TGA Therapeutic Goods Administration

AUSTRALIAN

Code of GMP for Therapeutic Goods

Sunscreen Products

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PREFACE

The Australian Code of Good Manufacturing Practice was developed in 1969 as an Industry-Government document reflecting agreed standards and practices for the manufacture of therapeutic goods. Commonwealth and State Health Ministers agreed that the Code should constitute the criteria to be used by GMP auditors for evaluating pharmaceutical manufacturing establishments and that this evaluation should be the basis for the granting of licences by State authorities under the guidance of the Commonwealth GMP Audit and Licensing Section. That Code has in fact been used in this way up to the present, with revisions to accommodate new technology and new concepts of control and with necessary changes in emphasis to minimise the risk of error.

1989 saw the introduction of a single, National, licensing scheme under a re-enacted Therapeutic Goods Act in 1989. Under the original regulations, manufacturers of sunscreens were not required to be licensed. 1994 will see the revocation of the exemption with the basis for the granting of a licence to be conformity to a stand alone Code of GMP, tailor made for sunscreen manufacture.

After consultation with industry groups, this Code of GMP for Sunscreens, intended specifically for manufacturers of sunscreen products which are required to be listed on the Australian Therapeutic Goods Register, was adapted using much of the material from Medicines Code but also drawing on experiences gained from implementation of quality systems, such as those based on the AS 3900/ISO 9000 series of Australian Standards.

The Sunscreen Code of GMP, whilst being an agreed reference point for licensing, is also a distillation of national and international experience regarding the principles, requirements and precautions necessary to safeguard product quality. Conformity provides a high degree of assurance that history will not repeat itself and recognised manufacturing problems recur.

All clauses are written using the term "should", which indicates requirements that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. However, it is not intended that the Code should place any restraint upon the development or introduction of new concepts or new technologies. Nor is it assumed that the Code covers every aspect of manufacture, control and quality assurance: the manufacturer bears the ultimate responsibility for the products made and distributed.

Development of the 1990's Codes of GMP coincided with a national movement towards Total Quality Commitment. Emphasis in manufacture generally is moving away from testing as a judgement on materials or products of essentially unknown quality to testing as a **confirmation** that standards have been met through dedication to quality.

The preparation of a Quality Manual, as the documentation of quality commitment and the quality management system, is commended as a key to the achievement of Total Quality. Australian Standard ASQS-1-1988 provides guidance on the preparation of a quality manual. It is expected, as always, that the sunscreen product will be able to meet

the requirements of the Australian Standard AS 2604 "Sunscreen products - evaluation and testing" **at any time in its shelf life**.

This philosophy may be expected to influence strongly the attitudes of the therapeutic goods manufacturers and the GMP Audit and Licensing Section of TGA.

The Australian Government and the Australian sunscreen industry are together committed to the achievement of high standards of quality assurance for sunscreens. This Code provides principles and practices by which this objective will be met.

INTRODUCTION

The Sunscreen Code has been written to allow it to be used both for inspection and for self-audit, following the flow of goods from receipt through storage, processing and packing to final testing and release. Additionally, in order to clarify the way in which the Code seeks to realise its objectives, a 'rationale' is added to each major section and, where special emphasis or explanation was considered desirable, to some subsections.

It was prepared by the Australian Therapeutic Goods Administration, GMP Audit and Licensing Section, with valuable assistance from consultants, individual companies and manufacturers' associations. An attempt was made to seek a balance between those who believed there should be no special Code of GMP prepared for what are now accepted to be therapeutic goods and those who sought to have no Code of GMP whatever.

Note was taken of the requirements of other national and international standards applicable to sunscreen manufacture and Australia's involvement in the WHO Certification Scheme for Quality of Pharmaceutical Products Moving in International Commerce.

The Code does not deal with common or statute law requirements such as the obligations of contractors, Occupational Health and Safety, Customs and Excise, Dangerous Goods, Poisons (including narcotics), Weights and Measures, animal welfare, waste disposal and pollution, radiation, or the many legal requirements surrounding building construction. These must be met by the manufacturer. However, interaction with the GMP Audit and Licensing Section is strongly recommended before major changes are made in such critical aspects as building construction or refurbishment, water or air purification or introduction of a computer system where material or batch status or batch documentation is involved.

Appendix D, "Guidelines on Instrumentation" and Appendix F "Guidelines for microbiological testing of process water", of the Australian Code of GMP for Therapeutic Goods - Medicinal Substances, have been cross referenced.

To assist the reader, a List of Abbreviations Used, a List of Key Interpretations from the Therapeutic Goods Act, a List of Referenced and Recommended Standards and Publications, a Glossary and an Index have been added.

It is hoped that manufacturers will indeed regard this edition as a ready reference to the achievement of quality and keep it within arm's reach for frequent use.

Although one of the objectives of the present Sunscreen Code of GMP was to produce a document that would stand for some years, it is recognised that amendment may be necessary to accommodate technology change, to clarify uncertainty, or to specifically recognise important alternatives. *Comments on the Code or on any of the Medicine Codes appendices are therefore invited at any stage in the life of this edition.*

ABBREVIATIONS

CFU: Colony-forming units. Each colony of micro-organisms is regarded as originating from a "unit" which is assumed to be single micro-organism, although this is not necessarily true.

GMP: Good Manufacturing Practice.

JAS-ANZ: Joint Accreditation Scheme - Australia New Zealand.

NATA: National Association of Testing Authorities. This Association operates a certification (registration) scheme for testing laboratories in 10 fields, including Chemistry and Biological Testing.

NH&MRC: National Health & Medical Research Council.

1. BUILDINGS AND GROUNDS

Rationale

100. Buildings are located, designed, constructed and utilised so as to ensure protection of the product from contamination, permit efficient cleaning and maintenance and minimise the risk of manufacturing error.

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 dispatch areas, should be designed, constructed and maintained so as to protect against the effects of weather or ground seepage and the entry and harbouring of vermin, birds, pests and pets. Cavities and voids should not be present unless sealed or provided with access for pest control.

103. Grounds should be established and maintained in an orderly condition so as to minimise ingress into the buildings of dust, soil, or other contaminants.

Pipes, ducts and service areas

104. 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.

Consideration should be given to product pipelines not being inter-connected or connectable in a manner that invites cross-contamination or product mix-up.

"Dead legs" (in which circulation cannot occur) should be minimised.

105. 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;

For new installations:

- exposed overhead roof joists, pipes and ducts should be avoided;
- exposed pipes should not touch walls, but be suspended from or supported by brackets, sufficiently separated to allow thorough cleaning;
- openings in walls, floors or ceilings through which piping, ducting or other nonstructural items pass should be sealed or have removable covers that permit cleaning; and

- light fittings should be located and/or sealed so as not to collect and deposit contamination.

106. For existing installations, where fittings are in place contrary to the above, such as exposed overhead roof joists, pipes, ducts, wall openings, and exposed light fittings, appropriate cleaning procedures and schedules should be written and followed.

107. Production areas should not normally contain service machinery, or its associated ductwork or pipework, except where the ducting or pipes connect directly to equipment. Rooms or areas containing service machinery should be readily cleanable.

Space, layout, compatibility

108. Sufficient space should be provided for orderly receipt, warehousing and processing so as to minimise clutter and the risk of material or product cross-contamination or mix-up.

109. The layout of rooms and the manufacturing instructions and procedures used in existing plants should together minimise 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 manufacturing areas where containers, starting materials or product is exposed should be controlled to minimise contamination.

Processing and packaging areas should not be used as thoroughfares or for storage, except for work in progress. Where unavoidable, these areas should be clearly defined and away from where product is exposed.

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 should be compatible.

113. Except where alternative arrangements are acceptable, a dispensary area (which does not necessarily have to be a separate room) should be provided for weighing and measuring out starting materials.

Air control

114. For new installations, fresh air intakes and stale air exhausts, and associated pipework and trunking should be suitably located, e.g., intakes and exhausts should not

be to close to each other to avoid "short circuiting" and intakes should be sited 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.

Existing installations should be evaluated to determine if the quality of the product is affected by the air control.

115. The air in work zones where containers, starting materials or product is exposed should be controlled to minimise airborne contamination.

116. In all rooms, air supply and extraction points should not be close to each other.

117. For new installations, 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.

For existing installations, any air ducts which are insulated internally should be assessed as to their continuing suitability.

All air ducts should be verified as clean by inspection or testing.

Floors, walls, ceilings and associated fittings

118. Surfaces in manufacturing areas should be designed to facilitate cleaning and be free from cracks and open joints.

119. The use of excess water should be avoided so that the processing environment remains as dry as possible.

120. Open drainage channels should be avoided where possible but if used should be shallow to facilitate cleaning and disinfection.

Drains should be of adequate size and have trapped gullies.

121. Joins between walls and floors should be easy to clean, adequately sealed and, where appropriate, coved, i.e., a smooth, generous radius is formed between wall and floor, instead of a 90° angle which is difficult to clean and keep clean.

122. 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.

123. 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.

124. Lighting should be adequate for particular tasks. Flush mounting is preferred for new installations.

Special facilities and provisions

125. The building design should include adequate provision for dismantling, cleaning, washing and, where necessary, sanitising and drying equipment.

Adequate facilities should be provided for the storage of equipment used by cleaning staff.

126. Suitable provision should be made for the safe storage of waste materials awaiting disposal (see also Section 4).

127. Where laboratories are provided on site, they should be designed, equipped, 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 is contained in the NATA publication "Microbiological Testing: Laboratory Accommodation Guidelines".

Chemical 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 microbiological laboratories should not contaminate other laboratories.

128. For new installations, adequate facilities should be provided for GMP training.

129. A plan of the building(s) showing air handling facilities should be available.

130. Buildings should be secure against entry of unauthorised personnel. Special precautions should be taken for non-employees entering the plant.

Goods receival and storage areas

131. Materials should not be stored without protection outside buildings except where their quality, labelling and containers cannot be affected adversely by the weather.

132. Arrangements should prevent the coupling of bulk tankers to receival points except by or under the supervision of an authorised person.

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

The arrangement of the receival areas and stores should minimise contamination and provide a protected environment.

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.

External doors should be kept closed when not in use.

134. Sampling should be conducted in such a way as to prevent contamination or cross-contamination.

135. Storage areas should be adequate and organised to permit suitable and effective separation and identification of the various materials and products stored.

136. Quarantined and reject goods should be stored in an identified area. See Table 136.1.

Any system replacing physical quarantine should give equivalent security.

137. Labels, and other pre-printed packaging materials, including "APPROVED" status labels, should be stored in an area with access only to authorised persons.

Storage arrangements should permit clear separation of different labels and of each kind of pre-printed packaging material, so as to minimise the risk of mix-ups.

138. 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.

139. Starting and intermediate materials and finished products should be stored in environments compatible with the specifications or labelling instructions for such goods. The conditions of storage for final packaged goods should be compatible with any storage conditions specified on the labels of the goods.

140. Except in special circumstances, stock rotation should be practised in storage areas for both starting materials and finished products. That is, the oldest approved stock should be used first.

Table 136.1 - Quarantine and Reject Areas

Material	**Quarantine (Q) or Reject (R) Area**
Starting materials on receipt	Q
Preprinted packaging materials	Q
Partially finished goods	Q
Finished goods awaiting transfer to the warehouse	Q
Finished goods quarantined within the warehouse awaiting release	Q
Returned finished goods	Q
Rejected starting materials	R
Rejected or recalled products	R

2. EQUIPMENT

Rationale

200. Equipment that is technically suitable, well sited (so as not to interfere with other operations) easy to clean and well maintained has a major role in ensuring the maintenance of good product standards. Such equipment will ensure that contamination from foreign material such as rust, lubricants and abraded particles or foreign ingredients will be minimal.

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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 surfaces 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 minimised 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, sanitised 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 approved coolants, lubricants and other like chemicals should be used.

212. Where practicable, equipment used for critical steps in processing should be:

- automatically controlled; or
- 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 utilised, that accuracy is guaranteed, for example 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 observed. The format of the records should be such that the permitted tolerances are evident to the person making each entry.

3. PERSONNEL AND TRAINING

Rationale

300. The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of sunscreen products relies upon people. For this reason there must be a sufficient number of qualified and experienced personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of good manufacturing practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

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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 should have the managerial and professional or technical skills and experience to assume and discharge responsibility for ensuring that the goods manufactured consistently meet standards and specifications.

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

303. The areas of responsibility and lines of authority of key personnel should be identifiable.

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 good manufacturing practice.

304. Persons in responsible positions should have adequate authority to discharge their responsibilities.

305. Key personnel 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 and/or cosmetics made under GMP.

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

306. Where 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 (see Glossary), 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 for microbiological audit may be waived by the licensing authority.

307. Where operators are required to accept and implement instructions exactly and, where their duties require it, fill out forms, they should be sufficiently fluent in the spoken and written language in which the documents and standard operating procedures are written. Fluency in spoken and written English may be waived provided that skills in other languages relevant to the employer's needs are demonstrated.

308. Operators should understand and be trained to follow standard operating procedures relevant to their work and in the principles and practice of tasks assigned to them.

309. 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.

A Register of signatures and initials should be maintained.

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

4. FACTORY SANITATION AND PERSONAL HYGIENE

Rationale

400. A high standard of factory sanitation and personal hygiene is necessary to achieve the objectives of protecting each product from contamination by the environment or by the operators, protecting products from cross-contamination with other products and protecting operators from the effects of hazardous materials. Emphasis is placed on written programs to ensure that the steps have been thought out and, where necessary, validated.

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, labelled containers for removal to collection points and from there disposed of safely at frequent intervals. Collection points should be remote from processing.

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 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, sanitising all equipment. Operators should be familiar with these procedures, which should include:

- the responsibility for cleaning;
- whether re-cleaning or sanitising 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, fibre-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 emphasise:-

- 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; and
- avoiding further dilution or storage or ‘topping up' during use but, where storage is not avoidable, labelling any stored dilution with an expiry date.

If contamination of finished products or colonisation 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 key personnel 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 the current Australian Standard AS3666: Air Handling and Water Systems of Buildings - Microbial Control.

409. A system should be in operation which ensures that cleaning and, where necessary, sanitising has occurred after use and, where necessary, before re-use of equipment.

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.

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.

Facilities and procedures for personal hygiene

413. Adequate changing rooms and clean and well-ventilated toilets provided with adequate hand washing facilities should be provided, toilets being adequately isolated from any manufacturing area by at least an air lock. 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 minimise 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 emphasising 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 carried out 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, beard and hand 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. Appropriate signage should specify dress code requirements.

420. Except for facilities designed into dedicated areas, eating, drinking or smoking must not be permitted in manufacturing areas or in any other area where these activities might adversely influence 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.

421. For people employed in direct contact with the product, there should be pre-employment and periodic medical checks.

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 sunscreen products.

Personnel should be required to report infections and skin lesions, and a defined procedure followed when they are reported.

Where appropriate, operators should be tested for colour-blindness and the results made known to supervisors under whom they work.

422. Training relating to factory sanitation and personal hygiene should be included in staff training programs.

423. If hazardous materials are handled, the staff should be provided with -
- training and written procedures to ensure the safe handling of these materials; and
- protective clothing and equipment necessary to implement these procedures.

5. DOCUMENTATION

Rationale

500. The objectives of thorough documentation are to define the manufacturer's system of information and control, to minimise the risk of misinterpretation and error inherent in oral or casually written communication, to provide unambiguous procedures to be followed, to provide confirmation of performance, to allow calculations to be checked and to allow tracing of a batch history.

Document creation, control and use

501. General Standard Procedures to control all documents and data that relate to the requirements of this Code should be established and maintained.

502. 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 master document or standard procedure should indicate or include:
- the user's company or trading name;
- its purpose or title;

- a document identity number which uniquely identifies the document and indicates revision, if any;
- date of authorisation;
- date of expiry (in the case of standard operating procedures), date of review;
- signatures of authorising persons and, when different, the signatures of the person who prepares the document;
- the distribution list. where copies are distributed (the list to appear on at least the master copy); and
- page numbers (of numbers of total pages) e.g., page 1 of 2, page 2 of 2.

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

505. The reason for revision should be documented.

506. Documents which require the entry of data should:
- provide sufficient space for the entry;
- allow adequate spacing between entries; and
- clearly indicate what is to be entered.

507. Where an issued document requires the entry of data or additional information, entries should be handwritten clearly and legibly in permanent ink.

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

509. Issued documents should not be handwritten. Reproduced or computer-printed documents should be clear and legible; in the case of batch documents or unit product records, each must be initialled to indicate a verified issue.

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

511. Manufacturers should have:
- specifications for materials used and products made (including test methods);
- master documents from which the unit product or batch records are derived;
- standard operating procedures to give directions for recurrent tasks;
- agreements covering external activities; and
- other records to provide a complete history of each batch made and the circumstances of its manufacture.

512. Specifications should conform to any accepted in Australia in connection with product registration.

513. All documents relating to product quality should be reviewed and approved for adequacy by authorised procedures prior to their issue.
A control procedure should ensure that:

- the pertinent issues of appropriate documents are available at all locations where operations essential to the effective functioning of the quality system are performed;
- obsolete documents are promptly removed from all points of issue or use.

514. Unless the document maintenance system specifically provides otherwise, changes to documents should be reviewed and approved by the same persons (or functions) as those who performed the original review and approval. These persons should have access to all pertinent information upon which to base their review and approval. Where practicable, the nature of the change should be indicated in the document.

A master list or equivalent document control procedure should be established to provide a revision history. Documents should be re-issued after a practical number of changes have been made.

515. Documents should be kept up to date. Any amendments should be formally authorised 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.

516. Master batch documents, standard operating procedures and other master documents having a direct bearing on product quality should be authorised by the person responsible for quality.

Product traceability

517. 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 utilisation and disposition (including destruction) of all starting materials and products.

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

Storage and retention of documents and records

519. 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 one year after the expiry date of the batch or, where there is no expiry date, for at least six years after the date of manufacture of the batch.

Records of complaints should be held for a corresponding period.

Obsolete or superseded documents should be filed and similarly retained.

520. There should be a copy made of master documents for secure storage to protect against theft, loss, or alteration of information of the original.

521. Records may be retained as microfilm or microfiche. The responsibility for 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 519.

522. Paper or film records should be stored in a restricted access area. Records should be protected from tampering or loss.

523. 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 file.

Specifications

524. Specifications for components should include

- a description of the material or component and drawings where appropriate;
- the material's standard name (see Glossary) and a code reference unique to that material;
- a reference to the approved supplier(s) of the material;
- any safety instructions for handling or use;
- arrangements for acceptance from certified suppliers or sampling instructions and details of quality control tests to be performed (including analytical methods where appropriate), classification of defects and acceptance limits;
- any requirements for standard reference samples;
- storage conditions; and
- frequency of re-testing the stored material, where appropriate.

Master and batch records

525. Master manufacturing and packaging records should include:

- a description of the equipment and materials to be used;
- details of all precautions to be taken;
- step by step instructions;
- details of any in-process quality control checks to be conducted by production personnel, including sampling instructions;

- instructions on the procedure to be followed in the event of the problems relating to product quality; and
- instructions for the disposition of accepted or rejected intermediate or finished products, e.g. transfer to work-in-progress stores or destruction.

526. Batch manufacturing and packaging records should be prepared from the currently approved version of the appropriate master documents. This system should be designed to avoid clerical errors and whenever possible, photocopying or other secure reproduction process should be utilised. An unambiguous batch number should be issued. Note that the date of manufacture is satisfactory where only a single batch of product is made on any one day.

527. During manufacture there should be entered into the batch manufacturing records the following:
- the lot or identifying number of each material and where appropriate the quantities of material used;
- the quantity of product manufactured using the given batch number and, where appropriate the number of bulk containers or finished product containers;
- the results of all in-process controls and the initials of personnel taking samples and carrying out the tests;
- where relevant, designation of the equipment and production line(s) on which the product was manufactured and the date(s);
- where necessary, authorisation by designated personnel that the manufacturing area had been checked prior to any change to ensure that products, materials and other items relating to previous operations had been completely removed; and
- details of any deviations from the manufacturing specifications.

528. After manufacture there should be entered into the batch manufacturing records a signed statement that the batch has been manufactured according to the processing instructions and that any deviations have been documented.

Finished products

529. Specifications for finished products should include:
- an exact statement of the sunscreening substances intended to be present together with those requiring assay and their concentrations in the product:
- the product code (if any):
- the physical form and appearance:
- tests and limits for identity, purity, physical and chemical characteristics, assay and (where appropriate) 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.

530. 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 acceptable 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 should show both specifications.

The expiry specifications must be consistent with any data accepted by the Therapeutic Goods Administration in connection with product registration and with any statutory standard applicable to the product.

531. 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.

Other supportive documents

532. Other documents may be necessary to support the quality, safety, traceability and process control of sunscreen manufacture.

6. MANUFACTURING PROCEDURES

Rationale

600. Reliability of products is secured by using only dependable and verified starting materials, by following exactly the specific, explicit and previously defined and validated manufacturing procedures set out for each product, guided by comprehensive general Standard Operating Procedures, and by protecting the products from external and cross-contamination.

Security of labelling is of equal importance: this is achieved through a rigorous system of controls on the text of the label, on printing procedures and on receipt, identification, storage, issue, usage and return to stock of the printed material.

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 Quality Assurance or their delegates.

602. Incoming starting materials should be checked, quarantined, sampled, tested (if required, see also 524.5) against written specifications and released before use following a standard operating procedure. This procedure should also apply to other materials such as gases and solvents used in production which may come in contact with the product. A

simplified system may be used for "Other Packaging Materials" (see "Packaging Materials" in Glossary).

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.

605. In processing areas, starting materials or product should be stored in a manner to prevent contamination.

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 standard operating procedures and product-specific processing or packaging instructions. (See Documentation).

607. Intermediate preparations, such as solutions used for pH adjustment not specific to one batch, should be prepared following the same system of Master Formulae and Processing Instructions and their batch numbers carried forward onto the documents for the finished products in which they are used.

608. Packaging and labelling 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 for sale or supply.

610. Products which have been diverted from standard flow patterns or subjected to non-standard procedures should be reintroduced into the process only after special inspection and investigation by authorised 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 occurs.

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 (see Glossary) 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.

Contamination control - general

Rationale

613. Risks of contamination or cross-contamination arise from starting materials (including water), from the environment and from uncontrolled release of dust, gases, vapours, sprays or organisms from materials or products in process, from residues in equipment, and from operators and their clothing. Special precautions are necessary to minimise these risks.

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614. Facilities, equipment, procedures and, as necessary, air-flow rates and directions, should be such as to minimise 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. 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 contamination control procedures should apply to the non-therapeutic products.

618. When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust.

619. At every stage of processing, products and materials, particularly primary packaging materials, should be protected from microbial and other contamination.

620. 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.

621. 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.

622. Essential supplies, such 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 labelled as to their contents.

623. Product containers to be filled should be supplied to the packaging line or station in a clean condition, or 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.

624. 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.

Contamination control - microbiological

625. Microbiological contamination of sunscreens should be minimised by a co-ordinated approach which should include:

- the training of all appropriate staff in matters relating to personal hygiene and factory sanitation (See Sections 3 and 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 emulsified products) and those difficult to preserve;
- establishment of action limits for quantitative microbiological test results;
- frequent monitoring of process water; and
- periodic microbiological monitoring of product contact surfaces and wet areas such as wash bays and, where practical, other areas that are likely to harbour and spread microbiological contamination.

Contamination control - process water

Introduction

626. Water for use in manufacture has been the 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 therapeutic goods standards. It is therefore necessary to substantially remove impurities and to control the microbial level in order to standardise products and avoid contaminating them.

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

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627. Water to be used as an ingredient should be purified before use.

628. 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;
- both a brief description of and a full specification for each element in the system including manufacturers' recommended flow rates;
- standard procedures for use, including startup, shutdown, backwashing, regeneration, sanitising 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 action 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 the operation and maintenance of the system and their deputies; and
- a periodic review which is not less frequent than annual.

629. 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 sample size selected for microbiological testing should be such as to give a countable number of colonies on the membrane or plate employed. A recommended test method is given as Appendix F to the Australian Code of GMP for Therapeutic Goods - Medicinal Products.

Micro-organisms recovered from total counts should occasionally be separately identified, as they do not always grow in selective media.

630. "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 10^2 cfu/mL at point of use but may be set at a figure orders of magnitude lower.

Chemical starting materials control

631. Where possible, chemical starting materials should be purchased only from approved or certified suppliers (see Glossary). They should be purchased to established specifications (see Section 5 - Documentation). Purchase orders should make adequate reference to these specifications.

632. At the time of receipt of chemical starting materials each delivery should be examined for damage to the containers and for visible contamination. Particular attention should be given to chemical 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 recorded and assessed.

Where practicable, badly damaged or soiled containers should be rejected. Where 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 protected environment and documented accordingly.

633. Within each delivery, active materials bearing different manufacturers' batch or lot numbers should be separated: each group bearing the same batch, lot or equivalent number should be regarded as a "separate material".
For these active materials subsequent deliveries of the same manufacturer's batch or lot number should also be regarded as "separate materials", but maybe eligible for reduced testing.

634. Active materials should not be accepted unless bearing the manufacturer's batch, lot or equivalent number.

635. Each "separate material" should be allocated a Unique Identifying Number from the Goods Received Register. This number and the standard name 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.

636. After examination, sorting and, where applicable, cleaning of incoming chemical starting materials a (single) conspicuous quarantine label should be affixed to each container as near as possible to the original label. All other status labels should be cancelled. All subsequent labelling 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, flammables stores and strong rooms.

637. Each active material should be sampled, tested and released before use.

638. Containers of material should not be removed from a quarantine area unless released for used unless they bear a RELEASED or APPROVED or REJECTED label cancelling the HOLD or QUARANTINE section of the original quarantine label.

639. Goods whose release has expired should be labelled as quarantined and promptly returned to a quarantine area. A system of drawing attention to the existence of previously released materials that have expired should be established.

Alternative systems of quarantine and release to those above which achieve equivalent control may be approved by the licensing authority.

640. Partly-used containers of materials should be periodically inspected to ensure that they are properly closed, stored, and identified and have not deteriorated.

641. 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.

642. 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 an identified reject 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.

Dispensing control

643. Starting Materials should be issued from stores only by authorised persons, following a standard operating procedure.

644. Stock records (such as Inventory Cards) should be maintained in such a way as to facilitate the reconciliation between "separate materials" 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.

645. Only approved materials should be permitted in the dispensing area.

646. Chemical starting materials should be dispensed only by authorised 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 to be dispensed should be available. Each dispensing operation of active materials (see glossary) should be witnessed and checked by a second person and the check recorded.

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

647. In order to minimise the possibility of cross-contamination and mix-up, as few materials as practicable should be brought into the dispensing area at any one time.

648. Each container of dispensed material not immediately processed should be tagged or labelled with the following minimum information:

- Standard Name;
- quantity;
- Unique Identifying Number; and
- product processing or batch number.

649. The collected dispensed materials for a given batch should be stored in such a way as to preserve the integrity of the batch.

Processing control

650. Batches should be processed in accordance with master documents.

651. Where the batch processing instructions make reference to a standard operating procedure, the operator should have ready access to that procedure.

652. At all times during manufacture all bulk containers and all major items of equipment or equipment groups in use should be adequately labelled or otherwise identified to indicate the name, strength and batch or processing number of the product being processed. When necessary such labelling 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.

653. 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.

654. 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 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 and documented.

655. 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.

Recovered or reprocessed materials

Product Residues

656. Where a residue is incorporated into a batch of a product on a non-routine basis, each instance should be specifically approved and recorded, taking into account:

- 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 utilisation and/or disposal that will facilitate overall reconciliation; and
- any necessary testing or approval, for example where microbiological quality may be affected.

Re-processing

657. 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 effectiveness or stability;
- for each instance of re-processing, such risks are evaluated and the manufacturing operations to be used are approved and recorded;
- 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.

Returned goods

658. All returned goods, other than products returned in the original shrink-wrapped packaging which show no evidence of tampering, should be examined to determine whether they should be released, reprocessed or destroyed.

659. 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-labelled, or bulked for repacking, provided that there is no risk to product quality and the operation is specifically authorised and documented. If such a product is re-labelled, the operation should be regarded as a formal packaging operation. If bulked, the operation should be regarded as a formal processing operation.

660. A finished product returned from the market (i.e. which has left the control of the manufacturer), returned because of complaints, damage or other circumstances which may prejudice the quality of the goods should *only* be considered for re-sale, re-labelling or bulking for repacking after it has been critically assessed.

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 relabelled material.

Labelling and packaging control

Rationale

661. Special emphasis needs to be given to the control of labels and pre-printed packaging materials to avoid mix-ups and product recalls.

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In this subsection, "pre-printed packaging materials" includes unit cartons, pre-printed product containers and leaflets.

662. Pre-printed packaging materials should be drafted and approved to ensure that aspects relevant to Production and to Quality Control are considered.

663. Labels and pre-printed packaging materials should be identified by a code number/letter as part of the printed text, unique to each amendment.

664. A master file of approved labels and all other pre-printed packaging material and their specifications should be held by a competent person.

665. General operating procedures describing the receipt, identification and storage of printed packaging and labelling material should be available.

666. On receipt, all labels and pre-printed packaging materials should be quarantined, examined and identified by a competent person 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.

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

668. Pre-printed labels must not be overprinted with a different name or strength of the product.

669. Where batch numbers or expiry dates are added to labels off-line the addition should be done in a segregated, secure area which may be a label store. The coding process should be documented and preceded by a line clearance check.

670. When setting up a production schedule for packaging operations, particular attention should be given to minimising 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 labelling operations carried out at the one time.

671. Each batch or part-batch should be packed utilising documents and batch records prepared in accordance with Section 5.

672. Where the instructions make reference to a standard operating procedure, the operator should have ready access to that procedure.

673. Before commencement of any packaging and labelling:

- 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 labelling record to show that this check has been carried out;
- if fitted, any label counters/readers should be tested to verify that they are functional;
- all packaging and labelling 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.

674. On-line controls should include checks of at least:

- bulk material, labelling and pre-printed packaging material supplied or in use;
- label appearance and adhesion;
- if fitted, label verifier function;
- coding;
- cap torque; and
- first and last packages;

675. Normally, filling and labelling 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 mislabelling can occur.

676. Upon completion of the run, unused, un-coded labels and pre-printed packaging materials should be returned into store; unused coded materials should be counted and held for destruction.

A reconciliation should 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 labelling records.

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

677. In the event of a significant discrepancy that could indicate a product or labelling 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.

7. CONTRACT MANUFACTURE

Assessment of contract manufacturers (contract acceptor)

700. Contract manufacturers (Contract Acceptors) should be selected on the basis of their ability to meet contract requirements, including quality requirements. The limits of the responsibilities of the parties should be defined in a "Specification of GMP Responsibilities". Records of contract manufacturers' performance, quality management and acceptability should be kept.

The Contract Giver should ensure that the contract manufacturer’s quality management system controls are effective such as:

- demonstrated consistent product quality through extensive testing; and/or
- assessment by the contract giver to an appropriate standard; and/or
- a third party audit and certification, such as by a JAS-ANZ certified auditing body.

The Contract Acceptor must not pass a contract or any part of it to a third party without the consent of the Contract Giver.

Contract review

701. The Contract Acceptor and Contract Giver should have a documented procedure for periodically reviewing the contract to ensure that:

- the requirements are adequately defined and documented;
- any requirements differing from those in the contract are resolved;
- the Contract Acceptor has the capability to meet all contract requirements.

The review should be documented.

702. 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. Any alterations to contract arrangements should be agreed in writing by both parties.

8. QUALITY MANAGEMENT

System

800. A quality system is the organisational structure, responsibilities, procedures, instructions, processes and resources for implementing quality management.

Management should develop, establish and implement a quality system as the means by which stated policies and objectives will be accomplished.

The quality system should be structured and adapted to the company's particular type of business and should take into account the appropriate elements outlined in this Code.

The quality system should function in such a manner as to provide confidence that:

- the system is well understood and effective;
- the products or services actually do satisfy customer expectations, as well as legal requirements; and
- emphasis is put on problem prevention rather than detection and correction after occurrence.

801. The quality system should operate to ensure that samples of starting materials (including relevant packing materials), intermediate products, finished products or samples from any material or substance relevant to product quality are taken, and tested (if required, see 524.5) to determine their release or rejection on the basis of test results and other available evidence as to their quality.

Functions and duties

802. The quality system should include the following functions (some or all of which may be delegated to a contractor):

- establish or approve quality control specifications for all starting materials and finished products, for packaging materials in contact with the products and for intermediate products;
- establish or approve master batch and packaging documents;
- establish or approve standard operating procedures 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 the microbiological testing and microbiological monitoring of materials, products and environment, including process water;
- revise or approve the revision of the established quality control specifications and sampling and testing instructions as necessary, replace superseded versions, and

maintain a complete written collection of the current versions and an historical record of amendments;

- monitor, sample and/or test starting materials (see 524.5), 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 finished products and of starting materials and intermediate products where necessary;
- where necessary, evaluate the stability of starting materials and intermediate products;
- establish instructions for the storage of materials and products within the manufacturer's premises;
- establish expiry periods and storage instructions for incorporation in the labelling 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 quality control 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. ;
- evaluate and authorise 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 authorising 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 to demonstrate that materials, methods, processes and equipment are capable of doing what they purport to do. Such studies may be necessitated by changes in the source or specifications for materials, or changes in processes 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 an active self-inspection program to determine compliance with GMP requirements.

Sampling

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

804. Sampling should be carried out so as to avoid contamination and other adverse effects.

805. Where feasible and appropriate, sufficient quantities of chemical starting materials and finished products should be taken for both control and retention samples.

Testing

806. Testing should be performed in accordance with methods detailed in or referenced in specifications.

807. A test for identification should be carried out on material from each container of active starting material sampled. Tests for identification should be as specific as is practicable and should unequivocally distinguish each active material from all other active materials used in the particular premises.

808. For excipients, 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.

809. Only valid certificates of analysis should be included with the analytical records for each material. Where test results from valid Certificates of Analysis are entered on Analytical Summary Records they should be entered in such a way as to distinguish them from internal test results.

A valid certificate of analysis is one from an approved or certified supplier (see Glossary) 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.

In-process and finished product testing

810. The quality system should include in-process and finished product sampling and testing. The quality system should ensure that:

- calibrated equipment is available to perform the tests;
- operators are trained; and
- independent quality control results are obtained from time to time as an audit and these results are entered in distinctive form on the test records.

811. Samples on which decisions to approve finished product may be based, should be taken only by persons appropriately trained and authorised.

Good control laboratory practice

812. The manufacturer should ensure that any quality control is carried out in a laboratory whose practices follows Australian Standard 2830.1: Good Laboratory Practice, Part I, Chemical Analysis and the requirements of Section 5 of this Code - Documentation.

813. 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.

Microbial limit test methods should be validated by the addition of small numbers of challenge organisms in the presence of the starting material or product.

814. Written records of all testing should be made and retained.

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.

Stability testing

815. The stability profile of each formulation, in its Australian sales pack type, should be available. Where it is not, it should be determined according to a written stability program.

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

816. 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.

Deviation and fault analysis

817. A procedure should be documented and established for the review of reports of deviations 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 supply

818. Goods should not be despatched unless release has been authorised under a formal release procedure.

819. Where goods are to be transferred from the packaging area to the warehouse before release for supply, an effective system of quarantine should apply.

820. Release for supply should require the examination and certification by a competent person nominated by management 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 check list system should be used for the collected documents to verify that all are present. The release should include the dated signature of the person authorised to approve the supply of the batch (see also Contract Manufacture).

The records may be certified at intermediate stages by authorised persons for completeness, conformity to standards for yield and in-process tests and conformity to final specifications. The final examination and evaluation of the consolidated records, however, should remain the responsibility of the nominated person.

Contract quality control

821. Some or all aspects of quality control 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.

822. 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 despatched. 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.

823. 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 to be employed or where such details may be obtained;
- arrangement for reporting test results and retention of records of test results; and
- arrangements for keeping retention samples.

Product complaints

824. Complaints or defects relating to product quality, including those made to non-technical personnel, should be reported, investigated and resolved following a written standard operating procedure. The procedure should ensure that all complaints or defects are reported and should specify the responsible persons(s) through whom they must be channelled. The procedure should also ensure that complaints concerning quality, including adverse drug reactions, are reported.

825. A file of complaints and defects should be maintained, 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 relevant departments.

Product recall

826. 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.

827. 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.

828. 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).

829. Recalls must not be undertaken without informing the officer in the Therapeutic Good Administration responsible for Government coordination of recalls and such other persons as may be nominated in the Uniform Recall Procedure.

Quality audits

830. All aspects of Good Manufacturing Practice 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.

831. Where an external audit by a qualified microbiologist (see Clause 306 and Glossary) is commissioned, the audit should include, where applicable -

- microbiological laboratory technique, performance and records;
- microbiological specifications, tests and controls;
- cleaning and sanitation procedures for the manufacturing areas; and
- environmental monitoring.

9. USE OF COMPUTERS

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 AS3563. 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 examples of each document produced by the program, instructions for testing, operating and maintaining the system and the names of the person or persons responsible for its development and operation.

906. When a computer system is in process of replacing a manual operation the two 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 cannot 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 a 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 authorised person (e.g. entering a master processing formula) should require independent verification and release for use by a second authorised person.

911. A hierarchy of permitted access to enter, amend, read, or print out data should be established according to user need. Suitable methods of preventing unauthorised entry should be available, such as pass cards 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 taken 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 523 and 520 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
- List of programs with brief description of each
- 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

REFERENCED AND RECOMMENDED STANDARDS AND PUBLICATIONS

Standards and Publications cited in the Code

Australian Standards - published by Standards Australia

QS1 1988	Guide to the preparation of quality manuals.
AS 2604	Sunscreen Products - evaluation and testing
AS 2830.1	Good laboratory practice Part 1-1985 Chemical Analysis ISBN O 7262 3954 2
AS 2982-1987	Laboratory construction ISBN O 7262 4692 1
AS 3563-1988	Software quality management system ISBN O 7262 5174 7
AS 3666-1989	Air-handling and water systems of buildings - Microbial control ISBN O 7262 5531 9
AS 3900/ISO 9000	Quality Systems Guide to Selection and Use

National Association of Testing Authorities

Microbiological Testing: Laboratory Accommodation Guidelines.

Technical Note No 4: A guide to Microbial Media Quality Control.

Selected Australian Standards Relevant to Quality Management

ASQ 119	Supplier Assessment Scheme Procedures and Rules
QS5	Guide to the Assessment and Auditing of Quality Management Systems
AS 1057	Quality Assurance and Quality Control - Glossary of Terms
AS 1095	Microbiological methods for the dairy industry (relevant parts and sections) (cited in Appendix F)
AS 1199-1988	Sampling procedures and tables for inspection by attributes ISBN O 7262 4901 7
AS 1399-1973	Guide to AS1199 - Sampling procedures and tables for inspection by attributes ISBN O 7262 0020 4
AS 1766	Methods for the microbiological examination of food (relevant parts and sections) (cited in Appendix F)
AS 2415	Calibration System Requirements
AS 2490	Sampling Procedures and Charts for Inspection by Variables for Percent Defective
AS 2561	Guide to the Determination and Use of Quality Control Costs
AS 2990	Quality Systems for Engineering and Construction Projects
AS 3900/ISO 9000	Quality Systems Guide to Selection and Use
AS 3901 /ISO 9001	Quality Systems for Design/Development, Production, Installation and Servicing

AS 3902/ISO 9002	Quality Systems for Production and Installation
AS 3903/ISO 9003	Quality Systems for Final Inspection and Test
AS 3904/ISO 9004	Quality Systems - Guide to Quality, Management and Quality System Elements

GLOSSARY

The following explanations of terms used in the Code are given to assist the reader and as source material for GMP training programs. They are not intended to be "definitions" in the scientific sense or "interpretations" in the legal sense, and are not meant to be read in any context other than the Code.

The Glossary also includes some terms not used in the Code but commonly used in its application. It does not include terms such as "therapeutic good" or "manufacture" which have "interpretations" in the legislation under which the Code applies and must be taken to have these interpretations for the purposes of the Act, such as licensing. Some of these terms are given in a separate list.

Quality Management terms are discussed under that heading in the main text.

ACCURACY: The closeness of the result obtained, during measurement or analysis, to the true value. Bias is a systematic deviation from the true value.

ACTIVE MATERIALS: Includes sunscreen agents and preservatives.

APPROVED SUPPLIER: A supplier of starting materials of known origin who is recognised as reliable, based on a history of deliveries which all met specifications and were well packaged and intact on receipt and, where possible, based also on a vendor audit (see also Certified Supplier).

BATCH: A defined quantity of material processed in one process or series of processes so that it may be expected to be uniform with respect to composition and probability of chemical and/or microbiological contamination. However, to complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub-batches, which are later brought together to forma final homogeneous batch. In the case of continuous processing, the batch is an arbitrarily defined fraction of the production, characterised by its intended homogeneity, e.g. from a shift or a day, or derived from a particular lot of active ingredient.

BATCH NUMBER: A number or combination of numerals, symbols and letters which uniquely distinguishes a batch of product from all other batches of that 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.

A number of sub-batches may be combined by mixing to form a single batch. However, where the bulk batch is divided into lots which are differently packaged or significantly

separated during manufacture (e.g. separated packaging runs) such lots are distinguished from one another, for the purposes of product labelling, by suitable means, usually an affix to the Batch Number.

It is permissible to use one unique series of numbers (processing numbers) on product up to the point of packaging and another for the packed product, with or without an affix as described above, provided that they are unambiguously correlated in batch records.

It is permissible to combine a series of batches of bulk product into a continuous series of packaging operations (not significantly separated in time, place or equipment) and apply a single batch number to the packaged batch, bearing in mind that if a fault occurs or reconciliation fails, the whole series may have to be rejected or recalled.

Incoming materials will usually carry the batch, lot or equivalent number of their manufacturer, but will be allocated instead a Unique Identifying Number by which they are identified within the premises of the user. This avoids the use of the term "batch number" with two different meanings.

CALIBRATION: The operations carried out to determine the accuracy of measuring instruments, of "material measures" such as masses or gauges and of measurement standards. Properly it does not include adjustment but in this Code it is assumed that adjustment follows the detection of unacceptable error.

CERTIFIED SUPPLIER: An Approved Supplier who has been formally audited by the purchaser and who meets AS3901 or 3902 requirements and is so certified by Standards Australia (see also Approved Supplier).

COMPUTER SYSTEM: The combination of hardware, software and operating procedures that determines computer functions.

EXISTING INSTALLATION: A facility in existence prior to the publication of this Code

IMPERATIVE (in relation to documents): A positive manner of expression, e.g. "Disassemble completely the Acme pump and associated hoses and clips"; NOT "the Acme pump is to be disassembled ....." or "The Acme pump is cleaned by .....".

LINEARITY (of analytical method): The ability of the method to produce results (within a defined range) that are directly or indirectly proportional to the concentration of the analyte in the sample.

MASTER DOCUMENT: A document from which copies are made for use in the manufacture or testing of individual batches of product. The master is checked, authorised and filed until required for copying. It is convenient to distinguish it by having some of the printing or the signatures in red ink: the red colour will not appear on copies.

NEW INSTALLATION: Any major structural change involving capital expenditure completed following publication of this Code. See also "existing installation"

PACKAGING MATERIAL: Any material used in the packaging of a product. The term is not normally extended to cover the delivery cases or outer packaging used for the transportation or shipment of orders.
Three categories of packaging materials may be distinguished:

- Packaging materials which come in contact with the product ;
- Printed Packaging Materials (carrying product labelling).
- Other Packaging Materials.

Although these categories are not necessarily mutually exclusive, the nature and extent of the control which needs to be applied to them may vary.

PRECISION (of analytical method): The degree of variation (hence, of agreement) between individual test results when the method is applied separately to separate samples drawn from the same homogeneous batch of material. This will include variation between analysts, between days, between tests on the same prepared extract of a given sample, between extracts and between laboratories conducting the same test. It is usually divided into two components:

- repeatability (within-laboratory); and
- reproducibility (between-laboratory).

QUALIFIED MICROBIOLOGIST: A person with an appropriate tertiary qualification in science or other relevant discipline (including a microbiology major) and having relevant experience.

QUALIFICATION (of equipment): The process of determining that a device, apparatus or piece of manufacturing or control equipment meets all design and performance specifications, including "boundary", "worst case" and "power failure" conditions. This is a necessary preliminary to ***process*** validation.

QUARANTINE: The status of starting materials, or intermediate, bulk or finished products isolated, whether physically or by a system, whilst awaiting a decision on their suitability for processing, or for sale or distribution.

RECONCILIATION: Comparison of and assessment of any discrepancy between the amounts of material entering and leaving a given operation or series of operations.

In the case of processing, this means the amount of materials theoretically entering a process compared to the amount actually obtained as product, plus known (unavoidable) and measured or estimated losses of material and calculable adjustments for moisture or other solvent.

In the case of a packaging process, it means the amount of product entering that process, compared to the amount actually packed as product (number of items packed x average fill) plus known (unavoidable) and measured or estimated losses.

In the case of packaging materials, it means the numbers counted or estimated to be issued for packaging purposes compared to the numbers applied to sound and defective product (including samples and cartons) plus numbers returned to store and numbers destroyed or defaced.

In these paragraphs "estimate" means as closely estimated as the circumstances permit and implies that a space is provided on the relevant form for the estimate and (in the case of packaging materials) the basis for the estimate.

SANITISER: A disinfecting agent used to reduce micro-organisms on surfaces to an acceptable level; usually following a cleaning step.

SPECIFICATION: A document or documents giving a description of a starting material, packaging material, intermediate, bulk or finished product in terms of its chemical, physical and (possibly) biological properties together with methods of test. A specification normally includes descriptive clauses and numerical clauses, the latter stating standards and permitted tolerances.

SPECIFICITY (of analytical method): The ability of the method to measure the analyte in a manner that is free from interference from other components that may normally be expected to be present, such as ingredients, impurities and degradation products.

STANDARD NAME: A name assigned to a starting material that uniquely identifies it within the manufacturing establishment. It is used to cite the material in specifications, on identity/status tags, in analytical reports, in stores records and in batch documents. It is chosen to avoid the possibility of confusion between similar-looking or similar-sounding names.

STARTING MATERIAL: Any material employed in manufacture and which may contact or be included in the finished product, including packaging materials. The term does not include ancillary chemicals such as cleaning and sanitising agents, deioniser regenerants, machine lubricants or adhesives, though these are not to be overlooked for their possible hazards or effects on the product. Starting materials that are not packaging materials are sometimes known as chemical starting materials or raw materials or ingredients, although not all such materials necessarily remain as ingredients of the final product.

STATUS: The classification of any goods, materials, containers equipment, facilities or machines in relation to their acceptance (or otherwise) for use, further processing or distribution (e.g. 'Quarantine', 'On Test', 'Released', 'Restricted Use', 'Hold', 'Rejected', 'To be Cleaned').

UNIQUE IDENTIFYING NUMBER: See Batch Number.

VALIDATION - GENERAL: The action of proving that any material, process, procedure, activity, system, equipment or mechanism used in manufacture or control can and will reliably achieve the desired and intended results.

VALIDATION - PROSPECTIVE: Validation of a process, procedure etc. before production begins - a part of orderly Product or Process Development.

VALIDATION - RETROSPECTIVE: The conduct of validation studies performed after production has begun and designed to show that the processes, procedures etc. are effective and robust (insensitive to variation) within the likely ranges of variables affecting them. The collection of data showing that batches always meet specifications is not, in itself, validation.

WORST CASE: A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

YIELD:

- ***Theoretical yield*** is the quantity of material or product that would be produced at an intermediate or final stage of manufacture, assuming that all starting materials, intermediates and final products met their average specifications and that no loss or error occurred in production.

- ***Expected yield*** is the quantity of material or product that is expected to be produced at an intermediate or final stage of manufacture, allowing for unavoidable losses (including moisture) under normal but controlled manufacturing practice, and any deliberate over-fill of product into its unit containers. "Expected yield" may also be varied batch by batch to allow for factors such as actual moisture content, where they are significant variables.

KEY INTERPRETATIONS FROM THE THERAPEUTIC GOODS ACT 1989

For information only; consult the exact text of the current legislation because it is amended from time to time.

"manufacture", in relation to therapeutic goods, means:
(a) to produce the goods; *or*
(b) to engage in any part of the process of producing the goods or of bringing the goods to their final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for sale of the goods or of any component or ingredient of the goods as part of that process;

"premises" includes:
(a) a structure, building, aircraft, vehicle or vessel; *and*
(b) a place (whether enclosed or built upon or not); *and*
(c) a part of a thing referred to in paragraph (a) or (b);

"manufacturing premises" means a building, a part of a building or a group of buildings on one or more sites:
(a) that is for use in the manufacture of a particular kind of therapeutic goods; *and*
(b) at which the same persons have control of the management of the production of the goods and the procedures for quality control;

"manufacturing principles" means the principles for the time being having effect under section 36 of the Act;

"therapeutic use" means use in or in connection with:

(a) preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons or animals; *or*

(b) influencing, inhibiting or modifying a physiological process in persons or animals; *or*

(c) testing the susceptibility of persons or animals to a disease or ailment;

and includes use in, or in connection with, contraception or testing for pregnancy;

Note, however, that some Parts of the Act do not apply to goods for animal use only.

"therapeutic goods" means goods:

(a) that are represented in any way to be, or that are, whether because of the way in which the goods are presented or for any other reason, likely to be taken to be:

  (i) for therapeutic use; or

  (ii) for use as an ingredient or component in the manufacture of therapeutic goods; or

  (iii) for use as a container or part of a container for goods of the kind referred to in subparagraph (i) or (ii);

or

(b) included in a class of goods the sole or principal use of which is, or ordinarily is, a therapeutic use or a use of a kind referred to in subparagraph (a) (ii) or (iii);

and includes goods declared to be therapeutic goods under an order in force under section 7 of the Act, but does not include:

(c) goods declared not to be therapeutic goods under an order in force under section 7 of the Act; or

(d) goods in respect of which such an order is in force, being an order that declares the goods not to be therapeutic goods when used or labelled in the way specified in the order where the goods are used or labelled in that way; or

(e) foods;