks, which do not adversely affect quality of water and ensure freedom from microbiological growth. The tank shall be cleaned periodically and records maintained by the licensee in this behalf.

VII. DISPOSAL OF WASTE

Schedule M :

- 1.4 (i) The disposal of sewage and effluents (solid, liquid and gas) from the manufactory shall be in conformity with the requirements of Environment Pollution Control Board.
- (ii) All bio-medical waste shall be destroyed as per the provisions of the Bio-Medical Waste (Management and Handling) Rules, 1996.
- (iii) Additional precautions shall be taken for the storage and disposal of rejected drugs. Records shall be maintained for all disposal of Waste.
- (iv) Provisions shall be made for the proper and safe storage of waste materials awaiting disposal. Hazardous, toxic substances and flammable materials shall be stored in suitably designed and segregated, enclosed areas in conformity with Central and state legislations.

# CHAPTER 2

## EQUIPMENT

TGA :

201. Equipment should be suitable for its intended use, designed to facilitate thorough cleaning and sanitation – both inside and out – and constructed of materials which do not react with or absorb materials or products.
202. Wood should be avoided as a material of construction or support for equipment, especially where it may be wetted. Where this is not possible, surfaces including downward – facing surfaces, should be sealed with a coating resistant to chipping.
203. Equipment should be located and installed in such a way as to safeguard against product mix-up and against contamination by the environment, operators or other products.
204. To facilitate cleaning, equipment should be mobile or clear of walls and floors, or, where this is not practicable, sealed to the surface which it touches.

Where possible, tanks and other permanently installed vessels should be connectable to drain points to collect washings and rinsings.

205. Product and process water pipelines should have sanitary couplings and be sloped for drainage.
206. Contamination from operations that generate dust or aerosols should be minimized by containing the dust or by extraction, filtration, or other appropriate means.
207. Equipment should be kept clean, dry and protected from contamination when not in use.
208. Equipment should be cleaned and, where necessary, sanitized before use in accordance with section 4.
209. Equipment and tooling should be kept in good repair and records of maintenance kept wherever the maintenance, or lack of it, may affect product quality.

210. Defective equipment should be tagged as defective and, where portable, removed from manufacturing areas.
211. Equipment should not create a hazard to the product through leaking glands, lubricant drips, and the like: or through inappropriate modifications or adaptations. Only coolants, lubricants and other chemicals approved Quality assurance should be used.
212. Where practicable, equipment used for critical steps in processing should be :
  - \* automatically controlled
  - \* monitored by devices which sense and record the pertinent parameters; or
  - \* equipped with cutouts and alarms
213. Weighing and measuring equipment used in processing, storage and quality control --- including time, temperature and pressure – measuring devices, recorders and alarms --- should be sufficiently accurate for their purpose and should be calibrated and checked at regular intervals in accordance with a standard operating procedure.

Where practicable, each item should bear a label or tag indicating that it has been calibrated and an expiry date for that calibration. Evidence should be available that the calibrating devices are themselves accurate, or, where contractors have been utilized, that accuracy is guaranteed, for e.g. by NATA certification of the contractor.
214. The schedule for checking weighing equipment for use in dispensing should include at minimum a check at values typical of the weights of material dispensed, on dates appropriate to the frequency of use.
215. The standard weights used for checking weighing equipment should be stored in a suitably protective container or location and their calibration confirmed at appropriate intervals.
216. Records of calibration should indicate actual results obtained. The format of the records should be such that the permitted tolerances are evident to the person making the entry.

**MCA :**

- 3.34 Manufacturing equipment should be designed, located and maintained to suit its intended purpose.
- 3.35 Repair and maintenance operations should not present any hazard to the quality of products.
- 3.36 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 clean and dry condition.
- 3.37 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.
- 3.38 Equipment should be installed in such a way as to prevent any risk of error or of contamination.
- 3.39 Production equipment should not present any hazard to 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 and thus present any hazard.

- 3.40 Balances and measuring equipment of an appropriate range and precision should be available for Production and control operations.
- 3.41 Measuring, Weighing, recording and control equipment should be calibrated and checked at definite intervals by appropriate methods. Adequate records of such tests should be maintained.
- 3.42 Fixed pipe-work should be clearly labeled to indicate the contents and, where applicable, the direction of flow.
- 3.43 Distilled, deionised 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.
- 3.44 Defective equipment should, if possible, be removed from production and QC areas, or at least be clearly labeled as defective.

**Schedule M :**

- 11.1 Equipment shall be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The lay out and design of the equipment shall aim to minimize 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. Each equipment shall be provided with a log book, wherever necessary.
- 11.2 Balances and other measuring equipment of an appropriate range, accuracy and precision shall be available in the raw material stores, production and in-process control operations and these shall be calibrated and checked on a scheduled basis in accordance with SOP and records maintained.
- 11.3 The parts of the production equipment that come into contact with the product shall not be reactive, additive or absorptive to an extent that would affect the quality of the product.
- 11.4 To avoid accidental contamination, wherever possible, non-toxic / edible grade lubricants shall be used and the equipment shall be maintained in a way that lubricants do not contaminate the products being produced.
- 11.5 Defective equipment shall be removed from Production and QC areas or appropriately labeled.

**MCC :**

- 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 QC areas, or at least be clearly labeled 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 microorganisms.
- 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 other 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 definite 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 program designed to ensure 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 back up 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 program (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 pipe-work should be clearly labeled 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 filter press. Filtration can be fine enough to exclude bacteria, if this is necessary. Filters should not shed fibers or adversely affect the product.

**WHO :**

- 12.1 **Principle :** Equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The lay out and design of equipment must aim to minimize 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.
- 12.2 Equipment should be installed in such a way as to minimize any risk of cross-contamination.
- 12.3 Fixed pipe-work should be clearly labeled to indicate the contents and, where applicable, the direction of flow.
- 12.4 All service pipings and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.
- 12.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.
- 12.6 Production equipment should be designed, located and maintained to serve its intended purpose.
- 12.7 Production equipment should be designed so that it can be easily and thoroughly cleaned on a scheduled basis.
- 12.8 Control-laboratory equipment and instruments should be suited to the testing procedures undertaken.
- 12.9 Washing and cleaning equipment should be chosen and used as not to be a source of contamination.
- 12.10 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to an extent that would affect the quality of the product.
- 12.11 Defective equipment should, if possible, be removed from production and QC areas, or at least be clearly labeled as defective.



## CHAPTER 3

# PERSONNEL & TRAINING

TGA :

301. Personnel should have the education, training, experience and skills or any combination of these elements that will ensure that they can perform assigned duties and functions at an acceptable level.
302. Key personnel, responsible for managing and supervising manufacture, quality assurance and quality control, should be adequate in number. They should have the managerial and professional or technical skills and experience to assume and discharge responsibility for ensuring that the goods manufactures consistently meet standards and specifications.

Suitable persons should be deputed to carry out the duties and functions of the key personnel in their absence.

303. By means of job descriptions and organizational charts, the areas of responsibility and lines of authority of key personnel should be identifiable. Organization charts, job descriptions and the names, qualifications and experience of key personnel and their deputies should be available.

There should be no gaps or unexplained or conflicting overlaps in the responsibilities of those concerned with GMP. The responsibilities placed on any one person should not be so extensive as to compromise the effective execution of assigned duties in relation to GMP.

304. Persons in responsible positions should have adequate authority to discharge their responsibilities.
305. The persons in-charge of production and of quality assurance respectively should usually have studied a relevant science (e.g. Pharmacy, Chemistry, Chemical engineering, microbiology, food technology) at university or technical institute level and have had practical experience under professional guidance in the manufacture and control of therapeutic goods made under GMP. They should be different persons, neither of whom is responsible to the other unless other arrangements acceptable to the inspecting authority are made, yet each should have a responsibility for the achievement of product quality.

Appointees with less than the indicated qualifications or experience should be provided with a training program designed to make up deficiencies.

306. Only in exceptional circumstances should persons engaged part-time or in a consultative capacity be appointed to key positions.

Where, in exceptional circumstances, there is no person wholly engaged in quality assurance, an annual external audit of quality specifications, tests and procedures should be commissioned.

Where the manufacturer does not employ a qualified microbiologist, an annual external audit by such a person should be commissioned.

Written reports of audits should be furnished. Evidence should be available that audits have

occurred essentially as programmed and that follow-up action occurred where recommended.

The requirement of microbiological audit may be waived by the licensing authority.

307. Operators should be sufficiently fluent in spoken English and sufficiently fluent in written English to respond to training, accept and implement instructions exactly, and where their duties require it, fill out forms correctly.
308. Where appropriate, operators should be tested for color-blindness and the results made known to supervisors under whom they work.
309. Operators should understand and be trained to follow SOP relevant to their work and in the principles and practice of tasks assigned to them.
310. Operators should not be permitted to sign or initial a document unless they have been trained in the task associated with the signature and in the significance of the signature.

Register of signatures and initials should be maintained.

311. Training of manufacturing personnel in the principles of GMP should be carried out as an induction exercise and at regular planned intervals in accordance with a formal training program. Records, specific for member of staff, should be made and retained. Casual or contract personnel (including cleaners) should also receive appropriate induction training in GMP.

MCA :

General :

- 2.1 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive so as to present any risk to quality.
- 2.2 The manufacturer must have an organization chart. People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of GMP.

Key personnel :

- 2.3 Key personnel include the Head of Production, the head of QC and if at least one of these persons is not responsible for the duties described in Article 22 of Directive 75/319/EEC, the Qualified Persons (QP) designated for the purpose. Normally, key posts should be occupied by full time personnel. The Heads of Production and QC must be independent from each other. In large organizations, it may be necessary to delegate some of the functions listed in 2.5, 2.6 and 2.7.
- 2.4 The duties of the QP(s) are fully described in Article 22 of Directive 75/319/EEC, and can be summarized as follows:

- (a) For medicinal products manufactured within the European Community, a QP must ensure that each batch has been produced and tested/checked in accordance with the directives and the marketing authorization.
- (b) For medicinal products manufactured outside the European Community, a QP must ensure that each imported batch has undergone, in the importing country, the testing specified in paragraph 1 (b) of Article 22.
- (c) A QP must certify in a register or equivalent document, as operations are carried out and before any release, that each production batch satisfies the provisions of Article 22.

The persons responsible for these duties must meet the qualification requirements laid down in Article 23 of the same Directive, they shall be permanently and continuously at the disposal of the holder of the manufacturing authorization to carry out their responsibilities. Their responsibilities may be delegated, but not to other QP(s).

2.5 The Head of Production Department generally has the following responsibilities:

- (i) To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality.
- (ii) To approve the instructions relating to production operations and to ensure their strict implementation.
- (iii) To ensure that the production records are evaluated and signed by an authorized person before they are sent to the QC Department.
- (iv) To check the maintenance of his department, premises and equipment.
- (v) To ensure that the appropriate validations are done.
- (vi) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

2.6 The Head of the QC Department generally has the following responsibilities:

- (i) To approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products.
- (ii) To evaluate batch records.
- (iii) To ensure that all necessary testing is carried out.
- (iv) To approve specifications, sampling instructions, test methods and other QC procedures.
- (v) To approve and monitor any contract analysts.
- (vi) To check the maintenance of his department, premises and equipment.

- (vii) To ensure that the appropriate validations are done.
- (viii) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

2.7 The heads of Production and QC generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, subject to any national regulations:

- \* The authorization of written procedures and other documents, including amendments;
- \* The monitoring and control of the manufacturing environment;
- \* Plant hygiene;
- \* Process validation;
- \* Training;
- \* The approval and monitoring of suppliers of materials;
- \* The approval and monitoring of contract manufacturers;
- \* The design and monitoring of storage conditions for materials and products;
- \* The 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.

#### Training

2.8 The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.9 Besides the basic training on the theory and practise 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. Training programs should be available, approved by either the head of Production or the Head of QC, as appropriate. Training records should be kept.

2.10 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.

2.11 Visitors or untrained personnel should preferably, not be taken into the Production and QC areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

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

#### Schedule M :

6.1 The manufacture shall be conducted under the direct supervision of competent technical staff with prescribed qualifications and practical experience in the relevant dosage form and / or active pharmaceutical products.

6.2 The head of the QC laboratory shall be independent of the manufacturing unit. The testing shall be conducted under the direct supervision of competent technical staff who shall be whole time employees of the licensee.

6.3 Personnel for QA and QC operations shall be suitably qualified and experienced.

6.4 Written duties of Technical and QC personnel shall be laid and followed strictly.

6.5 Number of personnel employed shall be adequate and in direct proportion to the workload.

6.6 The licensee shall ensure in accordance with a written instruction that all personnel in production area or into QC laboratories shall receive training appropriate to the duties and responsibility assigned to them. They shall be provided with regular in-service training.

#### MCC : Organization and personnel

##### 2.1 Principles

2.1.1 The establishment and maintenance of a satisfactory system of QA and the correct manufacture and control of medicines rely upon people. For this reason, there should be sufficient personnel at all levels with the ability, training, experience and, where necessary, the professional / technical qualifications and managerial skills appropriate to the tasks assigned to them. Their duties and responsibilities should be clearly explained to them and recorded as written job descriptions or by other suitable means. All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

##### 2.2 Responsibilities of key personnel

2.2.1 The firm must have an organization chart. People in responsible positions should have specific tasks recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties must be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of GMP. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

\* the organogram should clearly indicate the reporting lines and level of responsibility. The organogram should be authorized and be in accordance with the functional relationships described in the individual job descriptions of the functionaries referred to.

- \* proper job descriptions should include the responsibilities and document in detail the policy and requirements.
- \* responsibilities should be delegated and acceptance acknowledged in writing.

2.2.2 Key personnel include the Managing Director, the person responsible for Production and the person responsible for QA. The person responsible for Production and the person responsible for QA, should be different persons of equal level of authority, neither of whom should be responsible to the other, but who both have a responsibility for achieving the requisite quality.

Note : The duties of this person responsible for QA are wider than those which may be suggested by such terms as “Chief Analyst”, “Laboratory Head”, etc.

2.2.3 Persons in responsible positions should have sufficient authority to discharge their responsibilities. In particular, the person responsible for QA should be able to carry out his defined functions impartially.

2.2.4 Suitably qualified persons should be designated to take up the duties of key personnel during the absence of the latter.

2.2.5 Key personnel should be provided with adequate working staff.

2.2.6 The way in which the various key responsibilities which can influence product quality are allocated may vary with different manufacturers. These responsibilities should be clearly defined and delegated.

#### 2.2.7 Consultants

Only in exceptional circumstances should persons engaged part time or in a consultative capacity to be appointed to key positions. Consultants advising on the manufacture, processing, packing, or storage of medicines shall have sufficient education, training and experience, or a 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 QC.

#### 2.2.9 Head of QC

The person responsible for QC should have the authority to establish, verify and implement all QC 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 the 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 QC may include authorizing 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 QA Manager who oversees all the QA arrangements and reports to senior management. The person responsible for QC may report to the QA manager and share some of the responsibilities with him.

The person responsible for QA 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 the third party contractors.

## 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 the 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.

### WHO :

- 10.1 **Principle** : The establishment and maintenance of a satisfactory system of Quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly understood by the individuals concerned and recorded as written descriptions. All personnel should be aware of the principles of GMP that affect them.

### General

- 10.2 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.
- 10.3 The manufacturer should have an organization chart. All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP.
- 10.4 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.



10.5 Steps should be taken to prevent unauthorized people from entering production, storage and quality control areas. Personnel who do not work in these areas should not use them as a passageway.

#### Key personnel

10.6 Key personnel include the head of production, the head of QC, the head of sales/distribution and the authorized person(s). Normally, key-posts should be occupied by full-time personnel. The heads of production and QC should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility can not be delegated.

10.7 Key personnel responsible for supervising the manufacture and quality control of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of

- (a) chemistry (analytical or organic) or biochemistry
- (b) chemical engineering
- (c) microbiology
- (d) pharmaceutical sciences and technology
- (e) pharmacology and toxicology
- (f) physiology, or
- (g) other related sciences

They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products.

10.8 The heads of production and QC departments generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations;

- (a) the authorization of written procedures and other documents, including amendments;
- (b) the monitoring and control of the manufacturing environment;
- (c) plant hygiene;
- (d) process validation and calibration of analytical apparatus;
- (e) training, including the application and principles of quality assurance;
- (f) the approval and monitoring of suppliers of materials;
- (g) the approval and monitoring of contract manufacturers;
- (h) the designation and monitoring of storage conditions for materials and products;
- (i) the retention of records;

- (j) the monitoring of compliance with GMP.
- (k) the inspection, investigation and taking samples, in order to monitor factors that may affect product quality.

10.9 The head of the production department generally has the following responsibilities:

- (a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
- (b) to approve the instructions relating to production operations, including the in-process controls and to ensure their strict implementation;
- (c) to ensure that the production records are evaluated and signed by a designated person before they are made available to the QC department;
- (d) to check the maintenance of the department, premises and equipment;
- (e) to ensure that the appropriate process validation and calibrations of control equipment are performed and recorded and the reports made available.
- (f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

10.10 The head of the QC department generally has the following responsibilities:

- (a) to approve or reject starting materials, packaging materials and intermediate, bulk and finished products;
- (b) to evaluate batch records;
- (c) to ensure that all necessary testing is carried out;
- (d) to approve sampling instructions, specifications, test methods and other QC procedures;
- (e) to approve and monitor analysis carried out under contract;
- (f) to check the maintenance of the department, premises and equipment;
- (g) to ensure that the appropriate validations, including those of analytical procedures and calibrations of control equipment are done;
- (h) to ensure that the required initial and continuing training of QC personnel is carried out and adapted according to need.

#### Training

10.11 The manufacturer should provide training in accordance with a written program for all the personnel whose duties take them into production areas or into control laboratories (including the

technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

- 10.12 Besides 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. Training programs should be available, approved by the head of either production or QC, as appropriate. Training records should be kept.
- 10.13 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.
- 10.14 The concept of quality assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.
- 10.15 Visitors or untrained personnel should preferably not be taken into production and QC areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

## CHAPTER 4

# FACTORY SANITATION & PERSONNEL HYGEINE

TGA :

a. General :

401. The factory , including employee amenity areas, workshops and service rooms, should be clean, dry, sanitary, orderly and free from accumulated waste, dirt and debris.
402. Waste material should not be allowed to accumulate. It should be collected in sturdy, closable, labeled containers for removal to collection points and from there disposed off safely at frequent intervals. Collection points should be remote from processing.

b. Cleaning

403. A written cleaning and, where necessary, sanitation procedure should be established for all production areas and stores. Relevant sections should be readily available to staff and should specify, as appropriate :
  - \* the areas to be cleaned;
  - \* the frequency (and where necessary, the times) of cleaning;
  - \* the steps to be taken;
  - \* the responsibilities for cleaning operations;
  - \* the materials (e.g. detergent, disinfectant) and the equipment to be used;
  - \* methods for the cleaning, decontamination, drying and storage of mops, brushes and other cleaning equipment;
  - \* special precautions necessary in particular areas, e.g. wash-up areas or where work is in progress or uncovered;
  - \* specific methods for cleaning exhaust ducts, grilles, flues and, where appropriate, fan blades; and
  - \* record keeping
404. Written procedures should be established and available for cleaning and, where necessary, sanitizing all equipment. Operators should be familiar with these procedures, which should include:
  - \* the responsibility for cleaning;
  - \* whether re-cleaning or sanitizing is necessary before next use and the procedures that ensure that

these steps have occurred;

- \* materials and equipment to be used;
  - \* extent of disassembly
  - \* all necessary steps, including rinsing, drying and (preferably) covering and storage;
  - \* procedures for cleaning hoses and associated fittings;
  - \* documentation (tags, logs); and
  - \* special precautions, where applicable.
405. Cleaning equipment or materials that shed particles, raise dust, produce aerosols or otherwise generate contamination should be avoided where possible. These include compressed air, bristle brushes, fiber-shedding cloths and certain designs of floor-scrubbing machines. Vacuum or wet cleaning methods are preferred. Vacuum cleaners or polishers should be fitted with fine dust filters.
406. Instructions describing the correct storage and use of disinfectants should emphasize -
- \* ensuring that objects and surfaces to be treated are pre-cleaned;
  - \* disassembly of equipment being treated;
  - \* using only the specified disinfectants;
  - \* the dilution of each disinfectant and the correct choice of diluent;
  - \* avoiding further dilution or storage or 'topping up' during use but, where storage is not avoidable, labeling any storage dilution with an expiry date
- If contamination of finished products or colonization of equipment or the environment with pathogens or potential pathogens is discovered, the choice of disinfectant and the conditions of its use should be carefully reviewed by QA in connection with an investigation of the origin(s) of the contamination.
407. If wet areas or open drains are present in production areas there should be specific procedures for their cleaning and decontamination.
408. Air handling systems, including air ducts, ancillary components, humidifiers and cooling towers should be inspected and maintained in accordance with Australian standards AS3666-1989: Air handling and water systems of buildings – Microbial control.
409. A system should be in operation which ensures that cleaning and, where necessary, sanitizing has occurred after use and, where necessary, before re-use of equipment.

Where equipment is dedicated to one formulation only or used for a run of batches of the same formulation, cleaning should remove as much as practicable of each batch before proceeding to the next. In such cases, the maximum period or maximum number of batches that are permitted to

elapse before complete cleaning must be carried out should be specified in a standard procedure which should be supporting data.

410. Except where a specific program has been written for or a single written instruction issued to an external contractor, the manufacturer's cleaning and sanitation program should be used, in manufacturing areas, by all employees and all contractors.
411. Where the removal of traces of product or the establishment of microbiologically clean surfaces is critical, evidence should be available that the methods used are effective.

**c. Pest Control**

412. An officer responsible for pest control should be nominated by the manufacturer. This officer should ensure that pest control is carried out under specific instructions or agreements (including the mapping of any baits), should ensure that only nominated pest control agents are used, should take particular care that pest control chemicals do not contaminate materials, containers, products and should ensure that all treatments are logged.

**d. Facilities and procedures for personal Hygiene**

413. Adequate change rooms and clean and well-ventilated toilets provided with adequate hand washing facilities should be provided, toilets being adequately isolated from any manufacturing by atleast an airlock. Odour-masking agents should not be used in toilets.
414. Hand washing facilities should be provided near working areas. These should include -
- \* clean hand basins provided with running water.
  - \* soap or detergent dispensed so as to minimize contamination; and
  - \* single-use towels or hot-air hand dryers.
415. Hand-washing should be required of factory staff after using a toilet and whenever relevant to the operations being conducted. Notices emphasizing this requirement should be prominently displayed in relevant positions.
416. Direct contact between operators' hands and exposed product should be avoided.
417. A policy regarding the wearing of makeup and jewellery should be established and enforced, as appropriate to the circumstances.
418. Clean working-garments appropriate for the work should be worn by all staff. Where relevant to the protection of starting materials, work in process or finished exposed product, protective apparel such as hair, face, hand, shoe and arm coverings should be worn. Hair coverings should fully contain the hair. Working garments should not have pockets above bench level where the contents of pockets could fall into product.
419. Procedures should be written and enforced to ensure that all persons who do not work full-time in areas requiring special clothing (including maintenance personnel, pest controllers, laboratory staff,

consultants and visitors) wear the garments prescribed for those areas.

420. Garments supplied for use in processing or use in sterile production areas should not be worn outside the factory premises.
421. Except for facilities designed into dedicated areas, eating, drinking or smoking should not be permitted in manufacturing areas or in any other area where these activities might adversely affect product quality. If smoking is permitted on the premises, it is preferable that 'smoking' areas are positively designated : smoking is then clearly forbidden in any other area.
422. There should be pre-employment and periodic medical checks, 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.

Personnel 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.

423. Training related to factory sanitation and personnel hygiene should be included in staff training programs.
424. Where hazardous or physically potent drugs are manufactured or tested, the staff should be provided with –
  - \* Training and written procedures to ensure the safe handling of these drugs; and
  - \* Protective clothing and equipment necessary to implement these procedures.

MCA :

Personal Hygiene

- 2.13 Detailed hygiene programs should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into production and QC areas. Hygiene programs should be promoted by management and widely discussed during Training sessions.
- 2.14 All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.
- 2.15 Steps should be taken to ensure as far as practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.
- 2.16 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

- 2.17 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited . In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected, should be forbidden.
- 2.18 Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the product.
- 2.19 Personnel should be instructed to use the hand-washing facilities.
- 2.20 Any specific requirements for the manufacture of special groups, e.g. sterile preparations, are covered in the annexes.

Schedule M :

Health, clothing and sanitation of workers

- 7.1 The personnel handling Beta-lactum antibiotics shall be tested for penicillin sensitivity before employment and those handling sex hormones, cyto-toxic substances and other potent drugs shall be periodically examined for adverse effects. These personnel should be moved out of these sections (except in dedicated facilities), by rotation, as a health safeguard.
- 7.2 Prior to employment, all personnel, shall undergo medical examination including eye examination, and shall be free from Tuberculosis, skin and other communicable or other contagious diseases. Thereafter, they should be medically examined periodically, at least once a year. Records shall be maintained thereof. The licensee shall provide the services of a qualified physician for assessing the health status of personnel involved in different activities.
- 7.3 All persons, prior to, and during employment, shall be trained in practices which ensure personnel hygiene. A high level of personal hygiene shall be observed by all those engaged in the manufacturing processes. Instructions to this effect shall be displayed in change rooms and other strategic locations.
- 7.4 No person showing, at any time, apparent illness or open lesions which may adversely affect the quality of products, shall be allowed to handle starting materials, packaging materials, in-process materials, and drug products until his condition is no longer judged to be a risk.
- 7.5 All employees shall be instructed to report about their illness or abnormal health condition to their immediate supervisor so that appropriate action can be taken.
- 7.6 Direct contact shall be avoided between the unprotected hands of personnel and raw materials, intermediate or finished, unpacked products.
- 7.7 All personnel shall wear clean body coverings appropriate to their duties. Before entry into the manufacturing area, there shall be change rooms separate for each sex with adequate facilities for personal cleanliness such as wash basin with running water, clean towels, hand dryers, soaps, disinfectants etc. The change rooms shall be provided with cabinets for the storage of personal belongings of the personnel.
- 7.8 Smoking, eating, drinking, chewing or keeping plants, food, drink and personal medicines shall not



be permitted in production, laboratory, storage and other areas where they might adversely influence the product quality.

MCC :

## 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.

2.6.1.2 Personnel should be instructed to use the hand-washing facilities.

2.6.1.3 Detailed hygiene programs 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 taken 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 authorized 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.

WHO :  
Sanitation & Hygiene

4.1 A high level of sanitation and hygiene should be practiced in every aspect of the manufacture of drug products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive program of sanitation and hygiene.

Personal hygiene

- 10.16 All personnel, prior or and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.
- 10.17 All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.
- 10.18 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials, or drug products until the condition is no longer judged to be a risk.
- 10.19 All employees should be instructed and encouraged to report to their immediate superior any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.
- 10.20 Direct contact should be avoided between the operator's hand and starting materials, primary packaging materials and intermediate or bulk product.
- 10.21 To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if re-usable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.
- 10.22 Smoking, eating, drinking, chewing and keeping plants, food, drink, smoking material and personal medicines should not be permitted in production, laboratory and storage areas or in any other areas where they might adversely influence product quality.
- 10.23 Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees. E.g. contractors' employees, visitors, senior managers and inspectors.

# CHAPTER 5

# DOCUMENTATION

TGA :

a. Kinds of Document

501. Manufacturers should have specifications for materials used and products made (including test methods), master documents from which batch records are derived, Standard Operating procedures to give directions for recurrent tasks, agreements covering external activities and registers and other records to provide a complete history of each batch made and the circumstances of its manufacture, in accordance with the following clauses.

b. Preparation, issue and use of documents

502. Documents should be carefully and logically set out to encourage correct use and be easy to check. Documents should contain all necessary, but no superfluous data. Any headings, items or spaces on a master document that cease to be used should be removed at the earliest opportunity.

503. Each document should indicate or include -

- \* the user's company or trading name;
- \* purpose and title;
- \* a document identity number which uniquely identifies the document and indicates revision, if any;
- \* date of authorization;
- \* date of expiry or review (in the case of SOP)
- \* signatures of authorizing persons and, where different, the signature of the person who prepared the document.
- \* the distribution list, where copies are distributed (at least on master copy); and
- \* page numbers (of number of total pages).

The way in which the document is to be used, and by whom, should be clearly apparent from the document itself.

The reason for revision should be documented.

504. Issued documents should not be hand written. Reproduced or computer-printed documents should be clear and legible; in the case of batch documents each must be initialed to indicate a verified issue.

505. Any correction made to a document should be initialed or signed and dated and the correction should permit the reading of the original information. Where appropriate, the reason for correction should be recorded.

506. Documents which require the entry of data or additional information should:

- \* provide sufficient space for the entry;
- \* allow adequate spacing between entries; and
- \* clearly indicate what is to be entered.

Where any issued document requires the entry of data or additional information, entries should be handwritten clearly and legibly in permanent ink. If a handwritten entry is corrected, the correction should permit reading of original entry and should be initialed by the person making it.

507. Where documents bear instructions, they should be written in the imperative, ie. as a direct command, as numbered steps. They should be clear, precise and unambiguous and in plain English that the user can understand. Such documents should be readily available to all concerned with carrying out the instructions.

508. Documents should be kept up to date. Any amendments should be formally authorized before the document is used. In the case of permanent amendments, the amended document should be replaced at the earliest opportunity by a newly prepared document and the superseded document so marked and filed.

509. Master batch documents, SOPs and other master documents having a direct bearing on product quality should be authorized by the person responsible for QA or that person's delegate as well as by a responsible production or other relevant manager.

c. Product traceability

510. A system should be in operation whereby the complete and up-to-date histories of all batches of products from the starting materials to the completed forms are progressively recorded. The system should be adequate to determine the utilization and disposition (including destruction) of all starting materials and products.

511. Sales and distribution records should be readily available, complete and easy to follow so as to expedite the recall of goods whenever necessary.

d. Storage and retention of documents and records

512. Except where legislation requires longer retention periods, the complete records pertaining to each batch, including original data such as laboratory notebooks, should be retained for at least 1 year after the expiry date of the batch or, where there is no expiry date, for at least 6 years after the date of manufacture of the batch.

Records of complaints should be held for a corresponding period.

513. Master documents for batch processing and packaging should be copied and the copies and the copies secured against theft, loss or alteration of information.
514. Records may be retained as microfilm or microfiche. The responsibility of photo-reduction should be delegated to a specific person and the following procedures and controls adopted.
- \* a check should be made to ensure that all the necessary documents have been photo-reduced.
  - \* all photo-reduced documents should be checked to ensure that they are legible and accurate copies, showing all the information present on the originals;
  - \* Original documents relating to a batch should not be destroyed until the checks described above have been carried out.
  - \* all photo-reduced records should be available and readable. Provision should be made on site for making legible copies; and
  - \* the photo-reduced records of each batch should be retained for the period of time specified in Clause 512.
515. Paper or film records should be stored in a restricted access area. Records should be protected from tampering or loss.
516. Records may be retained by computer storage, but the procedures and checks in section 9 should be followed. Such records should be progressively backed up (e.g. daily) and the backup kept at a location remote from the active life.

MCA :

General

- 4.1 *Specifications* describe in detail the requirement with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

*Manufacturing formula, processing and packaging instructions* state all the starting materials used and lay down all processing and packaging operations

*Procedures* give directions for performing certain operations, e.g. cleaning, clothing, environmental control, sampling, testing, equipment operation.

*Records* provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product.

- 4.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorization dossiers.
- 4.3 Documents should be approved, signed and dated by appropriate and authorized persons.

- 4.4 Documents should have unambiguous contents; title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents should not allow any error to be introduced through the reproduction process.
- 4.5 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.
- 4.6 Documents should not be handwritten; although, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting. Sufficient space should be provided for such entries.
- 4.7 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.
- 4.8 The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable. They should be retained for at least one year after the expiry date of the finished product.
- 4.9 Data may be recorded by electronic data processing systems, photographic or other reliable 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 authorized persons should be able to enter or modify data in the computer and there should be a record of the changes and deletions; access should be restricted by password or other means and the result of 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 the data are readily available throughout the period of retention.

#### MCC : PRINCIPLES

- 8.1.1 Documentation is an essential part of the QA 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 utilization and disposal of starting materials, packaging materials and intermediate, bulk and finished products, may be determined.
- 8.1.3 There should be authorized (signed and dated) specifications for at 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 authorized, 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 the Master documentation.
- 8.1.8 There should be a written procedure for updating of master documentation and the system should ensure 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 master documentation is a pre-requisite for 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 in applicancy.

#### 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 space 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 color of the paper 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 documents should be checked against an authorized 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 authorized 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 authorized 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 note books should be retained for at least 1 year after the expiry date of the batch. Documents should be easily retrievable.



WHO :

14.1 Principle : Good documentation is an essential part of the QA system and, as such, should be related to all aspects of GMP. Its aims are to define the specifications for all materials and methods of manufacture and control, to ensure that all personnel concerned with manufacture know what to do and when to do it, to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of drug for sale, and to provide an audit trail that will permit investigation of the history of any suspected defective batch. The design and use of documents depend upon the manufacturer. In some cases, some or all of the documents described below may be brought together, but they will usually be separate.

General

14.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

14.3 Documents should be approved, signed and dated by appropriate authorized persons. No document should be changed without authorization.

14.4 Documents should have unambiguous contents: the title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. 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.

14.5 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.

14.6 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

14.7 Any alteration made to the document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

14.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records and associated SOPs should be retained for at least 1 year after the expiry date of the finished product.

14.9 Data may be recorded by electronic data processing systems or by photographic or other reliable means. Master formula and detailed SOPs 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 authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs or other means. It is particularly important that, during the period of retention, the data are readily available.

Schedule M :

Documents and records

- 12.1 Documents designed, prepared, reviewed and controlled, wherever applicable, shall comply with these rules.
- 12.2 Documents shall be approved, signed and dated by appropriate and authorized persons.
- 12.3 Documents shall specify the title, nature and purpose. They shall be laid out in an orderly fashion and be easy to check. Reproduced documents shall be clear and legible. Documents shall be regularly reviewed and kept up – to date. Any alteration made in the entry of a document shall be signed and dated.
- 12.4 The records shall be made or completed at the time of each operation in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records and associated SOP shall be retained for at least 1 year after the expiry date of the finished product.
- 12.5 Data may be recorded by electronic data processing systems or other reliable means, but Master Formulae and detailed operating procedures relating to the system in use shall also be available in a hard copy to facilitate checking of the accuracy of the records. Wherever documentation is handled by electronic data processing methods, authorized persons shall enter or modify the data in the computer. There shall be record of changes and deletions. Access shall be restricted by passwords or other means and the result of entry of critical data shall be independently checked. Batch records electronically stored shall be protected by a suitable back-up. During the period of retention, all relevant data shall be readily available.

#### ESSENTIAL DOCUMENTS

##### TGA :

##### α a. Specifications General

517. There should be authorized and dated specifications for starting materials and finished products. Where appropriate, specifications should be available for intermediate or bulk products.
518. Where a statutory standard is applicable to a starting material this is a minimum specification and the QC specifications used should at least confirm to it, except where it can be shown that particular tests are not relevant to the quality of the product. If alternative test methods are used, they should be shown to be at least accurate, precise and specific as the official method. Additional clauses may be necessary to meet the specific requirements of the manufacturer or of specific equipment or products.
519. The QC specifications should also conform to any specifications accepted by the department for approval of the product or in connection with its registration.

##### MCA :

#### 4.10 Specifications

There should be appropriately authorized and dated specifications for starting and packaging materials and finished products; where appropriate, they should be also available for intermediate or bulk products.

TGA :

Specifications

Starting materials :

520. Specifications for starting materials (other than packaging materials) should include, where applicable

- \* a Standard name to be used in production documents, with reference to compendial names (where different);
- \* suppliers' code or trade names;
- \* a code reference unique to the material specification
- \* tests and limits for identity, purity, physical and chemical characteristics, microbiological standards (where appropriate) and assay or potency. However, where potency and specific identification testing are impracticable, e.g. for certain materials of natural origin, the use of standard samples, microscopic examination and organoleptic identification testing may be applicable.
- \* details of, or reference to the test methods to be used by the manufacturer;
- \* approved or certified supplier(s) of the material;
- \* storage conditions and precautions;
- \* physical appearance and characteristics to be noted by the sampling officer;
- \* sampling plan and sampling instructions and precautions or reference to appropriate parts of a standard procedure; and
- \* period for which approval will remain valid.

MCC :

Master specifications :

##### 8.3.1 Starting materials

8.3.1.1 There should be an authorized 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.

#### Schedule M :

##### 17.1 For Raw materials and Packaging materials:-

They shall include -

- (a) the designated name and internal code reference;
- (b) reference, if any, to a pharmacopoeial monograph;
- (c) qualitative and quantitative requirements with acceptance limits;
- (d) name and address of manufacturer or supplier and original manufacturer of the material;
- (e) specimen of printed material;
- (f) directions for sampling and testing or reference to procedures;
- (g) storage conditions; and
- (h) maximum period of storage before re-testing.

##### 17.2 For product containers and closures -

17.2.1 All containers and closures intended for use shall comply with the pharmacopoeial requirements. Suitable validated test methods, sample sizes, specifications, cleaning procedure and sanitation procedure, wherever indicated, shall be strictly followed to ensure that these are not reactive, additive, adsorptive, or leach to an extent that significantly affects the quality or purity of the drug. No second hand or used containers and closures shall be used.

17.2.2 Whenever bottles are being used, the written schedule of cleaning shall be laid down and followed. Where bottles are not dried after washing, they should be rinsed with de-ionized water or distilled water, as the case may be.

17.3 For in-process and bulk containers – Specifications for in-process material, intermediate and bulk products shall be available. The specifications should be authenticated.

MCA :

Specifications for starting and packaging materials

4.11 Specifications for starting and primary or printed packaging materials should include, if applicable:

(a) A Description of the materials, including:

- \* the designated name and the internal code reference;
- \* the reference, if any, to a pharmacopoeial monograph;
- \* the approved suppliers and, if possible, the original producer of the products;
- \* specimen of printed materials.

(b) Directions for sampling and testing or reference to procedures.

(c) Qualitative and quantitative requirement with acceptance limits.

(d) Storage conditions and precautions.

(e) The maximum period of storage before re-examination.

WHO:

#### SPECIFICATIONS FOR STARTING AND PACKAGING MATERIALS

14.18 Specifications for starting and primary or printed packaging materials should provide, if applicable, a description of the materials, including:

- (a) the designated name (if applicable, the International Non-proprietary Name) and internal code reference;
- (b) the reference, if any, to a pharmaceutical monograph; and

- (c) qualitative and quantitative requirements with acceptance limits;

Depending on the company's practice, other data may be added to the specification, such as:

- (a) the supplier and the original producer of the materials;
- (b) a specimen of printed materials;
- (c) directions for sampling and testing, or reference to procedures;
- (d) storage conditions and precautions;
- (e) the maximum period of storage before re-examination.

Packaging material should conform to specifications, with emphasis placed on the compatibility of the material with the drug product it contains. The material should be examined for critical and major physical defects as well as for the correctness of identity markings.

- 14.19 Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

TGA :

Packaging materials :

521. Specifications for packaging materials (See note 1) should include:

- \* a standard name to be used on documents;
- \* suppliers' names (where different) (see Note 2);
- \* a code reference unique to the material, including a revision code (in the case of printed materials this code should be that used on the material. e.g. a label code)
- \* a description of the nature, dimensions and materials of construction of the component;
- \* quality standards, mould references and drawings as applicable;
- \* approved label copy (for pre-printed materials);
- \* bar codes, where applicable including a reference to the bar code register;
- \* details of, or references to, tests to be used to determine compliance with the specification;
- \* approved or certified suppliers (see Note 2);
- \* sampling plan and sampling instructions or reference to appropriate parts of a SOP; and

\* period for which approval will remain valid.

Notes :

1. See “Packaging Material” in glossary: the need for detailed specifications may not apply to “Other Packaging Materials”.
2. Optional for this document where adequately covered by Standard Names documentation. See also Glossary.

MCC :

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

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.

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

WHO :

#### SPECIFICATIONS AND TESTING PROCEDURES

14.13 Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.

14.14 There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for

water, solvents and reagents (e.g. acids and bases) used in production should be included.

- 14.15 Each specification should be approved and maintained by the QC unit. Specifications for starting materials, intermediates, bulk and finished products are referred to in sections 14.18 – 14.21.
- 14.16 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.
- 14.17 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the QC laboratory.

#### INTERMEDIATE AND BULK PRODUCTS:

##### TGA :

- 522. Specifications for bulk and intermediate products should be available if these are received or dispatched, or if data obtained from tests on intermediate or bulk products are used for the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

##### MCA :

- 4.12 Specifications for bulk and intermediate products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

##### MCC :

- 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. E.g. cores of coated tablets.

##### WHO :

- 14.20 Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used in the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

#### FINISHED PRODUCTS :

##### TGA :

- 523. Specifications for finished products should include :



- \* an exact statement of the therapeutically active substances intended to be present together with those requiring assay and their concentrations in the product.
- \* the product code (if any);
- \* the pharmaceutical dosage form and physical appearance;
- \* tests and limits for identity, purity, physical and chemical characteristics, assay or potency and (where applicable) microbiological standards
- \* details of, or reference to the test methods to be used by the manufacturer;
- \* sampling instructions ; and
- \* the shelf life and storage conditions in relation to the packaging used.

524. Where the stability profile of a finished product indicates that it may be subject to significant change from specifications on storage, the requirements which each batch must meet before it is released for distribution (the release specifications) should have different or narrower ranges of acceptance values than those to which the product must conform at any time during its shelf life (the expiry specifications).

Where this distinction is made, all relevant documents should refer clearly and unambiguously to “release” or “expiry” specifications respectively. A suitable master document show both specifications.

It is a requirement that expiry specifications must be consistent with any data accepted by the department in connection with product registration and with any statutory standard applicable to the product.

525. The release specifications for a finished product should include a specific test for its identification. Where the manufacturer makes other products which are clearly distinguishable from this product by visual examination, the identification test may be carried out on a sample of the bulk final product; where different products are not clearly distinguishable, the test should be carried out on a sample of the packaged product.

**MCA :**

4.13 Specifications for finished products should include:

- (a) The designated name of the product and the code reference, where applicable.
- (b) The formula or a reference to.
- (c) A description of the pharmaceutical form and package details
- (d) Directions for sampling and testing or a reference to procedures
- (e) The qualitative and quantitative requirements, with the acceptance limits.

- (f) The storage conditions and any handling precautions, where applicable.
- (g) The shelf life.

Schedule M :

17.4 For Finished products – Appropriate specifications for finished products shall include :-

- (a) the designated name of the product and the code reference;
- (b) the formula or a reference to the formula and the pharmacopoeial reference;
- (c) directions for sampling and testing or a reference to procedures;
- (d) a description of the dosage form and package details;
- (e) The qualitative and quantitative requirements, with the acceptance limits for release;
- (f) The storage conditions and precautions, where applicable, and
- (g) the shelf-life.

MCC :

8.3.4.1 There should be specifications, approved at least by the person responsible for QA, 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 specification document.

WHO :

14.21 Specifications for finished products should include:

- (a) the designated name of the product and the code reference, where applicable;
- (b) the designated name(s) of the active ingredient(s) (if applicable, the International Non-proprietary name(s));
- (c) the formula or a reference to the formula;
- (d) a description of the dosage form and package details;
- (e) directions for sampling and testing or a reference to procedures;
- (f) the qualitative and quantitative requirements, with acceptable limits;
- (g) the storage conditions and precautions, where applicable; and
- (h) the shelf life

TGA :

Goods Received register :

526. A register should be established showing the receipt of starting materials. The register should include -

- \* date of receipt;
- \* Standard name of material;
- \* supplier's name for materials (if different);
- \* supplier's batch or lot number(s);
- \* quantity and number of containers per suppliers' batch; and
- \* the unique identifying number(s) allocated (see clause 644).

Standard names list :

527. A list showing the standard name for each starting material should be established. Standard names should be sufficiently specific to indicate special quality characteristics and be designed to minimize mix-ups. The standard names specified on this list should be used to identify starting materials during storage and manufacture.

Status labels

528. Status labels should include:

- \* the company logo; and
- \* the words QUARANTINE or HOLD, RELEASED or APPROVED or REJECTED or equivalent terms acceptable to the inspecting authority;

Status labels for starting materials should also include provision for:

- \* the Standard Name of the material;
- \* a Unique identifying number;
- \* except where the correct number of labels is generated by a computer approval system, the signature or initials of the person authorized to assign approved status; and
- \* the date after which the release is no longer valid.

Status labels for work-in-progress should also include provision for an adequate description of the labeled material.

529. REJECT labels should be used only for materials that are unfit for use: those of uncertain status or destined for recovery, re-processing and the like should be designated HOLD, QUARANTINE or the equivalent.
530. The status of any material should be evident from the visual inspection of its status label.
531. Unless the standard quarantine and release procedure is utilized, a further visually distinct and different standard label should be used for substances used for production but not in the product. E.g. acids and alkalis for demineraliser regeneration, blue dye for leak testing.

#### Batch Register :

532. A register should be established showing, for each product made, the batch number(s) allocated, and the packaged batch numbers, where these differ from the processing batch number.

#### WHO : Labels

- 14.10 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colors to indicate status (for e.g. quarantined, accepted, rejected or clean).
- 14.11 All finished drug products should be identified by labeling, as required by the national legislation, bearing at least the following information:
- (a) the name of the drug product;
  - (b) a list of the active ingredients (if applicable, with the International Non-proprietary names), showing the amount of each present, and a statement of the net contents, e.g. number of dosage

units, weight or volume;

- (c) the batch number assigned by the manufacturer;
- (d) the expiry date in an uncoded form;
- (e) any special storage conditions or handling precautions that may be necessary;
- (f) directions for use and warnings and precautions that may be necessary; and
- (g) the name and address of the manufacturer or the company or the person responsible for placing the product on market.

14.12 For reference standards, the label or accompanying document should indicate the concentration, date of manufacture, expiry date, date the closure is first opened and storage conditions, where appropriate.

#### MASTER FORMULA AND PROCESSING INSTRUCTIONS :

##### TGA:

- 533. A Master formula and processing instruction for each batch size of each product should be prepared by a competent person and checked by a second, independent competent person. Where these data are transferred into / installed on a computer, or are prepared directly on a computer, an authorized duplicate should be kept.
- 534. Where the Master formula is to be scaled and is stored in a computer in unit form and Batch records are a printout from that computer, upper and lower limits to the batch size should be determined and be part of the program.
- 535. The processing instructions may be part of the Master formula or be separate. When separate, the two documents should be unambiguously cross-referred.
- 536. The Master Formula should include :
  - \* a reference which distinguishes the document from superseded documents for the same product.
  - \* the name of the product;
  - \* the pharmaceutical dosage form and strength;
  - \* the amount of each ingredient per dosage unit and a statement of the total weight or measure of the dosage unit or, where there is no dosage unit, the amount of each ingredient per unit of weight or measure of the finished product; and
  - \* a complete list of ingredients to be used in processing the product, listed by standard name (including any that may not appear in the final product) and the quantity of each. The quantities should appear in a position where they can not be confused with the amounts per dosage unit specified in the preceding paragraph.

537. The manufacturing documentation should be prepared with the intent to provide NLT 100% of the labeled or established amount of the active ingredient(s).
538. Necessary and reasonable variations in the amounts of other ingredients in the preparation are allowable, provided that the range of variation is stated in the master formula and provided that, in the case of registered products, the registered formula shows these variations.
539. Where any predetermined excess (overage) of an ingredient is used, the percentage excess should be shown.
540. Where material of variable potency is to be used, the document should provide a place for the relevant calculation.
541. All quantities should be stated in a consistent system of measurement. It is preferable for different units of quantity to appear in separate columns.
542. The master processing instructions should include:
- \* a reference which distinguishes the document from superseded documents for the same product.
  - \* the name of the product;
  - \* a statement of the manufacturing location (where relevant) and the equipment to be used;
  - \* the methods, or reference to the methods, to be used for preparing the equipment (e.g. cleaning, assembling, calibrating, sterilizing);
  - \* detailed stepwise processing instructions, including :
    - \* a check that the equipment to be used has been cleaned;
    - \* sequences for adding materials and for carrying out steps of the procedure
    - \* mixing times, temperatures and other relevant parameters or controls necessary to ensure a consistent product (as appropriate);
    - \* provision to insert actual lapsed times, temperatures, control or test results (as appropriate);
    - \* safety precautions to be observed.

For non-critical steps or series of steps in production, where there is no need to have each step signed off or to record data, the instructions and precautions may be given in brief together with a reference to a SOP.

Parameters for critical processing steps should be clearly specified. For e.g. for microdose products, critical parameters including mixing time, sequence of additions, and mixing equipment.

- \* directions for in-process sampling and testing, including the timing and quantity of samples to be taken and the sampling method and whether these samples are to be taken by (and the tests

conducted by) Production or QC personnel. These directions may be given in brief together with a reference to a SOP. Sampling methods should prevent microbial contamination;

- \* requirements for bulk storage of the product, including necessary containers, labels and special conditions of storage;
- \* a statement of the theoretical and / or expected amount of product at pertinent stages of processing and on completion, together with permitted tolerances; and
- \* provision for calculation of yields in the batch document.

#### MCA :

Formally authorized manufacturing formula and processing instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

#### 4.14 The manufacturing formula should include:

- (a) The name of the product, with a product reference code relating to its specification.
- (b) A Description of the pharmaceutical form, strength of the product and batch size.
- (c) A list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material; mention should be made of any substance that may disappear in the course of processing.
- (d) A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

#### 4.15 The processing instructions should include:

- (a) A Statement of the processing location and the principal equipment to be used.
- (b) The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. Cleaning, assembling, calibrating, sterilizing).
- (c) Detailed stepwise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures).
- (d) The instructions for in-process controls with their limits.
- (e) Where necessary, the requirements for bulk storage of the products, including the container, labeling and special storage conditions where applicable.
- (f) Any special precautions to be observed.

#### Packaging instructions

4.16 There should be formally authorized packaging instructions for each product, pack size and type. These should normally include, or have a reference to, the following:

- (a) Name of the product.
- (b) Description of its pharmaceutical form, and strength where applicable.
- (c) The pack size expressed in terms of the number, weight or volume of the product in the final container.
- (d) A complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material.
- (e) Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product.
- (f) Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin.
- (g) A Description of the packaging operation, including any significant subsidiary operations, and equipment to be used.
- (h) Details of in-process controls with instructions for sampling and acceptable limits.

Schedule M :

18. Master formula records

There shall be Master Formula records relating to all manufacturing procedures for each product and batch size to be manufactured. These shall be prepared and endorsed by the competent technical staff i.e. head of production and QC. The Master Formula shall include

- (a) The name of the product together with product reference code relating to its specifications;
- (b) the patent or proprietary name of the product along with the generic name, a description of the dosage form, strength, composition of the product and batch size.
- (c) name, quantity, and reference number of all the starting materials to be used. Mention shall be made of any substance that may disappear in the course of processing.
- (d) A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.
- (e) A Statement of the processing location and the principal equipment to be used.
- (f) The methods, or reference to the methods, to be used for preparing the critical equipment including Cleaning, assembling, calibrating, sterilizing.



- (g) Detailed stepwise processing instructions and the time taken for each step.
- (h) The instructions for in-process controls with their limits.
- (i) the requirements for storage conditions of the products, including the container, labeling and special storage conditions where applicable.
- (j) Any special precautions to be observed.
- (k) packing details and specimen labels.

19. Packaging records – There shall be authorized packaging instructions for each product, pack size and type. These shall include or have a reference to the following :-

- (a) name of the product;
- (b) description of the dosage form, strength and composition;
- (c) the pack size expressed in terms of the number of doses, weight or the volume of the product in the final container;
- (d) Complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specification of each packaging material;
- (e) reproduction of the relevant printed packaging materials and specimens indicating where batch number and expiry date of the product have been applied.
- (f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before the operations begin;
- (g) description of the packaging operation, including any significant subsidiary operations and equipment to be used;
- (h) details of in-process controls, with instructions for sampling and acceptance;
- (i) upon completion of the packing and labeling operation, a reconciliation shall be made number of labeling and packaging units issued, number of units labeled, packed and excess returned or destroyed. Any significant or unusual discrepancy in the numbers shall be carefully investigated before releasing the final batch.

**MCC :**  
**MASTER MANUFACTURING INSTRUCTIONS**

8.4.1 A formally authorized 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.
- (c) a list of all starting materials to be used, with the amount of each, whether or not they appear in the Finished Product. All quantities should be stated in an 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 mentioned.
- (d) a statement of the total expected final yield with the acceptable limits and of relevant intermediate yields as 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, sterilizing)
- (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.

## MASTER PACKAGING INSTRUCTIONS

8.5.1 A formally authorized 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) a code or reference number of each material which relates it to its specification
- (f) a specimen or facsimile of relevant printed packaging material, where applicable.
- (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, sterilizing)
- (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.

WHO :

## MASTER FORMULA

14.22 A formally authorized Master formula should exist for each product and batch size to be manufactured.

14.23 The Master formula should include:

- (a) the name of the product, with a product reference code relating to its specification;
- (b) a description of the dosage form, strength of the product, and batch size;
- (c) a list of all starting materials to be used (if applicable, with the International Nonproprietary

Names), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);

- (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
- (e) a statement of the processing location and the principle equipment to be used;
- (f) the methods, or reference to the methods, to be used for preparing the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing;
- (g) detailed stepwise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);
- (h) the instructions for any in-process controls with their limits;
- (i) where necessary, the requirements for storage of the products, including the container, the labeling, and any special storage conditions;
- (j) any special precautions to be observed.

#### Packaging instructions

14.25 Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to:

- (a) the name of the product;
- (b) a description of its pharmaceutical form, strength and method of application where applicable;
- (c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- (d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;
- (e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
- (f) special precautions to be observed including a careful examination of the packaging area and equipment in order to ascertain the line clearance before operations begins;
- (g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- (h) details of in-process controls with instructions for sampling and acceptance limits.

BATCH RECORD PROCESSING:

TGA:

543. A clear and complete (or appropriately abridged) copy of the Master formula and Processing instructions should be made for each batch of a product before it is processed. Transcription from the Master documents should be by photocopying or computer printout of each document should be initialed by a competent person before issue to signify that it is complete, legible and appropriate.

544. At the time of issue, the document should be marked with:

- \* a number, on which page, which uniquely distinguishes from all other batches of the same product or other products at all stages of manufacture and permits a correspondence to be established between the batch and all tests carried out on it in the course of processing and quality control; and
- \* the unique identifying numbers of particular starting materials to be used, where these are pre-allocated.

Where the batch number incorporates a date code, then the date should relate to a date of first processing and not to subsequent filling or packaging operations.

545. During processing, the following should be entered onto the batch record:

- \* the unique identifying number of each component or raw material actually used (unless pre-allocated), including, where necessary, the separate numbers and quantities of the two or more separate materials that may have been used to make up the quantity.
- \* the calculated quantities of particular starting materials to be used, where these are adjusted for moisture, potency, etc. in accordance with provision to do so on the Master Batch Record;
- \* where the Master Formula permits or requires a variation in the quantity of starting material, a record of the amount actually used.
- \* initials of the person(s) who first weighed or measured out each starting material and the initials of the person(s) who verified by direct observation that the weight or measure, labeled identity and unique identifying number of the material were correct and correctly recorded.
- \* dates of commencement and completion of processing and of any significant intermediate stages.
- \* the amount of product obtained at pertinent stages during processing as well as the total yield of the product and the final number of containers;
- \* the initials of the person responsible for each critical stage of manufacture;
- \* where several items of major equipment of the same type are available for use (i.e. where equipment is replicated), reference to the specific items used. Alternatively this information may be recorded -
  - \* In Plant cleaning logs, Plant usage logs or plant equipment logs(in which maintenance is also recorded); or

- \* by attaching cleaning tags to the Batch record.
  - \* details of, and signed authorization for, any deviation from the Master Formula and method;
  - \* where a specific stage of processing of a batch or product is carried out at other premises or by a contractor, a note to this effect;
  - \* identity and amounts of recovered or re-processed materials used, if any, together with signed authorization for their use;
  - \* notes or comments on any unusual occurrences, anomalies or discrepancies and the results of any investigation of these matters; and
  - \* a signature by the process supervisor indicating that, apart from any deviation noted above, manufacture had proceeded in accordance with the Master Formula and method, and that process or yield variations are adequately explained.
546. The results of any in-process testing should form part of the batch processing records. Identity and weighing dockets, tags, etc. from the weighing of starting materials, cleaning tags and equipment printouts or charts should also be retained where practicable.

Master Packaging Bill of materials and Packaging instructions :

547. A Master Packaging Bill of materials and Packaging instructions for each product should be prepared by a competent person. Where this data is transferred into or stored on a computer or is prepared directly on a computer, a printout should be signed and dated.

A second, independent, competent person or persons should have the duty of checking, reconciling, signing, dating and maintaining the currently approved originals or signed printouts of these documents – see also clause 509 regarding QA approval.

548. Where batch records are produced by photocopying from the master document, a separate master should be prepared for each pack type and size.

549. The Master Packaging Bill of materials and Packaging instructions should include

- \* a reference which distinguishes the document from superseded documents for the same product;
- \* the name of the product;
- \* a description of the pharmaceutical form and strength of the product and a brief description of the visual appearance;
- \* the pack size, expressed as the number, weight or volume of the product in the final container;

either

- \* a materials list based on one finished package or multiples thereof, with provision for multiplication to allow a desired size of packaging run;

or

- \* a materials list based on the theoretical yield from a fixed quantity or complete batch of product;

together with

- \* permitted tolerances for excess quantities that may be issued; being a practical allowance for wastage.
- \* the inventory code or reference number of each non-printed material which relates it to its specification.
- \* a specimen of each portion of the labeling materials, including inserts; unless the manufacturer elects to use a code system for the purpose of clause 683, in which case an up-to-date register should be maintained in the packaging section relating the codes to authorized specimens or copies of the labeling material;
- \* details of any required pre-treatment of packaging materials (e.g. washing, blowing, sterilizing) and of any over-printing necessary;
- \* instructions for the packaging operation or a reference to relevant SOP.
- \* the directions for any in-process controls to be applied during packaging. These may refer to written SOPs. The directions should include:-
  - \* the attributes to be checked;
  - \* the number and type of samples to be taken;
  - \* the tests and checks to be carried out, and their frequency;
  - \* the limits for acceptance or rejection; and
  - \* the job title of the person(s) responsible for performing the above.
- \* any special instructions or precautions, including safety precautions;
- \* provision for the calculation of product yield i.e. reconciliation of the actual quantity of material forwarded for packaging with the actual quantity of material in the finished packs (with permitted tolerances); and
- \* provision for calculation of yield of labels and pre-printed packaging materials, with permitted tolerances. Where these tolerances expressed as percentages, the percentages should be on a sliding scale that decreases with increasing batch size and should be based on historical data.

550. Where products may be stored in a partially packaged form, requirements for such storage should be

specified in the SOP or, if, routine, in the master documentation.

MCA :

Batch processing records

4.17 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved manufacturing formula and processing instructions. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

Before any processing begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use.

During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations;

- (a) The name of the product.
- (b) Dates and times of commencement of significant intermediate stages and of completion of production.
- (c) Name of the person responsible for each stage of production.
- (d) Initials of the operator of different significant steps of production and, where appropriate, of the person who checked each stage of these operations (e.g. weighing)
- (e) The Batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added)
- (f) Any relevant processing operation or event and major equipment used.
- (g) A record of the in-process controls and the initials of the persons carrying them out, and the result obtained.
- (h) The product yield obtained at different and pertinent stages of manufacture.
- (i) Notes on special problems including details, with signed authorization for any deviation from the manufacturing formula and processing instructions.

Schedule M :

21. Batch processing records :-

21.1 There shall be Batch Processing record for each product. It shall be based on the relevant parts of the currently approved Master Formula. The method of preparation of such records included in the



Master Formula shall be designed to avoid transcription errors.

- 21.2 Before any processing begins, check shall be performed and recorded to ensure that the equipment and work station are clear of previous products, documents or materials not required for the planned process are removed and that equipment is clean and suitable for use.
- 21.3 During processing, the following information shall be recorded at the time each action is taken and the record shall be dated and signed by the person responsible for the processing operations;
- (a) The name of the product.
  - (b) the number of the batch being manufactured.
  - (c) dates and time of commencement of significant intermediate stages and of completion of production.
  - (d) Initials of the operator of different significant steps of production and, where appropriate, of the person who checked each stage of these operations.
  - (e) The Batch number and/or analytical control number as well as the quantities of each starting material actually weighed
  - (f) Any relevant processing operation or event and major equipment used.
  - (g) A record of the in-process controls and the initials of the persons carrying them out, and the result obtained.
  - (h) The amount of the product obtained after different and critical stages of manufacture (yield).
  - (i) comments or explanations for significant deviations from the expected yield limits shall be given;
  - (i) Notes on special problems including details, with signed authorization for any deviation from the Master Formula.
  - (j) addition of any recovered or reprocessed material with reference to recovery or reprocessing stages.

**MCC :**

#### **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 COA.
- (g) analyst's signature and the signed release or rejection (or other status decision) by QC
- (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.

#### BATCH RECORDS (MANUFACTURING)

8.8.1 BMRs 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 BMRs 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 labeled 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 authorized 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 Records [BMR]
- (k) details of, and signed authorization 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

WHO :

## BATCH PROCESSING RECORDS

- 14.26 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved master formula. The method of preparation of such records should be designed to avoid transcription errors.
- 14.27 Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned process and that the equipment is clean and suitable for use. This check should be recorded.
- 14.28 During processing, the following information should be recorded at the time each action is taken and after completion, the record should be dated and signed by the person responsible for the processing operations:
- (a) the name of the product;
  - (b) the number of the batch being manufactured;
  - (c) dates and times of commencement, of significant intermediate stages, and of, completion of production;
  - (d) the name of the person responsible for each stage of production;
  - (e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing);
  - (f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
  - (g) any relevant processing operation or event and the major equipment used;
  - (h) the in-process controls performed, and the initials of the person(s) carrying them out, and the results obtained;
  - (i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
  - (j) notes on special problems including details, with signed authorization for any deviation from the master formula.

## BATCH RECORD – PACKAGING:

### TGA :

For the purposes of this sub-section packaging includes labeling

551. A clear and complete copy of the Master Packaging Bill of Materials and Packaging instruction should be made for each batch of a product before it is processed. Transcription from the master

document should be by photocopying or computer printout.

552. A competent person should:

- \* initial each document before issue to signify that it is complete, legible and appropriate;
- \* insert the number of each package size to be produced and related data;
- \* insert the batch number or numbers (or the numbers specified in clause 532 or 544) which identify the product or product components being packed.

553. During packaging, the following should be entered into the batch record:

- \* the total number, weight or measure of the product or product components supplied for packaging and the number of bulk containers in which they are contained (“product components” means finished product items that are to be assembled and packed with the product being filled: it does not include packaging materials);
- \* the batch numbers appearing on the labels of all therapeutic goods packaged from the batch, including affixes indicating sub-batches or split packaging runs;

Where the bulk batch is divided into lots which are differently packaged or significantly separated during packaging, i.e. different packaging runs, then all such lots should be distinguishable from one another, by label and in the records, either by suffixes to the main batch number or by another acceptable system.

Where the batch number on the label incorporates a date code, then the date should relate to a date of first manufacture and not to subsequent filling or packaging operations

- \* the “processing number” applicable to the bulk material where this differs from the packed batch number (see clause 663);
- \* a record of the packaging machines, lines or areas used;
- \* the signature of the person who conducted the line clearance check;
- \* the initials of the person(s) who issued the bulk product and printed packaging materials, confirmed their correct nature and quantities and confirmed that the packaging line was correctly set up in all respects.
- \* The Unique identifying Number of each packaging material actually used (unless pre-allocated or “other packaging material”) including, where necessary, the separate numbers and quantities of the two or more separate packaging materials that may have been used to make up the quantity;
- \* The initials of the persons who supervised any separated stage of the packaging operation;
- \* Dates of commencement and completion of packaging and of significant intermediate stages;
- \* the total number or quantity of the final packaged product and its reconciliation with the quantity supplied for packaging;

- \* the actual, or, where counting is impractical, the estimated numbers of pre-printed packaging components issued and returned; and the reconciliation of those numbers with the numbers used on product, on samples or destroyed;
- \* a specimen of each of the coded labeling materials actually used (an alternative system acceptable to the inspecting authority may be used);
- \* where a specific stage of packaging and/or labeling of a batch of product is carried out at other premises or by a contractor; a note to this effect;
- \* details of and signed authorization for any deviation from the issued packaging record and instructions; and
- \* a signature by the packaging supervisor indicating that, apart from any deviation noted above, packaging has proceeded in accordance with the packaging record and associated instructions and that yield variations are adequately explained.

554. The results of any in-process testing should form part of the batch packaging records.

MCA :

Batch Packaging records

4.18 A Batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the packaging instructions and the method of preparation of such records should be designed to avoid transcription errors. The record should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

Before any packaging operation begins, there should be recorded checks that the equipment and workstation are clear of previous products, documents or materials not required for the planned operations, and that equipment is clean and suitable for use.

The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

- (a) The name of the product.
- (b) The date(s) and times of the packaging operations.
- (c) The name of the responsible person carrying out the packaging operation.
- (d) The initials of the operators of the different significant steps.
- (e) Records of checks for identity and conformity with the packaging instructions including the results of in-process controls.
- (f) Details of the packaging operations carried out, including references to the equipment and the packaging lines used.

- (g) Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting.
- (h) Notes on any special problems or unusual events including details, with signed authorization for any deviation from the manufacturing formula and processing instructions.
- (i) The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

Schedule M :

20. Batch packaging records :-

20.1 A batch packaging record shall be kept for each batch or part batch processed. It shall be based on the relevant parts of the packaging instructions, and the method of preparation of such records shall be designed to avoid transcription errors.

20.2 Before any packaging operations begins, check shall be made and recorded that the equipment and work stations are clear of the previous products, documents or materials not required for the planned packaging operations, and that the equipment is clean and suitable for use.

MCC :

**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 batch or reference 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 QC

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.

## 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 the 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 authorized person or QC.

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 authorized 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 authorization by an appropriate person should be kept.

WHO :

#### BATCH PACKAGING RECORDS

14.29 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the packaging instructions, and the method of preparing such records should be designed to avoid transcription errors.

14.30 Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.

14.31 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by the signature or electronic password:

- (a) the name of the product, the batch number and the quantity of the bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
- (b) the date(s) and time(s) of the packaging operations;
- (c) the names of the responsible person carrying out the packaging operation;
- (d) the initials of the operators of the different significant steps;
- (e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
- (f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;

- (g) whenever possible, samples of the printed packaging materials used, including specimens bearing the batch number, expiry date and any additional overprinting;
- (h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
- (i) the quantities and reference number or identification of all printed packaging materials and bulk products issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

**PROCEDURES & RECORDS :**

**TGA:**

**Quality control records**

555. Quality control records or tests on starting materials, packaging materials, intermediate and bulk products and finished products should include:

- \* an unambiguous reference to the material being tested, its sample origin, sampling scheme and sampling officer;
- \* references to relevant specifications and (where separate) to testing procedures;
- \* dates of testing;
- \* test results, including observations, calculations, recorder charts and references to any valid COA.
- \* any consequent calculation of potency adjustment, batch pH correction etc;
- \* reasons for any variations, special procedures or repeats;
- \* a statement and justification of any departure from the established test methods or limits for the test;
- \* the initials of the person(s) performing the tests;
- \* a clear statement of approval, rejection or other status decision; and
- \* the signature of the person authorized to assign status

556. The method of recording should facilitate comparative reviews of past results and, where relevant, the detection of trends. See also Use of COA, Clause 814 & 815.

Complaints file :

557. A file of all complaints, other than those known to have no bearing on product quality, together with associated records, should be maintained in accordance with clause 834-835.

**Other supportive documents :**

558. Supportive documents that may be required to achieve complete documentation but which are not elaborated upon this section of the code include:

- \* inventory cards or other records showing receipt and disposition of starting materials
- \* cleaning tags and equipment records
- \* records of calibration
- \* in-process control records (these may be either separate documents or part of Batch Processing record)
- \* registers such as label and bar code registers, manuals such as Organization, Maintenance, Water processing, Environmental Monitoring.
- \* Release for sale documentation
- \* records of personnel training in GMP.
- \* SOPs referred to in brief in master processing instructions.
- \* SOPs not otherwise specified including that for the issue and maintenance of such procedures
- \* records of destruction of rejected material
- \* records of disposition of returned goods
- \* deviation reports, flagging unusual or unexplained events or departures from standards
- \* quality audit records, including action lists
- \* format for presentation of stability profiles

MCC :

## 1.7 CRITICAL PROCEDURES OR STANDARD OPERATING PROCEDURES

1.7.1 Certain procedures governing critical operations are key to the QA system. These procedures should be written and followed. All the relevant requirements under “Documentation” apply to critical procedures as well

1.7.2 Critical or Standard operating Procedures should include :

- (a) Self - inspection (audits)
- (b) recall of medicines from the market
- (c) handling of technical complaints
- (d) handling of returned goods

(e) vendor inspection / approval of printed packaging materials

(f) purchasing procedures

(g) procedures for handling and disposal of dangerous, highly toxic or sensitizing materials

(h) rodent and pest control

1.7.3 As and where the scale and nature of an operation demands, there should be written procedures covering other aspects, which could influence the quality of a product, for example:

(a) cleaning and maintenance of buildings and equipment

(b) setting-up and operating manufacturing and packaging equipment.

(c) control of the manufacturing environment and monitoring it for potential chemical, physical and biological contamination hazards.

(d) training of personnel, particularly with regard to the understanding of relevant procedures and hygiene.

(e) the return of unused material to store and the handling of reject material

(f) dress requirements

(g) set procedure to be followed in the case of reworks

(h) sampling

(i) manufacturing and analytical contract agreements

(j) minimum qualifications for key personnel

(k) waste disposal

1.7.4 SOPs should be prepared for all systems, procedures and operations which are required to be performed.

1.7.5 The distribution of new and the withdrawal of obsolete procedures should be controlled to ensure that only valid procedures are available.

All procedures should be reviewed on at least a bi-annual basis.

1.7.6 Major or critical equipment should be accompanied by log books recording, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including dates and identity of people who carried these operations out.

## 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) analysts signature and the signed release or rejection (or other status decision) by QC.

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 recognized and appropriate action taken. E.g. tracking of trends.

#### 8.10.5 Other Documents

8.10.5.1 Where relevant to the sale 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 1 year after the expiry date of the batch . Finished product samples should be retained at least until the expiry date of the product, plus 1 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.

### 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 QC (alternative arrangements may be made when an acceptable COA 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 QC.

#### 8.11.2 Sampling

8.11.2.1 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 the supporting document should be kept.

#### 8.11.4 Release and Rejection

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 SOPs 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.

#### 8.12.3 PLANNED PREVENTIVE MAINTENANCE PROGRAMME

A Planned Preventive Maintenance Program and SOP for carrying out the maintenance, should be in place. It should refer to all relevant equipment and apparatus to be included in the program. 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 QC 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.

MCA :

Procedures and records

##### *Receipt*

4.19 There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material.

4.20 The records should include the following

- (a) The name of the material on the delivery note and the containers;
- (b) The in-house name and/or code 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 number assigned after receipt;
- (h) Any relevant comment (e.g. state of the containers).

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

##### *Sampling*

4.22 There should be written procedures for sampling, which include the person(s) 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.

##### *Testing*

4.23 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be



recorded.

*Other*

- 4.24 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 Qualified person(s) (QP) in accordance with the requirements of article 22 of Directive 75/319/EEC.
- 4.25 Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.
- 4.26 There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for:
- \* Validation;
  - \* Equipment assembly and calibration;
  - \* Personnel matters including Training, clothing, hygiene;
  - \* Environmental monitoring;
  - \* Pest control;
  - \* Complaints;
  - \* Recalls;
  - \* Returns.
- 4.27 Clear operating procedures should be available for major items of manufacturing and test equipment.
- 4.28 Log books should be kept for major or critical equipment recording, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.
- 4.29 Log books should also record in chronological order, the use of major or critical equipment and the areas where the products have been processed.

**Schedule M :**

**22. Standard Operating Procedures (SOPs) and records, regarding :-**

**22.1 Receipt of materials;**

**22.1.1** There shall be written SOPs and records for the receipt of each delivery of raw, primary and printed packaging material.

**22.1.2** The records of the receipts shall include,

- (a) the name of the material on the delivery note and the number of the containers
- (b) the date of receipt;
- (c) the manufacturer's and/or supplier's name;
- (d) the manufacturer's batch or reference number;
- (e) the total quantity, and number of containers, quantity in each container received;
- (f) the control reference number assigned after receipt;
- (g) any other relevant comment or information.

22.1.3 There shall be written SOPs for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

22.1.4 There shall be SOP available for each instrument and equipment and these shall be placed in close proximity to the related instrument and equipment.

## 22.2 Sampling

22.2.1 There shall be written SOPs for sampling, which include the person(s) authorized to take the samples.

22.2.2 The sampling instructions shall include:

- (a) the method of sampling and the sampling plan,
- (b) the equipment to be used,
- (c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality,
- (d) the quantity of sample to be taken,
- (e) instructions for any sub-division or pooling of the samples,
- (f) the type of sample container to be used.
- (g) any special precautions to be observed, especially in regard to sampling of sterile or hazardous material.

## 22.3 Batch Numbering :-

22.3.1 There shall be SOP describing the details of the batch (lot) numbering set up with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

22.3.2 Batch numbering SOPs applied to a processing stage and to the respective packaging stage shall be same or traceable to demonstrate that they belong to one homogeneous mix.

22.3.3 Batch number allocation shall be immediately recorded in a log book or by electronic data processing system. The record shall include date of allocation, product identity and size of batch.

#### 22.4 Testing

22.4.1 There shall be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed shall be recorded.

#### 22.5 Records of analysis :-

22.5.1 The records shall include the following data.

- (a) name of the material or product and the dosage form.
- (b) batch number, and where appropriate, the manufacturer and / or supplier;
- (c) references to the relevant specifications and testing procedures;
- (d) test results, including observations and calculations, and reference to any specifications (limits);
- (e) dates of testing;
- (f) initials of the persons who performed the testing;
- (g) initials of the persons who verified the testing and the detailed calculations,
- (h) a statement of release or rejection, and
- (i) signature and date of the designated responsible person.

22.5.2 There shall be written SOPs and the associated records of actions taken for;

- (a) equipment assembly and validation;
- (b) analytical apparatus and calibration;
- (c) maintenance, cleaning and sanitation;
- (d) personal matters including qualification, training, clothing, hygiene;
- (e) environmental monitoring;
- (f) pest control;

- (g) complaints;
- (h) recalls made;
- (i) returns received.

23. Reference Samples:-

- 23.1 Each lot of every active ingredient, in a quantity sufficient to carry out all the tests, except sterility and Pyrogens/Bacterial Endotoxin Test, shall be retained for a period of 3 months after the date of expiry of the last batch produced from that active ingredient.
- 23.2 Samples of finished formulations shall be stored in the same or simulated containers in which the drug has been actually marketed.

25. Distribution records :

- 25.1 Prior to distribution or dispatch of given batch of a drug, it shall be ensured that the batch has been duly tested, approved and released by the QC personnel. Pre-dispatch inspection shall be performed on each consignment on a random basis to ensure that only the correct goods are dispatched. Detailed instructions for ware housing and stocking of Large Volume Parenterals, if stocked, shall be in existence and shall be complied with after the batch is released for distribution. Periodic audits of warehousing practices followed at distribution centers shall be carried out and records thereof shall be maintained. SOPs shall be developed by warehousing of products.
- 25.2 Records for distribution shall be maintained in a manner such that finished batch of a drug can be traced to the retail level to facilitate prompt and complete recall of the batch, if and when necessary.

WHO :  
STANDARD OPERATING PROCEDURES AND RECORDS

14.32 There should be SOPs and records for the receipt of each delivery of starting material and primary and printed packaging material.

14.33 The records of the receipts should include :

- (a) the name of the material on the delivery note and containers;
- (b) the “in-house” name and /or code of material if different from (a);
- (c) the date of receipt;
- (d) the supplier’s name and, if possible, manufacturer’s name;
- (e) the manufacturer’s batch or reference number;

- (f) the total quantity and number of containers received;
  - (g) the batch number assigned after receipt;
  - (h) any relevant comment (e.g. , state of the containers).
- 14.34 There should be SOPs for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.
- 14.35 SOPs should be available for each instrument and piece of equipment and placed in close proximity to the equipment.
- 14.36 There should be SOPs for sampling, which specify the person(s) authorized to take samples.
- 14.37 The sampling instructions should include :
- (a) the method of sampling and sampling plan;
  - (b) the equipment to be used;
  - (c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
  - (d) the amount(s) of sample(s) to be taken;
  - (e) instructions for any required subdivision of sample;
  - (f) the type of sample container(s) to be used and whether they are for aseptic sampling or for normal sampling;
  - (g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.
- 14.38 There should be a SOP describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.
- 14.39 The SOP for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.
- 14.40 The SOP for batch numbering should assure that the same batch numbers will not be repeatedly used; this applies also to reprocessing.
- 14.41 Batch number allocation should be immediately recorded e.g., in a log book. The record should include date of allocation, product identity and size of batch.
- 14.42 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be

recorded.

14.43 Analysis records should include at least the following data:

- (a) the name of the material or product and, where applicable, dosage form;
- (b) the batch number and, where appropriate, the manufacturer and/or supplier;
- (c) references to the relevant specifications and testing procedures;
- (d) test results, including observations and calculations and reference to any specifications (limits);
- (e) dates of testing;
- (f) the initials of the persons who performed the testing;
- (g) the initials of the persons who verified the testing and the calculations, where appropriate;
- (h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

14.44 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 an authorized person.

14.45 Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

14.46 SOPs and associated records of actions taken or, where appropriate, conclusions reached should be available for:

- (a) equipment assembly and validation;
- (b) analytical apparatus and calibration;
- (c) maintenance, cleaning and sanitization;
- (d) personal matters including qualification, training, clothing and hygiene;
- (e) environmental monitoring;
- (f) pest control;
- (g) complaints;
- (h) recalls;
- (i) returns.

14.47 Log books should be kept with major and critical equipment and should record, as appropriate, any

validations, calibrations, maintenance, cleaning or repair operations including dates and the identity of the people who carried these operations out.

14.48 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

14.49 There should be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities to be cleaned. Such written procedures should be followed.

**SITE MASTER FILE : -**

**Schedule M :**

The licensee shall prepare a succinct document in the form of Site Master File containing specific and factual GMP about the production and / or control of pharmaceutical manufacturing preparations carried out at the licensed premises. It shall contain the following. -

29.1 General information : -

- (a) brief information of the firm;
- (b) pharmaceutical manufacturing activities as permitted by the licensing authority;
- (c) other manufacturing activities, if any, carried out on the premises.
- (d) type of products licensed for manufacture with flowcharts mentioning procedures and process flow;
- (e) number of employees engaged in production, QC, storage and distribution.
- (f) Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis.
- (g) short description of the Quality Management System of the firm.
- (h) products details registered with foreign countries.

29.2 Personnel :-

- (a) organizational chart showing the arrangement for QA including production and QC;
- (b) Qualification, experience and responsibilities of key personnel;
- (c) outline for arrangements for basic and in-service training and how the records are maintained;
- (d) health requirements for personnel engaged in production;

- (e) personal hygiene requirements, including clothing.

29.3 Premises :-

- (a) simple plan or description of manufacturing areas drawn to scale;
- (b) nature of construction and fixtures / fittings;
- (c) brief description of ventilation systems. More details should be given for critical areas with potential risk of airborne contamination (schematic drawing of systems). Classifications of the rooms used for the manufacture of sterile products should be mentioned.
- (d) special areas for the handling of the highly toxic, hazardous and sensitizing materials;
- (e) brief description of the water systems (schematic drawings of systems), including sanitation;
- (f) description of planned preventive maintenance programs for premises and of the recording system;

29.4 Equipment -

- (a) brief description of major equipment used in production and QC laboratories (a list of equipment required);
- (b) description of planned preventive maintenance programs for equipment and of the recording system;
- (c) qualification and calibration, including the recording systems and arrangements for computerized systems validation;

29.5 Sanitation -

- (a) availability of written specifications and procedures for cleaning manufacturing areas and equipment;

29.6 Documentation -

- (a) arrangements for the preparation, revision and distribution of necessary documentation for the manufacture;
- (b) any other documentation related to product quality that is not mentioned elsewhere (e.g. microbiological controls about air and water).

29.7 Production :-

- (a) brief description of production operations using, where possible, flow sheets and charts specifying important parameters;
- (b) arrangements for the handling of starting materials, packaging materials, bulk and finished



products, including sampling, quarantine, release and storage.

(c) arrangements for the handling of rejected materials and products;

(d) brief description of general policy for process validation.

#### 29.8 Quality Control :-

(a) description of the QC system and of the activities of the QC department. Procedures for the release of finished products.

#### 29.9 Loan License manufacture and licensee :-

(a) description of the way in which compliance of GMP by the loan licensee shall be assessed.

#### 29.10 Distribution, complaints and product recall :-

(a) arrangements and recording system for distribution.

(b) arrangements for the handling of complaints and product recalls.

#### 29.11 Self – inspection :-

(a) short description of the self-inspection system indicating whether an outside, independent and experienced expert was involved in evaluating the manufacturer's compliance with GMP in all aspects of production.

#### 29.12 Export of drugs :-

(a) products exported to different countries;

(b) complaints and product recall, if any.

#### WHO :

#### SITE MASTER FILE :

A site master file is a document prepared by the manufacturer containing specific and factual GMP information about the production and/or control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, the site master file need describe only those operations, e.g. analysis, packaging.

A site master file should be succinct and, as far as possible, not exceed 25 A4 pages.

#### 1. General information

1.1 Brief information on the firm (including name and address), relation to the other sites, and, in particular, any information relevant to understanding the manufacturing operations.

1.2 Pharmaceutical manufacturing activities as licensed by the national authority.

- 1.3 Any other manufacturing activities carried out on site.
- 1.4 Name and exact address of the site, including telephone, fax and 24-hour telephone numbers.
- 1.5 Type of products manufactured on the site and information about any specially toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on a campaign basis).
- 1.6 Short description of the site (size, location and immediate environment and other manufacturing activities on the site).
- 1.7 Number of employees engaged in production, QC, storage and distribution.
- 1.8 Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis.
- 1.9 Short description of the quality management system of the firm responsible for manufacture.
2. Personnel
  - 2.1 Organization chart showing the arrangements for QA including production & QC.
  - 2.2 Qualifications, experience and responsibilities of key personnel.
  - 2.3 Outline of arrangements for basic and in-service training and how records are maintained.
  - 2.4 Health requirements for personnel engaged in production.
  - 2.5 Personnel hygiene requirements including clothing.
3. Premises and equipment
  - Premises
    - 3.1 Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings not required).
    - 3.2 Nature of construction and finishes.
    - 3.3 Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the rooms used for the manufacture of sterile products should be mentioned.
    - 3.4 Special areas for the handling of highly toxic, hazardous and sensitizing materials).
    - 3.5 Brief description of water systems (schematic drawings of the systems are desirable), including sanitation.

3.6 Description of planned preventive maintenance programs for premises and of the recording system.

Equipment

3.7 Brief description of major equipment used in production and control laboratories (a list of equipment is not required).

3.8 Description of planned preventive maintenance programs for equipment and of the recording system.

3.9 Qualification and calibration, including the recording system. Arrangements for computerized systems validation.

Sanitation

3.10 Availability of written specifications and procedures for cleaning manufacturing areas and equipment.

4. Documentation

4.1 Arrangements for the preparation, revision and distribution of necessary documentation for manufacture.

4.2 Any other documentation related to product quality that is not mentioned elsewhere (e.g. microbiological controls on air and water).

5. Production

5.1 Brief description of production operations using, wherever possible, flow sheets and charts specifying the important parameters.

5.2 Arrangements for the handling of starting materials, packaging materials and bulk and finished products including sampling, quarantine, release and storage.

5.3 Arrangements for the handling of rejected materials and products.

5.4 Brief description of the general policy for process validation.

6. Quality Control

6.1 Description of the QC system and of the activities of the QCD. Procedures for the release of finished products.

7. Contract manufacture and analysis

7.1 Description of the way in which the GMP compliance of the contract acceptor is assessed.

8. Distribution, complaints and product recall.

8.1 Arrangements and recording system for distribution.

8.2 Arrangements for the handling of complaints and product recalls.

9. Self-inspection

9.1 Short description of the self-inspection system.

# CHAPTER 6

## MATERIALS MANAGEMENT

MCC :

### 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 quality and grade of the material, but also the nature of the packaging and container to be used.

4.2.2 Material 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 from 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 labeling, (including name, batch number, expiry date, supplier) damage and contamination, and QC 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 (e.g. delivery note and COA) is accompanied.

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

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 labeled 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 labeling
- \* 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 QC 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 QC should be used.

4.5.4 Issuing of printed packaging materials requires strict and careful control, e.g.

- \* 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.

WHO :  
MATERIALS

13.1 Principle : The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (active, auxiliary, packaging). Special attention should be given to the materials as such.

General

13.2 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

13.3 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by a first-in, first-out rule.

Starting materials [Also refer Section 18]

13.4 The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.

13.5 Starting materials should be purchased only from suppliers named in the relevant specification and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting materials in question, including handling, labeling and packaging requirements as well as complaints and rejection procedures are discussed between the manufacturer and the supplier.

13.6 For each consignment, the containers should be checked for integrity of package and seal and for correspondence between the order, the delivery note and the supplier's labels.

13.7 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled, if required, with the prescribed data.

13.8 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the QC department and investigated.

13.9 If one delivery of material is made up of different batches, each batch number should be considered as separate for sampling, testing and release.

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

- (a) the designated name of the product and the internal code reference where applicable;
- (b) the batch number(s) given by the supplier and on receipt by the manufacturer, if any;
- (c) where appropriate, the status of the contents (e.g. on quarantine, on test, released, rejected, returned, recalled);
- (d) where appropriate, an expiry date or date beyond which resting is necessary.

When fully computerized storage systems are used, not all of the above information need be in a legible form on the label.

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

13.12 Only starting materials released by QCD and within their shelf life should be used.

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

13.14 Each dispensed material and its weight or volume should be independently checked and the check recorded.

13.15 Materials dispensed for each batch of the final product should be kept together and conspicuously labeled as such.

#### Packaging materials

13.16 The purchase, handling and control of primary and printed packaging materials shall be as for starting materials.

13.17 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.

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

13.19 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

13.20 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.

#### Intermediate and bulk products

- 13.21 Intermediate and bulk products should be kept under appropriate conditions.
- 13.22 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

#### Finished products

- 13.23 Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.
- 13.24 The evaluation of finished products and the documentation necessary for release of a product for sale are described in section 16 "Good practices in QC".

#### Rejected and recovered materials

- 13.25 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved by authorized personnel and recorded.
- 13.26 The reprocessing of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reprocessing. A reprocessed batch should be given a new batch number.
- 13.27 The introduction of all or part of earlier batches, conforming to the required quality into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.
- 13.28 The need for additional testing of any finished product that has been reprocessed, or into which a recovered product has been incorporated, should be considered by the QCD.

#### Recalled products

- 13.29 Recalled products should be identified and stored separately in a secure area until decision is taken on their fate. The decision should be made as soon as possible.

#### Returned goods

- 13.30 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; they may be considered for release, re-labeling or bulking with a subsequent batch only after they have been critically assessed by the QCD in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history and the time elapsed since it was issued should 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

reuse, although basic chemical reprocessing to recover the active ingredient may be possible. Any action taken should be appropriately recorded.

#### Reagents and culture media

- 13.31 All reagents and culture media should be recorded upon receipt or preparation.
- 13.32 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labeled. The label should indicate the concentration, standardization factor, shelf-life, the date when re-standardization is due and the storage conditions. The label should be signed and dated by the person preparing the reagent.
- 13.33 Both positive and negative controls should be applied to verify the suitability of culture media. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

#### Reference standards

- 13.34 Reference standards may be available in the form of official reference standards. Reference standards prepared by the producer should be tested, released and then stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.
- 13.35 Official reference standards should be used only for the purpose described in the appropriate monograph.
- 13.36 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization. All in-house reference standards should be based on official reference standards, when available.
- 13.37 All reference standards should be stored and used in a manner that will not adversely affect their quality.

#### Waste materials

- 13.38 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.
- 13.39 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

#### Miscellaneous

- 13.40 Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.

## CHAPTER 7

# MANUFACTURING PROCEDURES

TGA :

a. General

601. All handling of materials and product should follow written procedures or instructions.

Any deviation from defined procedures should be recorded and agreed by the person responsible for production and the person responsible for QA or their delegates.

602. Incoming starting materials should be checked, quarantined, sampled, tested against written specifications and released before use following a SOP. This procedure should also apply to other materials such as gases, solvents and tablet printing dyes used in production and in contact with the product. A simplified system may be used for “Other Packaging materials”.

603. Intermediate and bulk products purchased as such should be handled as though they were starting materials.

604. All starting materials and products should be stored in an orderly fashion to permit segregation by both batch and status and to permit stock rotation. They should be stored under the conditions specified in Clause 143.

605. In processing areas, starting materials or products should be stored only on pallets or other stands or racks made of smooth, impervious material.

606. Manufacture should be carried out following Master Formulae and Processing Instructions and Master Packaging Bills of Materials and Packaging Instructions. These instructions may be a combination of SOPs and product-specific processing or packaging instructions. (See Documentation).

607. Intermediate preparations, such as solutions used for pH adjustment or coating solutions, should be prepared following the same system of Master Formula and Processing Instructions and their batch numbers carried forward onto the documents for the finished products in which they appear.

608. Packaging and labeling should be carried out according to general standard procedures and specific packaging instructions.

609. Finished products in their final packaging should be quarantined until tested and until released by QA.

610. Products which have been diverted from standard flow patterns or subjected to non-standard procedures should be re-introduced into the process only after special inspection and investigation by authorized personnel. Detailed records should be kept of this operation.

611. When any new Master Formula and Processing Instruction is adopted, steps should be taken to demonstrate and document that it is suitable for routine production and that the defined process, using the materials and equipment specified, will consistently yield a product of the required quality.

A similar evaluation should be conducted when any significant change in batch size, processing, equipment or materials occur.

612. From time to time, processes and procedures should undergo critical appraisal to ensure that they remain capable of achieving the intended results. Where validation studies are indicated, they should be conducted in accordance with a carefully designed protocol and an established timetable. These documents and the results of validation studies should be systematically filed.

MCA :

5.1 Production should be performed and supervised by competent people.

5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled with the prescribed data.

5.4 Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the QC department.

5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

5.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

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

5.9 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.

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

5.11 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.

- 5.12 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, rooms used should be labeled 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.
- 5.13 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colors to indicate status (e.g. quarantined, accepted, rejected, cleaned etc.)
- 5.14 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.
- 5.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the QC department when appropriate.
- 5.16 Access to production premises should be restricted to authorized personnel.
- 5.17 Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

**Schedule M :**  
**Manufacturing Operations and Controls -**

- 8.1 All manufacturing operations shall be carried out under the supervision of technical staff approved by the Licensing authority. Each critical step in the process relating to the selection, weighing and measuring of raw material addition during various stages shall be performed by trained personnel under the direct personal supervision of approved technical staff.

The contents of all vessels and containers used in manufacture and storage during the various manufacturing stages shall be conspicuously labeled with the name of the product, batch no., batch size and stage of manufacture. Each label should be initialed and dated by the authorized technical staff.

Products not prepared under aseptic conditions are required to be free from pathogens like Salmonella, Escherichia coli, Pyocyanea etc.

**MCC :**  
**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**

- 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 might affect product quality and/or the reproductivity of the process should be validated. This includes changes o materials and equipment.
- 5.2.5 Periodic re-validation should become a routine procedure to ensure that processes and procedures remain capable of achieving the intended results.

WHO :

## 15. GOOD PRACTICES IN PRODUCTION

15.1 Principle : Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

### General

- 15.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.
- 15.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be approved in writing by a designated person, with the involvement of the QCD, when appropriate.
- 15.4 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- 15.5 Operations on different products should not be carried out be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.
- 15.6 At all times during processing, all materials, bulk containers, major items of equipment and where appropriate the rooms used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication should also mention the stage of production.
- 15.7 Access to production premises should be restricted to authorized personnel.
- 15.8 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.
- 15.9 In-process controls are mostly performed with the production area. They should not carry any risk for the quality of the product.

## CONTAMINATION CONTROL

### TGA :

614. Facilities, equipment, procedures and, as necessary, air flow rates and directions, should be such as to minimize the risk of cross contamination, although the precautions which need to be taken vary according to the type of potential contamination.
615. Before any manufacturing operation begins, steps should be taken to ensure that the work area and equipment are clean and free from any starting material, packaging material, products, product residues, documents or equipment not required for the current operation.
616. Personal medication should not be permitted in manufacturing areas except with management permission.
617. Product that has been dropped or diverted from its normal flow pattern, position or sequence should not be returned unless subject to an authorized deviation procedure.
618. Different operations should not be carried out simultaneously or consecutively in the same room where there is risk of mix-up or contamination.

Where non-therapeutic products are manufactured together with therapeutic products, compatible procedures should apply to the non-therapeutic products.

619. When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust.
620. Dispensing should be carried out in a separate area except in a dedicated product areas where separate dispensaries are inappropriate or where alternative acceptable arrangements apply.
621. At every further stage of processing, products and materials, particularly primary packaging materials, should be protected from microbial and other contamination.
622. Containers and closures used for materials awaiting processing, for in-process products, and for bulk products, should be clean and of a nature and type which will prevent contamination or deterioration of the product or material.
623. As far as practicable, packaging materials should be removed from the wrappings and packing or transport material in or on which they are delivered in an area where product is not exposed or packed (See also Space, Layout and Compatibility)
624. Essential supplies, such as lubricants, adhesives, inks, cleaning fluids, etc. should be kept in containers that look completely different from any container that is used for product packaging and should be prominently and clearly labeled as to their contents (see also Clause 531).

625. Product containers to be filled should be supplied to the packaging line or station in a clean condition, or to be cleaned on-line. The purity of cleaning agents such as rinse water or air should be controlled.

Residues blown from containers during cleaning should not be allowed to contaminate the packaging area.

626. Packaging areas should be cleaned at frequent intervals and at any time that a spill of material occurs.

Specific cleaning instructions for packaging equipment should be available.

Penicillin products, additional

627. Penicillins should be produced only in separate buildings, with separate air handling facilities, dedicated to these products and preferably on separated sites, except where the inspecting authority accepts a totally segregated internal unit with an adequate testing program.

However, penicillin products may be relabeled on dedicated equipment or by campaign packaging in segregated areas using validated cleandown procedures.

Cephalosporin products

628. Cephalosporins should be produced in segregated areas using dedicated equipment, including dedicated packaging lines or by campaign manufacture in segregated areas using validated cleandown procedures. Particular care should be taken to prevent contamination with penicillins.

However, Cephalosporins may be relabeled under the conditions specified in Clause 629.

Potent materials, additional

629. Cross-contamination of products by live biologicals, or by drugs such as certain steroids or anti-neoplastics which in trace amounts may produce physiological effects, should be prevented by methods such as :

- \* carrying out manufacturing operations in separate buildings or adequately isolating the operations by total enclosure or making successive batches in the same or in dedicated equipment followed by intensive cleaning and where appropriate, fumigation;
- \* controlling airborne contaminants by the use of an appropriate air pressure differential in processing areas or adequate exhaust systems and filters, together with control of re-circulated air;
- \* the siting and shielding of manufacturing equipment, and wherever possible the use of equipment solely for the one drug.
- \* containment of contaminant-transfer by means of air-locks, clothing change and the de-contamination of containers and other articles prior to their removal from the isolated area;
- \* separate cleaning of contaminated clothing;



- \* periodic testing of the environment around the manufacturing areas for the presence of the therapeutic substance being processed; and
- \* validation of cleaning procedures.

Antineoplastic drugs, additional

630. Air handling facilities for the manufacture of anti-neoplastic drugs should be in accordance with the principles for air handling given in Australian Standard 2639 – 1983: Cytotoxic Drug safety Cabinets – Installation and use. Where the manufacture involves handling only a few grams of active substance, the option of handling at positive pressure, with the anteroom at higher pressure is appropriate: for larger quantities, , the option of handling at negative pressure (again with the anteroom at relatively higher pressure) is appropriate.

Notes :

(1) The requirements of the Standard relating specifically to sterility may not be applicable to products not intended for parenteral administration. However, for sterile products, the requirements of the Standard are additional to those of part 2 of this code.

(2) The negative pressure mode is under review.

631. Filters in hoods and air handling systems should be serviced or replaced by specially trained personnel, following a SOP.

632. A SOP should be written to specify the procedures to be adopted if spillage occurs. Operators should be trained in these procedures.

633. SOPs for the safe storage and disposal of waste material should be enforced.

Microbiological Contamination of Non-sterile products

634. Microbiological Contamination of Non-sterile products should be minimized by a co-ordinated approach which should include:

- \* training of all appropriate staff in matters relating to personal hygiene and factory sanitation (See sections 3 & 5);
- \* effective operating, cleaning and sanitation procedures;
- \* a microbiological sampling and testing program for starting materials of natural origin and for final products of high water activity (such as aqueous and emulsions products) and those difficult to preserve;
- \* a program of microbiological testing of other starting materials and products to look for unusual results that might indicate a microbiological problem.
- \* establishment of action limits for quantitative microbiological test results;

- \* frequent monitoring of process water (see clause 636-639); and
- \* periodic microbiological monitoring of the processing environment, for eg. product contact surfaces and wet areas such as wash bays that are likely to harbour and spread microbiological contamination.

#### Process water

635. Water for use in manufacturing has not always been recognized to be a starting material and as a consequence, has been a source of many manufacturing problems internationally. Although tap water can be reasonably pure, it is always variable and in some regions of very poor quality by pharmaceutical standards, it is therefore necessary to substantially remove impurities and to control the microbial level in order to standardize products and avoid contaminating them.

A specification for “process water” should be developed based on sound physical, chemical and bacteriological principles.

#### GMP

636. Water to be used as an ingredient should be purified before use.
637. Where process water is used as an ingredient or as the in-feed for further purification for the manufacture of sterile goods (see part 2), a Water Quality Manual (or Water Quality Section of a Quality Manual) should be prepared. This document should include:
- \* a drawing of the purification, storage and (where applicable) reticulation system, showing all pipelines, valves, sample points, breather points, drain points, couplings, instrumentation, pipe slopes, flow rates and velocities of water flow;
  - \* both a brief description of and a full specification for each in the system including manufacturers’ recommended flow rates;
  - \* standard procedures for use, including startup, shutdown, backwashing, regeneration, sanitizing and filter maintenance and testing;
  - \* a log of system changes, routine and non-routine maintenance (unless routine maintenance is logged elsewhere and the log is readily available), investigations, corrective actions and validation studies
  - \* chemical and microbiological specifications including resample, action and shutdown limits;
  - \* sampling instructions and testing procedures, including validation of procedures;
  - \* results of tests, including graphical presentations;
  - \* the positions of persons responsible for operation and maintenance of the system and their deputies; and
  - \* periodic review which is not less frequent than annual.

638. Process water should be tested sufficiently frequently to demonstrate that the system is in control, the frequency being based on studies of microbial load with time at appropriate points in the system. Samples should be tested for microbial load and indicator organisms. Sampling procedures should include “worst case” results. The aliquot selected for microbiological testing should be such as to give a countable number of colonies on the membrane or plate employed. Micro-organisms recovered from total counts should occasionally be separately identified, as they do not grow in selective media.
639. “Target”, “Warning” and “Action” levels for microbiological load should be set, conveniently one order of magnitude/ml apart. The ‘Action’ limit should not generally exceed 10<sup>2</sup> cfu/ml at point of use but for the manufacture of products in which micro-organisms are likely to proliferate or for antiseptics, may be set at a figure orders of magnitude lower.

**MCA :**

Prevention of cross-contamination in production

- 5.18 Contamination of a starting material or of a product by another material or product must be avoided. This 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 on equipment, and from operator’s 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 containing living organisms, certain 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 over a long time.
- 5.19 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:
- (a) Production in segregated areas (required for products such as pencillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
  - (b) Providing appropriate air locks and air extraction;
  - (c) Minimizing the risk of contamination caused by re-circulation 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 de-contamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
  - (f) Using ‘closed systems’ of production;
  - (g) Testing for residues and use of cleaning status labels on equipment.
- 5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically

according to set procedures.

**Schedule M :**

**8.2 Precautions against mix-up and cross-contamination –**

- 8.2.1 The licensee shall prevent mix-up and cross-contamination of drug material and drug product (from environmental dust) by proper air-handling system, pressure-differential, segregation, status labeling and cleaning. Proper records and SOP thereof shall be maintained.
- 8.2.2 The licensee shall ensure processing of sensitive drugs like Beta-Lactum antibiotics, sex hormones and cytotoxic substances in segregated areas or isolated production areas within the building with independent air handling unit and proper pressure differentials. The effective segregation of these areas shall be demonstrated with adequate records of maintenance and services.
- 8.2.3 To prevent mix-ups during production stages, material under process shall be conspicuously labeled to demonstrate their status. All equipment used for production shall be labeled with their current status.
- 8.2.4 Packaging lines shall be independent and adequately segregated. It shall be ensured that all the leftovers of the previous packaging operations, including labels, cartons and caps are cleared before the closing hour.
- 8.2.5 Before packaging operations are begun, steps shall be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any products, materials and spillage. The line clearance shall be performed according to an appropriate checklist and recorded.
- 8.2.6 The correct details of any printing (for example of batch numbers or expiry dates) done separately or in the course of the packaging shall be re-checked at regular intervals. All printing and over-printing shall be authorized in writing.
- 8.2.7 The manufacturing environment shall be maintained at the required levels of temperature, humidity and cleanliness.
- 8.2.8 Authorized persons shall ensure change-over into specific uniforms before taking any manufacturing operations including packaging.
- 8.2.9 There shall be segregated enclosed areas, secured for recalled or rejected material and for such material which are to be re-processed or recovered.

**MCC :**

**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), or by campaign production (separation in time) followed by appropriate cleaning
- (b) providing appropriate air-locks and air extraction
- (c) minimizing the risk of contamination caused by re-circulation 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 contamination). Vacuum and wet cleaning methods are preferred.
- (f) using “closed systems” of production
- (g) testing for residues and use of cleaning status labels in production

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.

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

WHO :

## PREVENTION OF CROSS-CONTAMINATION & BATCHERIAL CONTAMINATION IN PRODUCTION

- 15.10 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust.
- 15.11 Contamination of starting material or of a product by another material or product has to be avoided. The risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapors, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects and from operators' clothing, skin etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.
- 15.12 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:
- (a) production in segregated areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
  - (b) providing appropriate air locks, pressure differentials and air extraction;
  - (c) minimizing the risk of contamination caused by re-circulation or re-entry of untreated or insufficiently treated air;
  - (d) wearing protective clothing in areas where products with special risk of cross-contamination are processed;
  - (e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
  - (f) using a "closed system" of production;
  - (g) testing for residues;
  - (h) using cleanliness status labels on equipment.
- 15.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to SOPs.
- 15.14 Production areas where susceptible products are processed should undergo periodic microbiological monitoring.

## STARTING MATERIALS CONTROL

TGA :

640. Where possible, starting materials should be purchased only from approved or certified suppliers. They should be purchased to established specifications. Purchase orders should make adequate reference to these specifications.

641. At the time of receipt of starting materials, each delivery should be examined for damage to the containers and for visible contamination. Particular attention should be given to starting materials packed in paper or plastic bags, broached containers and containers visibly soiled by liquid. Any damage or contamination likely to prejudice the integrity of the contents should be reported to and assessed by QC.

Where practicable, badly damaged or soiled containers should be rejected. When rejection is not practicable, they should be cleaned and/or the contents transferred to suitable alternative containers. Transfer should be regarded as a manufacturing process, carried out in a protective environment and documented accordingly.

642. Within each delivery, containers bearing different manufacturers' batch or lot number should be separated: each group bearing the same batch, lot or equivalent number should be regarded as a "separate material".

Subsequent deliveries of the same manufacturers' batch or lot number should also be regarded as "separate materials", but may be eligible for reduced testing.

643. Active materials should not be accepted unless bearing the manufacturers' batch, lot or equivalent number.

644. Each "separate material" should be allocated a Unique Identifying number from the goods received register. This number and the standard name (see Clause 527) should be used throughout storage and processing to identify that material. In order to prevent confusion with product batches, the number should not be called a batch number and should be derived from a different system to that used for finished product batches. Alternative systems may be approved by the inspecting authority.

645. Starting materials should be stored under appropriate conditions: See Goods Receiving and Storage areas in Section 1.

646. After examination, sorting and, where applicable, cleaning of incoming materials a (single) conspicuous quarantine label should be affixed to each container as near as possible to the original label. All other status label should be cancelled. All subsequent labeling or marking should be as near as possible to the quarantine label. The marked goods should then be stored in a quarantine area.

The quarantine label should continue to be visible until cancelled. The method of cancellation should be such as to show that the quarantine label was originally present.

Equivalent acceptable systems may be required for cases such as bulk tanker loads of liquids, pallet loads of bagged material with high turnover, goods of awkward physical dimensions or weight and goods stored in special conditions such as cold stores, flammable stores and strong rooms.

647. Each material should be sampled, tested and released before use.
648. Containers of material should not be removed from a quarantine area unless released for use by QC and unless they bear a RELEASED or APPROVED or REJECTED labeling canceling the HOLD or QUARANTINE section of the original quarantine label.
649. Goods whose release has expired should be labeled as quarantined and promptly returned to a quarantine area. A system of drawing attention to the existence of expired release should be established.

Alternative systems of quarantine and release (to those of clauses 646, 648, 649) which achieve equivalent control may be approved by the licensing authority.

650. Partially used containers of materials should be periodically inspected by QC staff to ensure that they are properly closed, stored, and identified and have not deteriorated.
651. Where appropriate, labile materials should be re-tested to ensure that they conform with specifications at the time of use and to allow factoring if necessary.
652. Materials which have been rejected upon examination, after testing, after re-testing or for any other reason should be identified with a "REJECT" Label. These rejected materials should be segregated, stored in a designated reject quarantine area and returned to the supplier, destroyed or otherwise disposed of without undue delay. Records should be maintained of their disposal. Where the reason for rejection is failure to meet specifications, a note of the rejection should appear on the analytical summary record.
653. Dry chemical starting materials should be sieved before use unless this step has been shown to be unnecessary or inappropriate.

#### Dispensing Control

654. Starting materials should be issued from stores only by authorized persons, following a SOP.
655. Stock records (such as inventory cards) should be maintained in such a way as to facilitate the reconciliation between "separate materials" (see clause 642) entered into stock and the quantities issued for dispensing and manufacture. This reconciliation should be regarded as an element of the control of quality: Deviation reports should be raised for any significant discrepancy.
656. Only approved materials should be permitted into the dispensary area.
657. Starting materials should be dispensed only by authorized persons, following a standard procedure which ensures that the correct materials are accurately weighed or measured. Scales and measures with accuracy appropriate to the various quantities should be dispensed should be available. Each dispensing operation should be checked and the check recorded (see Clause 545).

Labels on emptied containers should be defaced, cancelled or removed. Except where the original container is itself suitable for forwarding to compounding areas, new cleaned containers should be used for this purpose. All such containers should be properly labeled.



658. In order to minimize the possibilities of cross-contamination and mix-up, as few materials as practicable should be brought into the dispensary area at any one time. Specially equipped and/or dedicated areas may be necessary for dispensing hazardous, toxic or sensitizing materials .
659. Each container of dispensed material should be tagged or labeled with the following minimum information:
- \* Standard Name;
  - \* Quantity;
  - \* Unique Identifying Number; and
  - \* Product processing or batch number.
660. The collected dispensed materials for a given batch should be stored in such a way as to preserve the integrity of the batch.

**MCA :**  
Starting materials

- 5.25 The purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers.
- 5.26 Starting materials should only be purchased from approved suppliers named in the relevant specification, and where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of production and control of the starting material in question, including handling, labeling and packaging requirements, as well as complaints and rejection procedures are discussed with the manufacturer and supplier.
- 5.27 For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's label.
- 5.28 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.
- 5.29 Starting materials in the storage area should be appropriately labeled. Labels should bear at least the following information:
- \* The designated name of the product and the internal code reference where applicable;
  - \* A batch number given at receipt;
  - \* Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
  - \* Where appropriate, an expiry date or date beyond which re-testing is necessary.

When fully computerized storage systems are used, all the above information need not necessarily

be in a legible form on the label.

- 5.30 There should be appropriate procedures or measures to assure the identity of contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.
- 5.31 Only starting materials which have been approved by the QC department and which are within their shelf life should be used.
- 5.32 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 labeled containers.
- 5.33 Each dispensed material and its weight or volume should be independently checked and the check recorded.
- 5.34 Materials dispensed for each batch should be kept together and conspicuously labeled as such.

#### Schedule M :

##### 10. Raw materials

- 10.1 The licensee shall keep an inventory of all raw materials to be used at any stage of manufacture of drugs and maintain records as per Schedule U.
- 10.2 All incoming materials shall be quarantined immediately after receipt or processing. All materials shall be stored under appropriate conditions and in an orderly fashion to permit batch segregation and stock rotation by a "first in/first expiry"- "first-out" principle. All incoming materials shall be checked to ensure that the consignment corresponds to the order placed.
- 10.3 All incoming materials shall be purchased from approved sources under valid purchase vouchers. Wherever possible, raw materials should be purchased directly from the producers.
- 10.4 Authorized staff appointed by the licensee in this behalf, which may include personnel from the QC department, shall examine each consignment on receipt and shall check each container for integrity of package and seal. Damaged containers shall be identified, recorded and segregated.
- 10.5 If a single delivery of material is made up of different batches, each batch shall be considered as a separate batch for sampling, testing and release.
- 10.6 Raw materials in the storage area shall be appropriately labeled. Labels shall be clearly marked with the following information:
  - (a) designated name of the product and the internal code reference, where applicable, and analytical reference number.
  - (b) manufacturer's name, address and batch number;
  - (c) the status of the contents (e.g. quarantine, under test, released, approved, rejected);

(d) the manufacturing date, expiry date and retest date.

10.7 There shall be adequate separate areas for materials “under test”, “approved” and “rejected” with arrangements and equipment to allow dry, clean and orderly placement of stored materials and products, whenever necessary, under controlled temperature and humidity.

10.8 Containers from which samples have been drawn shall be identified.

10.9 Only raw materials which have been released by the QC department and which are within their shelf life shall be used. It shall be ensured that shelf-life of formulation product shall not exceed with that of active raw materials used.

10.10 It shall be ensured that all the containers of raw materials are placed on the raised platforms / racks and not placed directly on the floor.

**MCC :**

### **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 labeled. Labels should bear at least the following information :

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

(b) a the 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 re-testing 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 QC 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 labeled 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 labeled 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.

#### PROCESSING CONTROL

TGA :

661. Batches should be processed in accordance with master documents specified in clause 553 and batch documents prepared and completed in accordance with Clauses 543 – 545.
662. Where the batch processing instructions make reference to a SOP, the operator should have ready access to that SOP.
663. At all times during manufacture, all bulk containers and all major items of equipment or equipment groups in use should be adequately labeled or otherwise identified to indicate the name, strength and batch or processing number of the product being processed. When necessary, such labeling should also identify the stage of manufacture and status.

The processing number need not be identical with the batch number that appears on the label of the finished product, but if not it should be easily related to that number.

664. Before applying labels or marks to materials or equipment, all inappropriate labels or marks previously applied should be removed or permanently defaced. Labels should be applied or attached securely. Labels should not be applied to lids.
665. The final yield and any significant intermediate yield of each production batch should be recorded and checked against the expected yield. In the event of a significant variation, steps should be taken to prevent release or further processing of the batch (or of any other batches, or of products processed concurrently with which it may have become admixed) until an adequate explanation can be found which permits release or further processing.
666. Records of any processing or testing carried out at other premises or by a contractor and records of any in-process testing or copies of such records should be consolidated with the principal records for review before the batch is released for sale.

#### Microdose Formulations – Validation and control

668. *For the purposes of this sub-section, a microdose product is a solid dosage form containing 5 mg or less of an active ingredient per unit dose of the product; multi-vitamin, multi-vitamin and trace mineral, unscheduled herbal and homeopathic formulations excepted.*

*However, products for which microdose specifications have been required in connection with registration may also require the studies and controls specified in this subsection.*

669. The parameters influencing unit dose uniformity of microdose products should be established and the appropriate instructions, controls, limits and tests built into the Master Processing Instructions.

Repeat studies should be undertaken periodically and in any case, whenever a significant change in starting materials or method of manufacture is introduced. Records of validation should be available

for inspection.

670. The uniformity of drug content of microdose products should be assessed according to a written testing program.

Recovered and reprocessed materials  
Product residues

671. Product residues should not be incorporated into subsequent batches of product on a routine basis except where this is provided for in the master formula or processing instructions and where limits are prescribed for the proportion of residue. In addition, a standard operating procedure should specify at least:

- . limits on the age and total quantity of residue that may be accumulated;
- . limits on the number of batches of residue that may be incorporated in a single batch of product;
- . limits on the total quantity or proportion of residue that may be incorporated in a single batch of product;
- . a procedure for utilization and or/disposal that will facilitate overall reconciliation; and
- . any necessary testing or approval, for example where dissolution rate may be affected or is required in relation to registration.

672. Where a residue is incorporated into a batch of a product on a non-routine basis, each instance should be specifically approved by Quality Assurance. The batch records should show the written Quality Assurance approval.

Re-processing

673. The re-processing of material which fails any intermediate or final specifications should be exceptional. However, the use of a second cycle or part-cycle of manufacture or the working-off of a failed batch in subsequent batches is permitted provided that:

- . it has been established that there are negligible risks that the re-processed product has diminished therapeutic effectiveness or stability;
- . for each instance or re-processing, such risks are evaluated and the manufacturing operations to be used are approved in writing by Quality Assurance;
- . the circumstances, rationale for approval and procedure are fully documented; and
- . the possible need for tests beyond those specified for the standard product has been considered.

MCA :

Processing operations: intermediate and bulk products

5.35 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.

- 5.36 Intermediate and bulk products should be kept under appropriate conditions.
- 5.37 Critical processes should be validated.
- 5.38 Any necessary in-process controls and environmental controls should be carried out and recorded.
- 5.39 Any significant deviation from the expected yield should be recorded and investigated.

Rejected, recovered and returned materials

- 5.61 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers, or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorized personnel.
- 5.62 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. Records should be kept of the reprocessing.
- 5.63 The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.
- 5.64 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the QC department.
- 5.65. Products returned from the market and which have left the control of the manufacturer should be destroyed unless there is no doubt that their quality is satisfactory; they may be considered for resale, re-labeling or recovery in a subsequent batch only after they have been critically assessed by the QC department in accordance with a written procedure. 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 reuse, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately recorded.

MCC :

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 labeled 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 colors to indicate status (for eg. 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 QC 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 as necessary.

## 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 QC 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 QC, should be established for the amount of any such material which may be added to subsequent batches.
- 5.7.5 Batches incorporating residues should not be released until the batches from which 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 reprocessed (or to which residues have been added) should be considered.

WHO :

Processing operations: intermediate and bulk products

- 15.15 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.
- 15.16 Any necessary in-process controls and environmental controls should be carried out and recorded.
- 15.17 Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. Production equipment should be cleaned according to detailed written procedures and stored only under clean and dry conditions.
- 15.18 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.
- 15.19 Any significant deviation from the expected yield should be recorded and investigated.
- 15.20 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.
- 15.21 Pipes used for conveying distilled or de-ionized water 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.
- 15.22 Measuring, weighing, recording and control equipment and instruments should be serviced and



calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when re-calibration is due should be clearly indicated.

15.23 Repair and maintenance operations should not present any hazard to the quality of products.

Schedule M :

Sanitation in the manufacturing premises –

- 9.1 The manufacturing premises shall be cleaned and maintained in an orderly manner, so that it is free from accumulated waste, dust, debris and other similar material. A validated cleaning procedure shall be maintained.
- 9.2 The manufacturing areas shall not be used for storage of materials, except for the material being processed. It shall not be used as a general thoroughfare.
- 9.3 A routine sanitation program shall be drawn up and observed, which shall be properly recorded and which shall indicate -
  - (a) specific areas to be cleaned and cleaning intervals;
  - (b) Cleaning procedure to be followed, including equipment and materials to be used for cleaning; and
  - (c) personnel assigned to and responsible for the cleaning operation.
- 9.4 The adequacy of the working and in-process storage space shall permit the orderly and logical positioning of equipment and materials so as to minimize the risk of mix-up between different pharmaceutical 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.
- 9.5 Production areas shall be well lit, particularly where visual on-line controls are carried out.

Reprocessing and recoveries :-

- 24.1 Where reprocessing is necessary, written procedures shall be established and approved by the QA department that shall specify the conditions and limitations of repeating chemical reactions. Such re-processing shall be validated.
- 24.2 If the product batch has to be reprocessed, the procedure shall be authorized and recorded. An investigation shall be carried out into the causes necessitating re-processing and appropriate corrective measures shall be taken for recurrence. Re-processed batch shall be subjected to stability evaluation.
- 24.3 Recovery of product residue may be carried out, if permitted, in the master production and control records by incorporating it in subsequent batches of the product.

RETURNED GOODS

**TGA:**

674. All returned goods should be quarantined and examined by Quality Assurance or Quality Control to determine whether they should be released, reprocessed or destroyed.
675. A finished product returned from the manufacturer's own stores or warehouse [for example, because of soiled or damaged labels or outer packaging] may be re-labeled, or bulked for re-packing, provided that there is no risk to product quality and the operation is specifically authorized and documented. If such a product is re-labeled, the operation should be regarded as a formal packaging operation. If bulked, the operation should be regarded as a formal processing operation.
676. A finished product returned from the market [i.e. which has left the control of the manufacturer], returned because of complaints, damage, age or other circumstances which may prejudice the quality of the goods should be considered for re-sale, re-labeling or bulking for re-packing only after it has been critically assessed by Quality Assurance. The nature of the product, any special storage conditions it requires, its condition [especially any evidence of packs having been opened or tampered with], its history, the time elapsed since it was issued and the possible need for re-testing 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 chemical re-processing to recover active ingredient may be possible.  
A suffix or new batch number should be used to distinguish any bulked or relabeled material.
677. The person responsible for Release for Sale should oversee these procedures for returns, which should be subject to formal documentation and control.

**MCC :**

**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 eg. of soiled or damaged labels or outer packaging) may be relabeled or bulked for inclusion in subsequent batches, provided that there is no risk to product quality and the operation is specifically authorized and documented. If such products are re-labeled, extra care is necessary to avoid mix-up or mis-labeling.

## LABELING AND PACKAGING CONTROL

### TGA :

#### Rationale

678. Special emphasis needs to be given to the control of labels and pre-printed packaging materials. International experience has shown that only a total system of the most rigorous control, from the draft label through artwork approval, printing, receipt and quality control, storage, verification, issue application to the product and disposal or return of surplus, together with in-line quality control and strict discipline in packaging areas can insure against error. Very detailed procedures are prescribed to pre-empt “learning by experience”, as experience already has shown that taking fewer precautions that these results in mix-ups and product recalls.

### GMP

In this subsection, “pre-printed packaging materials” includes unit cartons, pre-printed product Containers and leaflets.

679. Pre-printed packaging materials should be drafted and approved following a standard operating procedure which ensures that aspects relevant to Production and to Quality Control are considered.

680. Labels & pre-printed packaging materials should be identified by a code number/letter as part of the printed text, unique to each amendment. They should also include an optical bar code for verification, and, in the case of cut labels or unit cartons a bar code for visual checking, especially “families” of look-alike labels or unit cartons.

681. A master file of approved labels and all other pre-printed packaging material and their specifications should be held by a competent person. Approved copies of the file should be maintained by and issued by that person to relevant departments, including Quality Control.

682. General operating procedures describing the receipt, verification, storage, issue and reconciliation of printed packaging and labeling material should be available.

683. On receipt, all labels and pre-printed packaging materials should be quarantined, examined and verified by Quality Control against standard specimens and specifications before being released for use. Particular care should be given to ‘families’ of related products and to labels on which similar information appears on multiple panels.

684. Outdated or obsolete labels or printing packaging material should be removed, quarantined and destroyed and this disposal recorded.

685. All approved labels and pre-printed packaging materials [including “APPROVED” status labels] should be stored separately in a locked area or otherwise adequately segregated [see Clause 140]. Access to the area should be restricted to authorized persons. Only a designated person or alternate should be restricted to authorized persons. Only a designated person or alternate should be permitted to issue these materials in accordance with documented procedures.

686. Pre-printed labels must not be overprinted with a different name, dosage form or strength of the product.

687. Labels should be counted either on receipt or before issue and verified either before issue or on-line.

Label counters and code verifiers should be checked for accuracy and response using test reels which include known [and appropriately large] numbers of labels and examples of typical defects. A record should be kept of these checks.

688. Where batch numbers or expiry dates are added to labels off-line the addition should be done in a segregated, lockable area which may be a label store. The coding process should be documented and preceded by a line clearance check.
689. When setting up a production schedule for packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Products of similar appearance should not be packaged simultaneously unless there is physical segregation. Adequate separation should be provided between all different packaging and labeling operations carried out at the one time. Special precautions may be required for toxic, sensitizing or other physiologically active materials.
690. Each batch or part-batch should be packed utilizing documents prepared in accordance with Clause 547 and batch records prepared and completed in accordance with Clauses 551-554.
691. Where the instructions make reference to a standard operating procedure, the operator should have ready access to that procedure.
692. A known number of each label or pre-printed packaging material should be issued, in closed containers, for each packaging run. Where exact counting is impractical, a close estimate should be made by suitable means and a record kept of the calculation and its basis. Where a surplus is included, this should be only the amount determined by experience to be likely to be needed, or else comprise the excess in the nearest complete package or roll. Where additional labels or pre-printed packaging materials are issued during the packaging run, each additional issue should be shown on the batch document.
693. Before commencement of any packaging and labeling:
- . the packaging line for that operation should be thoroughly examined, following a standard operating procedure, to ensure that all materials, products and records from previous operations have been removed.
  - . the person responsible should initial the batch packaging and labeling record to show that this check has been carried out;
  - . any label counters/readers should be tested to verify that they are functional;
  - . all packaging and labeling materials should be carefully checked by a competent person for identity and conformity to the descriptions in the batch packaging record;
  - . pipelines and other pieces of equipment used for the transportation of products from one area to another should be checked to ensure that they are connected in a correct manner; and
  - . the line should be conspicuously identified to show the product and strength to be packed.
- A simplified line clearance may be specified for the packaging of successive batches of the same product.
694. On-line Controls should include checks of at least

- \* bulk material, labeling and pre-printed packaging material supplied or in use;
- \* count or measure;
- \* label appearance and adhesion
- \* coding;
- \* cap torque
- \* seal integrity of strips and allied packs; and
- \* first and last packages

Where these checks are done by production staff, they should be audited by QC staff.

695. Normally, filling and labeling should be an integral process. Where this is not possible, special procedures including segregation, marking and identification should be applied to ensure that no mix-ups or mislabeling occurs.
696. Upon completion of the run, unused, un-coded labels and pre-printed packaging materials should be counted and held for destruction or be counted back into store; unused coded materials should be counted and held for destruction; damaged or defaced labels should be counted or closely estimated.

A reconciliation should then be made, using prepared spaces on the packaging documents, between the numbers of items issued for packaging (including additional issues if any) and the numbers accounted for. The latter should include, as appropriate, the number used on sound or defective product, on samples, and on cartons, the number returned to store, and the numbers to be destroyed or defaced.

A reconciliation should also be made, using prepared spaces on the packaging documents, between the quantity of product bulk material issued for packaging and the amount accounted for. The latter should include, as appropriate, the amount packed (number of product containers X average actual fill) amounts returned, known (unavoidable) losses, amounts estimated as spilled and amounts destroyed. "Estimated" implies an estimate made as closely as circumstances permit but does not include a guess where estimation is not possible.

Where a batch is part-filled, the material reconciliation for the part-run should deduce the amount of bulk issued from the amount of bulk remaining unpacked, which should be re-measured if necessary.

Any significant or unusual discrepancy should be investigated.

The results of the reconciliation and any investigation should be recorded on or attached to the batch packaging and labeling records.

When the above steps are complete, materials held for destruction should then be destroyed.

. Note: Unit recently, the discipline of issuing only counted numbers of pre-printed packaging materials and of reconciling this number with the numbers used on product or destroyed or returned to stock has been emphasized as an important element of control. However, the emphasis world-wide, is moving towards optical verification at the point of labeling or cartooning. Bar code reading

at this point provides high assurance; complete label scanning even higher. Where manufacturers employ on-line optical verification with suitable controls on the verification process, they may elect to reconcile by count at the packaging line, rather than from the store.

697. In the event of a significant discrepancy that could indicate a product or labeling mix-up, steps should be taken to prevent release of the batch or of any batches of the product or products in question, unless an adequate explanation is found which may permit release for sale.

**MCA :**

**Packaging materials**

- 5.40 The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.
- 5.41 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. Packaging materials should be issued for use only by authorized personnel following and approved and documented procedure.
- 5.42 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.
- 5.43 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

Packaging operations :

- 5.44 When setting up a program for the packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packed in close proximity unless there is physical segregation.
- 5.45 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 checklist.
- 5.46 The name and batch number of the product being handled should be displayed at each packaging station or line.
- 5.47 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity to with the packaging instructions.
- 5.48 Containers for filling should be clean before filling. Attention should be given to avoiding any contaminants such as glass fragments and metal particles.
- 5.49 Normally, filling and sealing should be followed as quickly as possible by labeling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.

- 5.50 The correct performance of any printing operation (e.g. code numbers, expiry dates) to be done separately or in the course of packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.
- 5.51 Special care should be taken when using cut- labels and when over-printing is carried off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.
- 5.52 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
- 5.53 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- 5.54 On-line control of the product during packaging should include at least checking the following:
- \* General appearances of the packages;
  - \* Whether the packages are complete;
  - \* Whether the correct products and packaging materials are used;
  - \* Whether any over-printing is correct;
  - \* Correct functioning of line monitors.
- Samples taken away from the packaging line should not be returned.
- 5.55 Products which have been involved in an unusual event should only be re-introduced into the process after special inspection, investigation and approval by authorized personnel. Detailed records should be kept of this operation.
- 5.56 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.
- 5.57 Upon completion of packaging operation, any unused batch coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

#### Schedule M :

##### Labels and other Printed materials :

Labels are absolutely necessary for the identification of the drugs and their use. The printing shall be done in bright colors and in a legible manner. The labels shall carry all the prescribed details about the product.

- 13.1 All containers and equipment shall appropriate labels. Different color coded labels shall be used to indicate the status of a product (for example : under test, approved, passed, rejected).



- 13.2 To avoid chance mix-up of printed packaging materials, product leaflets relating to different products, shall be stored separately.
- 13.3 Prior to release, all labels for containers, cartons and boxes and all circulars, inserts and leaflets shall be examined by the QC department of the licensee.
- 13.4 Prior to packaging and labeling of a given batch of a drug, it shall be ensured by the licensee that samples are drawn from the bulk and duly tested, approved and released by the QC personnel.
- 13.5 Records of receipt of all labeling and packaging materials shall be maintained for each shipment received indicating receipt, control reference numbers and whether accepted or rejected. Unused coded and damaged labels and packaging materials shall be destroyed and recorded.
- 13.6 The label or accompanying document of reference standards and reference cultures shall indicate concentration, lot number, potency, date on which container was first opened and storage condition, where appropriate.

**MCC :**  
**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 labeling 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 e.g. 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 program for the packaging operation, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutes. 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 e.g. 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 the 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 labeling. If it is not the case, appropriate security procedures should be applied to ensure that no mix-ups or mislabeling can occur.
- 6.3.6 The correct performance of any printing operation (for e.g. 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 rechecked 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 labeled according to a specific written procedure.
- 6.3.12 Hand packaging 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 re-introduced 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 checklists 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.

WHO :

#### PACKAGING OPERATIONS

- 15.24 When the program for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packed in close proximity unless there is physical segregation or the use of electronic surveillance.
- 15.25 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 and not required for the current operation. The line clearance should be performed according to an appropriate checklist and recorded.
- 15.26 The name and batch number of the product being handled should be displayed at each packaging station or line.
- 15.27 Normally, filling and sealing should be followed as quickly as possible by labeling. If labeling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.
- 15.28 The correct performance of any printing (e.g. code numbers, expiry dates) done separately or in the course of packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.
- 15.29 Special care should be taken when cut- labels are used and when over-printing is carried out off-line, and in hand packaging operations. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups, but checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
- 15.30 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- 15.31 On-line control of the product during packaging should include at least checking the following:
  - (a) The general appearances of the packages;

- (b) Whether the packages are complete;
- (c) Whether the correct products and packaging materials are used;
- (d) Whether any over-printing is correct;
- (e) Correct functioning of line monitors.

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

- 15.32 Products which have been involved in an unusual event during packaging should be re-introduced into the process only after special inspection, investigation and approval by authorized personnel. A detailed record should be kept of this operation.
- 15.33 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.
- 15.34 Upon completion of packaging operation, any unused batch coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

#### FINISHED PRODUCTS RELEASE

##### MCA :

- 5.58 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.
- 5.59 The evaluation of finished products and documentation which is necessary before release of product for sale are described under QC.
- 5.60 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

##### MCC :

#### 6.6 FINISHED PRODUCTS 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 QC laboratory and for retention purposes.
- 6.6.3 Documentation should be reconciled, completed / and sent for a complete documentation audit by QA.
- 6.6.4 When all required parameters are satisfied, including the document audit, QC may recommend release of the product from its quarantine status.

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

# CHAPTER 8

# VALIDATION

MCA :

- 5.21 Validation studies should reinforce GMP and be conducted in accordance with defined procedures. Results and conclusions can be recorded.
- 5.22 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.
- 5.23 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.
- 5.24 Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

Planning for Validation :(Annex 15)

2. All validation activities should be planned. The key elements of a validation program should be clearly defined and documented in a Validation Master Plan (VMP) or equivalent documents.
3. The VMP should be a summary document which is brief, concise and clear.
4. The VMP should contain data on at least the following :
  - (a) Validation policy;
  - (b) organizational structure of validation activities;
  - (c) summary of facilities, systems, equipment and processes to be validated;
  - (d) documentation format; the format to be used for protocols and reports;
  - (e) planning and scheduling;
  - (f) change control;
  - (g) reference to existing documents.
5. In case of large projects, it may be necessary to create separate VMPs.

Documentation

6. A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps

and acceptance criteria.

7. A report that cross-references the qualification and / or validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.
8. After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorization.

### **Qualification**

#### Design qualification (DQ)

9. The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).
10. The compliance of the design with GMP should be demonstrated and documented.

#### Installation qualification (IQ)

11. IQ should be performed on new or modified facilities, systems and equipment.
12. IQ should include, but not limited to the following :
  - (a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
  - (b) collection and collation of supplier operating and working instructions and maintenance requirements;
  - (c) calibration requirements;
  - (d) verification of materials of construction.

#### Operational qualification (OQ)

13. OQ should follow IQ
14. OQ should include, but not limited to the following :
  - (a) tests that have been developed from knowledge of processes, systems and equipment;
  - (b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as “worst case” conditions
15. The completion of a successful OQ should allow the finalization of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal “release” of the facilities, systems and equipment.

#### Performance qualification (PQ)

16. PQ should follow successful completion of IQ and OQ.
17. PQ should include, but not be limited to the following:
  - (a) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;
  - (b) tests to include a condition or set of conditions encompassing upper and lower operating limits.
18. Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

#### Qualification of established (in-use) facilities, systems and equipment

19. Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventative maintenance, operating procedures and operator training procedures and records should be documented.

#### Process validation

##### General

20. The requirements and principles outlined in this chapter are applicable to the manufacture of pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and revalidation.
21. Process validation should normally be completed prior to the distribution and sale of the medicinal product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes in use for sometime should also be validated (retrospective validation)
22. Facilities, systems and equipment to be used should have been qualified and analytical testing methods should be validated. Staff taking part in the validation work should have been appropriately trained.
23. Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

##### Prospective validation

24. Prospective validation should include, but not be limited to the following;
  - (a) short description of the process;
  - (b) summary of the critical processing steps to be investigated;



- (c) list of the equipment, facilities to be used (including measuring / monitoring / recording equipment) together with its calibration status;
  - (d) finished product specifications for release;
  - (e) list of analytical methods, as appropriate;
  - (f) proposed in-process controls with acceptance criteria;
  - (g) additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
  - (h) sampling plan;
  - (i) methods for recording and evaluating results;
  - (j) functions and responsibilities;
  - (k) proposed timetable.
25. Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that 3 consecutive batches / runs with the finally agreed parameters, would constitute a validation of the process.
26. Batches made for process validation should be of the same size as the intended industrial scale batches.
27. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of GMP, including the satisfactory outcome of the validation exercise and with the marketing authorization.

#### Concurrent validation

28. In exceptional circumstances, it may be acceptable not to complete a validation program before routine production.
29. The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel.
30. Documentation requirements for concurrent validation are the same as specified for prospective validation.

#### Retrospective validation

31. Retrospective validation is only acceptable for well-established processes and will be inappropriate

where there have been recent changes in the composition of the product, operating procedures or equipment.

32. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.
33. The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance log books, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.
34. Batches selected for Retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications and should be sufficient in number to demonstrate process consistently. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.
35. For Retrospective validation, generally data from 10 to 30 consecutive batches should be examined to assess process consistently, but fewer batches may be examined if justified.

#### **Cleaning Validation**

36. Cleaning Validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carry over of product residues, cleaning agents and microbial contamination should be logically based on materials involved. The limits should be achievable and verifiable.
37. Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.
38. Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts. The intervals between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined.
39. For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilizing a "worst case" approach can be carried out which takes account of the critical issues.
40. Typically, 3 consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.
41. 'Test until clean' is not considered an appropriate alternative to cleaning validation.
42. Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

#### **Change Control**

43. Written procedures should be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.
44. All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, re-qualification and revalidation should be determined.

#### Revalidation

45. Facilities, systems, equipment and processes, including cleaning should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.

#### Schedule M :

##### 26. Validation and Process Validation :-

- 26.1 Validation Studies shall be an essential part of GMP and shall be conducted as per the pre-defined protocols. These shall include validation of processing, testing and cleaning procedures.
- 26.2 A written report summarizing recorded results and conclusions shall be prepared, documented and maintained.
- 26.3 Processes and procedures shall be established on the basis of validation study and undergo periodic re-validation to ensure that they remain capable of achieving the intended results. Critical processes, shall be validated, prospectively or retrospectively.
- 26.4 When any new master formula or method of preparation is adopted, steps shall be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified shall be demonstrated to yield a product consistently of the required quality.
- 26.5 Significant changes to the manufacturing process, including any change in equipment or materials that may affect product quality and / or the reproducibility of the process, shall be validated.

#### MCC :

##### VALIDATION MASTER PLAN

The validation program 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 VMP 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
- \* SOPs
- \* 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), SOPs 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 authorized (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, programs 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 parenteral 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 GMP.

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 authorized personnel. The document may comprise the following :

- \* introduction and objectives
- \* plant inventory number
- \* SOP 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 qualifications commences.

9.3.2 An **operational 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, the 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 as 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, airflow 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 specification results are obtained)
- \* re-qualification time-scales 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 of time, and to create a PQ protocol which is then used as the vehicle for amassing the ongoing data.

#### 9.4 PROCESS VALIDATION

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

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 is 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 3 batches (including at least 2 production batches in the final batch size) should be validated, to show consistency. Worst case situations should be considered.

9.4.2.1 Where 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 confirms to the in-process control and final product specifications.

9.4.2.2 There should be 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 that 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 GMP or QA 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. 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. sterilization, 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 fulfil the relevant requirements and that no negative influence on product quality or measured value 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 should be carried out on-site or off-site, either by the user or 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 of an analytical system at the time the test is performed.

#### 9.6.4 Methods, (other than pharmacopoeial 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 analytical procedure.

### 9.7 CLEANING VALIDATION

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

#### 9.7.2 There should be written SOPs detailing the cleaning process for equipment and apparatus.

#### 9.7.3 There should be 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 of 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.

### 9.9 GENERAL

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

9.9.1 **Validation of tableting** : In the case of an oral tablet manufactured by granulation and compression, the critical process parameters may include (but not 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 w.r.t water content, friability, disintegration and dissolution
- \* lubrication level w.r.t 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 w.r.t. tablet 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 sterilization process for terminally sterilized products, or of the sterilization, 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 sterilized products:

- \* bioburden before sterilization
- \* heat distribution
- \* influence of container size (minimum of three batches of each size)
- \* influence of chamber loading patterns (minimum of 3 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.

WHO :

5.1 Validation studies are an essential part of GMP and should be conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions should be prepared and stored. Processes and procedures should be established on the basis of a validation study and undergo periodic revalidation to ensure that they remain capable of achieving the intended results. Particular attention should be accorded to the validation of processing, testing and cleaning procedures.

Process validation

5.2 Critical processes should be validated, prospectively and retrospectively.

5.3 When any new master 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.

5.4 Significant amendments to the manufacturing process, including any change in equipment or materials that may affect product quality and / or the reproducibility of the process, should be validated.

Validation of manufacturing processes:

General

Definition : The collection and evaluation of data, beginning at the process development stage and continuing through the production phase, which ensure that the manufacturing processes – including equipment, buildings, personnel and materials – are capable of achieving the intended results on a consistent and continuous basis. Validation is the establishment of documented evidence that a system does what it is supposed to do.

Validation is an integral part of QA, but the use of this term in connection with manufacturing often gives rise to difficulties. As defined above, it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated operation is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications, and has therefore been formally approved.

Unlike many other requirements of GMP, validation in itself does not improve processes. It can only conform (or not, as the case may be) that the process has been properly developed and is under control. Ideally, any development activity in the later stages should be finalized by a validation phase. This includes, in particular, the manufacture of investigational products and the scaling up of processes from pilot plant to production unit. In this event, GMP as manufacturing practice may only be concerned with revalidation, e.g. when processes are transferred from development to production, after modifications are introduced (in starting materials, equipment, etc) or when periodic revalidation is performed. (It may be noted that in some countries data on process validation are required at the pre-registration stage (in the submission of, or application for, marketing authorizations)).

However, it cannot be assumed that all processes in the pharmaceutical industry worldwide have been properly validated at the development stage. Consequently validation is discussed here in a broader context as an activity which is initiated in development and is continued until the stage of full-scale production is reached. In fact, it is in the course of development that critical processes, steps or unit operations are identified.

Good validation practice requires the close collaboration of departments such as those concerned with development, production, engineering, QA and QC. This is most important when processes go into routine full-scale production following pharmaceutical development and pilot-plant operations. With a view to facilitating subsequent validation and its assessment in the course of quality audits or regulatory inspections, it is recommended that all documentation reflecting such transfers be kept together in a separate file (“technology transfer document”).

Adequate validation may be beneficial for the manufacturer in many ways:

- \* It deepens the understanding of processes, decreases the risks of processing problems and thus assures the smooth running of the process.
- \* It decreases the risk of defect costs.
- \* It decreases the risks of regulatory non-compliance.
- \* A fully validated process may require less in-process control and end-product testing.

#### 1. Types of process validation

Depending on when it is performed in relation to production, validation can be prospective, concurrent, retrospective or revalidation (repeated validation).

- a. *Prospective validation* is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps; these are then evaluated on the basis of past experience to determine whether they might lead to critical situations. Where possible, critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. The trials are then performed and evaluated, and an overall assessment is made. If at the end, the results are acceptable, the process is satisfactory. Unsatisfactory processes must be modified and improved until a validation exercise proves them to be satisfactory. This form of validation is essential in order to limit the risk of errors occurring on the production scale i.e. in the preparation of injectable products.

- b. *Concurrent validation* is carried out during normal production. This method is effective only if the development stage has resulted in a proper understanding of the fundamentals of the process. The first 3 production – scale batches must be monitored as comprehensively as possible. (This careful monitoring of the first 3 production batches is sometimes regarded as prospective validation.) The nature and specifications of subsequent in-process and final tests are based on the evaluation of the results of such monitoring.

Concurrent validation together with a trend analysis including stability should be carried out to an appropriate extent throughout the life of the product.

- c. *Retrospective validation* involves the examination of past experience of production on the assumption that composition, procedures and equipment remain unchanged; such experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failures in production are analysed to determine the limits of process parameters. A trend analysis may be conducted to determine the extent to which the process parameters are within the permissible range.

Retrospective validation is obviously not a QA measure in itself and should never be applied to new processes or products. It may be considered in special circumstances only, e.g. when validation requirements are first introduced in a company. Retrospective validation may then be useful in establishing the priorities for the validation program. If the results of a Retrospective validation are positive, this indicates that the process is not in need of immediate attention and may be validated in accordance with the normal schedule. For tablets, which have been compressed under individual pressure sensitive cells, and with qualified equipment, Retrospective validation is the most comprehensive test of the overall manufacturing process of this dosage form. On the other hand, it should not be applied in the manufacture of sterile products.

- d. *Revalidation* is needed to ensure that changes in the process and/or in the process environment, whether intentional or unintentional, do not adversely affect process characteristics and product quality.

Revalidation may be divided into 2 broad categories:

- \* Revalidation after any change having a bearing on product quality.
  - \* Periodic revalidation carried out at scheduled intervals.
- e. *Revalidation after changes*. Revalidation must be performed on introduction of any changes affecting a manufacturing and / or standard procedure having a bearing on the established product performance characteristics. Such changes may include those in starting material, packing material, manufacturing processes, equipment, in-process controls, manufacturing areas or support systems (water, steam etc.) Every such change requested should be reviewed by a qualified validation group, which will decide whether it is significant enough to justify revalidation and, if so, its extent.

Revalidation after changes may be based on the performance of the same tests and activities as those used during the original validation, including tests on sub-processes and on the equipment concerned. Some typical changes which require revalidation include the following:

- \* Changes in the starting material(s). Changes in the physical properties, such as density, viscosity,

particle size distribution and crystal type and modification, of the active ingredients or excipients may affect the mechanical properties of the material; as a consequence, they may adversely affect the process or the product.

- \* Changes in the packaging material. e.g. replacing plastics by glass, may require changes in the packaging procedure and therefore affect product stability.
  - \* Changes in the process. E.g. changes in mixing time, drying temperature and cooling regime, may affect subsequent process steps and product quality.
  - \* Changes in equipment, including measuring instruments, may affect both the process and the product; repair and maintenance work, such as the replacement of major equipment components, may affect the process.
  - \* Changes in the production area and support system. E.g. the rearrangement of manufacturing areas and/ or support systems, may result in changes in the process. The repair and maintenance of support systems, such as ventilation, may change the environmental conditions and, as a consequence, revalidation / re-qualification may be necessary, mainly in the manufacture of sterile products.
  - \* Unexpected changes and deviations may be observed during self – inspection or audit, or during the continuous trend analysis of process data.
- f. *Periodic Revalidation.* It is well known that process changes may occur gradually even if experienced operators work correctly according to established methods. Similarly, equipment wear may also cause gradual changes. Consequently, revalidation at scheduled times is advisable even if no changes have been deliberately made.

The decision to introduce periodic revalidation should be based essentially on a review of historical data, i.e. data generated during in-process and finished product testing after the latest validation, aimed at verifying that the process is under control. During the review of such historical data, any trend in the data collected should be evaluated.

In some processes, such as sterilization, additional process testing is required to complement the historical data. The degree of testing required will be apparent from the original validation.

Additionally, the following points should be checked at the time of a scheduled revalidation:

- \* Have any changes in MFR and methods, batch size, etc., occurred ? If so, has their impact on the product been assessed.
- \* Have calibrations been made in accordance with the established program and time schedule ?
- \* Has preventive maintenance been performed in accordance with the program and time schedule ?
- \* Have the SOPs been properly updated ?
- \* Have the SOPs been implemented ?
- \* Have the cleaning and hygiene programs been carried out ?

- \* Have any changes been made in the analytical control methods ?

## 2. Prerequisites for process validation

Before process validation can be started, manufacturing equipment and control instruments, as well as the formulation, must be qualified. The formulation of a pharmaceutical product should be studied in detail and qualified at the development stage, i.e. before the application for the marketing authorization is submitted. This involves pre-formulation studies, studies on the compatibility of active ingredients and excipients, and of final drug product and packaging material, stability studies, etc.

Other aspects of manufacture must be validated, including critical services (water, air, nitrogen, power supply, etc.), and supporting operations such as equipment cleaning and sanitation of premises. Proper training and motivation of personnel are prerequisites to successful validation.

## 3. Approaches

Two basic approaches to the validation of the process itself exist (apart from the qualification of equipment used in production, the calibration of control and measurement instruments, the evaluation of environmental factors etc.), namely the experimental approach and the approach based on the analysis of historical data

The experimental approach, which is applicable to both prospective and concurrent validation, may involve:

- \* Extensive product testing
- \* Simulation process trials
- \* Challenge / worst case trials
- \* Controls of process parameters (mostly physical)

One of the most practical forms of process validation, mainly for non sterile products, is the final testing of the product to an extent greater than that required in routine QC. It may involve extensive sampling, far beyond that called for in routine QC & testing to normal QC specification, and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the "Normality" of the distribution, and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirement if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, eg., Dozen of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Products (intermediate or final) may occasionally be tested for non-routine characteristics. Thus, sub-visual particulate matter in parenteral preparations may be determined by

means of electronic devices, or tablets/capsules tested for dissolution profile if such tests are not performed on every batch.

Simulation process trials are used mainly to validate the aseptic filling of parenteral products that cannot be terminally sterilized. This involves filling ampoules with culture media under normal conditions, followed by incubation and control of microbial growth. In the past, a level of contamination of less than 0.3% was considered to be acceptable; however, the current target level should not exceed 0.1%.

Challenge experiments are performed to determine the robustness of the process, i.e. its capacity to operate smoothly when parameters approach acceptable limits. The use of ranges of parameters for the quality of the starting materials in experimental batches may make it possible to estimate the extent to which the process is still capable of producing an end-product that meets the specifications.

The physical parameters of the process are monitored in normal production runs to obtain additional information on the process and its reliability. Extra temperature-sensitive devices installed in an autoclave or dry-heat sterilizer (in addition to probes used routinely) will permit an in-depth study of the heat distribution for several loads. Heat-penetration measurements are recommended for injectable products of higher viscosity or with volumes larger than 5ml.

A tableting press equipped with pressure-sensitive cells will be helpful in collecting statistical data on the uniformity of die-fill and therefore on mass uniformity.

In the approach based on the analysis of historical data, no experiments are performed in retrospective validation, but instead all available historical data concerning a number of batches are combined and jointly analyzed. If production is proceeding smoothly during the period preceding validation, the data from in-process inspection and final testing of the product are combined and treated statistically. The results, including the outcome of process capability studies, trend analysis, etc., will indicate whether the process is under control or not.

Quality control charts may be used for retrospective validation. A total of 10-25 batches or more are used for this purpose, preferably processed over a period of no longer than 12 months, and reviewed together. (Batches rejected during routine quality control are not included in this review since they belong to a different "population", but failure investigations are performed separately.) A critical quality parameter of the end-product is selected, e.g., the assay value or potency, unit dose uniformity, disintegration time, or extent of dissolution. The analytical results for this parameter for the batches under review are extracted from past batch release documentation and pooled together, while the results from each batch are treated as subgroups. The grand average ("process average") and control limits are calculated and plotted on graphs or charts in accordance with the instructions given in numerous publications on control charts (see Bibliography, page 63).

A careful review of the charts will enable the reliability of the process to be estimated. A process may be considered reliable if the plotted data are within the control limits and the variability of individual results is stable or tends to decrease. Otherwise, an investigation and possibly an improvement are needed. (It may be noted that, once control charts for past batches have been prepared, they become a powerful tool for prospective quality management. Data for new batches are plotted on the same charts and, for every result outside control limits, a reason, that is a new factor affecting the process, is sought and when found, eliminated. By consistently applying this approach over a period of time the process may be considerably improved.)



In addition, information on product-related problems is also analyzed. The reliability of the process is demonstrated if, for a considerable time, there are no rejections, complaints, returns, unaccountable adverse reactions, etc. The process may be certified as retrospectively validated if the results of statistical analysis are positive and the absence of serious problems is documented. However, it should be emphasized that this approach is not applicable to the manufacture of sterile products.

#### 4. Organization

Several possible methods of organizing validation are available, one of which is the establishment of a validation group. For this purpose, the management appoints a person responsible for validation (validation officer), who then forms the group (team, committee). This is headed by a group leader and represents all major departments : development, production, engineering, QA and QC. The composition of the group should be changed from time to time to give opportunities to other people to generate new ideas and to gain experience. The validation group then prepares a program, which determines the scope of its work, its priorities, the time schedule, the resources needed, etc. The program is sent for review and approval to the departments and functions concerned. The final review and approval are the responsibility of the validation officer.

Table 1 : Example of priorities for a process validation program

Type of process	Validation requirements
New	Every new process must be validated before approval for routine production
Existing : Processes designed to render a product sterile	All processes affecting sterility and manufacturing environment must be validated; the most important is the sterilization stage
Non-sterile production	Low – dose tablets and capsules containing highly active substances; validation of mixing and granulation in relation to content uniformity Other tablets and capsules : validation of tablet compressing and capsule filling in relation to uniformity of mass

#### 5. Scope of a process validation program

Suggested priorities for a validation program are listed in Table 1. For new processes, it is recommended that the first few full-scale production batches (e.g. 3 batches) should not be released from quarantine after approval by the QC department until the validation has been completed, the results presented and reviewed and the process approved (certified).

#### 6. Validation protocol and report

A suggested scheme for the validation protocol and subsequent report concerning a particular process is shown below:

Part 1. Purpose (the validation) and prerequisites

Part 2. Presentation of the entire process and sub-processes, flow diagram, critical steps/risks

Part 3. Validation protocol, approval

Part 4. Installation qualification and drawings

Part 5. Qualification protocol / report

5.1 Sub-process 1

5.1.1 Purpose

5.1.2 Methods / procedures, list of manufacturing methods, SOPs and written procedures, as applicable

5.1.3 Sampling and testing procedures, acceptance criteria (detailed description of, or reference to, established procedures, as described in pharmacopoeias)

5.1.4 Reporting

5.1.4.1 Calibration of test equipment used in the production process

5.1.4.2 Test data (raw data)

5.1.4.3 Results (summary)

5.1.5 Approval and re-qualification procedure

5.2 Sub-process 2 (same as for sub-process 1)

5.n Sub-process n

Part 6. Product characteristics, test data from validation batches

Part 7. Evaluation, including comparison with the acceptance criteria and recommendations (including frequency of revalidation / re-qualification)

Part 8. Certification (approval)

Part 9. If applicable, preparation of an abbreviated version of the validation report for external use, for example by the regulatory authority.

The validation protocol and report may also include copies of the product stability report or a summary of it, validation documentation on cleaning and analytical methods

# CHAPTER 9

## QUALITY MANAGEMENT

TGA:

a. Concepts and rationale

800. The management of quality generally has progressed from testing finished product in order to determine whether it meets specifications or not (and if not, how to correct) to an involvement with every aspect of manufacture and testing which will assure senior management that the product will always meet corporate quality criteria, i.e. that the assurance is not conditional upon a favourable test result.

Quality begins with the product design and development. It is then assured by following good manufacturing practice, including QC test procedures, and by a continuing review and overview QA activity that extends beyond day-to-day compliance with specifications. QA is sometimes viewed as an overall management or enterprise concept philosophy but in this code it is treated as a function.

The allocation of duties between QA and QC may vary considerably between manufacturers because of their diversity both in type and size. This is acceptable, provided that all the functions are specified and carried out.

The Code provides that QA, including some aspects of QC, is to be set up as a department independent of production. This does not imply that Production personnel are not committed to producing quality therapeutic goods. However, it does provide a detailed overview, independent of the daily pressures of achieving production targets and provides a separate assurance function as a skilled resource.

Quality Assurance is presently recognized in the Australian pharmaceutical industry to include the following duties:

- \* creating quality systems and procedures;
- \* authorizing key procedures;
- \* reviewing and challenging specifications and test methods;
- \* reviewing vendor quality management;
- \* interacting with product development and manufacturing personnel to validate processes and procedures;
- \* interacting with manufacturing and engineering personnel in planning for the construction, alteration, renovation, or purchase of premises, plant or equipment.
- \* interacting with the personnel of other departments concerned with the development of electronic

data processing systems, whenever these are concerned with materials or products;

- \* evaluating Deviation and Fault reports and complaints;
- \* improving in-process controls;
- \* critically examining the environment with a view to minimizing product contamination;
- \* monitoring product stability;
- \* internal auditing;
- \* ensuring that goods are produced according to protocols accepted for registration; and
- \* releasing batches of product for sale on the basis of a certified package of production and laboratory documents.

It also includes QC, though the two activities may be administratively separate.

Quality Control involves the actual sampling and testing procedures and the actual sampling and testing of starting materials, intermediate products and finished products to verify that they meet specifications before release for further manufacture or sale. It includes on-line QC, though administratively it may be more convenient and philosophically more correct to exert intermediate and in-process controls using Production staff, while QC provides technical support and audit.

#### b. General

801. There should be a comprehensive system for the quality management of all therapeutic goods manufactured. There should be a separate department responsible for this system unless other arrangements acceptable to the inspecting authority are made.
802. Provision for the management of quality should include a laboratory adequately staffed and fully equipped for performing all QC tests and analysis (including any environmental tests) required before, during and after manufacture, except where arrangements for contract testing, acceptable to the inspecting authority, are made.
803. The person in-charge of QA should:
  - \* be qualified, authorized and responsible as specified in Section 3.
  - \* be notified promptly of all proposed changes in, and departures from, the master formulae and processing instructions and packaging and labeling instructions for products;
  - \* be notified of all circumstances which may affect the quality of products, whether before or after release for sale;
  - \* ensure that production is compatible with registration protocols; and
  - \* have the final responsibility to management for the testing and release or rejection of all materials

and products subject to the quality control system.

804. QA or QC should:

- \* take and test samples of starting materials (including relevant packaging materials), relevant intermediate products and finished products, to determine their release or rejection on the basis of test results and other available evidence as to their quality; and
- \* be empowered to take samples for testing from any material or substance relevant to product quality.

c. Functions and duties

805. In order to discharge its obligation to ensure that materials and products released for use or distribution are of satisfactory quality, the QA or QC department should;

- \$ establish or approve QC specifications for all starting materials and finished products, for packaging materials in contact with the products and for intermediate products and other packaging materials where appropriate;
- \$ establish or approve master batch and packaging documents;
- \* establish or approve SOPs relevant to or affecting product quality;
- \$ maintain or hold a current file of approved labels, pre-printed packaging material and other specified packaging material.
- \$ establish or approve written procedures and plans for the sampling of materials, work in progress and products to be tested;
- \$ establish or approve adequately detailed instructions for carrying out all tests required in connection with the quality control of materials and products;
- \$ establish or approve procedures for microbiological testing and microbiological monitoring of materials, products and environment, including process water.
- \* revise or approve the revision of the established QC specifications and sampling and testing instructions as necessary, replace superseded versions, and maintain a complete written versions of the current versions and an historical record of amendments;
- \* sample and test all batches of starting materials, finished products, specified intermediate products and specified packaging materials for compliance with their specifications, using the established sampling and test procedures.
- \$ evaluate the stability of all finished products and of starting materials and intermediate products where necessary, and, on the basis of appropriate stability data
- \* establish instructions for the storage of materials and products within the manufacturers' premises;
- \* establish expiry periods and storage instructions for incorporation in the labeling of products; and

- \* periodically review the status of materials or products, should their storage be prolonged to a period which may cause failure to comply with the relevant QC specifications (a standard procedure for re-examination of starting materials should be written);
- \* assess suppliers of starting materials (where possible by direct audit) and assign, where appropriate “approved supplier” or “certified supplier” status;
- \* Note : Starting material should not be granted “approved supplier” status except in relation to materials in sealed containers bearing the manufacturers’ original label and batch, lot or equivalent number.
- \* evaluate and authorize any re-processing or re-working of products or materials (See recovered or Reprocessed material)
- \* assemble and review all documentation relating to the processing, packaging and testing of each batch of product before authorizing release for sale;
- \* participate in the investigation of deviations, discrepancies or test failures (See also deviation and fault analysis);
- \$ carry out, co-ordinate or participate in initial and periodic process validation studies, including those described in clauses 611-612, 688-670 and 1631-1643, to demonstrate that materials, methods, processes and equipment are capable of doing what they purport to do. Such studies may be necessiated by changes in the source or specifications for materials, or changes in process or equipment. The studies should also show that a process is effective over the range of variation selected for a particular processing parameter.
- \* evaluate complaints relating to product quality received from any source (See also Complaints);
- \* review periodically the records relating to each product and report on compliance with standards, problems if any and recommended action;
- \* maintain all quality functions and procedures under review for appropriateness and validity;
- \* audit and approve contract analysts (jointly with Production where appropriate); audit and approve contract manufacturers, where these are to be employed;
- \* examine returned goods, to determine whether they should be released, reprocessed or destroyed; and
- \* establish and maintain, jointly with production, an active self inspection program to determine compliance with GMP requirements.

806. Certain of the functions shown as \$ sub-clauses in Clause 805 may be delegated to the development department of a manufacturer.

MCA :

- 6.1 Each holder of a manufacturing authorization should have a QC department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate sources must be available to ensure that all the QC arrangements are effectively and reliably carried out.
- 6.2 The QC Department as a whole will also have other duties, such as to establish, validate and implement all QC procedures, keep the reference samples of materials and products, ensure the correct labeling of containers of materials and products, ensure the monitoring of stability of the products, participate in the investigation of complaints related to the quality of the product etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.
- 6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished product specification and examination of final Finished pack.
- 6.4 QC personnel should have access to production areas for sampling and investigation as appropriate.

Schedule M :  
Quality Control system

- 16.1 Every manufacturing establishment shall establish its own QC laboratory manned by qualified and experienced staff.
- 16.2 The area of the QC may be divided into Chemical, Instrumentation, Microbiological and Biological testing.
- 16.3 Adequate area having the required storage conditions shall be provided for keeping reference samples. The QC department shall evaluate, maintain and store reference samples.
- 16.4 SOPs shall be available for sampling, inspecting, and testing of raw materials, intermediate, bulk finished products and packaging materials and, wherever necessary, for monitoring environmental conditions.
- 16.5 There shall be authorized and dated specifications for all materials, products, reagents and solvents including test of identity, content, purity and quality. These shall include specifications for water, solvents and reagents used in analysis.
- 16.6 No batch of the product shall be released for sale or supply until it has been certified by the authorized person(s) that it is in accordance with the requirements of the standards laid down.
- 16.7 Reference/retained samples from each batch of the products manufactured shall be maintained in a quantity which is at least twice the quantity of the drug required to conduct all the tests, except sterility and pyrogen / Bacterial endotoxin test performed on the active material and the product manufactured. The retained product shall be kept in its final pack or a simulated pack for a period of 3 months after the date of expiry.

- 16.8 Assessment of records pertaining to finished products shall include all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack. Assessment records should be signed by the in-charge of production and counter-signed by the authorized QC personnel before a product is released for sale or distribution.
- 16.9 QC personnel shall have access to production areas for sampling and investigation, as appropriate.
- 16.10 The QC department shall conduct stability studies of the products to ensure and assign their shelf life at the prescribed conditions of storage. All records of such studies shall be maintained.
- 16.11 The in-charge of QA shall investigate all product complaints and records thereof shall be maintained.
- 16.12 All instruments shall be calibrated and testing procedures validated before these are adopted for routine testing. Periodical calibration of instrument and validation of procedures shall be carried out.
- 16.13 Each specifications for raw materials, intermediates, final products and packing materials shall be approved and maintained by the QC department. Periodic revisions of the specifications shall be carried out whenever changes are necessary.
- 16.14 Pharmacopoeia, reference standards, working standards, reference spectra, other reference materials and technical books, as required, shall be available in the QC laboratory of the licensee.

**MCC :**  
**QUALITY CONTROL**

**7.1 PRINCIPLES**

- 7.1.1 In order to achieve reliable results, QC 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 satisfactorily. QC should be independent from Production. QC should adopt procedures necessary to ensure that the relevant tests and checks are carried out.

**7.2 RESPONSIBILITIES**

- 7.2.1 The QCD 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 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 QC is not confined to laboratory operations but must be integrated into the QA 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 QCD will also have the following responsibilities

- \* sampling of materials subject to QC and the keeping of retention samples and records.
- \* monitoring of 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 QCD 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 and 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 SOPs 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 QC 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 QC staff should be suitably educated, trained and motivated to perform their tasks adequately.

### SAMPLING

#### TGA:

807. There should be written sampling plans and procedures for starting materials, goods in-process and finished products.

Sampling plan for starting materials (excluding packaging materials) should:

- \$ differentiate between Certified, Approved and other suppliers, including unknown suppliers, as appropriate;
- \* differentiate between starting materials that do not bear a manufacturer's batch number and those that do;
- \$ take account of the nature of each material, for example its potency and whether its place and method of manufacture may insure against mix-up or even mix-up impossible;
- \* take account of the use to which the material is to be put, for example an injectable product;
- \$ differentiate between materials that may be expected to vary from container to container (for example, by segregation or moisture uptake) and those that may not;
- \$ prescribe the action to be taken where a delivery from a certified or approved supplier has failed;
- \* prescribe an increased sampling rate for damaged containers or where lots do not appear to be homogeneous;
- \* specify the extent of pooling of samples destined for tests other than identification; and
- \* require the Sampling officer or Analyst to initially examine each sample for evidence of deterioration, inhomogeneity or other visible defect.

808. Sampling plans for packaging materials should take into account:

- \* the items shown as (\$) listed above for starting materials;

- \* the need to check the identity of each container or reel of labels and pre-printed packaging materials; and
  - \* the number of samples needed to reach a valid decision to approve or reject a delivery in relation to quality-related defects.
809. Sampling should be carried out so as to avoid contamination and other adverse effects on quality. Containers which have been sampled should be marked and numbered accordingly and should be adequately re-sealed after sampling. Samples should be marked to indicate the containers from which they were drawn.
810. Unless the nature of the material precludes it, sufficient quantities of chemical starting materials and finished products should be taken for both control testing and retention samples.
- \* In the case of starting materials, at least twice the quantity necessary for the tests required to establish identity and purity should be retained for at least 2 years after use.
  - \* In the case of finished products, the number of product units retained should be adequate to permit re-examination at suitable intervals and the investigation of possible complaints. Such samples should be retained for at least 1 year after their expiry date or, where there is no expiry date, for at least 6 years from the date of manufacture.
811. Retention samples of product should include the finished, packaged and labeled product, except where alternatives are approved by the licensing authority.

**MCA :**

- 6.11 The sample taking should be done in accordance with appropriate written procedures that describe;
- \* The method of sampling;
  - \* The equipment to be used;
  - \* The amount of the sample to be taken;
  - \* Instructions required for any sub-division of the sample;
  - \* The type and condition of the container to be used;
  - \* The identification of containers sampled;
  - \* Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
  - \* The storage conditions;
  - \* Instructions for the cleaning and storage of sampling equipment.

612. Reference samples should be representative of the batch of the materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process)
- 6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.
- 6.14 Reference samples from each batch of finished products should be retained until 1 year after the expiry date. Finished products should usually kept in their final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) should be retained for at least 2 years after the release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. Reference samples of materials should be of a size sufficient to permit at least a full re-examination.

**MCC :**

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 the 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.

## TESTING

### TGA :

812. Testing should be performed in accordance with methods detailed in referenced in specifications.
813. A test for identification should be carried out on material from each container of starting material sampled. Tests for identification should be as specific as is practicable and should unequivocally distinguish each material from all other materials used in the particular premises.
814. Testing schedules may take into account the nature and age of the material, the grading and history of the supplier, and any valid certificate of analysis. A valid COA is one from an approved or certified supplier which relates to a specific batch of material and which is in the proper form, dated and signed. It does not include a certificate of average or typical composition.
815. Only valid COA should be included with the analytical records for each material. Where test results from valid COA are entered on Analytical Summary Records, they should be entered in such a way as to distinguish them from internal test results.

## IN-PROCESS TESTING

816. QC is responsible for in-process sampling and testing. However, it may delegate authority in writing to operators to carry out certain in-process sampling and testing, provided that-
  - \* calibrated equipment is available to perform the tests;
  - \* operators are trained; and
  - \* independent QC results are obtained from time to time as an audit and these results are entered in distinctive form on the test records.
817. Samples on which decisions to approve finished product may be based should be taken only by QA or QC personnel or by persons appropriately trained and authorized by them.

### MCA :

- 6.15 Analytical methods should be validated. All testing operations described in the marketing authorization should be carried out according to the approved methods.
- 6.16 The results obtained should be recorded and checked to make sure that they are consistent with each

other. Any calculations should be critically examined.

- 6.17 The tests performed should be recorded and the records should include at least the following data;
- (a) Name of the material or product and, where applicable, dosage form.
  - (b) Batch number and, where appropriate, the manufacturer and/or the supplier.
  - (c) References to the relevant specifications and testing procedures.
  - (d) Test results, including observations and calculations, and reference to any Certificate of Analysis.
  - (e) Dates of Testing.
  - (f) Initial of the person who performed the testing.
  - (g) Initials of the person who verified the testing and the calculations, where appropriate.
  - (h) A clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.
- 6.18 All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by QC and the results recorded.
- 6.19 Special attention should be given to the quality of laboratory reagents, volumetric glass ware and solutions, reference standards and culture media. They should be prepared in accordance with written procedures.
- 6.20 Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated.
- 6.21 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. 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.
- 6.22 Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

**MCC :**

- 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 QC 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.

#### MCC : 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, labeling should indicate the concentration, standardization factor, shelf – life and storage conditions. If relevant, a date for re-standardization should be recorded. The label should be signed and dated by the persons 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 QC 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 QCD.
- \* specifications
  - \* sampling procedures
  - \* testing procedures and records (including analytical worksheets and/or laboratory note books)
  - \* analytical reports and/or certificates
  - \* data from environmental monitoring, where required
  - \* validation records of test methods, where applicable

- \* procedures for and the 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 QC documentation relating to a batch record should be retained for at least one year after the expiry date of the batch.

## GOOD CONTROL LABORATORY PRACTICE

### TGA:

818. Laboratory practice should follow Australian Standard 2830.1: Good Laboratory Practice, Part I, Chemical Analysis and the requirements of Section 5 of this code – Documentation. Particular emphasis should be given to the provision of a comprehensive system of calibration and to the systematic filing of superseded methods and the dating of revisions.

819. Control laboratories and equipment should be kept clean.

820. Reagents made up in the laboratory should be prepared following standard procedures. As applicable, labeling should indicate the concentration, standardization factor, shelf life and storage conditions. The label should be dated and signed or initialed by the person preparing the reagent.



Where relevant, a date for re-standardization should be recorded. In certain cases, it may be necessary to carry out tests to confirm that the reagent is suitable for the purpose for which it is to be used: a record of these tests should be maintained.

Where appropriate, purchased reagent solutions should be dated on receipt.

821. Samples of reference substances specified in the current instructions for testing should be obtained. Reference standards and any secondary standards prepared from them should be dated and be stored, handled and used so as not to prejudice their quality.

A register should be used to record the source, identity and any other available information concerning the preparation and characterization of these substances as well as the date put into service and date taken out of service.

822. Microbiological culture media should be prepared according to written standard procedures and subjected to quality control. The preparation should be logged and the product batch numbered and expiry dated. Test records should refer to these batch numbers.

Both positive and negative controls should be applied to the use of media. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

823. Animals used for testing components, materials or products should, where appropriate, be quarantined before use. They should be maintained and quarantined according to a standard procedure that assures their suitability for the test to be performed. They should be identified and adequate records kept showing the history of their use.

Animal usage should comply with the current edition of the NH&MRC/CSIRO/AAC Code of practice for the care and Use of Animals for Experimental purpose.

824. Written records of all testing should be made and kept in accordance with Clause 512 and 555-556.

The record for a test should be sufficient to identify the test method employed and to enable a check of the calculation of the results.

## MCA

### GOOD QUALITY CONTROL LABORATORY PRACTISE

- 6.5 Control laboratory premises and equipment should meet the general and specific requirements for QC areas as under "Premises and equipment".
- 6.6 The personnel, premises and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed under "Contract manufacture and analysis" can be accepted for particular reasons, but this should be stated in the QC records.

### *Documentation*

- 6.7 Laboratory documentation should follow the principles given under Chapter 4 :Documentation. An important part of this documentation deals with QC and the following details should be readily

available to the QC 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.
- 6.8 Any QC documentation relating to a batch record should be retained for one year after the expiry date of the batch and at least 5 years after the certification referred to in article 22.2 of Directive 75/319/EEC.
- 6.9 For some kinds of data (e.g. Analytical test results, yields, environmental controls etc.) it is recommended that records be kept in a manner permitting trend evaluation.
- 6.10 In addition to the information which is part of the batch record, other original data such as laboratory note book and/or records should be retained and readily available.

WHO :

#### GOOD PRACTICE IN QUALITY CONTROL

16.1 Principle : QC is concerned with sampling, specifications and testing as well as with the organization, documentation and release procedures that ensure that the necessary and relevant tests are carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. QC is not confined to laboratory operations, but must be involved in all decisions that may concern the quality of the product. The independence of QC from production is considered fundamental.

#### Control of starting materials and intermediate, bulk and finished products

- 16.2 All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should be checked by the supervisor before the material or product is released or rejected.
- 16.3 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure.
- 16.4 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling.

- 16.5 Care should be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment that comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.
- 16.6 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.
- 16.7 Each sample container should contain a label indicating :
- (a) the name of the sampled material;
  - (b) the batch or lot number;
  - (c) the number of the container from which the sample has been taken;
  - (d) the signature of the person who has taken the sample; and
  - (e) the date of sampling.

#### Test requirements

#### Starting and packaging materials

- 16.8 Before releasing a starting or packaging material for use, the QC manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.
- 16.9 An identity test should be conducted on a sample from each container of starting material.
- 16.10 Each batch (lot) of printed packaging material must be examined following receipt.
- 16.11 In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results and through on-site audits of the supplier's capabilities. Certificates must be originals or otherwise have their authenticity assured. Certificates must contain the following information:
- (a) identification of the issuing supplier, signature of the competent official and statement of his or her qualifications;
  - (b) the name and batch number of the material tested;
  - (c) a statement of specifications and methods used; and
  - (d) a statement of test results obtained and the date of testing.

#### In-process control

- 16.12 In-process control records should be maintained and form a part of the batch records.

#### Finished products

- 16.13 For every batch of drug product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.
- 16.14 Products failing to meet the established specifications or any other relevant quality criteria should be rejected. Reprocessing may be performed, if feasible, but the reprocessed product should meet all specifications and other quality criteria prior to its acceptance and release.

#### Production record review

- 16.15 Production and control records should be reviewed and any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.
- 16.16 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least 1 year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases and water) should be retained for a minimum of 2 years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least 2 full re-examinations.

#### STABILITY TESTING

##### TGA :

825. The stability profile of each product, in its Australian sales pack, should be available. Where it is not, it should be determined according to a written stability program. The profile should be verified at appropriate intervals by supplementary testing of further batches of product. The program should include dissolution, microbiological and preservative efficacy testing where appropriate.

Note : Supplementary stability data may be obtained by testing retained batch samples before they are discarded.

826. Records of stability for all products should be maintained in a systematic tabular or equivalent form.

The collected data should be reviewed at appropriate intervals. The assessments leading to the determination or amendment of shelf life and storage conditions should be documented.

##### MCC :

- 7.9.1 A written program 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.

WHO :  
STABILITY STUDIES

- 16.17 The QC department should evaluate the quality and stability of finished pharmaceutical product and, when necessary, of starting materials and intermediate products.
- 16.18 The QC department should establish expiry dates and shelf – life specifications on the basis of stability tests related to storage conditions.
- 16.19 A written program for ongoing stability determination should be developed and implemented to include elements such as:
- (a) a complete description of the drug involved in the study;
  - (b) the complete testing parameters and methods describing all tests for potency, purity and physical characteristics and documented evidence that these tests indicate stability;
  - (c) provision for the inclusion of a sufficient number of batches;
  - (d) testing schedule for each drug;
  - (e) provision for special storage conditions;
  - (f) provision for adequate sample retention; and
  - (g) a summary of all the data generated, including the evaluation and the conclusions of study.
- 16.20 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

DEVIATION AND FAULT ANALYSIS

TGA :

827. A procedure should be documented and established for the review of Deviation Reports (see Other supportive Documents – Clause 558) and other indicators of quality or procedural problems. The procedure should require analysis of the data, assessment of whether a significant problem exists and allocation of the task(s) for corrective action.

Release for sale

828. Goods should not be dispatched unless release has been authorized under a formal Release for Sale procedure.
829. Where goods are to be transferred from the packaging area to the warehouse before release for sale, an effective system of quarantine should apply.
830. Release for Sale should require the examination and certification by QA of consolidated records of processing, packaging and quality control, to ensure compliance with the Master Formula, compliance with all procedures, acceptable yields and reconciliations and compliance with product specifications. A checklist system should be used for the collected documents to verify that all are present. The release should include the dated signature of the person authorized to approve the distribution of the batch (see also Contract Manufacture).

**QUALITY ASSURANCE :**

**Schedule M :**

14.1 The system of QA appropriate to the manufacture of pharmaceutical products shall ensure that :

- (a) the pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of GLP and GCP [Good clinical practice].
- (b) adequate arrangements are made for manufacture, supply and use of the correct starting and packaging materials;
- (c) adequate controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;
- (d) the finished product is correctly processed and checked in accordance with established procedures.
- (e) the pharmaceutical products are not released for sale or supplied before authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the label claim and any other provisions relevant to production, control and release of pharmaceutical products.

**MCA :**

The holder of a manufacturing authorization must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of QA incorporating GMP and thus QC. It should be fully documented and its effectiveness monitored. All parts of the QA system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of a manufacturing authorization and for the QPs.

1.1 The basic concepts of QA, GMP and QC are inter-related. They are described here in order to emphasize their relationships and their fundamental importance to the production and control of medicinal products.

1.2 QA is a wide ranging concept which covers all matters which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the object of ensuring that medicinal products are of the quality required for their intended use. QA therefore incorporates GMP plus other factors, including those outside the scope of this guide.

The system of QA appropriate to the manufacture of medicinal products should ensure that :

- (i) Medicinal products are designed and developed in a way that takes account of the requirements of GMP and GLP
- (ii) Production and control operations are clearly specified and GMP adopted.
- (iii) Managerial responsibilities are clearly specified;
- (iv) Arrangements are made for the manufacture, supply and use of the correct starting and packaging arrangements;
- (v) All necessary controls on intermediate products, and any other in-process controls, and validations are carried out;
- (vi) The finished product is correctly processed and checked, according to the defined procedures.
- (vii) Medicinal products are not sold or supplied before a QP has certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of medicinal products.
- (viii) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life.
- (ix) There is a procedure for self – inspection and / or quality audit which regularly appraises the effectiveness and applicability of the QA system.

MCC :

1.1.1 Quality is not merely a regulatory requirement; it is also a crucial determinant for business success or failure in modern performance-oriented markets. The **business strategic value** of quality relates **inter alia** to improvement of the enterprise's competitive position, increased productivity, improved risk management and increased profitability.

1.1.2 There should be comprehensively designed and correctly implemented quality management system which is fully documented, effectively controlled and adequately staffed with competent personnel, suitable and sufficient premises, equipment and facilities, so as to provide the assurance that

products have the necessary quality, safety, efficacy and therapeutic availability, comply with the requirements of the regulatory authorities and are fit for their intended use.

1.1.3 This Quality Management System is the responsibility of senior management and involves them and all those concerned with the design, development, manufacture, packaging, control, purchasing, storage, handling and distribution of medicinal products or their ingredients and components.

1.1.4 Many of the factors which affect product quality lie outside the scope of this guide. All members of the pharmaceutical industry are therefore encouraged to adopt quality management systems that are based on the **total quality** approach, which includes the following principles.

1.1.4.1 Basic quality responsibility rests with top management

1.1.4.2 Top management should identify and communicate company quality objectives by means of a formal quality policy statement.

1.1.4.3 Quality is affected at every stage of the industrial cycle; i.e. during new design control, incoming materials control, production control and post marketing surveillance activities.

1.1.4.4 Quality knows no functional boundaries; quality is everybody's job and requires carefully planned organization wide integration.

1.1.5 The basic concepts of QA, GMP & QC are inter-related. They are of fundamental importance to the production and control of medicinal products.

## 1.2 QA

1.2.1 QA is the sum total of all organized arrangements made with the objective of ensuring that medicines are of the quality required for their intended use. It is thus a wide-ranging concept which covers all matters affecting quality. It is the sum total of the organized arrangements made with the object of ensuring that medicinal products are of the quality required for their ultimate use.

1.2.2 The requirements and objectives of QA are as follows :

- (a) medicines are designed and developed in such a way that they can be produced to comply with the quality requirements and lot to lot conformity to specifications can be maintained.
- (b) production operations and GMP are clearly specified and adhered to
- (c) the production environment and services to the production operation are monitored.
- (d) deviations are adequately recorded, investigated and responded to
- (e) the supply and use of adequate starting materials and packaging materials is assured
- (f) all the necessary controls on intermediate and final products and other in-process controls, validation and, if necessary, trend analysis to be carried out.



- (g) no product is sold or supplied until a responsible pharmacist has ensured that each batch has been produced and controlled in accordance with legal and other requirements
- (h) medicines are stored, handled and distributed so that quality is maintained throughout their shelf life.
- (i) laboratory operations and GLP are clearly specified and adhered to
- (j) the QA system is regularly audited by self-inspection for effectiveness and applicability.

**WHO :**

1.1 Principle : “Quality Assurance” is a wide ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. QA therefore incorporates GMP and other factors, including those outside the scope of this guide such as design and development.

1.2 The system of QA appropriate to the manufacture of pharmaceutical products should ensure that :

- (a) pharmaceutical products are designed and developed in such a way that takes account of the requirements of GMP and other associated codes such as those of Good laboratory practice (GLP) and Good clinical practice (GCP);
- (b) production and control operations are clearly specified in a written form and GMP requirements are adopted;
- (c) managerial responsibilities are clearly specified in job descriptions;
- (d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- (e) all necessary controls on starting materials, intermediate products and bulk products and other in-process controls, calibrations and validations are carried out;
- (f) the finished product is correctly processed and checked, according to the defined procedures.
- (g) pharmaceutical products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products.
- (h) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed and subsequently handled so that quality is maintained throughout their shelf-life.
- (i) there is a procedure for self – inspection and / or quality audit that regularly appraises the effectiveness and applicability of the QA system.

1.3 The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure

that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company's suppliers and the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of QA incorporating GMP and QC. It should be fully documented and its effectiveness monitored. All parts of the QA system should be adequately staffed with competent personnel and should have suitable and sufficient premises, equipment and facilities.

## GOOD MANUFACTURING PRACTICE [GMP]

### MCA :

1.3 GMP is that part of QA which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization or product specification.

GMP is concerned with both production and QC. The basic requirements of GMP are that :

- (i) All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;
- (ii) Critical steps of manufacturing processes and significant changes made to the process are validated;
- (iii) All necessary facilities for GMP are provided, including:
  - (a) appropriately qualified and trained personnel;
  - (b) adequate premises and space;
  - (c) suitable equipment and services;
  - (d) correct materials, containers and labels;
  - (e) approved procedures and instructions;
  - (f) suitable storage and transport.
- (iv) Instructions & procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
- (v) Operators are trained to carry out procedures correctly;
- (vi) Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are

fully recorded and investigated;

- (vii) Records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- (viii) The distribution (wholesaling) of the products minimizes any risk to their quality;
- (ix) A system is available to recall any batch of product from sale or supply;
- (x) Complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent re-occurrence.

**MCC :**

1.3.1 GMP is that part of QA which ensures the products are consistently produced and controlled to the quality standards appropriate for their intended use and the legal requirements. GMP is thus concerned with both production and quality control matters.

1.3.2 The basic requirements and objectives of GMP are as follows :

- (a) the production processes are clearly defined, systematically reviewed and validated to ensure products of the required quality.
- (b) all the necessary facilities are provided, including:
  - \* appropriately qualified and trained personnel
  - \* adequate premises and space
  - \* suitable equipment and services
  - \* correct materials, containers and labels
  - \* approved procedures and instructions
  - \* suitable storage and transport
- (c) critical processing steps, key equipment and services are validated
- (d) all production operations are conducted in such a way as to produce products of the required quality
- (e) instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided.
- (f) operators are trained to carry out procedures correctly
- (g) records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and

investigated.

- (h) in-process and final controls for materials, processes, intermediates and products are adequate to determine suitability.
- (i) records of production, control and distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form.
- (j) distribution (wholesaling) of the products minimizes any risk to their quality
- (k) system is available to recall any batch of product from sale to supply.
- (l) complaints about marketed products are examined, the causes of quality defects investigated and interpreted and appropriate measures taken in respect of the defective products to prevent recurrence.

WHO :

## 2. GMP FOR PHARMACEUTICAL PRODUCTS

2.1 GMP is that part of QA which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP rules are directed primarily to diminishing the risks, inherent in any pharmaceutical production, that cannot be prevented completely through the testing of final products. Such risks are essentially of 2 types : cross-contamination (in particular by unexpected contaminants) and mix-ups (confusion) caused by false labels being put on containers.

Under GMP :

- (a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
- (b) critical steps of manufacturing processes and any significant changes made to the processes are validated;
- (c) all necessary facilities are provided, including:
  - (i) appropriately qualified and trained personnel;
  - (ii) adequate premises and space;
  - (iii) suitable equipment and services;
  - (iv) correct materials, containers and labels;
  - (v) approved procedures and instructions;
  - (vi) suitable storage and transport; and
  - (vii) adequate personnel, laboratories and equipment for in-process controls under the responsibility of their production management.

- (d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
- (e) operators are trained to carry out procedures correctly;
- (f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;
- (g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- (h) the proper storage and distribution of the products minimizes any risk to their quality;
- (i) a system is available to recall any batch of product from sale or supply;
- (j) complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products to prevent recurrence.

#### QUALITY CONTROL [QC]

##### MCA :

1.4 QC is the part of GMP which is concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of QC are that:

- (i) Adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediates, bulk and finished products and where appropriate for monitoring environmental conditions for GMP purposes.
- (ii) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and methods approved by QC.
- (iii) Test methods are validated.
- (iv) Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually been carried out. Any deviations have been fully recorded and investigated.
- (v) The finished products contain active ingredients complying with the qualitative and quantitative composition of the marketing authorization; are of the purity required, and are enclosed within their proper container and correctly labeled.

- (vi) Records are made of the results of inspection and that testing of materials, intermediate, bulk and finished products is formally assessed against specifications. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures.
- (vii) No batch of product is released for sale or supply, prior to certification by a QP that it is in accordance with the requirements of the marketing authorization.
- (viii) Sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

MCC :

#### 1.4 QUALITY CONTROL

1.4.1 QC is that part of GMP which is concerned with sampling, specifications and testing and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

1.4.2 The basic requirements and objectives of QC are as follows:

- (a) adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediates, bulk and finished products and where appropriate for monitoring environmental conditions for GMP purposes.
- (b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by the methods approved by QC.
- (c) test methods are validated
- (d) adequate standards and reagents are maintained
- (e) records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated.
- (f) the finished product complies with all legal requirements and is enclosed within its specified container and correctly labeled.
- (g) records are made of the results of inspection and testing of materials, intermediates, bulk and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures.
- (h) no batch of product is released for sale or supply prior to certification by a qualified pharmacist that it is in accordance with all legal requirements.
- (i) sufficient reference samples of starting materials and products are retained to permit future

examination of the product if necessary, and the product is retained in its final pack unless exceptionally large packs are produced.

- (j) follow-up stability trails in final packaging are conducted to assess the validity of the shelf life.

WHO :

### 3. QUALITY CONTROL [QC]

3.1 QC is the part of GMP concerned with sampling, specifications and testing and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. QC is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

3.2 Each holder of a manufacturing authorization should have a QC department. The independence of QC from production is considered fundamental. The QC department should be independent of other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his or her disposal. Adequate resources must be available to ensure that all the QC arrangements are effectively and reliably carried out. The basic requirements and objectives of QC are as follows:

- (a) adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting and testing starting materials, packaging materials, intermediates, bulk and finished products and where appropriate for monitoring environmental conditions for GMP purposes.
- (b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the QCD.
- (c) test methods must be validated
- (d) records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated.
- (e) the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container and correctly labeled.
- (f) records must be made of the results of inspecting and testing materials, intermediates, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.
- (g) no batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of marketing authorization. In certain countries, by law, the batch release is a task of the authorized person from the production department together with the authorized person from the QCD.
- (h) sufficient reference samples of starting materials and products must be retained to permit future

examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

- 3.3 The QC department as a whole will also have other duties, such as to establish, validate and implement all QC procedures, to evaluate, maintain and store the reference standards for substances, to ensure the correct labeling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.
- 3.4 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product and an examination of the finished pack.
- 3.5 QC personnel must have access to production areas for sampling and investigation as appropriate.



## CHAPTER 10

# CONTRACT MANUFACTURE & ANALYSIS

TGA :

In this section, contract manufacture means the manufacture in part or whole of a product by one [or More] manufacturer(s)[Contract Acceptor] for another party [Contract Giver]. Contract Quality Control is discussed in Clauses 831-833.

698. The Contract Giver must ascertain that where a license is required for the class of goods and operations being contracted, the Contract Acceptor is appropriately licensed.  
The Contract Giver should also be satisfied that the Contract Acceptor has the capability to do the Work and that the operations can be carried out in the agreed manner.  
Initial and periodic audits of the Contract Acceptor should be carried out and documented. Where necessary these audits may be carried out by an agreed third party Quality Representative [see AS3901: Quality Systems for Design/Development, Production, Installation and Servicing].
699. To ensure that the responsibilities of both parties are clearly understood and recorded, the arrangements and responsibilities of both parties are clearly understood and recorded, the arrangements and responsibilities for every aspect of manufacture and quality control that is relevant Good Manufacturing Practice, for each product made under contract, must be unambiguously specified in writing in a “Specification of GMP Responsibilities”, or equivalent document, signed by a representative of both parties. The signatories should be the persons primarily responsible for Quality Assurance [see also Clauses 803 and 805].
- Note: It is recommended that commercial arrangements be the subject of a separate agreement or contract.
- The Specification should include where applicable: -
- the arrangements for the specification, design, supply and approval of starting materials; components and printed packaging and labeling materials;
  - the party or parties responsible for the preparation of appropriate master formulae and processing instructions, master packaging and labeling instructions and product specifications, as specified in Section 5;
  - where necessary, additional information to the Contract Acceptor regarding any potential hazard to premises, plant, personnel, other materials or other products;
  - the title of the person responsible for quality control and release of the bulk product and/or final release for sale. This person should meet the requirements specified in Section 3, and may be an employee of or a Quality Representative of either the Contract Giver or the Contract Acceptor [see also Contract Quality Control];
  - where the quality control testing is to be carried out by the Contract Acceptor the Contract Giver should formally record that the quality control specifications exist and have been approved by him;
  - the responsibility for stability testing as specified in Clauses 825-826;
  - the party responsible for investigating complaints relating to each product made under contract;

- the party responsible for the taking and keeping of retention samples of materials and products, and the maintenance of records of manufacture and testing.

700. The specification of GMP responsibilities should be accessible at the premises of both the Contract Giver and Contract Acceptor for examination by the inspecting authority. It should be formally Reviewed at appropriate intervals. Any alterations to contract arrangements should be agreed in writing by both parties.
701. 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 consented to them. Any arrangements made with a third party should be in accordance with all the provisions of this sub-section.

#### Contract Quality Control

831. Some or all aspects of QC may be carried out by a person not solely employed by the manufacturer. External laboratories should be adequately equipped, staffed and experienced to undertake the work contracted to them.
832. Where samples are sent to external laboratories for occasional testing only, the purchase order or letter should specify the tests required, as specific a reference as possible to the test method and the designation of the samples dispatched. The report of results should make reference to the method used. It may include a statement that a particular specification is or is not complied with, but should not indicate approval or rejection.
833. Where sampling, testing and consequent reporting are to be routinely carried out, the following details should be included in an Agreement:
- \* procedures for taking samples and delivery of these samples to the contract tester;
  - \* full details of the test method of where such details may be obtained;
  - \* arrangement for reporting test results and retention of records of test results; and
  - \* arrangements for keeping retention samples

#### MCA :

##### a. General

- 7.1 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.
- 7.2 All arrangements for contract manufacture and analysis including any proposed changes in technical or other arrangements should be in accordance with the marketing authorization for the product concerned.

##### b. The Contract giver

7.3 The Contract Giver is responsible for assessing the competence of the Contract Acceptor to carry out successfully the work required and for ensuring by means of the Contract that the principles and guidelines of GMP as interpreted in this guidelines.

7.4 The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

7.5 The Contract Giver should ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or the products have been released by a QP.

c. The Contract Acceptor

7.6 The Contract Acceptor must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver. Contract manufacture may be undertaken only by a manufacturer who is the holder of a manufacturing authorization.

7.7 The Contract Acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.

7.8 The Contract Acceptor should not pass to a third party any of the work entrusted to him under the Contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the Contract Giver and Contract Acceptor.

7.9 The Contract Acceptor should refrain from any activity which may adversely affect the quality of the product manufactured and/or analyzed for the Contract Giver.

d. The Contract

7.10 A Contract should be drawn up between the Contract Giver and Contract Acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the Contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and GMP. All arrangements for manufacture and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.11 The Contract should specify the way in which the QP releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of marketing authorization.

7.12 The contract should describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and quality controls, including in-process controls, and who has the responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the Contract Acceptor should take samples at the premises of the manufacturer.

- 7.13 Manufacturing, analytical and distribution records, and reference samples should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of a complaint or a suspected defect must be accessible and specified in the defect/recall procedures of the Contract Giver.
- 7.14 The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.
- 7.15 In the case of Contract Analysis, the Contract Acceptor should understand that he is subject to inspection by the competent authorities.

MCC :

## 12. CONTRACT MANUFACTURE, ANALYSIS AND SERVICING

### 12.1 PRINCIPLES

- 12.1.1 The relative responsibilities of the Contract Giver and 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 Contract 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 authorize a Contract Acceptor to commence manufacture / packaging / testing of a medicine, until he has assured himself and authorized in his own handwriting, that all 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 Documentation (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 authorized 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 the 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

specification, 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 SOPs.

The technical agreement should address all aspects relating to change control. The Technical agreement may refer to SOPs 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 MCC, 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 MCC, prior to implementation of the change. Where necessary, master documentation and registration dossiers should be updated in accordance with SOPs and policy.

Where changes took place during manufacturing / 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 CoA 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 contract where applicable. A Contract Acceptor, should on receipt of materials, take all material into his own system of receipt 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 labeled in accordance with GMP requirements.

- 12.2.16 The guidelines under 12.2 should also be used for sale / distribution contracts where applicable

### 12.3 CONTRACT ANALYSIS

- 12.3.1 As appropriate, the provisions under “Contract Manufacture and / or packaging” may apply also to contract analysis.
- 12.3.2 Although analysis and testing may be undertaken by a Contract Analyst, the responsibility for QC 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 under Chapter “Quality Control” 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 SOP should specify the acceptable limits between services or maintenance of equipment, systems etc.

WHO :

#### 8. CONTRACT PRODUCTION AND ANALYSIS

8.1 Principle : Contract production and analysis must be clearly defined, agreed and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality. There must be a written contract between the contract giver and the contract acceptor which clearly establishes the duties of each party. The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility.

##### a. General

8.2 All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements should be in accordance with the marketing authorization for the product concerned.

8.3 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

8.4 The contract should permit the contract giver to audit the facilities of the contract acceptor.

8.5 In the case of contract analysis, the final approval for release must be given by the authorized person(s).

The Contract giver



- 8.6 The Contract Giver is responsible for assessing the competence of the Contract Acceptor in successfully carrying out the work or tests required and for ensuring by means of the Contract that the principles of GMP described in this guide are followed.
- 8.7 The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract acceptor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials, or other products.
- 8.8 The Contract Giver should ensure that all processed products and materials delivered by the Contract Acceptor comply with their specifications or that the product has been released by the authorized person.

#### The Contract Acceptor

- 8.9 The Contract Acceptor must have adequate premises, equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization.
- 8.10 The Contract Acceptor should not pass to a third party any of the work entrusted to him under the Contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original Contract Giver and Contract Acceptor.
- 8.11 The Contract Acceptor should refrain from any activity which may adversely affect the quality of the product manufactured and/or analyzed for the Contract Giver.

#### The Contract

- 8.12 A Contract should be drawn up between the Contract Giver and Contract Acceptor that specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the Contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and GMP. All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.
- 8.13 The Contract should specify the way in which the authorized person releasing the batch for sale ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.
- 8.14 The contract should describe clearly who is responsible for purchasing, testing and releasing materials and for undertaking production and quality controls, including in-process controls, and who has the responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the Contract Acceptor should take samples at the premises of the manufacturer.
- 8.15 Manufacturing, analytical and distribution records, and reference samples should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the



event of a complaint or a suspected defect must be accessible and specified in the defect/recall procedures of the Contract Giver.

- 8.16 The Contract should describe the handling of starting materials, intermediate and bulk products, and finished products if they are rejected. It should also describe the processing of information if the contract analysis shows that the tested product must be rejected.

# CHAPTER 11

## COMPLAINTS & PRODUCT RECALL

### PRODUCT COMPLAINTS

#### TGA :

834. Complaints or defects relating to product quality including those made to non-technical personnel should be reported, investigated and resolved following a written SOP. The procedure should ensure that all complaints or defects are reported (including those arising from returned goods handling) and should specify the responsible persons through whom they are to be channeled. The procedure should also ensure that complaints concerning quality, including adverse drug reactions, are reported at least to the quality department.
835. The quality department should maintain a file of complaints and defects, together with the results of evaluation, investigation and, (where applicable), action taken, structured to facilitate review. The file should be reviewed periodically to check for trends or the recurrence of a particular problem and the review documented and circulated to the relevant departments.

#### Product Recalls

836. There should, at all times, be a person, group or committee nominated to assess the need for and where necessary, to initiate and coordinate product recalls.
837. A written procedure for product recall based upon the Australian Uniform Recall Procedure for Therapeutic Goods and the requirements of the Trade Practices Act should be developed. The procedure should specify the actions to be taken for all reasonable contingencies that may be anticipated. It should be capable of being put into operation at any time, inside or outside normal working hours and should include emergency and 'out of hours' contacts and telephone numbers.
838. 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).
839. Recalls must not be undertaken without informing the officer in the Commonwealth department of Community Services and Health responsible for Government coordination of recalls and such other persons as may be nominated in the Uniform Procedure.

#### MCA :

- 8.1 A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him. If this person is not the QP, the latter should be made aware of any complaint, investigation or recall.
- 8.2 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

- 8.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for QC should normally be involved in the study of such problems.
- 8.4 If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches which may contain re-works of the defective batch should be investigated.
- 8.5 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- 8.6 Complaint records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.
- 8.7 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.
- 8.8 A person should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organization. If this person is not the QP, the latter should be made aware of any recall operation.
- 8.9 There should be established written procedures, regularly checked and updated when necessary, in order to organize any recall activity.
- 8.10 Recall operations should be capable of being initiated promptly and at any time.
- 8.11 All competent authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or suspected of being, defective.
- 8.12 The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, telephone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medicinal samples.
- 8.13 Recall products should be identified and stored separately in a secure way while awaiting a decision on their fate.
- 8.14 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.
- 8.15 The effectiveness of the arrangements for recalls should be evaluated from time to time.

Schedule M :

28. Complaints and Adverse Reactions :-

- 28.1 All complaints thereof concerning product quality shall be carefully reviewed and recorded according to written procedures. Each complaint shall be investigated / evaluated by the designated personnel of the company and the records of investigation and remedial action taken thereof shall be maintained.
- 28.2 Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned Licensing Authority.
- 28.3 There shall be written procedures describing the action to be taken, recall to be made of the defective product.
- 27.1 A prompt and effective product recall system of defective products shall be devised for timely information of all concerned stockists, wholesalers, suppliers, up to the retail level within the shortest period. The licensee may make use of both print and electronic media in this regard.
- 27.2 There shall be an established written procedure in the form of SOP for effective recall of products distributed by the licensee. Recall operations shall be capable of being initiated promptly so as to effectively reach at the level of each distribution channel.
- 27.3 The distribution records shall be made readily available to the persons designated for recall.
- 27.4 The designated person shall record a final report issued, including a reconciliation between the delivered and the recovered quantities of the products.
- 27.5 The effectiveness of the arrangements for recalls shall be evaluated from time to time.
- 27.6 The recalled products shall be stored separately in a secured segregated area pending final decision on them.

**MCC :  
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 casual 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 casual relationship is suspected between drug and event.

Unexpected Adverse drug Reaction

An adverse reaction, the nature and severity of which is not consistent with applicable product information or labeling 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 1 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 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 a 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 and 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 persons.

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 and 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 and 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.

WHO :

## 6. COMPLAINTS

6.1 Principle : All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures.

6.2 A person responsible for handling the complaints and deciding the measures to be taken should be designed, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation, or recall.

6.3 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

6.4 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for QC should normally be involved in the study of such problems.

6.5 If 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 reprocessed product from the defective batch should be investigated.

- 6.6 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.
- 6.7 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- 6.8 Complaint records should be regularly reviewed for any indication of specific recurring problems requiring attention and possibly the recall of marketed products.
- 6.9 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration or any other serious quality problems with a product.

## 7. PRODUCT RECALLS

- 7.1 Principle : There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.
- 7.2 A person responsible for the execution and coordination of recalls should be designated, as well as sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency. This person should normally be independent of the sales and marketing organization. If this person is different from the authorized person, the latter should be made aware of any recall operation.
- 7.3 There should be established written procedures, regularly checked and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly at least down to the level of the hospital or pharmacy.
- 7.4 All competent authorities of all countries to which a given product may have been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being defective.
- 7.5 The distribution records should be readily available to the person(s) responsible for recalls and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.
- 7.6 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.
- 7.7 The effectiveness of the arrangements for recalls should be evaluated from time to time.
- 7.8 An instruction should be included to store recalled products in a secure segregated area while their fate is decided.



## CHAPTER 12

# SELF INSPECTION / QUALITY AUDITS

### TGA :

840. All aspects of GMP should be audited periodically and thoroughly by a competent person, team or consultant, according to a written program. A “rolling” audit of individual sections that nevertheless covers all aspects in a prescribed time is preferred to a single, exhaustive audit.

Audit by a parent or affiliated company may be acceptable, depending on its frequency and depth. Audit by an internal team is preferred: where possible, the composition of such a team should be varied from time to time.

A written report of each audit should be prepared.

Evidence should be available that the program is written and followed and that follow-up activity results.

841. Where an external audit by a qualified microbiologist (see Clause 306) is commissioned, the audit should include, where applicable -

- \* sterility and pyrogen testing;
- \* microbiological laboratory technique, performance and records;
- \* microbiological specifications, tests and controls;
- \* cleaning and sanitation procedures for the manufacturing areas; and
- \* environmental monitoring.

### MCA :

9.1 Personnel matters, premises, equipment, documentation, production, QC, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self-inspection, should be examined at intervals following a pre-arranged program in order to verify their conformity with the principles of QA.

9.2 Self-inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits from external experts may also be useful.

9.3 All self-inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

Schedule M :

15. SELF INSPECTION & QUALITY AUDIT

- 15.1 To evaluate the manufacturer's compliance with GMP in all aspects of production and QC, concept of self inspection shall be followed. The manufacturer shall constitute a team of independent, experienced, qualified persons from within or outside the company, who can audit objectively the implementation of methodology and procedures evolved. The procedure for self inspection shall be documented, indicating self-inspection results, evaluation, conclusions and recommended corrective actions with effective follow up program. The recommendations for corrective actions shall be adopted.
- 15.2 The program shall be designed to detect shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections shall be performed routinely and on specific occasions, like when product recalls or repeated rejections occur or when an inspection by the licensing authorities is announced. The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of GMP objectively, all recommendations for corrective actions shall be implemented.
- 15.3 Written instructions for self-inspection shall be drawn up which shall include the following :
- (a) Personnel
  - (b) Premises including personnel facilities
  - (c) Maintenance of buildings and equipment
  - (d) Storage of starting materials and finished products
  - (e) Equipment
  - (f) Production and in-process controls
  - (g) Quality Control
  - (h) Documentation
  - (i) Sanitation and Hygiene
  - (j) Validation and revalidation programs
  - (k) Calibration of instruments or measurement systems
  - (l) Recall procedures
  - (m) Complaints management
  - (n) Labels control

- (o) Results of previous self-inspections and any corrective steps taken

MCC :

## 1.5 AUDITS

1.5.1 Audits on all systems, procedures and operations should be regularly conducted in order to monitor compliance with and the effectiveness of GMP and QA principles in the various operations and to allow for improvement and corrective measures where required.

Audits may be in-house or carried out by local regulatory authorities or the regulatory authorities of countries to which companies wish to export.

1.5.2 Audits should follow a pre-arranged program and include inspection of the following:

- (a) organizational matters and responsibilities
- (b) qualifications and training programs
- (c) compliance with hygiene requirements and entry restrictions
- (d) cleaning and disinfection programs
- (e) medical checks on personnel
- (f) production facilities, premises and equipment, including QC
- (g) production operations, procedures and documentation including QC
- (h) storage, handling, distribution and materials management
- (i) QA aspects such as complaints, returned goods and validation
- (j) suppliers of starting and packaging (especially printed) material
- (k) third party contractors for manufacturing, packaging, analysis and where required distribution of medicines.

1.5.3 Audits should be detailed and conducted by competent and impartial persons from the Company. External auditors may also be useful.

1.5.4 Audit reports should be made and corrective measures agreed upon, recorded and followed up.

## 1.6 QUALITY EVALUATION AUDITS

1.6.1 Written records as detailed under “Documentation” should be maintained so that data therein can be used for evaluating the quality standards of each product to determine the need for changes in product specifications or manufacturing and control procedures.

1.6.2 Written procedures should be established and followed for such evaluations and should include provisions for :

- \* a review of every batch, whether approved or rejected, and where applicable, records associated with the batch.
- \* a review of complaints, recalls, returned or salvaged products and investigations conducted during normal product record reviews before a batch is released.

1.6.3 Procedures should be established to ensure that the responsible official of the firm, if not personally involved in or immediately aware of recalls, salvaged products, complaints etc. be notified in writing of such issues.

WHO :

## 9. SELF-INSPECTION AND QUALITY AUDITS

An inspection team comprising of appropriate personnel should participate in inspections. The operational limitations and validation of the critical processing steps of a production process should be examined, to make sure that the manufacturer is taking adequate steps to check that the process works consistently.

A good starting point for an excipient plant inspection is a review of the following areas.

- \* Non-conformance, such as rejection of a batch not complying with specifications, return of a product by a customer, or recall of a product. The cause of non-conformance should have been determined by the manufacturer, a report of the investigation prepared, and subsequent corrective action initiated and documented. Records and documents should be reviewed to ensure that such non-conformance is not the result of a poorly developed or inconsistent process.
- \* Complaint files. Customers may report some aspects of product attributes that are not entirely suitable for their use. These may be caused by impurities or inconsistencies in the excipient manufacturing process.
- \* Change control documentation
- \* Master Formula and batch production records. Frequent revisions may reveal problems in the production process.
- \* Specifications for the presence of unreacted intermediates and solvent residues in the finished excipient.
- \* Storage areas for rejected products.

In evaluating the adequacy of measures taken to preclude contamination of materials in the process, it is appropriate to consider the following factors:

- \* Type of system (e.g. open or closed)
- \* Form of the material ( e.g. wet or dry)

\* Stage of processing and use of equipment and / or area (e.g. multipurpose or dedicated)

9.1 Principle : The purpose of self – inspection is to evaluate the manufacturer’s compliance with GMP in all aspects of production and QC. The self – inspection program should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self – inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. In the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self – inspection should consist of personnel who can evaluate the implementation of GMP objectively; all recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up program.

Items for self inspection

9.2 Written instructions for self-inspection shall be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

- (a) Personnel
- (b) Premises including personnel facilities
- (c) Maintenance of buildings and equipment
- (d) Storage of starting materials and finished products
- (e) Equipment
- (f) Production and in-process controls
- (g) Quality Control
- (h) Documentation
- (i) Sanitation and Hygiene
- (j) Validation and revalidation programs
- (k) Calibration of instruments or measurement systems
- (l) Recall procedures
- (m) Complaints management
- (n) Labels control
- (o) Results of previous self-inspections and any corrective steps taken

#### Self – inspection team

9.3 Management should appoint a self – inspection team from local staff who are expert in their own fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

#### Frequency of self – inspection

9.4 The frequency at which self – inspections are conducted may depend on company requirements.

#### Self – inspection report

9.5 A report should be made at the completion of self – inspection. The report should include:

- (a) self – inspection results
- (b) evaluation and conclusions
- (c) recommended corrective actions

#### Follow – up action

9.6 The Company management should evaluate both the self – inspection report and the corrective actions as necessary.

#### Quality audit

9.7 It may be useful to supplement self – inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors.

#### Suppliers' audit

9.8 The QC department should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

9.9 Before suppliers are approved and included in the specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the suppliers' ability to conform with GMP standards for active pharmaceutical ingredients.

# CHAPTER 13

## USE OF COMPUTERS

TGA :

900. Where a computer is used in connection with any procedure or process associated with the production of therapeutic goods, the computer system employed should meet the requirements of this code for those manual functions which it replaces.
901. The responsibilities of the key persons in manufacturing and quality departments are not changed by the use of computers.
902. Persons with appropriate expertise should be responsible for the design, introduction and regular review of a computer system.
903. The development, implementation and operation of a computer system should be carefully documented at all stages and each step proven to achieve its written objective under challenging test conditions.
904. Software development should follow the principles of Australian Standard AS 3563: Software Quality Management System.

Similarly, where a purchased source code is used or modified, the vendor's attention should be directed to AS 3563. Vendors should be asked to provide written assurance that software development or modification has followed the quality management system of that standard or of an equivalent system.

A logic flow diagram or schematic for software should be prepared for critical evaluation against system design/requirements/criteria.

905. A control document should be prepared specifying the objectives of a proposed computer system, the data to be entered and stored, the flow of data, the information to be produced, the limits of any variables and the operating program(s) and test programs, together with each document produced by the program, instructions for testing, operating and maintaining the system and the names of the person(s) responsible for its development and operation.
906. When a computer system is in process of replacing a manual operation, the 2 systems should be operated in parallel until it has been shown that the computer system is operating correctly. Records of the parallel operation and the defects found and resolved should be added to the history document in the following Clause.
907. Any change to an existing computer system should be made in accordance with a defined change control procedure which should document the details of each change made, its purpose and its date of effect and should provide for a check to confirm that the change has been applied correctly.
908. Where development has progressed to a point where the system can not readily be assessed by

reading the control and development documents together, a new control document incorporating all amendments should be prepared and the original retained.

909. Data collected directly from manufacturing or monitoring equipment should be checked by verifying circuits or software to confirm that it has been accurately and reliably transferred.

Similarly, data or control signals transmitted from computer to equipment involved in the manufacturing process should be checked to ensure accuracy and reliability.

910. The entry of critical data into a computer by an authorized person (e.g. entering a master processing formula) should require independent verification and release for use by a second authorized person.
911. A hierarchy of permitted access to enter, amend, read, or printout data should be established according to user need. Suitable methods of preventing unauthorized entry should be available, such as passcards or personal user-identity codes. A list of forbidden codes, e.g. names, birthdays, should be issued and a procedure for regular change of codes should be established.
912. The Computer system should create a complete record (“audit trail”) of all entries and amendments to the data base.
913. The recovery procedure to be followed in the event of a system breakdown should be defined in writing. This procedure should be designed to return the system to a previous state. A check should be made periodically that all programs and data necessary to restore the system will be available in case of breakdown. Any such breakdown and the recovery action should be recorded.
914. The computer system should be able to provide printed copies of relevant data and information stored within it. Hard copies of master documents should be signed, dated and filed in accordance with Section 5.
915. Printed matter produced by computer peripherals should be clearly legible and, in the case of printing onto forms, should be properly registered onto the forms.
916. Storage of live and master data should be in accordance with Clauses 516 and 513 respectively.
917. Records should be available for the following aspects of a computer system validation:
- \* Protocol for validation
  - \* General description of the system, the components and the operating characteristics
  - \* Diagrams of hardware layout/interaction
  - \* System logic diagrams or other schematic form for software packages
  - \* Current configuration for hardware and software
  - \* Review of historical logs of hardware and software for development, start-up and normal run periods



- \* Records of evaluation data to demonstrate system does as intended (verification stage and ongoing monitoring)
- \* Range of limits for operating variables
- \* Details of formal change control procedure
- \* Records of operator training
- \* Details of access security levels/controls
- \* Procedure for ongoing evaluation

MCA : (Annexure 11)

## COMPUTERISED SYSTEMS

### Personnel

1. It is essential that there is the closest co-operation between key personnel and those involved with computer systems. Persons in responsible positions should have the appropriate training for the management and use of systems within their field of responsibility which utilizes computers. This should include ensuring that appropriate expertise is available and used to provide advice on aspects of design, validation, installation and operation of a computerized system.

### Validation

2. The extent of validation necessary will depend on a number of factors including the use to which the system is to be put, whether the validation is to be prospective or retrospective and whether or not novel elements are incorporated. Validation should be considered as part of the complete life cycle of a computer system. This cycle includes the stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and modifying.

### System

3. Attention should be paid to the siting of equipment in suitable conditions where extraneous factors cannot interfere with the system.
4. A written detailed description of the system should be produced (including diagrams as appropriate) and kept up to date. It should describe the principles, objectives, security measures and scope of the system and the main features of the way in which the computer is used and how it interacts with other systems and procedures.
5. The software is a critical component of a computerized system. The user of such software should take all reasonable steps to ensure that it has been produced in accordance with a system of QA.
6. The system should include, where appropriate, built-in checks of the correct entry and processing of data.
7. Before a system using a computer is brought into use, it should be thoroughly tested and confirmed as

- being capable of achieving the desired results. If a manual system is being replaced, the 2 should be run in parallel for a time, as part of this testing and validation.
8. Data should only be entered or amended by persons authorized to do so. Suitable methods of deterring unauthorized entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals. There should be a defined procedure for the issue, cancellation and alteration of authorization to enter and amend data, including the changing of personal passwords. Consideration should be given to systems allowing for recording of attempts to access by unauthorized persons.
  9. When critical data are being entered manually (for e.g. the weight and batch number of an ingredient during dispensing), there should be an additional check on the accuracy of the record which is made. This check may be done by a second operator or by validated electronic means.
  10. The system should record the identity of operators entering or confirming critical data. Authority to amend entered data should be restricted to nominated persons. Any alterations to an entry of critical data should be authorized and recorded with the reason for the change. Consideration should be given to building into the system the creation of a complete record of all entries and amendments (an “adult trail”)
  11. Alterations to a system or to a computer program should only be made in accordance with a defined procedure which should include provision for validating, checking, approving and implementing the change. Such an alteration should be implemented with the agreement of the person responsible for the part of the system concerned and the alteration should be recorded. Every significant modification should be validated.
  12. For quality auditing purposes, it should be possible to obtain clear printed copies of electronically stored data.
  13. Data should be secured by physical or electronic means against willful or accidental damage. Stored data should be checked for accessibility, durability and accuracy. If changes are proposed to the computer equipment or its programs, the above mentioned checks should be performed at a frequency appropriate to the storage medium being used.
  14. Data should be protected by backing-up at regular intervals. Back-up data should be stored as long as necessary at a separate and secure location.
  15. There should be available adequate alternative arrangements for systems which need to be operated in the event of a breakdown. The time required to bring the alternative arrangements into use should be related to the possible urgency of the need to use them. For e.g., information required to affect a recall must be available at short notice.
  16. The procedures to be followed if the system fails or breaks down should be defined and validated. Any failures and remedial action taken should be recorded.
  17. A procedure should be established to record and analyze errors and to enable corrective action to be taken.
  18. When outside agencies are used to provide a computer service, there should be a formal agreement including a clear statement of the responsibilities of that outside agency.

19. When the release of batches for sale or supply is carried out using a computerized system, the system should allow for only a QP to release the batches and it should clearly identify and record the person releasing the batches.

MCC :

## 19. ELECTRONIC DATA PROCESSING

### 19.1 PRINCIPLES

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

### 19.2 RESPONSIBILITIES

- 19.2.1 The responsibilities of key personnel described in the guide are not changed by the use of computers and it is essential that there is the closest co-operation between Production, QC and Electronic Data Processing Departments.
- 19.2.2 Persons with appropriate expertise should be responsible for the design and introduction of a proposed computer system. These or other expert persons should be retained to review the system at appropriate intervals.
- 19.2.3 Employees whose duties involve the use of a computer system should be appropriately trained in its correct use. Written operating procedures should be readily available to these employees. On-line help screens could be used for this purpose. Records of operator training should be kept.

### 19.3 VALIDATION

- 19.3.1 The development, implementation and operation of a computer system should be carefully documented at all stages and each step proven to achieve its written objective under challenging test conditions.
- 19.3.2 The extent of validation necessary will depend on a number of factors
- the use to which the system is to be put
  - whether the validation is to be prospective or retrospective
  - whether novel elements are incorporated

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

- 19.3.3 A control document (system specification) should be prepared specifying the objectives of a proposed computer system, the data to be entered and stored, the flow of data, how it interacts with other systems and procedures, the information to be produced, the limits of any variable and

the operating program(s) and test programs. Examples of each document produced by the program should be included. A functional specification should also be prepared to provide instructions for testing, operating and maintaining the system and the names of the person or persons responsible for its development and operation.

- 19.3.4 Computers should be protected from disturbances caused by fluctuations in the electrical supply and from loss of memory due to supply failure, electrical / magnetic disturbances or high temperatures.
- 19.3.5 Before a system using a computer is brought into use, it should be tested and confirmed as being capable of achieving results. If a manual system is being replaced, it is advisable to run the two in parallel for a time, as part of this testing and validation.
- 19.3.6 At installation and after a suitable period of running a new system, it should be independently reviewed and compared with the system specification and functional specification to ascertain whether it is meeting all of its requirements.
- 19.3.7 Alterations to a system or to a computer program should only be made in accordance with a defined procedure which should include provision for checking, approving and implementing the change. Such an alteration should be implemented with the agreement of the person responsible for the part of the system concerned and the alteration should be recorded.
- 19.3.8 Data collected directly from manufacturing or monitoring equipment should be checked periodically to confirm that it has been accurately and reliably transferred. Similarly, data or control signals transmitted from a computer to equipment involved in the manufacturing process should be checked periodically to ensure accuracy and reliability.

#### 19.4 SECURITY

- 19.4.1 Data should only be entered or amended by persons authorized to do so. Suitable methods of deterring unauthorized entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals. The method of final release by computer of a batch for sale or supply should uniquely identify the person effecting the release. There should be a defined procedure for the issue, cancellation and alteration of authorization to amend data, including the changing of personal codes.
- 19.4.2 The entry of critical data into a computer by an authorized person (e.g. entering a master processing formula) should require independent verification and release of use by a second authorized person.
- 19.4.3 The computer program should create a complete record (“audit trail”) of all entries and amendments to the data base.
- 19.4.4 Adequate alternative arrangements should be available, i.e. disaster recovery procedure, for systems which need to be operated in the event of a breakdown. The procedures to be followed if a system fails or breaks down, should be defined and tested. Regular back-ups of all files should be stored in a secure location to prevent willful or accidental damage. Any failure and remedial action taken should be recorded.
- 19.4.5 It should be possible to obtain printed copies of electronically stored data.

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

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

## CHAPTER 14

# SECURITY GUIDELINES

MCC :

### 20.1 PRINCIPLE

- 20.1.1 Adequate security measures are essential to protect pharmaceutical installations against unauthorized entry or deliberate adulteration of products.
- 20.1.2 Legitimate procedures should be followed for the removal / transportation of stock and materials to prevent pilferage or theft.

### 20.2 SECURITY PERSONNEL

- 20.2.1 Sufficient resources should be provided to establish an adequate security force on a 24 hour, 7 days per week basis.
- 20.2.2 A Security manager should be appointed in writing to identify, evaluate and propose corrective measures to reduce risk to acceptable levels. He should be conversant with the Criminal Procedures Act and Labour Legislation.
- 20.2.3 Security staff should be security vetted and should be adequately trained and knowledgeable about company procedures and practices as they impact on Security operations.

### 20.3 ENTRY TO SITE

- 20.3.1 A risk evaluation is recommended to identify potential means of unauthorized entry during daylight as well as after hours.
- 20.3.2 The following security measures may be appropriate:
  - \* a perimeter fence of good quality
  - \* adequate security lighting
  - \* limited and restricted access to all production and storage areas, (especially scheduled) medicines
  - \* adequate gates of sound construction, that are lockable
  - \* security guards patrolling the grounds during the day and night. A telephone for the use of night security staff to use in the event of unlawful entry or fire, or an adequate electronic alarm system
  - \* guard dogs and handlers for night patrol

### 20.4 ENTRY TO BUILDINGS

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

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

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

## 20.5 INTERNAL SECURITY

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

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

## CHAPTER 15

# SAFETY AND ENVIRONMENTAL PROTECTION

MCC :

### 21.1 PRINCIPLES

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

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

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

### 21.2 SAFETY

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

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

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

21.2.4 The following should always be considered:

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

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



### 21.3 ENVIRONMENTAL PROCEDURES

- 21.3.1 In addition to all applicable legal requirements, pharmaceutical companies may institute additional in-house requirements.
- 21.3.2 Procedures and controls to minimize the discharge to the environment of hazardous substances may include the following:
- \* procedures and controls regarding the discharge of hazardous substances into sewage and storm water drains where the material could accumulate or interfere with treatment processes.
  - \* emission to the atmosphere from process vents, storage vessels, area ventilating systems, incinerator stacks and fugitive emissions.
  - \* contamination of soil, water or the atmosphere due to spill, leakage from any source (storage tanks etc), malfunction of control equipment, fire or explosion or from inadequate or improper treatment, storage or disposal practices.
- 21.3.3 Where possible, the company should have methods of rendering waste substances harmless to the environment.
- 21.3.4 There should be procedures to control the generation, transportation, storage, treatment or disposal of hazardous wastes. The most effective control of hazardous waste is the reduction or elimination of the waste. To that end, re-use, recycling, reclamation, inactivation or destruction is more desirable than land disposal or deep well injection. Other techniques should be thoroughly investigated before land disposal is selected.
- 21.3.5 Emergency procedures to minimize hazards associated with discharges to the environment should be developed. Procedures to co-ordinate internal and emergency groups should be considered.
- 21.3.6 The capabilities of vendor suppliers and contract-acceptors should also be evaluated from an environmental point of view.
- 21.3.7 Monitoring programs should be developed to determine that compliance with legal and/or in-house specifications is maintained.
- 21.3.8 Procedures should be developed for the operation and maintenance of pollution control and monitoring equipment and should include preventive maintenance.
- 21.3.9 Records should be retained in accordance with legal and / or in-house requirements.
- 21.3.10 The integrity of underground storage tanks and associated piping and equipment should be routinely verified. Alternatives to underground storage of potentially hazardous substances should be considered.
- 21.3.11 The preferred strategy for all waste management is reduction of waste at source.

## CHAPTER 16

# QUALIFIED PERSON (QP)

MCA :

Routine duties of a Qualified Person (QP)

8.1 Before certifying a batch prior to release, the QP doing so should ensure that at least the following requirements have been met:

- (a) The batch and its manufacture comply with the provisions of the marketing authorization (including the authorization required for importation where relevant);
- (b) manufacture has been carried out in accordance with GMP or, in the case of batch imported from a third country, in accordance with GMP standards at least equivalent to EC GMP.
- (c) the principle manufacturing and testing processes have been validated; account has been taken of the actual production conditions and manufacturing records;
- (d) any deviations or planned changes in production or QC have been authorized by the persons responsible in accordance with a defined system. Any changes requiring variation to the marketing or manufacturing authorization have been notified to and authorized by the relevant authority;
- (e) all the necessary checks and tests have been performed, including any additional sampling, inspection, tests or checks initiated because of deviations or planned changes;
- (f) all necessary production and QC documentation has been completed and endorsed by the staff authorized to do so;
- (g) all audits have been carried out as required by the QA system;
- (h) the QP should in addition take into account any other factors of which he is aware which are relevant to the quality of the batch.

A QP may have additional duties in accordance with national legislation or administrative procedures.

8.2 A QP who confirms the compliance of an intermediate stage of manufacture has the same obligations as above in relation to that stage unless otherwise specified in the agreement between the QPs.

8.3 A QP should maintain his knowledge and experience up to date in the light of technical and scientific progress and changes in quality management relevant to the products which he is required to certify

8.4 If a QP is called upon to certify a batch of a product type with which he is unfamiliar, for e.g. because the manufacturer for whom he works introduces a new product range or because he starts to work for a different manufacturer, he should first ensure that he has gained the relevant knowledge and experience necessary to fulfil this duty. In accordance with national requirements the QP may be required to notify the authorities of such a change and may be subject to renewed authorization.

WHO :

#### AUTHORIZED PERSON – ROLE, FUNCTIONS AND TRAINING

##### 1. The role and position of the authorized person in the company

The authorized person as the overall quality controller will be a member of a team whose function includes the following major areas :

- implementation (and, when needed, establishment) of the quality system;
- participation in the development of the company's quality manual;
- supervision of the regular internal audits or self-inspections;
- oversight of the QC department;
- participation in external audit (vendor audit);
- participation in validation programs;

Although authorized persons may not have line management responsibility for many activities within this function, they must be aware of any changes that may affect compliance with technical or regulatory requirements related to the quality of finished products. When any aspect of the company's operations is not in accordance with GMP guidelines or relevant registration in force, the authorized person must bring this to the attention of senior management. This duty should be reflected in the authorized person's job description.

The availability of an authorized person should be a pre-requisite for issue of a manufacturing license (authorization). The authorized person (as well as persons responsible for production & QC) must be approved by the drug regulatory authority. The license holder is obliged to inform the drug regulatory authority, or other responsible authority depending on national (regional) regulations, immediately if the authorized person is replaced unexpectedly. Such provisions will assure to a considerable degree, the independence of the authorized person from the management of the company in the fulfillment of his or her duties even when under pressure to depart from professional and technical standards.

As indicated in the GMP guidelines published in WHO, in certain countries, depending on the national legislations or regulations, two authorized persons are designated: one for production and another for QC. A company may have a complex structure, or operate at several locations, or both, and sometimes a separate authorized person may be designated who is responsible for manufacture of clinical trial materials. Consequently it may be necessary to nominate several authorized persons, one of them having the responsibilities of the overall quality controller and the others responsible for site or branch operations. The person authorizing batch release should be independent from production activities.

The drug regulatory authority should approve the authorized person on the basis of his or her professional curriculum vitae. Authorized persons have duties not only to their employer but also to the competent authorities such as the drug regulatory authority. They should establish good working relations with inspectors and as far as possible provide information on request during site

inspections.

The authorized person depends upon many working colleagues for the achievement of quality objectives, and may delegate some duties to appropriately trained staff while remaining the overall quality controller. It is therefore of paramount importance that he or she establish and maintain a good working relationship with other persons in positions of responsibility, especially those responsible for production and QC.

## 2. Implementation of the quality system

Authorized persons have a personal and professional responsibility for ensuring that each batch of finished products has been manufactured in accordance with the marketing authorization, GMP rules and all related legal and administrative provisions. This does not necessarily mean that they must have directly supervised all manufacturing and QC operations. They must be satisfied either directly or, more usually, by proper operation of quality systems, that manufacturing and testing have complied with all relevant requirements. Therefore it is recommended that the manufacturer establishes and maintains a comprehensive quality system, covering all aspects of GMP.

## 3. Routine duties of an authorized person

Before approving a batch for release, the authorized person doing so should always ensure that the following requirements have been met:

- \* The marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned.
- \* The principles and guidelines of GMP, as laid down in the guidelines published by WHO, have been followed.
- \* The principal manufacturing and testing processes have been validated, if different.
- \* All the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records.
- \* Any planned changes or deviations in manufacturing or QC have been notified in accordance with a well-defined reporting system before any product is released. Such changes may need notification to and approval by the drug regulatory authority.
- \* Any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations.
- \* All necessary production and QC documentation has been completed and endorsed by supervisors trained in appropriate disciplines.
- \* Appropriate audits, self-inspections and spot checks are being carried out by experienced and trained staff.
- \* Approval has been given by the head of the QC department.

- \* All relevant factors, have been considered, including any not specifically associated with the output batch directly under review (e.g. subdivision of output batches from a common input, factors associated with continuous production runs.

In certain circumstances, the authorized person may be responsible for the release of intermediates manufactured on contract.





#### 4. Education and training

The pool of expertise drawn upon for candidates for the position of authorized person may differ from country to country. The basic qualifications of a scientific education and practical experience for key personnel, including authorized persons, are outlined in the GMP guidelines published by WHO (Section 10, personnel).

Additional requirements may include subjects such as principles of QA and GMP, principles of GLP as applicable to research and development as well as to QC, detailed knowledge of the authorized/qualified person's duties and responsibilities, of International standards ISO 9000 – 9004 and relationships with suppliers, principles and problems of formulation of pharmaceutical preparations, pharmaceutical microbiology and principles and practice of sampling and testing of starting materials, packaging components and finished dosage forms

# REQUIREMENTS OF GOOD MANUFACTURING PRACTICE

## COMPILATION OF THE FOLLOWING GUIDELINES

NAME OF GUIDELINE	COLOUR OF TEXT
1. THERAPEUTIC GOODS ADMINISTRATION (TGA)	
2. MEDICINES CONTROL AGENCY (MCA)	
3. SCHEDULE M	
4. MEDICINES CONTROL COUNCIL (MCC)	
5. WORLD HEALTH ORGANIZATION (WHO)	