

Standard for the Preparation of Pharmaceuticals in Australian Hospital Pharmacy Departments

National Coordinating Committee on Therapeutic Goods
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Background

The National Coordinating Committee on Therapeutic Goods (NCCTG) at its 41st meeting, October 1991, recommended that guidelines be developed against which preparative activities (often termed 'manufacturing') in hospital pharmacy departments could be monitored. It was intended that the guidelines would substitute for the now outdated Appendix B (1976) of the *Australian Code of Good Manufacturing Practice for Medicinal Products 1990 (Code of GMP)*, but would not form part of that Code.

It is emphasised that the document is written as a set of principles to assist in the preparation of quality pharmaceuticals in hospitals and, to facilitate its implementation, will need to be complemented by existing Standards, Codes or Guidelines and elaborated by specifically developed written procedures or practice guidelines.

This approach is consistent with the policy of the Society of Hospital Pharmacists of Australia (SHPA) which had been working towards the development of guidelines and an effective accreditation procedure, and whose views have been taken into account by the NCCTG Working Party.

This Standard has been prepared by an NCCTG Working Party whose members were drawn from the Therapeutic Goods Administration (TGA) of the Commonwealth Department of Health, Housing and Community Services, the SHPA, the Victorian Health Department and the NSW Health Department under the chairmanship of its Chief Pharmacist Mr Barry Mewes.

In preparing the Standard, the Working Party incorporated the principles of quality management as outlined in Australian Standard AS3900 Series (ISO 9000): Quality Systems, and the *Code of GMP 1990*. Other documents utilised were:

SHPA Guidelines for Hospital Pharmacy Quality Assurance Programs

The Australian Council on Healthcare Standards' (ACHS) Accreditation Guide — Standards for Australian Healthcare Facilities, 11th edition, July 1992

NSW Health Department Circular 83/65 —

Guidelines for the Preparation of Pharmaceuticals in Hospitals.

Scope

In Australian hospital pharmacy departments a range of preparative activities is carried out in relation to pharmaceutical preparations used to treat patients. The range extends from individual patient items for immediate use (commonly termed 'dispensing') to more extensive activities, such as batches of products made in advance for potential patients (commonly termed 'bulk manufacture'). The procedures may range from labelling to aseptic manipulation.

Preparative activities on a larger scale are likely to involve additional costs or resources in establishing and maintaining Quality Management Systems. Hospitals may therefore consider:

- cooperative arrangements between hospitals for procurement and testing of starting materials; and
- rationalisation of specialist manufacturing activities.

Irrespective of the scale or complexity of preparation, the objective remains the same i.e. to consistently produce a safe and effective preparation for **every** patient, known or unknown.

This objective can be best achieved by implementing a Quality Management System (QMS) as defined in AS3900:

'The organizational structure, responsibilities, procedures, processes and resources for implementing quality management'.

This Standard provides the principles of a Quality Management System in relation to the preparation of pharmaceuticals in hospitals. It is appropriate to extend the application of these principles to the preparation of pharmaceuticals by externally contracted pharmacists servicing hospitals and nursing homes.

Successful quality management is not achieved without cost, but one objective of the preparation of the Standard was the provision of a cost-effective system.

The Quality Management System is intended to apply to the following range of activities:

Hospital Pharmacy Preparative Activities

A. Preparations for Individual Patients for 'Immediate' Use

- (i) Issuing of pre-prepared pharmaceuticals which may include:
 - counting/packing/labelling of solid dose units (tablets etc.)
 - measuring/packing/labelling of semi-solids (creams etc.)
 - measuring/packing/labelling of liquids (non-sterile)
 - issuing of injections.
- (ii) Compounding of non-sterile dosage forms which includes:-
 - blending of raw materials
 - addition to proprietary or other base products
 - blending or diluting base products.
- (iii) Aseptically prepared items.
- (iv) Terminally sterilised items.

B. Preparations Made in Advance

- (i) for individual patients — includes aseptically prepared items made for use over week-ends/public holidays when the pharmacy is closed or for supply to other or remote institutions (scale of preparation is small).
- (ii) for potential patients — includes:
 - non-sterile or aseptically prepared or terminally sterilised preparations made in batch quantities for issue over a period of time;
 - preparations made in bulk quantities for repacking later into smaller quantities for issue to patients;
 - repacking of pre-prepared pharmaceuticals into smaller amounts for issue to wards (e.g. as imprest stock).
- (iii) for non-patient use — such as dilution of disinfectants.

The Components of the Quality Management System

Interpretation: In this Standard the term 'should' 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.

1. Personnel

General

- 101 A suitably qualified person, preferably a pharmacist, should be designated as having overall responsibility for quality management.
- 102 A pharmacist should be designated to be in charge of each preparation area.

- 103 Pharmacy management should determine the level of competence, experience and training necessary to ensure the capability of personnel in the activities undertaken by the pharmacy.

Pharmacy management should define the level of qualification required and the role of persons working in the area (e.g. in preparing a topical cream, a pharmacy assistant who has received suitable training may weigh out the ingredients, but each step must be checked and signed as correct in the records by a registered pharmacist).

[Reference 1]

- 104 Pharmacy management should ensure that all personnel receive sufficient training to carry out their activities and are able to follow standard operating procedures relevant to their work.

- 105 Pharmacy management should ensure that personnel who are trained in a particular area maintain that level of capability. Their competence and skills should be validated on a regular basis. Individual records should be kept of training and competencies.

- 106 Training should include the principles of quality management relevant to the particular activities for which persons are qualified or undergoing qualification.

- 107 Written job descriptions should be available to staff which detail responsibilities of the position and which reflect the commitment of management to quality management principles. They should be regularly reviewed and updated.

Specific

108 Personnel in Preparation Areas

[Reference 2]

Health

Personnel involved in the preparation of pharmaceuticals should maintain high standards of personal hygiene and cleanliness and be instructed to report any condition (e.g. diarrhoea, coughs, colds, infected or infested skin or hair, wounds) which may cause the shedding of abnormal numbers or types of contaminants.

Personnel subject to any chronic disease or condition which would present an abnormal microbiological hazard to products should not be allowed to work in aseptic or sterile preparation areas.

The nature of the action to be taken regarding personnel hazard should be decided by a designated competent person.

Visitors

Visitors should be subject to the same procedural rules as staff where the visitor's presence could compromise the quality of the product. Visitors should be discouraged from entering aseptic or sterile preparation areas and, if permitted entry, should be subject to the same health rules as applied to staff.

109 Occupational Health and Safety

Where staff are required to handle hazardous substances (such as strong acids or formaldehyde) or where they are handling substances which may affect their health (such as antibiotic tablets which release dust), measures must be taken to protect them from exposure such as provision of a fume cupboard, protective masks and goggles. **Material Safety Data Sheets** for any hazardous substance should be available for reference.

All staff engaged in the preparation of cytotoxic products (whether in aseptic preparation or dispensing solid forms) must be advised of the risks of exposure to these substances and have regular medical examinations to assist in the monitoring of exposure to them.

Individual records should be kept of all exposures to cytotoxic substances as specified in the *Practice Guidelines of the Society of Hospital Pharmacists of Australia*.

[References 3 and 4]

110 Maintenance and Service

All personnel concerned with cleaning and maintenance should receive regular training in procedures and disciplines relevant to their activities, including hygiene, the basic elements of microbiology and advice on the hazards of exposure to cytotoxic substances. When external staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their supervision.

2. Facilities and Equipment

Facilities and equipment should be provided appropriate to the type and the level of activity.

The following factors should be taken into account:

201 Preparation areas should provide the following:

- sufficient space, with adequate separation of activities where necessary;
- sufficient light and controlled temperature and humidity;
- air supply of appropriate cleanliness level;
- air pressure differentials with adjoining areas where necessary;
- appropriate directional control of airflow

and air exchange rates, where necessary.

Specialised facilities, such as **cleanrooms** and **clean workstations**, must comply with the relevant Australian Standards (including testing and certification).

[Reference 5]

The TGA also publishes information bulletins on cleanrooms.

[Reference 6]

202 Controlled storage environments such as refrigerators should be monitored and temperature readings recorded. As a minimum, thermometers of the minimum/maximum type can be used and readings made at least once daily. Refrigerators holding a significant quantity of pharmaceuticals should be fitted with an alarm, permanently set, to indicate when the temperature in the refrigerator moves outside set limits.

203 Facilities and equipment should be designed and constructed to facilitate the necessary levels of **hygiene**. Written procedures must be available to ensure that the required standards of hygiene are achieved and maintained and that cleanliness and hygiene are regularly monitored.

204 Equipment should be kept clean, dry and protected from contamination when not in use. All equipment should be inspected for cleanliness and, where necessary, sanitised before any operation begins. Specific written cleaning instructions should be available to the staff at the point of use.

205 Programs and procedures should be developed for the **testing and calibration** of electro/mechanical measuring and recording equipment and thermometers. Appropriate records should be kept.

206 Adequate equipment should be available for monitoring of the environment of cleanrooms such as manometers to measure air pressure differentials, alarms to indicate failure of the air supply and air and surface samplers to determine microbial contamination levels. Procedures for the use of such equipment and the interpretation of results should be available.

207 All equipment should be properly **maintained** in accordance with written procedures and records of maintenance kept wherever the maintenance or lack of it may affect product quality.

208 Equipment used for **terminal sterilisation** of products and equipment, i.e. steam or gas sterilisers and sterilising ovens, should comply with the requirements of the *Code of GMP*,

[Reference 7]

and the relevant Australian Standards.

[Reference 8] 308

3. Materials

- 301 Raw materials should be procured to established specifications.
- 302 At the point of receipt, the container of the raw material should be visually examined. Particular attention should be given to raw materials packed in plastic or paper bags and to containers visibly soiled by liquid. Any damage or contamination likely to prejudice the integrity of the contents should be reported and assessed by a nominated staff pharmacist. All reject materials should be destroyed or quarantined and clearly marked 'rejected' for return to the supplier.
- 303 A recording system should be in operation which allows complete traceability of all materials at all stages from the patient who receives the product, to the material, to the supplier.
- [Reference 9]
- 304 Labels and packaging materials should also be subject to quality control procedures. Empty containers should be accepted only if packed so as to exclude dust or other contamination in transit, and should be appropriately stored to prevent contamination on storage.
- 305 **Raw Material Testing**
Although it would not normally be expected that hospital pharmacies are able to carry out their own raw material testing, it is expected that a system would be established to ensure that all materials meet the required specification at the time of receipt and throughout the period of use. This system should include:
- purchase from a supplier of starting materials of known origin who is recognised as reliable, based on a history of deliveries which all met specifications;
- and
- valid certificates of analysis (provided by the supplier);
- [Reference 10]
- and where considered necessary
- testing and analysis, whether in-house or contracted.
- 306 All raw materials which are not given an expiry date by the supplier must be given a shelf life and at the end of this period, validated for further use. The shelf life will be arbitrary to an extent but should be based on knowledge of the material.
- 307 All raw materials should be stored and used

under appropriate conditions.

Water to be used as an ingredient should be purified before use or purchased sterile. Purified water should be tested sufficiently frequently to demonstrate acceptable microbiological quality. Standard procedures should ensure that the quality of stored water is maintained.

4. Documentation

An effective Quality Management System rests on the development of Standard Procedures.

There should be a management system for the creation, authorisation and use (including security) of documentation.

401 Standard Procedures

All handling of pharmaceuticals should follow written standard procedures which are regularly reviewed and updated.

Some examples of especially important activities which require standard procedures are:

- donning of cleanroom garments and scrubbing prior to entry into cleanroom;
- procedure to be followed in the event of a spill in the cytotoxic drug preparation area;
- quarantining of raw materials or batches awaiting test results;
- aseptic processing validation.

402 Master Formulae and Processing and Packaging Instructions

Where a standard formula is used regularly to prepare single patient items and for any larger scale of production, master formula documents should be kept.

The Master Formula and Processing and Packaging Instruction should:

- identify the hospital;
- be prepared by a pharmacist who signs and dates the document to authorise it for use;
- be reviewed regularly by a designated pharmacist;
- preferably be typed (or printed from a computer) so that it is clear and legible;
- include a document identity number which uniquely identifies the document and its revisions;
- include the name and strength of the product and a description of its dosage form;
- include a standard formula reference (e.g. APF) and/or a list of ingredients together with the amount of each ingredient per dosage unit or per unit of weight or measure of the finished product; and a statement of the total weight or measure of such dosage unit. Where material of variable potency is

to be used, a place for the relevant calculation;

- include a statement of the equipment to be used and any steps to be taken in preparing the equipment (e.g. cleaning, assembling, calibrating, sterilising);
- include detailed stepwise processing instructions e.g. order of addition of ingredients, the mixing of specific ingredients prior to adding to the base;
- include the total quantity of product expected;
- include an example of the label to be used and any advisory/auxiliary labels;
- include sufficient space for entry of the details on the batch record as given in 403;
- include the appropriate type of packaging to be used.

403 **Batch or Individual Preparation Records**

A photocopy or reprint of the Master Formula or an individual patient worksheet should be used to make the record.

Records must permit complete traceability of the disposition of the product and the source of all raw materials.

If the copy is prepared by a staff member who is not a registered pharmacist, it should be checked as appropriate by a pharmacist and initialled.

The following information should be included in the record (except where irrelevant in the case of individual patient worksheets):

- the date of preparation
- the name of the operator and his/her signature
- batch numbers of ingredients
- quantities of ingredients used
- any relevant calculations as mentioned in 402
- signature of person measuring each ingredient and where this person is not a pharmacist, the signature of the pharmacist checking
- total quantity prepared
- confirmation of packaging used
- example of label to be used
- a unique batch or other identifying number
- expiry date of the product where appropriate
- yield or reconciliation of bulk and of packaged product
- signature of the pharmacist checking the final product against the record
- signature to verify destruction of all unused

batch-coded labels.

404 **Repacking Records**

Repacking of (non-sterile) dosage forms into multiple packs for storage and future use must be accompanied by similar documentation to that described above. In the case of tablets or capsules, those which are packed by the original manufacturer in foil or blister packages can be repacked more readily and with greater assurance than loose tablets or capsules since the immediate container does not have to be breached.

Written procedures must be available to avoid mix-ups and cross-contamination of products and materials.

In all cases, a **Master Process Card** should be prepared containing details of starting materials, processing instructions and final product and should include:

- the generic name and strength of the product
- the quantity per pack
- the labelling requirements with a sample label and any auxiliary stickers
- the type of container and closure
- adequate working instructions
- the usual number of packs to be packed
- sufficient space on the form to record the details as shown below in the Batch Record.

The Master Process Card should be reviewed regularly.

The **Batch Record** may be made on a photocopy of the Master Process Card or on a separate sheet or in a logbook and should contain the following details of the repackaging operation:

- the date of packing
- the name and signature of the person carrying out the repacking
- the generic and brand name and strength of the product
- the name of the manufacturer and manufacturer's batch number or hospital batch number
- the type of container used
- the quantity of product remaining
- yield or reconciliation of bulk and of packaged product
- a sample label
- the expiry date (will be either the original manufacturer's expiry date or in the case of extemporaneously prepared items the date set by the hospital pharmacy at time of preparation)
- the name and signature of the pharmacist

- preparing or checking the batch
- signature to verify destruction of all unused batch-coded labels.

405 Aseptic Preparation Area Records

In addition to batch or individual preparation records as described in 403, a logbook or similar record of sterile operations should be kept, showing dates, times of preparation, operator's name and product batch number.

406 Adverse Reaction Reporting

Any suspected patient reactions to products compounded by pharmacy should be reported to pharmacy and these should be logged against the batch record and log, and follow-up action taken as necessary.

407 Quality Control Records

Refer *Code of GMP 1990*.

[Reference 11]

408 Personnel Records

Records should be kept of:

- training of personnel and should be specific for each staff member;
- staff members' signatures against their names;
- exposure of staff to cytotoxic agents.

5. Preparation Methods

501 General

Adequate precautions should be taken to prevent contamination, cross-contamination and product mix-up in all stages of preparation. Standard procedures should specify the requirements for adequate separation of products in preparation areas including the assembling and dispensing of materials for aseptic preparation, repacking and the return of surplus materials to stores.

502 Packing and Labelling

- Labels should be of sufficient material quality, printing quality and size to ensure identification and permanence.
- Precautions must be taken to ensure that mistakes do not occur during labelling. Thus, particular attention should be paid to label security storage and verification of label text with the information on the master process card. All unused batch-coded labels should be destroyed.
- Before any labelling operation is commenced the area should be checked to ensure that all materials, labels and products of previous operations have been removed. For more complex packing and labelling situations and wherever equipment should be inspected for residual product, the documentation should include space for signature veri-

fyng that all materials, labels and product from previous operations have been removed and equipment inspected.

The control or batch number system employed should give ready access to all information required to establish the integrity of ingredients and the procedures used in preparing the finished products. Policy on the method of batch numbering should be set down.

Labels should contain the following typewritten or printed information:

- approved name and strength of product or full list of ingredients;
- batch number or identification number;
- storage conditions where necessary;
- expiry date and, where appropriate, time of expiry;
- quantity of preparation, i.e. volume, weight or count (in aseptically prepared products this is the final volume including the volume of all additives);
- name and address of hospital; and
- other wording as may be required legally or by the hospital.

503 Packaging Materials

Containers and closures should be selected having regard to the following considerations:

- compatibility and fit of individual components;
- protecting the product from light and moisture;
- preventing contamination of the product, including microbial contamination when necessary;
- preventing deterioration of the product through chemical reaction with either the materials of the containers or substances leached from the containers or through loss of substances from the containers;
- compliance with any official requirements for the packaging of products, e.g. child-resistant closures and tamper-evident measures;
- appropriateness in size and type for product concerned.

6. Process Validation and Testing

- 601** A **program** of chemical, physical and microbiological testing should be established to adequately assure the quality of the product. The selection of product to be tested should be based primarily on an analysis of hazard i.e. an analysis to assess which materials, steps and products are most likely to contribute to loss of purity, potency or sterility.

[Reference 12]

602 Physical and chemical stability testing would not be required for most pharmaceutical preparations made in hospital pharmacies due to the availability of stability data in texts and the expected short use-by period. However, where stability data are not available, and the pharmacy is compounding batch quantities for extended use, then stability testing should be performed.

A guideline to the design of a stability testing program is available — see Reference.

[Reference 13]

603 Sterility Testing and Validation

Processes designed to produce sterile products should be validated.

Heat sterilisation validation should follow the guidance given in the *Code of GMP*. Batches of these products should be sampled for sterility testing.

[Reference 14]

Validation of **aseptic preparation** should include:

- environmental testing (settle plates, surface samples, air samples, personnel);
- broth transfers mimicking actual transfers and reflecting both time and operator variables;
- sterility tests on randomly allocated duplicate products.

Note: Random sterility tests on aseptically prepared products need not include cytotoxic drugs due to the occupational hazard of extra handling of these substances.

604 Pyrogen testing

Section 1708, *Code of GMP*, is applicable wherever products are made from other than pyrogen-free ingredients.

Section 1708 states:

'1708. Unless the nature of the product makes pyrogen testing impossible, pyrogen testing should be carried out on all batches of parenteral products and solutions for irrigation of body cavities, wounds, operation cavities or the urogenital system where:

- the volume to be administered or used in a single or application dose is 15 mL or more; or
- the label on the container indicates that the preparation is apyrogenic; or
- directed by a statutory requirement.

Pyrogen testing should be replaced by testing for bacterial endotoxin wherever practicable and approved.'

7. Contracted Services

Where any tests, services or activities of the pharmacy department are provided by an external supplier or hospital department, the provider should be evaluated for its competence and monitored for its performance by the pharmacy in relation to the services contracted.

8. Audit

A documented system for in-house auditing of the quality management system, based on a step by step assessment of conformity to each of the components of these guidelines, should be in operation and should include procedures for implementation of corrective action and follow up.

The internal auditing program should be complemented by a program of independent auditing by a recognised authority.

References

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3. The Society of Hospital Pharmacists of Australia Committee of Specialty Practice in Oncology. SHPA policy guidelines for the safe handling of cytotoxic drugs in pharmacy departments. Aust J Hosp Pharm 1990: 20: 391-4.
4. SHPA policy guidelines for the transportation and handling of cytotoxic drugs by lay personnel. Aust J Hosp Pharm 1988: 18: 355.
5. AS 1386 - 1989: Cleanrooms and clean workstations
AS 2639 - 1983: Cytotoxic drug safety cabinets - installation and use
AS 2567 - 1982: Cytotoxic drug safety cabinets
AS 1807 - 1989: Cleanrooms, workstations and safety cabinets - methods of test.
6. Guidelines for preparing plans and specifications for an 'aseptic' (clean room) suite, 'cytotoxic' drug suite or combined suite in a hospital or related facility. TGA Technical Bulletin No. 3, August 1990.
7. Code of GMP 1990 - Medicinal Products - Part 2, Sections 1303-1309.
8. AS 1410 - 1987 Sterilizers - steam - pre-vacuum
AS 1714 - 1975 Ethylene oxide sterilizers
AS 1862 - 1976 Aeration cabinets (for use with ethylene oxide sterilizers)
AS 2182 - 1981 Portable electrically heated steam sterilizers
AS 2192 - 1978 Horizontal sterilizers (downward displacement pressure steam type)
AS 2487 - 1981 Dry heat sterilizers (hot air type)
9. Code of GMP 1990 - Medicinal Products - Part 1, Sections 510-511.
10. Code of GMP 1990 - Medicinal Products - Part 1, Sections 814-815.
11. Code of GMP 1990 - Medicinal Products - Part 1, Sections 555-556.
12. Baird-Parker T. HACCP and Food Control. Food Control 1990; (July): 131-3.
13. Australian Guidelines for Registration of Drugs (available from TGA).
14. Code of GMP 1990 - Medicinal Products - Part 2, Section 1632.