New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods

Part 2: Manufacture of Blood and Blood Products
FOREWORD

This Code of Good Manufacturing Practice (GMP) is the first specifically written for those engaged in blood collection and processing in New Zealand. The Blood Transfusion Service and the Department of Health have consulted and agreed that the Australian Code of Good Manufacturing Practice for Blood and Blood Products is a suitable document for application in New Zealand. The code is essentially the Australian code with some minor modifications for New Zealand use.

Codes of Good Manufacturing Practice have been developed throughout the world to guide those engaged in the manufacture and distribution of therapeutic goods. They describe proven systems and procedures for the production of quality products.

A code of GMP must be regarded as the minimum standard. Some operators may choose alternative systems to those outlined in the code. This is acceptable if they achieve the same objectives as the code. Systems that go beyond the guidelines are encouraged. Everyone engaged in the activity of processing blood or blood products should be aware of this document and apply its principles. The code represents the standard against which the Department of Health audit programme will be conducted.

The pursuit of high quality is a basic principle for any health enterprise. Both the Department of Health and the Blood Transfusion Service are committed to the maintenance of high standards in the operation of blood and blood product collection and processing facilities. The philosophy embodied within this Code and the others in this series can be applied to a wide range of products and services intended for therapeutic benefit.

Christopher Lovelace
Director-General of Health
ACKNOWLEDGEMENTS

The Department wishes to acknowledge assistance it has received from:

- The Blood Transfusion Service of New Zealand
- The Therapeutic Goods Administration of Australia who have allowed us to adopt their code and to present it in this format for New Zealand use.
The Manufacture of Blood and Blood Products in New Zealand

Introduction

New Zealand has adopted the Australian Code of Good Manufacturing Practice for Blood and Blood Products. The Code printed in this document is the Australian Code. It contains many references to the Australian situation.

Immediately following this Introduction is a list of references indicating where it is important to be aware that a New Zealand alternative exists. In some cases standards have been modified for the New Zealand situation.

The list is followed by a table of cross references between the Australian and New Zealand Codes of GMP for Manufacture and Distribution of Therapeutic Goods.

You may find it useful to familiarise yourself with the lists of modifications before reading and applying the text of the Australian Code of Blood and Blood Products in New Zealand.
New Zealand List of Alternatives, Additions and Exceptions to the
Australian Code of Good Manufacturing Practice for Therapeutic Goods -
Blood and Blood Products

1. Alternatives

The New Zealand equivalent is given in italics after the Australian term in each numbered section.

1.1 Australia, Australian, State of Australia:
   New Zealand.

1.2 Therapeutic Goods Administration:
   Therapeutics Section, Department of Health.

1.3 Australian Code of Good Manufacturing Practice (GMP) for Therapeutic Goods - Medicinal Products (ISBN 0644 137630):
   New Zealand Code of Good Manufacturing Practice, Part I Manufacturing of Medicines.

1.4 National Guidelines for the selection of blood donors, National Blood Transfusion Committee, Australian Red Cross Society, ISBN 0 909896 42 9:
   New Zealand Guide for the selection of blood donors. (This document is regularly updated by the Blood Transfusion Advisory Committee and is published as Appendix IV of the Guide to Standards for Transfusion Medicine Services in New Zealand.)

1.5 National Association of Testing Authorities (NATA):
   Testing Laboratory Registration Council of New Zealand (TELARC).

1.6 National Blood Transfusion Committee of the Australian Red Cross Society:
   Blood Transfusion Advisory Committee (BTAC) of the Department of Health.

1.7 Red Cross:
   The various health care providers which operate transfusion services in New Zealand. (The New Zealand Red Cross does not have an equivalent managerial and operational role in transfusion activities in New Zealand.)
1.8 Red Cross Blood Transfusion Service (RC BTS):

The various Transfusion Medicine Services operated by health care providers in New Zealand.

1.9 State or Territory Red Cross BTS Director:

Regional Transfusion Advisor (and member of the Blood Transfusion Advisory Committee).

1.10 Labelling of blood and blood products: Therapeutic Goods Order No 32: General requirements for labels for therapeutic goods, ISBN 0644 10595 X and Therapeutic Goods Order No 37: General requirements for labels for Therapeutic Devices ISBN 0644 13698 X, and other references to information required on labels:

The requirements for labelling blood and blood products in New Zealand are set out in Appendix VII of the Guide to Standards for Transfusion Medicine Services in New Zealand, together with specimen labels.

1.11 Uniform Recall Procedure for Therapeutic Goods:

Recall of medicines in New Zealand must follow the procedures set out by the Therapeutics Section of the Department of Health.

1.12 Therapeutic Goods Act (1989) - premises where plasma is prepared must be licensed:

Premises where any therapeutic blood product is prepared, processed or stored at any stage of production must be licensed. The requirement for licensing is not confined to preparation of plasma for fractionation.

1.13 Registered anticoagulant:

There is no process for registration of anticoagulants in New Zealand. Anticoagulants employed will form part of the medicine registration for each product.

1.14 Printing errors which result in duplicate copies of unique numbers must be reported to the Chairman of the National ADP standing committee of the NBTC (ref. para 321):

Errors should be notified to the BTAC through the Regional Transfusion Advisor.

1.15 National Health and Medical Research Council:

Health Research Council of New Zealand (HRC).
1.16 Audits of premises and procedures will be performed by GMP auditors of the Compliance Branch of the TGA:

*Audits will be performed by, and under the supervision of, inspectors of the Therapeutics Section of the Department of Health.*

1.17 Adverse reactions in apheresis donors must be notified to the TGA if due to a therapeutic good, ref. para 2017:

*Adverse reactions to a registered medicine must be notified to the Medicines Adverse Reactions Committee (MARC) and to the BTAC through the Regional Transfusion Advisor.*

1.18 Australian Standard AS 3864-1991: Medical refrigeration equipment - For the storage of blood and blood products and containers for the transport of blood and blood products.

(1) Permitted range of storage temperatures:

- 5±1°C for liquid blood products

  *NZ alternative: 4±2°C*

- less than minus 30°C (-30°C) for frozen products

  *NZ alternative: less than minus 30°C (-30°C) but a storage temperature of less than minus 17°C (-17°C) may be used as a temporary expedient, as set out in the Guide to Standard Operating Procedures for Transfusion Medicine Services prepared by the Blood Transfusion Advisory Committee.*

(2) Appendix A2. Frequency of tests on recording thermographs and alarm systems:

The test specified in Appendix G is to be performed at least once each week.

  *NZ alternative: The test frequency shall be at least once each month.*

(3) The tests of refrigeration performance specified in AS 3864-1991 require controlled temperature environments and other specifications which cannot be met for equipment in operational use. Equipment should be certified by the manufacturer to the standard described, before purchase.
Refrigeration equipment must also be assessed using the tests for on-site assessment described in Section 9 of the Guide to Standard Operating Procedures for Transfusion Medicine Services prepared by the Blood Transfusion Advisory Committee. The tests must be performed at least once each year. The frequency of testing should be increased for older equipment.

1.19 Plasma for transfusion as Fresh Frozen Plasma, para 829. Factor VIII:C greater than 0.7 iu/mL:

The mean value for Factor VIII:C is not less than 0.7 iu/mL.

1.20 Specification for haemolysis on units of Plasma - haemolysis at expiry less than 1 g Hb/L:

The test for haemolysis may be performed at any time after preparation of the Plasma.

1.21 Specifications for blood products in Chapter 8 - various requirements exist for microbial testing:

There is no specific New Zealand requirement for microbial testing where blood and blood components are handled in a closed system* from the time of collection and the collecting system is an integral set which is not opened at any site during the collection procedure. Quality control of sterility is based on:

(i) adherence to relevant Codes of Good Manufacturing Practice at all times,

(ii) clearly written Standard Operating Procedures which are available to, and are followed by, all staff, and

(iii) careful investigation of adverse reactions to blood and blood components which includes assessment for potential microbial infection. If evidence of a microbial infection problem is found a programme for surveillance monitoring should be instituted promptly.

* for definition see glossary, Annex 3k, ACGMP - B & BP

1.22 Plasma recovered, para 836 - volume specified as stated volume ±10%:

There is no requirement to show the volume on a pack of recovered plasma.

1.23 Interpretation of the Therapeutic Goods Act 1989 - Persons exempt from the requirement to have a manufacturing licence:

In New Zealand a person who operates a centre which produces any therapeutic blood product or undertakes part of the processing of therapeutic blood products is required to have a manufacturing licence.
1.24 Notification of defects found in therapeutic devices, including diagnostic reagents (ref. para 254):

*In the first instance, notification of a defect should be made to the Therapeutics Section of the Department of Health (Tel: (04) 496 2000, Fax (04) 496 2340). Notification should also be made to the manufacturer and the BTAC (through the Regional Transfusion Advisor).*

2. Additions

2.1 Standards Australia and the New Zealand Standards Organisation.

2.2 Suppliers of materiel should provide evidence of certification of their quality systems to the requirements of AS3901 or 3902 or satisfy an equivalent specification.

2.3 Materiel supplies must meet AS 3901 or 3902, and be so certified by Standards Australia or an equivalent specification.

2.4 Animal houses must comply with the current edition of the NH & MRC/CSIRO/AAC Code of Practice for the Care and Use of Animals for Experimental Purposes or an equivalent code.

3. Exceptions

3.1 Australian Register of Therapeutic Goods:

*No alternative in New Zealand.*

3.2 The Health Research Council of New Zealand has not been requested to undertake the activities described in relation to transfusion practice performed by the NH&MRC in Australia. These activities are largely performed by the BTAC or a delegated agent for the BTAC.

3.3 National Pathology Accreditation Advisory Council:

*No alternative in New Zealand.*

3.4 Records of blood donations and blood products must be signed (ref: paras 223, 226).

*A computer system may be used to maintain records of blood donors, blood donations and blood products. All records should be accessible in printed format and there must be a reliable record of the identity of the operator who performed tests and entered data.*
It must not be possible to change a record without the system retaining the previous result, the date of the transaction, and the identity of the operator who performed the change. Computer systems must have appropriate safeguards to prevent unauthorised persons gaining access or staff performing unauthorised transactions.

3.5 AS3787 General requirements for single use, sterile, plasticised polyvinylchloride (PVC) blood packs for whole blood and blood components:

The requirements of AS3787 are modified as follows for New Zealand purposes: the requirement for not more than 5mL of air in each pack of a multipack system is modified to not more than 10mL of air in each pack in a multipack system.
Cross References: Australian and New Zealand Codes of Good Manufacturing Practice

The code makes several references to the Australian Code of Good Manufacturing Practice for Medicinal Products. The following list provides a cross reference with the New Zealand Code of Good Manufacturing Practice, Part 1 (for pharmaceuticals). Where mention is made of the Australian code, the appropriate section of the New Zealand code is indicated.

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Code of Good Manufacturing Practice
For Therapeutic Goods -

Blood and Blood Products

July 1992
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Chapter 1

Preface

The past

A n Australian Code of Good Manufacturing Practice for Therapeutic Goods - Medicinal Products 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 a Commonwealth inspection unit. That Code was, in fact, 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.

In 1975, the Twenty-eighth World Health Assembly adopted an important resolution (resolution WHA28.72) on the utilization and supply of human blood products. It requested, inter alia, that steps should be taken to develop good manufacturing practices specifically for blood and blood components in order to protect the health of both the donors and recipients.

1978 saw the publication of the WHO Expert Committee on Biological Standardisation’s Technical Report Series No 626, Annex 1 “Requirements for the collection, processing and quality control of human blood and blood products”.

The preparation of an Australian Code of GMP specifically intended for use by the Australian Red Cross Society's Blood Transfusion Services and other blood collection centres coincided with the introduction of a single, national, licensing scheme of manufacturers of Therapeutic Goods under a re-enacted Therapeutic Goods Act 1989. The Act commenced the day after regulations were accepted by Parliament on the 14th February, 1991. This, amongst other things, required the licensing of blood collection centres which supplied plasma to other fractionation centres.

This Code was developed as a collaborative project by the National Pathology Accreditation Advisory Council (NPAAC), the GMP Audit and Licensing Section of the Australian Therapeutic Goods Administration, the National Blood Transfusion Committee (NBTC) and the Australian Red Cross Society’s Blood Transfusion Service. Other parallel industry associations – the Australian Pharmaceutical Manufacturers Association (APMA), Proprietary Medicines Association of Australia (PMAA) and the Medical Industry Association of Australia (MIAA) – were also consulted during its preparation.

The present

T his Code, 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. The sensitive nature of blood and blood products requires this assurance. The text therefore goes into some detail, although it is acknowledged that there can be alternatives to many of the detailed provisions that may conform to the same basic principles, achieve the same end and prove acceptable.

Therefore, it is not intended that this Code should place any restraint upon the development or introduction of new concepts or new technologies. Nor is it assumed that this Code covers every aspect of manufacture, control and quality assurance: the manufacturer bears the ultimate responsibility for the products made and distributed.

This Code also coincides 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. This philosophy may be expected to influence strongly the attitudes of Australian organisations, including therapeutic goods manufacturers and indeed the GMP Audit and Licensing Section, towards closer attention to quality management systems in the years in which the present edition of the Code takes effect.

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 ASQ5-1-1988 provides guidance on the preparation of a quality manual.

There are many reasons why blood collection centres should achieve and maintain the highest standard of operations. Uniformity of procedures amongst blood collection centres should be engendered by following these Code's requirements so as to ensure maximum safety of blood and its products.

Under the provisions of the Therapeutic Goods Act 1989, premises where plasma is separated for supply to a fractionation centre are required to be licensed. However, licenses may not be approved if the BCC producing the source plasma was found to be not operating within agreed standards.

This Code provides principles and practices by which this objective will be met. Conformity to the Code will be the basis for the assessment of eligibility for initial and continued licensing for production of plasma. The interpretation and application of this Code also requires the judgement of an experienced GMP Audit and Licensing Section.

The Australian Government, industry and Red Cross Society are together committed to the achievement of high standards of quality assurance for manufactured blood products.

The future

Although one of the objectives of the present Code was to produce a document that would stand for some years, it is recognised that amendment may be necessary to accommodate technological change, to clarify uncertainty, or to specifically recognise important alternatives.

It is intended to regularly review this Code. Comments on it or its Annexes are therefore invited at any stage in the life of this edition.

Comments should be forwarded to:

The GMP Audit & Licensing Section
Therapeutic Goods Administration
PO Box 100
WODEN ACT 2606

Acknowledgement

The preparation of this Code would not have been possible without the work previously done by the group who prepared the United Kingdom Department of Health's "Guidelines for the Blood Transfusion Services in the United Kingdom" which served as a foundation for modification and addition to prepare a Code relevant to the collection and processing of blood in Australia.

Grateful acknowledgement is given to the UK DH for permission to use its copyright material.

DOCUMENT HISTORY

The following list shows the revision history of the Codes of GMP.

- Abbreviations 1990
- Referenced and Recommended Standards and Publications 1996
- Glossary 1990
- Key Interpretations from the Therapeutic Goods Act 1989
- Appendix A 1971 (withdrawn for revision)
- Appendix B 1976 (withdrawn for revision)
- Appendix C 1981 (edited August 1992)
- Appendix D 1992
- Appendix E 1986
- Appendix F 1990
Introduction

The Code of GMP for Blood and Blood Products (the Code) has been written in a style intended to be readable rather than regulatory, intended to allow it to be used both for inspection and for self-audit, following the flow of Australian Standard AS 3902 (ISO 9002) Quality Systems for Production and Installation. Additionally, in order to clarify the way in which the Code seeks to realise its objectives, a 'rationale' has been added to some sections where special emphasis or explanation was considered desirable.

Further, almost 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. Where must is used this is shown in bold type. Notes have been added occasionally to provide guidance and interpretation and are shown in italics.

The Code does not deal with common or statute law requirements such as the obligations of employees, Occupational Health and Safety, Customs and Excise, Dangerous Goods, Poisons, Weights and Measures, waste disposal and pollution, or the many legal requirements surrounding building construction. These must be met by the blood collection centre (BCC). 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.

There are three publications that should be considered as follows:

- the Code — after the Introduction, Chapter 2 deals with the general requirements for a quality system suitable for the collection and processing of blood and its products, Chapters 3 and 4 build on this framework with specific Guidelines for blood and plasma donor sessions. Chapter 5 relates to donors in general, and, 6 and 7 to apheresis and hyperimmune donors. Chapter 8 contains Guidelines for blood component specifications. Chapter 9 relates to specifications for plasma intended for fractionation. Finally, to assist the reader, a Document History, a List of Abbreviations Used and an Index have been added; and

- the Annexes, which provide guidance to the interpretation of the Code, presented in two publications as follows:
  
  - the first part contains seven annexes which have information thought to be useful on topics such as an example document for the preparation of an standard operating procedure, requirements for premises, personnel, key interpretations from the Therapeutic Goods Act; a list of referenced and recommended standards and publications, and a glossary; and
  
  - the second part is a special annex (Annex 8) relating to guidelines on technical matters.

It is not intended that the Code be used to replace detailed specifications and standard operating procedures but that it be used in their preparation. It should also be used in conjunction with the:

- current "Code of Good Manufacturing Practice for Therapeutic Goods - Medicinal Products" (for ease of use some of the relevant sections are adapted as annexes), ISBN 0 64413763 0;

- "Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives" (WHO: Requirements for Biological Substances, No. 27, revised 1988), ISBN 92 4 154158 X; and


  Note: this document is regularly updated.

Reference is made to other texts where they are relevant.

It is hoped that blood collection centres will regard this Code as a ready reference to the achievement of quality and keep it within arm's reach for frequent use.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab</td>
<td>Antibody</td>
</tr>
<tr>
<td>ABO</td>
<td>Landsteiner's blood groups for individuals who have an A, B, both A and B, or neither A nor B (i.e. O) antigen on their red blood cells.</td>
</tr>
<tr>
<td>Ag</td>
<td>Antigen</td>
</tr>
<tr>
<td>ADP</td>
<td>Automated data processing</td>
</tr>
<tr>
<td>AHF</td>
<td>Anti-haemophilic factor</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase (enzyme)</td>
</tr>
<tr>
<td>ARTG</td>
<td>Australian Register of Therapeutic Goods</td>
</tr>
<tr>
<td>AS</td>
<td>Australian Standard</td>
</tr>
<tr>
<td>BB</td>
<td>Blood Bank</td>
</tr>
<tr>
<td>BCC</td>
<td>Blood Collection Centre. BCCs may be licensable if any blood is processed (even after expiry) into plasma, e.g., for supply to CSL.</td>
</tr>
<tr>
<td>BCCD</td>
<td>Blood Collection Centre Director</td>
</tr>
<tr>
<td>BS</td>
<td>British Standard</td>
</tr>
<tr>
<td>BTS</td>
<td>Blood Transfusion Service</td>
</tr>
<tr>
<td>CFU</td>
<td>Colony-forming units. Each colony of micro-organisms is regarded as originating from a &quot;unit&quot; which is assumed to be single micro-organism, although this is not necessarily true.</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus.</td>
</tr>
<tr>
<td>EVF</td>
<td>Erythrocyte volume fraction.</td>
</tr>
<tr>
<td>FFP</td>
<td>Fresh frozen plasma</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice.</td>
</tr>
<tr>
<td>HAV</td>
<td>Hepatitis A virus</td>
</tr>
<tr>
<td>Hb</td>
<td>Haemoglobin</td>
</tr>
<tr>
<td>HBcAg</td>
<td>Hepatitis B core antigen</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Hepatitis B e antigen</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C virus</td>
</tr>
<tr>
<td>HEPA</td>
<td>High efficiency particulate arresstance (air filter).</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus; the WHO preferred name for the aetiological agent responsible for AIDS (cf. LAV: lymphadenopathy-associated virus; HTLVIII; human T-cell lymphotropic virus; and ARV: AIDS related virus)</td>
</tr>
<tr>
<td>HLA</td>
<td>Human leucocyte antigens</td>
</tr>
<tr>
<td>HPLC</td>
<td>High performance liquid chromatography.</td>
</tr>
<tr>
<td>K</td>
<td>Kell is the third commonest blood group classification after ABO and Rh.</td>
</tr>
<tr>
<td>LAL</td>
<td>Limulus amoeocyte lysate. The reagent used in the test to detect pyrogenic endotoxin.</td>
</tr>
<tr>
<td>NATA</td>
<td>National Association of Testing Authorities. This Association operates a certification (registration) scheme for testing laboratories in 10 fields, including Chemistry and Biological Testing.</td>
</tr>
<tr>
<td>NBTC</td>
<td>National Blood Transfusion Committee</td>
</tr>
<tr>
<td>NH&amp;MRC</td>
<td>National Health &amp; Medical Research Council.</td>
</tr>
<tr>
<td>NPAAC</td>
<td>National Pathology Accreditation Advisory Council</td>
</tr>
<tr>
<td>RC</td>
<td>Red Cross</td>
</tr>
<tr>
<td>RC BTS</td>
<td>Red Cross Blood Transfusion Service.</td>
</tr>
<tr>
<td>Rh</td>
<td>The Rhesus system of classifying antigens on red blood cells.</td>
</tr>
<tr>
<td>Rh (D)</td>
<td>The most potent of the Rh antigens in provoking antibody formation.</td>
</tr>
<tr>
<td>SA</td>
<td>Standards Australia.</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration.</td>
</tr>
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</table>

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Chapter 2

Guidelines for a quality system for the collection and processing of blood and blood products

Rationale

201 Quality Assurance is a total scheme to ensure that the product meets specification and includes all those planned and systematic actions necessary to provide adequate confidence that the product will satisfy given requirements for quality. In terms of the RC BTS the objective is to ensure the availability of a sufficient supply of blood and components of adequate and specified quality with maximum efficiency and with minimum risk to donors, processing staff and patients.

202 In order to achieve satisfactory quality assurance it is essential that there should be a structured and organised approach. This is the quality system.

203 In this chapter the principles for the establishment of a quality system will be presented. They are derived from the Australian Code of Good Manufacturing Practice for Therapeutic Goods - Medicinal Products (August 1990), and from the Australian Standards AS 3900 series, which equate to the International Standards ISO 9000 series and the British Standard BS 5750. These deal with establishment and maintenance of Quality Systems.

A full list of references is given in the referenced and recommended standards and publications in Annex 3. In addition, a full list of referenced and recommended standards and publications is given in Annex 3).

204 The principles outlined in the standards cited above apply to BCC's although some may argue that:

- each donation represents a batch and testing of an individual donation is restricted to tests that do not lead to its destruction.

However, the quality systems described in the above standards have been shown to apply to many different situations (as diverse as a solicitor's office and a bicycle factory) and have been shown to be applicable to similar manufacturing situations analogous to blood processing such as device manufacturing. For instance, the manufacturer of a heart pacemaker may be said to have concerns similar to those of blood products suppliers. That is, single, high-value units not able to be subjected to destructive tests, but expected to be subject to a comprehensive quality system established.

It is often considered that quality assurance is exclusively a laboratory function. This is not so. Every person in the BCC who is involved with the collection, testing, processing and release of products for issue, the selection of venues for blood collection, the cleaning of premises or the maintenance of equipment is responsible for quality.

205 The formal style of the ISO 9000 series is used in this chapter, but the implications of each recommendation are interpreted when appropriate.

206 The word materiel (sic) is used frequently in this chapter. For those readers who may not be familiar with its use, it can be defined as "all components, materials or other supplies which are to be incorporated or to be used in the testing or processing of product". Materiel is to material as person is to personnel. Thus, materiel may comprise a pack for the collection of blood or plasma, the donation of whole blood or plasma, components, plasma fractions, the test reagents used during their preparation or pieces of equipment. By use of this word, lengthy explanations of the different component parts of products or materials can be avoided.
A quality system

207 Each BCC should establish, document and maintain an effective and economical quality system to ensure and demonstrate that the material and services conform to specified requirements.

The documented quality system should include quality management objectives, policies, organization and procedures to demonstrate compliance with the requirements of this Code.

208 The documentation of the quality management system should be presented as a quality manual.

209 Blood Collection Centre Directors (BCCDs) have to consider the overall operational plan for their BCC. In conjunction with staff with specialised skills, the policy for the BTS should be compiled and recorded. The principles involved in the production of safe, efficacious products should be defined together with the principles involved in determining specifications for material and services. These should include general principles of quality management to ensure that the stated requirements can be met.

Organisation

Quality Assurance Manager

210 Each BCC should appoint a management representative, independent of production and preferably of other functions, who should have the necessary authority and the responsibility for ensuring that the requirements of this Code are implemented and maintained.

Note: for small centres, this person need not be on the premises if it can be demonstrated that the net overall control of quality is the same.

211 The quality assurance (Q.A.) manager should report directly to the BCCD or to another person, deputed by the BCCD, who is entirely independent of production.

212 In the event of conflict arising between the Q.A. manager and blood processing staff, the BCCD (or the person nominated by the BCCD) should have the authority to make a decision after consultation with the State or Territory RC BTS director. The circumstances and the decision taken should be fully documented.

Staff responsible for functions affecting quality

213 BCC staff members should be aware that each has responsibility for functions affecting quality. The level of responsibility should be defined for each group or individual members of staff. The degree of authority allocated to each staff member to evaluate quality problems and to initiate, recommend and provide effective outcomes should be determined.

214 Each BCC should regularly re-appraise the quality assurance program and the part played in it by all members of staff.

Note: see also Annex 3c.

Review of the quality system
(quality audits)

215 The quality system should be periodically and systematically reviewed to ensure its continued effectiveness; records of the review should be maintained.

216 The quality audits should be performed by:

- trained BCC personnel who do not have direct responsibilities in the procedures being audited;

and/or

- qualified external auditors.

217 External assessments should also be part of quality audits.

218 When an audit demonstrates that a procedural change should be made, the revised procedure should be validated before introduction.

Standard operating procedures
(work instructions)

219 Each BCC should develop and maintain clear and documented instructions that set out, for all staff involved in functions affecting quality, the procedures
which they will use. Standard Operating Procedures should be written at a level which allows a skilled employee from a different area to understand an operation.

BCC documentation should be written in the imperative.

Each procedure which affects the quality of a product should have a standard operating procedure.

Records

Each BCC should develop and maintain records that demonstrate that:

- the required quality has been achieved and that the quality system has operated effectively;
- records stored electromagnetically are able to be reproduced as a hard copy at any time during their required storage period;
- documents are securely stored to prevent, e.g., illicit copying;
- documents can be traced to their location;
- new documents are introduced only with a formal commissioning and training period;
- superseded documents are withdrawn and accounted for; and
- copies of superseded documents are archived.

Specific requirement: product history file

Records should be maintained in a product history file for a suitable period of time.

- Note: it is suggested that this be at least twenty years for BCCs or fifteen years for hospitals, although longer periods may be needed in order to defend against possible litigation.

Records should include or refer to the location of the following:

- the donation number allocated to each donation of whole blood or plasma from which products are derived. It is advisable that the donation number should not be cycled within the duration of the product history file;

- Note: when plasma is collected by apheresis from a single donor into more than one pack, BCCs should build in a security system so that if more than one pack bears the same donation number, the total number of packs to trace in the event of a recall can be identified by, e.g., labelling with "pack 1 of 3" (2 of 3, 3 of 3).

- the session record (see glossary) of each donation of whole blood or plasma from which the products are derived;

- the processing record incorporating the date performed, the designated individual or where appropriate, the names of team members performing critical steps relating to collection and any open processing together with, where applicable, the major equipment used;

- the inspection checks and quality control tests performed, the methods and equipment used, results and the date and signature of the person carrying out the inspection or tests; and

- a record of the label or, if appropriate, the package insert and the control number (i.e. a distinctive combination of numbers or letters which uniquely identifies an individual product) for each product produced.

The records for each product should be such that the origin of the product can be traced to the donor of the whole blood or plasma, and from the donor to other donations he or she may have made.

Corrective action

Each BCC should establish and maintain documented procedures to provide for:

- a continuing analysis of production losses to determine the cause and the corrective action needed;

- a continuing monitoring of processing and analysis of records to detect and eliminate potential causes of lost production; and

- records which give assurance that the corrective actions were effective.
Documentation control and change procedures

General guidelines

225 Each BCC should establish and maintain control of all documentation to ensure that:

- the pertinent parts of appropriate documents are available to blood processing staff and other appropriate personnel, at all locations, including mobile collection sites, where operations are performed which are essential to the effective functioning of the quality system;

- all changes to documentation are in writing, dated and signed by the person designated by the BCCD;

- all changes to documentation are provided to specified staff responsible for the procedure and steps are taken to ensure that the revised instructions are understood and will be acted upon promptly;

- documents are reissued after a practical number of changes have been made;

- provision is made for the prompt removal of obsolete documents from all points of issue or use; and

- a copy of an obsolete document is archived.

Note: see also Annex 6.

Documentation for products derived from pooled donations i.e., a product master file.

226 If the BCC prepares products from pooled donations (such as cyroprecipitate from pooled plasma) then it should establish and maintain detailed documentation on a product master file for each product. This document should be prepared, dated and signed by a designated person(s). Any changes should be dated and authorised in writing by the signature of the designated person.

The product master file should include or refer to the location of the following information:

- specifications;
- standard operating procedures (work instructions);
- quality control procedures and the apparatus used;
- full information concerning the selection of donors and the donations to be used for the preparation of the product;
- full information concerning suppliers of critical components such as blood packs, including the specification for those components and written copies of any agreements made with these suppliers; and
- complete labelling procedures for the donations and products together with copies of all approved labels and other labelling.

Control of inspection of test materiel

227 Each BCC should ensure that there is provision of suitable equipment and reagents for the preparation and testing of products prepared from whole blood and plasma.

228 Each BCC should control the calibration and maintenance of equipment used in the preparation of products prepared from whole blood and plasma. Procedures for calibration and maintenance should be suitable to demonstrate the conformance of this materiel to the specified requirements.

229 Each BCC should ensure by means of suitable quality control that all reagents conform to specified requirements.

Note: this should be by both the use of internal and, where appropriate or available, external control materiel.

Note: see also "The Australian Code of GMP – Blood and Blood Products - Laboratory Guidelines".
Control of purchased material and services

Purchasing

230 Each BCC should ensure that all material and services used conform to specified requirements.

Note: the selection of sources and the type and extent of control exercised by the BCC will be dependent on the type of material and the demonstrated capability of the suppliers.

231 Each BCC should require the supplier of a registered product to provide information to confirm that it conforms to the terms of the registration.

Purchasing data

232 Each purchasing document should contain a clear description of material and services ordered.

Manufacturers should be able to provide evidence of certification of their quality systems to the requirements of Australian Standards AS 3901 or AS 3902.

Inspection on receipt

233 Each BCC should ensure that no material is used until it has been inspected and verified as conforming to the agreed specifications. The BCC and the supplier should be in agreement with specifications, including limits for rejection, in advance of the supply.

Collection of whole blood and plasma and production control

234 Each BCC should ensure that blood and plasma collection and processing are carried out under appropriately controlled conditions.

Note: “Controlled conditions” includes, when appropriate, the use of suitable processing equipment and a special working environment, e.g., the use of laminar flow cabinets in environmentally controlled areas. It also includes documented standard operating procedures in which the manner of collection and processing are defined.

235 Each BCC should ensure that after each stage that affects quality there is either an inspection or a quality control test. For instance, the following stages would require inspection and quality control for the preparation of platelets from donations of whole blood:

- initial selection of the collected donations for processing. For instance, elimination of donations for platelet preparation from persons who have recently taken aspirin, and elimination of donations which have not been collected into appropriate packs or have not been transported to the BCC at appropriate temperature;
- verification of correct centrifugation speeds;
- examination for pack defects during processing;
- specified volumes of defects during processing and final suspension of the platelets;
- labelling of product;
- release of platelets from quarantine after all mandatory tests have been completed on the whole blood donation;
- conditions of transportation; and
- performance of quality control tests (Chapter 8).
Specific requirements

236 If open systems* of processing blood or blood products are used then each BCC should ensure that requirements under the following headings in the current Code of Good Manufacturing Practice for Therapeutic Goods – Medicinal Products are followed:

- Personnel, training, hygiene and clothing;
- Buildings and grounds;
- Environmental control;
- Sanitation and monitoring;
- Equipment; and
- Manufacturing procedures and controls.

*Note: Commonwealth Serum Laboratories Ltd. will not accept pooled plasma for processing.

Finished product inspection and product release

237 At release, all blood and blood components should be appropriately labelled in conformity with Guidelines outlined in Annex 4.

238 There should be a system of quarantine for all blood and blood products to ensure that they cannot be released for issue until approved documentation indicates that they have undergone mandatory testing with satisfactory results.

239 Each BCC should perform all inspections and tests on the finished product to complete the evidence of full conformance to specified requirements.

In exceptional circumstances only blood and/or blood products may have to be issued when full testing may not have been completed.

Note: smaller centres may adopt other procedures which meet these requirements, for instance, by having inspections and tests conducted by an accredited external laboratory.

240 Before a product is released for distribution, all test results and acceptance records should be checked by a designated person(s). Release should be authorised by the signature of a designated person.

Note: other means, such as a validated computer release system, may be acceptable to the auditing authority.

241 Where release is subject to computer-derived information the computer system should be validated to be fully secure against the possibility of un inspected or defective materials being released.

Note: the computer should be secure against tampering; see Annex 3 for more information on requirements for computer systems.

Quality control tests

242 The quality control test procedures used by the BCC should be in accordance with the Guidelines given for each product (see Chapter 8).

243 Quality control test procedures should be regularly reviewed.

Note: the frequency of review will depend on factors such as products not conforming to specification, or as the result of information obtained from quality audits.

Control of non-conforming materiel

244 Each BCC should establish and maintain procedures for controlling materiel that does no conform to specified requirements.

Note: non-conforming materiel may consist of any materiel used in the collection and processing of whole blood and plasma such as the reagents used in testing, the donations of whole blood and plasma, or product which have not met specified requirements.

245 As appropriate, the procedures should include provision for identification, segregation and disposal. All non-conforming materiel should be clearly identified to prevent unauthorised use or mixing with materiel which conforms to specified requirements.
Identification of processing status of pooled products

246 Each BCC should establish and maintain a system for the identification of product status of pooled products during all stages of processing and for those tests which have been carried out.

Identification of product

247 Each BCC should ensure by means of suitable identification that products which have not been released for issue can be distinguished from those which conform to specification and have received their final inspection.

In addition, this should also be by storage in a separate location.

Protection and preservation of product quality

248 Each BCC should establish and maintain a system to control the packing and preservation of products during their shelf life, including any transportation that may be required.

Material that has been out of the control of the BCC and then returned to it for further processing should be clearly identified.

- Note: for instance, plasma sent to a hospital and then returned should be clearly marked so that if sent to a fractionation centre, it can determine whether to process it.

249 The requirements in the following should be followed:

- labelling – Therapeutic Goods Order No 32 “General Requirements for Labels for Therapeutic Goods” (ISBN 0 644 10595 X), if appropriate Therapeutic Goods Order No 37 “General Requirements for Labels for Therapeutic Devices” (ISBN 0 644 13898 X), as well as Chapter 8, Annex 4 and 7;

- storage – Chapter 8, Annex 4; and

- transportation – Chapter 8, Annex 4.

Training

250 Each BCC should establish a system for identifying and implementing training needs and certification requirements for all staff.

Note: see also Annex 3c

Specific requirement

251 Personnel working in controlled environments should be given training related to maintaining the integrity of that controlled environment.

Product recall and notification of defects

252 Each BCC should establish a standard operating procedure whereby adverse effects caused by the administration of any component of a donation of blood or plasma can result in the recall of:

- all unused components derived from a donation of blood or plasma suspected or known to be defective or hazardous; or

- a set of donations of blood or plasma suspected or known to be defective or hazardous.
Recalls

253 Any recall of a product should lead to a thorough investigation of the causative factors of the adverse effects with a view to their elimination.

Note: Information concerning complaints and recalls together with copies of The Uniform Recall Procedure for Therapeutic Goods may be obtained from:

- The Australian Recall Co-ordinator, Recalls Section, Compliance Branch Therapeutic Goods Administration.
  PO Box 100
  Woden ACT 2606

- Tel (06) 286 0200 (0244) (0270)

- Fax (06) 286 1386

Defects

254 Any defect found in a therapeutic device (such as a blood collection bag), should be reported to the Medical Device Branch, TGA.

Note: reply-paid letter report forms and information concerning the Therapeutic Device Problem Reporting Scheme may be obtained from:

- The Assistant Secretary
  Medical Device Branch
  Therapeutic Goods Administration.
  PO Box 100
  Woden ACT 2606

- Tel (06) 286 0205 (0222)

- Fax (06) 286 1386
Chapter 3

Quality assurance at blood donor sessions

Rationale

301 This section applies to the collection of donations of whole blood at permanent sites or by mobile blood collection teams.

302 The BCCD is ultimately responsible for the correct and safe procedures for the collection of blood.

The medical practitioner or senior nurse in charge is immediately responsible for the operation of the blood collection session.

Records

Donation identification

305 Sessional reception staff must ensure that a unique number set is assigned to each donation. Great caution is necessary to avoid crossover or duplication of numbers.

306 Sets of numbers allocated but not used should be placed in a container for destruction and must be accounted for.

307 If there is need to renumber a blood pack system, new numbers should be used; labels and leftover numbers which have been discarded must not be retrieved.

Labelling

308 Donor session staff must ensure that the unique number assigned to the donation appears on the donor session record, on the primary and secondary collection packs and on all the sample tubes used.

309 The organisation should be such as to avoid the possibility of errors in the labelling of blood containers and blood samples.

For example:

- there should be the minimum possible elapsed time when taking samples following cessation of the donation;
- the blood bag and the corresponding samples should not be removed from the donor's couch until a satisfactory check on correct labelling has been carried out; and
- each donor couch should have its own individual facilities for the handling of samples during donation and labelling.

Note: Guidance for the following procedures is given in Annex 1.

- Donor identification
- Preparation of the venepuncture site
- Preparation of antiseptic solutions
- Preparation of the blood pack
- Performance of the venepuncture
- Blood donation
- Blood anticoagulation
- Blood flow
- Blood volume monitoring
- Sample collection
- Completion of the donation
- Final inspection
- Safety related defects
310 When not under the direct control of an authorised person, critical labels should be secured in a locked storage area accessible only to authorised personnel.

*Note: the term critical labels is defined in glossary.*

# Donor session records

311 A record must be maintained of:

- the sessional venue;
- the date; and
- the donation number and the identity of all donors attending.

For any donors who are deferred, permanently deferred or retired the full details should be recorded and the reasons given for the action taken.

312 The records of blood donation sessions should allow identification of each important step associated with the donation.

Records should include unexpected occurrences. For instance:

- all unsuccessful donations must be recorded together with the reason;
- all adverse reactions must be recorded together with the action taken; and
- full details of any other incidents, including those involving only staff, should be recorded.

313 The records should be used for the regular compilation of statistics which should be studied regularly by those responsible for activities concerned with the organisation and management of blood collection sessions.

## Control of purchased materiel and services

### Specification and inspection of blood bags

314 Blood collection should be by aseptic techniques using a sterile closed system and a single venepuncture. The integrity of the system should be checked prior to use and measures should be taken to prevent unsterile air entering the system.

315 Blood should be collected into packs that:

- are pyrogen free and sterile, containing sufficient registered anticoagulant for the quantity of blood to be collected; and
- which comply with the requirements of Australian Standard AS 3767 “General requirements for single-use, sterile, plasticized polyvinylchloride (PVC) blood packs for whole blood and blood components”.

316 The container label should state the kind and volume of anticoagulant, the volume of blood that can be collected and the required storage temperature for red cells. Blood packs may be supplied in containers holding 1-12 bags.

317 Where the outer packaging of blood packs has been opened and resealed, manufacturers’ directions regarding storage, use and expiry dates of the pack should be adhered to.

If a number of packs is removed from their outer packaging at one time (“opened”) they should be marked with the date, time and initials to ensure the expired containers are promptly discarded.

The shelf life of opened packs should be validated they are not discarded:

- at the end of each working day; or
- according to the manufacturer’s directions.

318 There should be a system in place to readily link the blood pack manufacturer’s batch number to the donor session and ultimately the donor forms.

*Note: this may be achieved by recording the number on the donor form or by other appropriate systems such as a diary that records the date, batch numbers were started and finished.*
The donation number on the pack and sample tubes must be checked at the end of the donation to ensure that those for a given donation are identical.

Prior to release from the blood collection session the pack and its associated tubing should be reinspected for defects and its integrity should be checked. Any defective pack should be marked for disposal and held separately from intact packs. Details of the defect(s) should be recorded for future analysis and action (see Annex 1).

Inspection of labels for printing errors

All donor records and labels should be checked for printing errors. Duplicate number sets must not be used and these and missing numbers must be reported via a designated senior manager to the printer concerned and to the Chairman of the National ADP standing committee of the NBTC.
Cross references

Documentation

Donor selection - see Chapter 5.
Specification of blood and blood products - see Chapter 8.

Control of inspection of test material

See 227 and the Code of GMP – Blood and Blood Products - Laboratory Guidelines

Collection control

Selection of premises for donation sessions - see Annex 3.
Specification and care of equipment for plasmapheresis - see Annex 2.

Protection and preservation of product quality

See 248 and Annex 4

Labelling

See 249 and Annex 6.

Storage

See Annex 4.

Transportation

See Annex 4.
Chapter 4

Quality assurance at apheresis donor sessions

Rationale

401 This section only applies to manual plasmapheresis and automated machine plasma and platelet apheresis procedures.

Reference should be made to Clin Lab Haematol 1990; 12(2) : 141-158, "Guidelines for the clinical use of blood cell separators" by the Clinical Haematology Task Force of the British Committee for Standards in Haematology.

Responsibility

402 A qualified medical specialist fully experienced in apheresis procedures must be ultimately responsible for the selection, health and welfare of the apheresis donors as well as responsible for the organisation of satisfactory staff training programmes and proficiency testing either in his/her own unit or by secondment to a unit where there is greater experience.

403 The specialist should ensure that standard operating procedures and documentation, as outlined in Chapter 2, are prepared for each procedure undertaken and that these are available at each session.

General specifications

Note: Guidance for the following procedures is given in Annex 2.

- Donor identification;
- Preparation of the venepuncture site;
- Performance of the venepuncture;
- Preparation of the machine/manual plasmapheresis set;
- Plasmapheresis equipment;
- Apheresis equipment;
- Adverse donor reactions; and
- Care and cleaning of apheresis machines.

Plasma, leucocyte and platelet donations

404 A standard operating procedure should be prepared for each apheresis procedure in use and any deviations from it should be recorded.

405 The return of red blood cells to donors undergoing manual plasmapheresis should be subject to stringent controls.

406 Particular attention should be given to the donor's extracorporeal blood volume when employing machine apheresis. The written protocol for each type of machine and procedure should state what the maximum allowable extracorporeal volume is and that it should not be exceeded.

Post-donation inspection

407 Post-donation inspection should be conducted as in Annex 1. In addition the plasma donation should be inspected for the presence of any clots and any colour change that might suggest the presence of haemolysis. Such changes may require a review of the apheresis procedures and/or equipment.

408 Any suspected abnormality should also be recorded on the donor record card. If any of the sessionsal staff is in doubt as to whether the donation is suitable for the purpose for which it was intended, the donation should be marked for inspection by the blood product laboratory staff before further processing.
Donor session records

Donor session records should be completed as in Chapter 3. Written evidence of informed consent must be retained.

Note: informed consent may not be legally required to be obtained before each apheresis procedure other than before the first such procedure. However, the BCC should ensure that it complies with any relevant state or territory legislation.

Control of purchased materiel and services

Specification and inspection of blood packs

The complete harness/appheresis set should be thoroughly inspected for faults prior to use and during the setting up procedure as follows:

- the set should be in date; and
- before the donor is attached to the set particular attention should be given to checking for the following faults which may become more detectable during the setting up and priming procedure:
  - kinks;
  - occlusions;
  - points of weakness; and
  - leaks.

If an occlusive kink or a leak becomes apparent during a machine procedure then that procedure should be abandoned and any remaining blood constituents should not be returned to the donor.

Any faults detected before or during a procedure should be reported on the daily worksheet for in-house quality control of the sets in use.

If there is any doubt about the integrity of any set, it should not be used but retained for inspection and reported to the Medical Devices Branch, TGA. See also 253, 254 and 255.
Cross references

Documentation
Donor selection - see Chapters 5, 6 and 7.
Specification of blood and blood products - see Chapter 8.

Control of inspection of test material
See 227 and the Code of GMP – Blood and Blood Products - Laboratory Guidelines

Collection control
Selection of premises for donation sessions - see Annex 3.
Specification and care of equipment for apheresis - see Annex 2.

Protection and preservation of product quality
See 248 and Annex 4

Labelling
See 249 and Annex 6.

Storage
See Annex 4.

Transportation
See Annex 4.
Chapter 5

Selection of donors

Rationale

501 Donations of whole blood or blood components provide the material from which all blood products are derived. The basic criteria for selection of blood donors apply equally to donors of whole blood and of cellular or plasma components collected by apheresis.

502 Procedures should have the purpose of ensuring that the potential donor is in good health for two reasons:

- to protect the recipient from any ill-effect through transmission of disease or drugs by blood transfusion; and

- to protect the volunteer from any harm to his or her health.

503 As this Code of GMP is concerned with the quality of the final product, issues relating solely to donor safety, donor ill-effects and donor care are largely excluded although these considerations form an important part of donor selection.

504 Special consideration should be given to documented procedures and adequate safeguards for patients referred for autologous donations or therapeutic venesection.

General Considerations

505 The requirements and procedures outlined in the NBTC's publication "Guidelines for Selection of Blood Donors" ISBN 0 909896 42 9 must be followed.

Note: this document is regularly updated.

Only persons in good health should be accepted as donors of blood for therapeutic use.

506 The prospective donor's medical history should be evaluated on the day of donation by a suitably qualified person who has been trained to utilise accepted guidelines for the selection of blood donors.

507 If there is doubt about the suitability of a prospective donor a donation should not be taken and the details should be referred to a medical practitioner for a decision.

508 The ultimate responsibility for the selection of donors rests with the BCCD; the immediate responsibility is that of the medical practitioner or senior nurse in charge of the session.

Donor declaration form

509 Each donor must receive and read the statutory donor declaration form concerning participation in activities at high risk of transmitting the AIDS virus.

Each donor must be questioned in a private interview as to whether he or she has understood the questions. Each donor must then sign that he or she does not fall into any of the risk categories listed. The signature must be witnessed by an authorised person.

Note: visual and auditory privacy may be obtained at mobile sites by e.g., screening and having background music.
The questions, and the preamble, must meet the criteria of the NBTC and any legislation relevant to that State or Territory.

The questionnaire must identify the donation to which it refers.

The signed questionnaire, or a suitably authorised and legally acceptable facsimile copy, must be retained for twenty (20) years.

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**Medical Assessment**

510 A medical assessment must be made.

*Note: in practice it is impossible to perform a complete medical and physical examination of every prospective donor. A significant part of the assessment procedure will usually rely on answers to simple standard questions relating to general health, past medical history and medication. This is combined with simple visual assessment of the donor and selected testing of samples collected at the time of donation.*

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**Medical history of donors**

**General considerations**

511 All donors should be questioned about the conditions listed in the NBTC’s publication “Guidelines for Selection of Blood Donors”, ISBN 0 909896 42 9.

*Note: this document is regularly updated.*

Any condition declared should be discussed with the medical practitioner or registered nurse in attendance at the blood collection session unless clear, unequivocal instructions regarding the responses are available to the member of staff conducting the questioning.

512 Donors whose serum or plasma or cells are to be used for laboratory as opposed to therapeutic purposes should be submitted to the same routine as other donors, but obviously some decisions regarding their suitability to donate may be different (e.g. treatment with certain medication, medical history or allergy).

513 Donors should be made aware that recipients experience risk from transfusion and donors should therefore be asked to report any illness developing subsequent to the donation.

514 Information which is, or may be, of relevance to the health of the recipient and which arises subsequent to the transfusion of the blood should be reported to the appropriate party (i.e. the fractionator or Consultant in charge of the hospital blood transfusion laboratory) so that further action may be taken if deemed necessary.

515 The record of physical assessment and medical history of the donor should be identified by the examiner’s signature. Any reason for exclusion should be recorded; lists of conditions necessitating permanent or temporary exclusion from blood donation are found in the NBTC’s publication “Guidelines for Selection of Blood Donors”.

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Selection of donors for apheresis

Supervision and medical care

601 A medical practitioner specially trained in apheresis procedures should be directly responsible for the supervision and medical care of apheresis donors.

Criteria for acceptance

602 Other than in exceptional circumstances (to be decided by a designated medical practitioner), donors for apheresis procedures should meet the usual criteria for ordinary whole blood donations given in Chapter 5. They should preferably have given at least 2 routine blood donations without untoward effect.

603 In addition the following criteria should be observed for apheresis donors:

- ordinarily, the donors should be between 16 and 70 years of age; and
- first time donors should not normally be less than 50 kg in weight. The donor weight should be assessed to ensure that the maximum extracorporeal volume during plasmapheresis does not exceed 15% of the total blood volume.

- serum proteins.

605 The results obtained should be within the normal range for the age and sex of the donor.

For platelet donation, the pre-donation platelet count at recruitment must be greater than 150 x 10^9/L. At subsequent platelet donations the platelet count should be measured retrospectively.

606 Follow up investigations should be carried out on all regular apheresis donors. Detailed haematological and serum protein assays including immunoglobulin levels should be carried out at regular intervals during the year. A medical specialist should review these laboratory investigations and assess the donor’s fitness to continue on the apheresis program.

Note: the regularity of the investigations is dependent on the frequency and volume of donations and should be specified in the BCC standard operating procedures.

Medical examination

607 For donors under 45 years of age, a minimum requirement is the examination of blood pressure and pulse. For donors over 45 years of age it may be necessary to extend the examination.

Volume of plasma donated

608 Not more than 15 litres of plasma should be donated by any one donor in a year.

609 The quantity of plasma donated per donation and per week should be specified in the BCC standard operating procedures.

610 Erythrocyte loss should preferably be kept below 20 mL of packed red cells per week.
The interval between one apheresis procedure and a whole blood donation should be at least 48 hours. If a plasma donor donates a unit of whole blood or does not have the erythrocytes returned during a plasma donation then further donation should be delayed for a period decided by the designated medical practitioner.

**Donors for plateletapheresis and leukapheresis**

In general, donors for plateletapheresis and leukapheresis must meet the criteria for whole blood and plasmapheresis donors. The RC BTS Guidelines should be followed.

**General specifications for plasma donor sessions**

These can be found in Annex 2.
Chapter 7

Selection of hyperimmune donors

Rationale

701 The need for certain specific immunoglobulins, for example anti-hepatitis B, anti-tetanus and anti-Rh (D) is such that an adequate supply is unlikely to be obtained from the general population. In these circumstances, deliberate immunisation of suitable donors has to be undertaken.

The donors must be fully informed of the procedure and the risks involved. Suitable donors may be selected by random screening in order to detect those with pre-existing but low levels of the particular immune antibody required; this may be preferable to immunisation de novo.

Criteria for selection of donors is given in Chapters 5 and 6.

Immunisation of donors

707 Immunisation of donors with antigens should be carried out only when sufficient supplies of material of suitable quality cannot be obtained by the selection of appropriate donors from donations identified as suitable by screening.

708 Donors must be fully informed of the risk of any proposed immunisation procedure, and pressure should not be brought to bear on a donor to agree to immunisation.

709 Donors of blood and those undergoing plasmapheresis should be asked for a history of hypersensitivity to a proposed antigen. Immunisation should be performed using registered vaccines. The choice of immunisation with vaccines or erythrocytes is discussed below.

710 The three main preparations used for immunisation in Australia are hepatitis B vaccine (for the production of anti-hepatitis B), tetanus toxoid (for the production of anti-tetanus), and Rh (D) positive red cells for the production of anti-Rh (D).

711 Where erythrocyte or other cellular antigens are used, they should be appropriately selected and tested to reduce as much as is reasonably possible any risk to the recipient of the antigen, particularly with respect to disease transmission and production of other (unwanted) antibodies.
712 Only erythrocytes obtained from donors which meet the criteria of Annex 5 should be used for immunisation.

713 The number and dose of injections of antigen should be restricted to the minimum required to obtain a satisfactory response.

714 A donor who has been deliberately immunised with erythrocytes should not be subsequently immunised with other erythrocytes for the purpose of producing a second (different) immune antibody.

715 When immunisation is intended, the donor should be:

- informed of the procedures by a qualified medical practitioner and encouraged to take part in a discussion;
- encouraged to seek advice from his or her family medical practitioner before agreeing to immunisation;
- informed that any medical practitioner of his or her choice will be sent all information about the proposed immunisation procedure;
- required to indicate his or her agreement by signing an informed consent form; and
- informed and understand that he or she is free to withdraw consent at any time.
Guidelines for blood component specifications

Rationale

801 These guidelines apply to single donations prepared either from units of whole blood or from the products of apheresis.

802 Specific tests should be carried out to establish that the product meets the requirements of this chapter.

Frequency of tests

803 Every donation must be tested and found negative for:

- HIVAb;
- HBsAg;
- HCVAb; and
- a syphilis screening test.

804 Every donation should be tested and labelled with the ABO and Rh (D) blood group.

Setting of requirements

805 The wide variability of the source materials used to make blood components makes it difficult to set stringent limits within which a production laboratory should operate. Nevertheless, realistic minimum requirements should be set and complied with.

Microbial contamination

806 All surfaces that come into contact with blood products intended for transfusion must be sterile and pyrogen-free.

807 Any new development in component preparation involving a change in preparative procedures or storage conditions or involving an open system or the breaching of a closed system in any way must be validated during the development stage to ensure the maintenance of sterility.

808 Each donation intended for transfusion and each component preparation constitutes a single batch.

It must not be tested for microbial contamination by a method that entails breaching the final container before the unit is transfused.

809 Tests for microbial contamination should be conducted on a statistically significant number of samples which for convenience may be time-expired units.

Notes:

- the test selected may be a sterility test. Guidelines for sterility testing are given in the Code of GMP for Therapeutic Goods - Medicinal Products - Appendix C - Guidelines for Sterility Testing;

- it is suggested that samples for periodic testing, such as microbial contamination testing, be selected using a sampling plan such as that of Dodge HF: Sampling Plans for Continuous Production, Journal of Quality Technology, 9:120-4, (July) 1977, or those in Australian Standard AS 1195-1988 Sampling Procedures And Tables For Inspection By Attributes, ISBN 0 7262 4901 7; and

- see also Annex 3i.
Product release

810 At release, all components should be appropriately labelled in conformity with Guidelines outlined in Annex 4.

811 There should be a system of quarantine for all blood products to ensure that they cannot be released for issue until approved documentation indicates that they have undergone mandatory testing with satisfactory results.

812 Only in exceptional circumstances may blood and/or blood components be issued when they may not have been fully tested.

Each BCC must have a standard operating procedure which details the circumstances under which such issues can be made.
Whole blood

General description

A unit of blood collected into a registered anticoagulant and not further processed.

Technical description

A unit of whole blood consists of up to 450 mL ± 10% of blood from a suitable donor in an approved container containing anticoagulant at a ratio of approximately 7 parts of blood to 1 of anticoagulant and an erythrocyte volume fraction (EVF) between 0.35 and 0.45.

For paediatric purposes it may be considered necessary to produce a unit of lesser volume than 450 mL. This may be achieved by dividing in a closed system the unit of whole blood, or by collecting a smaller quantity of blood whilst maintaining the same ratio of blood to anticoagulant. This procedure must be documented and validated.

Labelling

For general guidelines see Annex 4. In addition, the following should be included on the label:

- "Whole Blood"
- approximate volume
- the name and address of the responsible blood transfusion service;
- Note: the address may be just the RC BTS state or territory
- the donation number;
- the ABO group;
- the Rh (D) group stated as positive or negative;
- the composition and volume of the anticoagulant solution;
- the date of collection;
- the expiry date of the whole blood;
- the storage temperature;
- "Warning - this product may transmit infectious agents";
- a statement to the effect that the blood must not be used if there are visible signs of deterioration;
- Note: such as "Do Not Use If Contents Show Visible Signs of Deterioration";
- a statement to the effect that the blood must be filtered before administration; and
- Note: such as "Use Transfusion Set With a Filter".
- a statement to the effect that adverse transfusion reactions should be reported to the Divisional RC BTS director.

Storage

For general guidelines see Annex 4.

Testing

Tests should be performed as described in the Code of GMP for Therapeutic Goods - Blood and Blood Products – Annex 8 - Technical Guidelines.

Note: Annex 8 was still in preparation at the time of publication of this Code of GMP. Draft copies for review only are available from the address on page 6.
Additional tests

819 One percent of all units of whole blood should be weighed. From the tared weight of the pack assembly and anticoagulant the actual volume of blood should be calculated using the nominal specific gravity of 1.058.

- Note: it is the usual practice to weigh the blood pack as the donation is being taken. Other methods may be acceptable, provided that they have been calibrated.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donation volume*</td>
<td>450 mL ≤ 10%</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>&lt;1 g Hb L⁻¹</td>
</tr>
<tr>
<td>Microbial contamination*</td>
<td>&lt;10 aerobic CFU mL⁻¹</td>
</tr>
</tbody>
</table>

* Note: any microbial contamination should be fully investigated.

Transportation

(for general guidelines see Annex 4)

820 The temperature of the units of whole blood should be maintained at 2 – 6°C during transportation from the BCC to the intended place of use.

821 A despatch note detailing the unique identifying numbers of each unit of whole blood by blood group should accompany the units during the transportation.

The despatch note should contain the signature(s) of the designated person(s) responsible for the issue.
Plasma, fresh frozen

General description

822 Plasma is the liquid fraction of WHOLE BLOOD containing anticoagulant.
It may be obtained:
• from whole blood; or
• by plasmapheresis.
It should be frozen:
• for fractionation – within 24 hours; or
• for clinical use – within 8 hours without further processing.
The method of preparation should ensure the maintenance of an acceptable level of Factor VIII and a minimum contamination with cellular material.
Separated plasma donations with red cell contamination or which are grossly lipaemic should not be sent for fractionation.

Technical Description

823 For fractionation, plasma should be separated within 24 hours and frozen quickly to a core temperature of minus 30°C or below.
824 For clinical use, plasma should be separated within 8 hours and frozen quickly to a core temperature of minus 30°C or below.

Labelling

825 For general guidelines see Annex 4. In addition, the following should be included on the label:
• the name of the product –
  "FFP" means fresh frozen plasma
  "FFP for AHF" means fresh frozen plasma for fractionation;
• the name and address of the responsible blood transfusion service;
• Note: the address may be just the RC BTS state or territory
• the donation number;
• the ABO group;
• the Rh (D) group stated as positive or negative;
• the date of collection;
• the storage temperature; and
• "Warning - this product may transmit infectious agents”

Additional Labelling for FFP

826 In addition to 825, the following:
• the expiry date;
• instructions for thawing;
• a requirement to report adverse transfusion reactions; and
• a statement to the effect that the product should be used within 4 hours of thawing.

Storage

827 For general guidelines see Annex 4. Variation of storage period needs adequate documentation approved by the BCCD.

Testing

828 This should be performed as described in the Code of GMP for Therapeutic Goods - Blood and Blood Products – Annex 8 - Technical Guidelines.

Note: Annex 8 was still in preparation at the time of publication of this Code of GMP. Draft copies for review only are available from the address on page 6.
Additional tests

829

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>Stated volume ± 10%</td>
</tr>
<tr>
<td>Factor VIII:C (FFP)</td>
<td>&gt;0.7 IU mL⁻¹</td>
</tr>
<tr>
<td>Factor VIII:C (FFP for AHF)</td>
<td>as agreed with the fractionation centre</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>&lt;1 g Hb L⁻¹</td>
</tr>
<tr>
<td>Microbial contamination*</td>
<td>&lt;10 aerobic CFU mL⁻¹</td>
</tr>
</tbody>
</table>

* Note: any microbial contamination should be fully investigated.

Transportation

(for general guidelines see Annex 4)

830 The storage temperature should be maintained during transportation. For FFP the receiving hospital should ensure that the packs have remained frozen during transit. Unless the plasma is for immediate use the packs should be transferred to storage at the recommended temperature.
Plasma, recovered

General description

831 “Plasma, recovered” is the liquid fraction of WHOLE BLOOD containing anticoagulant separated no later than 5 days after its nominal expiry date and frozen prior to transport. Recovered plasma is intended only for recovery of components by the fractionation centre and is not intended for transfusion.

Separated plasma with red cell contamination or which is grossly lipaemic should not be sent for fractionation.

Technical Description

832 Plasma separated from WHOLE BLOOD and frozen quickly to a core temperature of minus 20°C or below, within a day of separation from time-expired blood. See also Annex 4.

Labelling

833 For general guidelines see Annex 4. In addition, the following should be included on the label:

- the name of the product;
- the name and address of the responsible blood transfusion service;
  
  Note: the address may be just the RC BTS state or territory
- the donation number;
- the ABO group;
- the Rh (D) group stated as positive or negative;
- the date of preparation;
- the storage temperature; and
- "Warning - this product may transmit infectious agents".

Storage

834 For general guidelines see Annex 4. Variation of storage period needs adequate documentation approved by the BCCD.

Testing

835 This should be performed as described in the Code of GMP for Therapeutic Goods - Blood and Blood Products - Annex 8 - Technical Guidelines.

Note: Annex 8 was still in preparation at the time of publication of this Code of GMP. Draft copies for review only are available from the address on page 6.

Additional tests

836

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>Stated volume ± 10%</td>
</tr>
<tr>
<td>Haemoglobin at expiry</td>
<td>&lt;1 g Hb L⁻¹</td>
</tr>
<tr>
<td>Microbial contamination*</td>
<td>&lt;10 aerobic CFU mL⁻¹</td>
</tr>
</tbody>
</table>

* Note: any microbial contamination should be fully investigated.

Transportation

837 For general guidelines see Annex 4. The storage temperature should be maintained during transportation.
Chapter 9

Guidelines for specifications for plasma intended for fractionation

Features common to all plasma types

Donor qualifications

901 Each donor must meet all donor health criteria as defined in Chapter 5.

902 Each donation must be tested and found non-reactive for antibody to Hepatitis C virus (HCV) and for HBsAg.

903 Each donation must be tested and found to be non-reactive for antibody to HIV.

Donation handling

904 Handling techniques should comply with good manufacturing practice at each stage of plasma preparation.

905 Plasma is either collected by plasmapheresis or is obtained from anticoagulated whole blood.

Any anticoagulant used should be:

- registered; and
- agreed with by the fractionator.

906 The plasma separation technique should ensure minimal cellular content. The haemoglobin, cellular or free, should be less than 1g L⁻¹.

907 The plasma donation should be frozen in a plastic pack of a type agreed with by the fractionation centre.

908 Minimal acceptable storage conditions should ensure that the plasma temperature during storage or transportation does not exceed:

- -30°C for plasma for coagulation factor concentrate manufacture; or
- -20°C for recovered plasma.

Note: transient temperature perturbations in the plasma should be kept to a minimum and should not exceed 5°C during storage or transportation.

Documentation

909 Each plasma donation must be labelled clearly with:

- a unique donation number.

The donation number should be both machine- and eye-readable. They should be of a type as agreed between the BCC and the fractionation centre; and

- a label indicating the plasma type:

- plasma for coagulation factor harvesting should be labelled "FFP for AHF";
- plasma selected for specific antibody harvesting should be labelled appropriately; or
- plasma from time-expired blood should be labelled "Recovered plasma".
Frozen plasma packs of an identical plasma type may be packaged together for transportation in containers approved by the fractionation centre.

Each container should be clearly labelled with:
- contents;
- container number;
- BCC of origin;
- plasma type; and
- the words "Human plasma for fractionation".

Note: BCCs should use the special labels for transport available from the fractionation centre.

Each consignment of plasma must be accompanied by a consignment note.

The consignment note should have the following information:
- a serial number to allow identification;
- the number of individual packs in the consignment; and
- total number of donations in each consignment.

The format and contents of the consignment note should be as agreed between the BCC and the fractionation centre.

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**Plasma notifications**

Once plasma has been sent, the fractionation centre must be notified by the BCCD or delegate if:

- the donor did not meet the current donor health criteria;
- Note: failure to meet health criteria may not result in a recall of the plasma provided that the fractionation centre agrees that the failure does not compromise the plasma pool. Nevertheless, each notification should be formally recorded.
- there is reason to suspect within 6 months of despatch that there has been a breakdown in testing and/or labelling for:
  - HBsAg testing, or
  - HCV antibody testing; or
  - HIV antibody testing.
- if there is evidence of donor seroconversion at a previous or subsequent donation for any of the above.
Features specific to defined plasma types

Fresh frozen plasma

913  The requirements for FFP for AHF are as given in 822 to 830.

915  Each BCC should establish appropriate quality control procedures to monitor the FVIII content of the frozen plasma (chapter 8).

Recovered plasma

916  The requirements for "Plasma, recovered" are as given in 831 to 837.

Hyperimmune donor plasma

917  The requirements for plasma from hyperimmune donors are as given in Chapter 7.

918  BCCs should be able to demonstrate, if necessary, acceptable antibody potency using an assay system as agreed between it and the fractionation centre.

Requirements for specific plasma types

919  Anti-Rh (D)

The minimum acceptable titre for the starting pool is as agreed between the BCC and the fractionation centre.

Notes:

- with high potencies achieved in plasma from boosted donors, low titre plasma from other sources serves as a useful diluent for the fractionation centre;
- all donations marked as Anti-Rh (D) Plasma may be acceptable for an Rh (D) Immunoglobulin Pool; and
- potencies from individual BCCs are monitored by the fractionation centre testing the individual subpools.

920  Cytomegalovirus

The minimum acceptable titre for the starting pool is as agreed between the BCC and the fractionation centre.

Suitable donations should have a potency of at least 80% of a control preparation provided by the fractionation centre.

921  Hepatitis B

The minimum acceptable titre for the starting pool is as agreed between the BCC and the fractionation centre.

922  Tetanus

The minimum acceptable titre for the starting pool is as agreed between the BCC and the fractionation centre.

The minimum potency for a starting pool for Tetanus Immunoglobulin manufacture is 5 International Units per mL.

923  Zoster (varicella)

The minimum acceptable titre for the starting pool is as agreed between the BCC and the fractionation centre.

The minimum level of antibody in individual donations is a titre of 1:32 in a complement fixation test system, which incorporates a selected varicella antigen and a standardised reference plasma supplied by the fractionation centre.

The fractionation centre re-tests plasma donations on receipt and a labelled 100mm tubing sample is required of each donation for the test. The sample should be packed with the parent donation in a separate bag which can stand temperatures of -30°C or less.
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AUSTRALIAN

Code of Good Manufacturing Practice
For Therapeutic Goods -

Blood and Blood Products
Annexes 1-7

July 1992
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Preface

This document contains Annexes 1-7 which are intended to supplement and give guidance to requirements of the Australian Code of GMP for Therapeutic Goods - Blood and Blood products; they should be used in conjunction with that document. Annex 8 "Technical Guidelines" is published separately.

"Guideline" documents should NOT be regarded as mandatory. Systems which are different from those described in this publication are acceptable if they are equal to, or better than them. The onus is on the BCC to demonstrate the validity of the quality system implemented.

The annexes are presented as documents separate from the Code of GMP in order that they may be more readily amended, updated or altered. Comments on all or parts of any annexes are welcome at any stage of its publication.

Comments should be addressed to:

GMP Audit and Licensing Section
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

It is intended to subject all annexes to regular review on the same basis as the Code of GMP or more frequently if necessary depending on feedback.
Introduction

This publication comprises 7 annexes as follows:

Annex 1 gives general specifications for blood donor sessions including guidance on –
  • donor identification;
  • preparation of the venepuncture site;
  • preparation of the blood pack;
  • performance of the venepuncture; and
  • blood donation; and

Annex 2 gives guidance for apheresis sessions and is similar to Annex 1;

Annex 3, the longest in this publication, relates directly to headings taken from the Australian Code of GMP for Therapeutic Goods - Medicinal Products and has passages adapted from it as well as new material directly relating to blood collection centres;

Annex 4 gives direction on specifications for labelling, storage and transport of blood and blood products;

Annex 5 gives guidance on accreditation of donors of red blood cells for immunisation;

Annex 6 is a list of labels for blood and blood products; and

Annex 7 gives a list of required standards.
Donor-donation identification

1001 Before the venepuncture the identity of the donor must be checked. At the end of each step, the donation number allocated should be checked on all items to ensure that those on the blood packs and sample tubes are identical with that on the paperwork.

Preparation of the venepuncture site

1002 Blood should be drawn from a suitable vein in the antecubital fossa in an area that is free of skin lesions.

Note: the veins can be made more prominent by using a blood pressure cuff inflated to 40-60 mm Hg and by asking the donor to open and close his or her hand a few times.

1003 A prolonged cuff pressure of greater than 60mm Hg should not be employed.

Note: pressures greater than 60mm Hg could alter some blood constituents and reduce the quality of the blood collected; particularly with regard to the number of functional platelets obtained and Factor VIII recovery.

1004 A strictly standardised procedure for the preparation of the venepuncture site should be in operation to achieve:

• surgical cleanliness; and

• to provide maximum assurance of a sterile product.

Note: it is not possible to guarantee sterility of the skin surface for venepuncture.

Antiseptic solutions

1005 Suppliers to the BJC of the antiseptic solution should be able to provide evidence to the BCCD that the antiseptic solution, when used at the recommended dilution, meets the requirements of the Australian antiseptic performance test known as the "TGA" test, option D, as required by Regulation 23F made under the New South Wales Therapeutic Goods and Cosmetics Act, 1972 and other States' equivalent legislation.

Note: Particulars of the test are contained in the article by Graham, B. M.; in The Australian Journal of Hospital Pharmacy, Volume 8, No 4, 1978, 152-4.

1006 Antiseptic solutions should be made up according to manufacturer's directions.

1007 The antiseptic solution should be allowed to dry completely or wiped dry with sterile gauze before venepuncture. The prepared area should not be touched with fingers before the needle is inserted.

Preparation of the blood pack

1008 Standard operating procedures must document the procedure for ensuring that the blood collection pack is:

• in date; and

• inspected for any defects before use.

1009 If the pack is leaking, it should be rejected and the failure recorded. Moisture on the surface of a plastic pack after unpacking may indicate a leak. If one or more packs in any packet is found to be abnormally damp, all the packs should be rejected.

1010 If the anticoagulant solution is not clear the pack should be rejected.

1011 The blood pack should be positioned below the level of the donor's arm and the blood collection tube clamped off.
1012 The method used for monitoring the volume of blood removed should be checked to be in working order and the pack placed in the correct position for the method to be effective. The method chosen should be objective, such as measurement by weight determination. Subjective methods, such as observation of the amount in the bag, should not be used.

Performance of the venepuncture

1013 Venepuncture should only be undertaken by authorised and trained personnel according to the policy of the BCC.

Note: a phlebotomist holding a qualification from an accredited tertiary institution may be acceptable.

1014 If local anaesthetic is used, it should:

- be a registered medicinal product;
- be injected in a manner which avoids any chance of donor-to-donor cross infection; and

Note: using individual disposable syringes and needles reduces the risk of cross infection.
- have a record of the batch number(s) for each blood collection session.

1015 Containers of local anaesthetic should be inspected for any leakage and if glass, inspected for cracks. Any suspect containers should be rejected.

1016 Unused material should be discarded at the end of each donor session.

1017 An aseptic technique should be used for drawing up the local anaesthetic into the syringe and the needle changed prior to the injection of the local anaesthetic.

1018 Items used for venepuncture should be obtained in a sterile, single use disposable form. If the dry outer wrapping of sterile packs becomes wet, the contents should not be used. Containers of bulk sterilised items should be labelled and dated when they were sterilised and when opened. Unopened sterilised containers may be stored for 2 or 3 weeks provided the outer package is sealed.

1019 Prior to use, sessional staff should ensure that the material used for venepuncture are sterile, in date and suitable for procedure to be undertaken. The sterile donor needle should have its tamperproof cover checked for integrity but it should not be uncovered until immediately prior to the venepuncture.

1020 As soon as the venepuncture has been performed, the clamp on the bleed line should be released.

Note: it is important that a clean, skillful venepuncture is carried out to ensure the collection of a full, clot free unit of blood suitable for the preparation of labile blood components.

1021 The tubing attached to the needle should be taped to hold the needle in place during the donation.

Blood donation

1022 If necessary, the donor should be asked to open and close his or her hand, over a suitable hand grip slowly every 10-12 seconds to encourage a free flow of blood.

1023 The donor should never be left unattended during or immediately after donation and should be kept under observation throughout the phlebotomy.

Blood anticoagulation

1024 The blood and anticoagulant should be mixed gently and periodically (approximately every 30 seconds) during collection.

Note: mixing may be:

- manually - by inversion of the blood pack every 30 seconds, or
- automatically - by placing the blood pack on a mechanical agitator or by using a rocking device.
Blood flow

1025 Blood flow should be frequently observed to ensure that the flow remains fairly brisk so that blood coagulation is not initiated.

1026 If a 450 mL blood donation takes longer than 12 minutes, the donor session record of that blood pack should be marked accordingly.

Note: it is inadvisable to use “Slow bleed” donations for the preparation of platelet concentrates, fresh frozen plasma, cryoprecipitate.

Blood volume monitoring

1027 The volume of blood withdrawn should be controlled to protect the donor from excessive loss of blood and to maintain the correct proportion of anticoagulant to blood.

Notes:

- the most efficient way of measuring the blood volume in plastic bags is by weight. The mean weight of 1 ml of blood is 1.06 g; a unit containing 405 – 495 mL should therefore weigh 425 – 520 g plus the weight of the container and its anticoagulant; and

- if it is not possible to adjust the weighing device in use for the tare weight of the container and anticoagulant solution, it is advisable to record the minimum and maximum weight for the brand of pack in use as products from different manufacturers may vary considerably.

1028 Equipment for weighing blood into its plastic pack should be used according to the manufacturer’s instructions and periodically calibrated by appropriate techniques.

Sample collection

1029 Any reusable equipment should be cleaned between donations, e.g. scissors and haemostat. The methods employed should be clearly defined in the sessional procedures manual.

Note: at the end of the donation, the tubing can be temporarily clamped with a haemostat. The donor samples can then be collected by a method that precludes contamination of the donor unit.

Completion of the donation

1030 The pressure cuff should be deflated and then the needle removed followed by immediate pressure applied to the venipuncture site with a sterile cotton wool ball or gauze.

1031 The needle must be discarded into a special container designed to prevent any risk to personnel.

1032 The bag should be inverted several times to mix the contents thoroughly.

1033 The free end of the tubing should be sealed immediately. The blood contained in the collection tubing should be expressed into the pack containing the blood donation and allowed to flow back into the tube to ensure anticoagulation.

Note: this is not necessary if samples are taken separately for crossmatching purposes and the tubing is sealed close to the bag.

If the sealed off tubing left attached to the bag is further sealed into segments for crossmatching purposes (preferably using a heat sealer), each segment number should be clearly and completely readable. It must be possible to separate the segments from the container without breaching the sterility of the container.
Annex 2

General specifications for apheresis sessions

Rationale

2001 These operating procedures provide guidance only. Further specific definition is required by individual BCC's. Reference should also be made to "Guidelines for the clinical use of blood cell separators", Clin. Lab. Haematol., 1990, 12, 141-158

Cross references

Donor identification

As in Annex 1.

Preparation of the venepuncture site

As in Annex 1.

Performance of the venepuncture

As in Annex 1; but once the venepuncture has been performed, subsequent procedures, such as releasing the clamp on the bleed line, should follow the protocol for the particular type of apheresis procedure being undertaken.

Preparation of the machine/manual apheresis set

2002 The apheresis harness or manual plasmapheresis set should be for single use, preferably preconnected by the manufacturer to ensure a safe sterile pathway once the venepuncture needle is in place and designed in such a way that whole blood can be collected, separated and non-harvested cellular elements safely returned to the donor.

Note: the return of cells to donors undergoing manual apheresis should be subject to particularly stringent control.

The biggest inherent danger is confusion between two packs of concentrated cells during centrifugation and return to individual donors.

A proper identification system to avoid this is essential: e.g. the donor may be asked to sign the label on the pack and to confirm his or her signature before the return of the red cells. In addition, use can be made of the integral numbering system on the pilot tube of plastic bags, perhaps by transferring this number to the wrist of the donor.

Plasmapheresis equipment

2003 On sites where manual plasmapheresis is performed, a blood bag centrifuge is required for plasma separation. The operating procedure for using this centrifuge should be available at the session. It should be checked every 2 months by a designated engineer using a precision RPM meter and stopwatch to check speed, acceleration and retardation.

Apheresis equipment

2004 Automated apheresis machines should have the following features:

- a manual override system;
- a blood flow monitor;
- an in-line air detector;
- a control system to ensure any automatic pressure cuff is deflated during the donor return cycle;
• a blood filter integral with the harness to prevent any aggregates formed during the procedure from being returned to the donor.

• an anticoagulant flow indicator or regulator;

• a device for presetting the volume of plasma required and monitoring the volume of plasma collected; and

• a means of preventing unauthorised personnel from making procedural changes on a machine capable of more than one type of donor apheresis procedure.

2005 Automated plasma filtration machines must be provided with a monitoring device to record the transmembrane pressure. If the transmembrane pressure falls outside the preset safe operating range, an alarm should be activated.

2006 In the event of a power failure, the machine should automatically enter a standby mode once power returns, and a manual system should exist for the return of the remaining donor cells.

Blood volume monitoring

2010 Blood volume monitoring:

• as in Annex 1 for manual plasmapheresis; and

• occurs automatically in machine apheresis.

Sample collection

2011 Sample collection:

• as in Annex 1 for manual plasmapheresis;

• for machine procedures sampling usually takes place at the beginning of the donation.

The methods employed –

• must ensure an aseptic technique with no risk of contaminating the donation, and

• should be clearly defined in the sessional procedures manual.

2012 Extra samples are required at specified intervals from frequent apheresis donors to ensure their continued suitability and safety. The samples required should be recorded on the donor session record together with information as to when they were last collected.

2013 A system, organised by the medical specialist in charge of apheresis, should be in operation for regular review of these results with a written protocol of the action to be taken if any are abnormal.
Completion of the donation

2014 Completion of the donation as in Annex 1.

Note: Further segmentation of the sealed off tubing is unnecessary. A length of tubing should only be left attached to the pack of plasma if samples of the plasma are required for testing purposes. Any side tubing left attached to the plasma bag is more likely to fracture when the plasma bag is frozen.

2015 Tubing containing samples required for testing should be aseptically separated from the plasma pack prior to freezing. Regular quality control of the plasma and platelets collected should be undertaken on these samples.

2016 All disposable used equipment should be discarded safely according to documented instructions.

Care and cleaning of apheresis machines

2018 Apheresis machines should be:

- serviced in accordance with the manufacturer's instructions (services should be logged);
- maintained according to a planned scheme; and
- cleaned daily with a suitable decontaminating agent.

2019 There should be a standard operating procedure for dealing with blood spillage.

Adverse donor reactions

2017 For donor apheresis procedures, any potentially serious procedural problem should be reported to the state or territory RC BTS Director who will ensure that all other BCCs are informed of the potential hazard without delay.

The TGA should also be informed if the reaction is due to any therapeutic good used during the procedure; see also the Australian Code of GMP - Blood & Blood Products, Chapter 2, clauses 252 and 254.
Annex 3

Adaptions and Extracts from the Code of Good Manufacturing Practice for Therapeutic Goods - Medicinal Products

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Annex 3a

Premises

General considerations

3a 01 Premises and equipment used for the preparation of components from blood and plasma will be subjected to audit by GMP auditors from the Compliance Branch of the Therapeutic Goods Administration. The premises and equipment chosen must comply with the requirements of the Australian Code of Good Pharmaceutical Manufacturing Practice for Therapeutic Goods - Medicinal Products. The clauses adapted from that Code are given below for convenience.

Premises: mobile donor sessions

Rationale

3a 02 Although premises used for mobile donor sessions may often be accepted as the only local venue available, they should be of:

- sufficient size;
- construction; and
- location
to allow:

- proper operation;
- cleaning; and
- maintenance.

in accordance with accepted rules of hygiene and in compliance with revised Requirements for Biological Substances No. 1 (General Requirements for Manufacturing Establishments and Control Laboratories, WHO Technical Report Series No. 323, 1966).

The person in charge of the blood collection team should be provided with a written plan of action appropriate to each venue.

Note: this can be used if conditions on arrival are not found to be acceptable. Care must be taken to avoid disturbances of any other activities within the venue if it is being shared.

Activities to be borne in mind when accepting a venue

3a 03 The following activities should be planned for:

- donor registration and interviewing;
- data processing where necessary;
- laboratory and medical examination of donors, as appropriate, to determine fitness to donate;
- storage of equipment, reagents and disposables which may involve allocation of adequate space for transit containers and other equipment;
- blood donation without risk of contamination and errors:
- seating should be sufficient for donors and staff, with allowance made for possible queues during busy periods;

Annex 3  Code of GMP-Medicinal Products: adaptions and extracts   page 15
- apheresis - performance of apheresis, where applicable, by single-arm techniques only. When apheresis machines are used, the flooring should conform to the appropriate manufacturer’s recommendations;
- social and medical care of donors, including those who suffer reactions;
- storage of blood and components during the session unless they are to be transferred immediately to the BCC or to appropriate storage in the team vehicle;
- electrical supply - an adequate electrical supply for any onboard refrigerator of the sessional vehicle, and for all electrical equipment used on the session; and
- telephone or, e.g. two way radio.

Note: the space required for these activities will obviously depend on the workload and rate.

Health and safety factors to be considered

3a 04 The requirements of any local or State legislation concerning occupational safety and health should be taken into account when selecting sessional venues. In particular, the following points should be borne in mind:

- environmental control may not be within the power of a mobile team, but every effort should be made to ensure that the space does not become too hot, too cold or stuffy. Subsidiary cooling fans and heating should be carried on sessional vehicles, and used as necessary. This equipment should be subjected to a planned maintenance programme at the BCC;
- fire exits should be unobstructed and operational. All session staff should be aware of their location and that of the fire extinguishers. Standard operating procedures should include the planned management of donors in the event of a fire;
- flooring should be nonslip, whether for a routine or an apheresis session;

Note: signs may be required warning of a possible slippery floor.
- furniture and equipment should be arranged within the available space so as to minimise crowding (with its increased possibility of mistake or accident), enabling adequate supervision and ensuring a smooth and logical work-flow;
- ground to be covered by staff carrying equipment should be even and well lit. Preferably, the space to be used should not entail carriage of equipment on stairs. A similar safe approach should be ensured for donors;
- lighting should be adequate for all the required activities. Provision should be made for the use of emergency lighting in the event of interruption of the electricity supply;
- notices should be displayed, directing donors to the appropriate entry point of the building, and to the room being used;
- parking - it should be possible for the sessional vehicle(s) to park in close proximity to the access doors, to facilitate off-loading together with adequate parking for donors' cars;
- proximity - the venue should be as close as possible to the centre of population being served;
- refreshment facilities for donors and staff should be separated from the other activities of a donor session whenever possible. Every effort should be made to ensure that equipment used in this area poses the minimum threat of danger to all persons;
- toilet facilities for male and female donors and staff should be provided. Separate washing facilities are desirable for those staff involved in 'clean' procedures;
- vermin - the premises should be free from vermin; and
- waste disposal facilities should be available and adequate for the disposal of waste. Solid waste should be collected and contained in a suitable manner for return to the BCC and subsequent disposal.
Premises: permanent buildings and grounds

Note: the following is adapted from the Australian Code of GMP for Therapeutic Goods – Medicinal Products, 1991. That Code should be referred to for the original text.

Rationale

3a 05 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

3a 06 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.

3a 07 Buildings, including receiving and despatch areas, should be designed, constructed and maintained so as to protect against the effects of weather or ground seepage and the entry and harbouring of vermin, birds, pests and pets. Cavities and voids should not be present unless sealed or provided with access for pest control.

3a 08 Animal houses should be isolated from production areas, with separate entrances and air handling facilities, and should comply with the current edition of the NH&MRC/CSIRO/AAC Code of Practice for the Care and Use of Animals for Experimental Purposes.

3a 09 Grounds should be established and maintained so as to minimise ingress into the buildings of dust, soil, or other contaminants and should be maintained in an orderly condition.

Pipes, ducts and service areas

3a 10 Pipelines carrying services or products between rooms or areas should be identified by colour or by standard markings at suitable intervals and the direction of flow shown.

Particular care should be taken that product pipelines are not inter-connected or connectable in a manner that invites cross-contamination or product mix-up.

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

3a 11 In production areas where processing is not in sealed bag systems:

- extraction ducts should be designed to be cleanable and to prevent condensate or accumulated dust from falling back into product or equipment;

- there should be no recesses that cannot be cleaned and a minimum of projecting ledges, shelves, cupboards, pipes, fixtures and fittings;

- exposed overhead roof joists, pipes and ducts should be avoided. Where they are unavoidable, special cleaning procedures and schedules should be written and followed;

- exposed pipes should not touch walls, but be suspended from or supported by brackets, sufficiently separated to allow thorough cleaning;

- 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.

3a 12 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

3a 13 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.

3a 14 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.

3a 15 Access to environmentally controlled areas should be only from corridors or other manufacturing areas.

Processing and packaging areas should not be used as thoroughfares or, except for work in progress, for storage.

3a 16 Doors that lead from manufacturing areas directly to the outside, eg 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.

3a 17 The operations carried out in any particular area of the premises, whether storage, processing or packaging and whether involving therapeutic or non-therapeutic goods, should be compatible.

3a 18 Except where alternative arrangements are acceptable, a dispensary should be provided for weighing and measuring out starting materials that appear in the final product if produced by an open system, e.g. the manufacture of anti-coagulants.

Air control if products are produced in open systems

3a 19 Air intakes and exhausts, and associated pipework and trunking should be located so as to avoid any hazard to product and to avoid overloading air filters. In particular, intakes should not be sited near wet drains, air exhausts or sources of dust. Provision should be made to clean dust filters and air conditioning filters away from the air handling systems or production areas.

3a 20 The air supplied to work zones in which starting materials are sampled or dispensed, where product is made or filled or where equipment is dried should be supplied through filters certified to have an average arrestance of at least 80% when tested by AS1132:1973 - Methods of Test for Air Filters for Use in Air Conditioning and General Ventilation, using Test Dust No. 1. Storage or processing in sealed systems may be excepted from this provision.

Notes:

(1) The air so supplied is likely to be equal to or better than the equivalent of a “Class 7000” (approximately 300 particles of 2 micrometres particle size per liter) as extrapolated from AS1386-1989: Cleanrooms and Clean Workstations.

(2) Consideration should be given to temperature and relative humidity control; once a significant volume of filtered air is delivered across operators, comfort conditioning is usually found necessary.

3a 21 In all rooms, air supply and extraction points should not be so close or so disposed as to restrict or negate the supply of clean air to worksites and/or the sweep of dust or other contaminants away from worksites.

3a 22 The air flow pattern, throughput rate and proportion of recirculated air should be selected to afford adequate protection to the product as well as operator safety.

3a 23 The selection of pressure differentials should take into account the relative hazards of incoming and outgoing contamination in each work zone.

3a 24 Air ducts should not be insulated internally except for non-fibrous, non-porous insulation used to avoid or reduce condensation near cooling units or used to reduce the risk of fire near heating units. They should be verified as clean by inspection or testing.
Floors, walls, ceilings and associated fittings

3a 25 Floors, walls and ceilings in manufacturing areas should be designed so as not to shed more than a minimum of particles and be free from cracks and open joints. Floors and walls should be nonporous, nonslip and resistant to cleaning agents and to any disinfecting agent used. Floors should be smooth, except for wash bays housed in manufacturing areas or mezzanine or platform floor structures.

3a 26 As far as practicable, processing should occur in a dry environment. Where it is essential to provide for spillage or a high volume of floor rinsing, floors should be adequately sloped for drainage. Drains should be of adequate size and have trapped gullies. Open channels should be avoided where possible but if used should be shallow to facilitate cleaning and disinfection.

3a 27 Joins between walls and floors should be easy to clean, adequately sealed and, where appropriate, coved (sic). Coving should form a smooth curve between floor and wall of sufficient radius to minimise soil accumulation and to make cleaning easier.

3a 28 Doors (including door edges) and window frames should have a hard, smooth, impervious finish and should close tightly. It is desirable that door and window frames are fitted flush with surrounding walls. The conduct of operations carried out in production rooms should be visible from the outside where necessary for supervision or management.

3a 29 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.

3a 30 Lighting should be adequate for particular tasks.

Note: flush mounting is preferred for new installations.

Special facilities and provisions

3a 31 The building design should include adequate provision for dismantling, cleaning, washing and, where necessary, sanitising and drying equipment such as refrigerated centrifuges.

This should usually be a separate room or area.

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

3a 32 Suitable provision should be made for the safe storage of waste materials awaiting disposal.

3a 33 Laboratories should be designed, equipped, maintained and of sufficient size 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.

Note: additional guidance for the design and construction of microbiological laboratories (excluding sterility testing laboratories) is contained in the NATA publication “Microbiological Testing: Laboratory Accommodation Guidelines”.

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

3a 34 Adequate facilities should be provided for GMP training.

3a 35 A plan of the building(s) showing air handling facilities including key air handling equipment and showing air quality standards, flow rates, proportions recirculated and relative pressures should be available for inspection.

3a 36 Noise should be minimised.

3a 37 Buildings should be secure against entry of unauthorised personnel. Special precautions should be taken to check the bona fides and activities of visitors, external maintenance people and contractors such as pest controllers.
Goods Receipt and Storage Areas

3a.38 Material should not be stored unprotected outside buildings except where their quality, labelling and containers cannot be affected adversely by the weather.

3a.39 Security arrangements should prevent the coupling of bulk tankers to receipt points except by or under the supervision of an authorised person.

3a.40 The goods received at receiving bays, docks, platforms or areas should be protected from dust, dirt and rain.

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

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

3a.41 Storage areas should be adequate and organised to permit suitable and effective separation and identification of the various materials and products stored.

3a.42 Except where an acceptable alternative system is installed, there should be separate storage areas for "quarantine" or "reject" goods.

3a.43 Labels and other pre-printed packaging materials, including "APPROVED" status labels, should be stored in a secure manner that will permit access by and issue only to authorised persons in accordance with documented procedures.

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

3a.44 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.

3a.45 Material 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 the storage conditions specified on the labels of the goods.

3a.46 Controlled storage environments, eg deep freeze, refrigerated, air-conditioned, should be monitored using suitable temperature - recording devices and the records reviewed and filed. Temperatures in other storage areas should be monitored and the results tabulated and analysed so as to demonstrate the suitability of these areas for their purposes.

Refrigerated and freezing storage environments should comply with AS 3864-1991 "Medical refrigeration equipment - for the storage of blood and blood products, and containers for the transport of blood and blood products".

3a.47 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.
Annex 3b

Equipment

Note: the following is adapted from the Australian Code of GMP for Therapeutic Goods – Medicinal Products. That Code should be referred to for the original text.

Rationale

3b 01 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.

GMP

3b 02 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.

3b 03 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.

3b 04 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.

3b 05 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.

3b 06 Contamination from operations that generate dust or aerosols should be minimised by containing the dust or by extraction, filtration, or other appropriate means.

3b 07 Equipment should be kept clean, dry and protected from contamination when not in use.

3b 08 Equipment should be cleaned and, where necessary, sanitised before use, servicing or maintenance.

3b 09 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.

3b 10 Defective equipment should be tagged as defective and, where portable, removed from manufacturing areas.

3b 11 Equipment should not create a hazard to the product through leaking glands, lubricant drips, and the like; or through inappropriate modifications or adaptations. Only coolants, lubricants and other chemicals approved by Quality Assurance should be used.

3b 12 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.

3b 13 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
- 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.

3b14 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.

3b15 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.

3b16 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.
Personnel and training

Note: the following is adapted from the Australian Code of GMP for Therapeutic Goods – Medicinal Products. That Code should be referred to for the original text.

Rationale

3c 01. The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of medicinal 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.

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.

3c 05 Persons in responsible positions should have adequate authority to discharge their responsibilities.

3c 06 The persons in charge of production and of quality assurance respectively should usually have studied a relevant science* at university or technical institute level and have had practical experience under professional guidance in the manufacture and control of therapeutic goods made under GMP. They should be different persons, neither of whom is responsible to the other unless other arrangements acceptable to the inspecting authority are made, yet each should have a responsibility for the achievement of product quality.

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

* Note: for example, pharmacy, chemistry, chemical engineering, microbiology, food technology, pathology, or another relevant scientific discipline.

3c 07 Only in exceptional circumstances should persons engaged part-time or in a consultative capacity be appointed to key positions.

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

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.

3c 08 Operators should be sufficiently fluent in spoken English and sufficiently fluent in written English to respond to training, accept and implement instructions exactly and, where their duties require it, fill out forms correctly.

GMP

3c 02 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.

3c 03 Key personnel, responsible for managing and supervising manufacture, quality assurance and quality control, should be adequate in number. They should have the managerial and professional or technical skills and experience to assume and discharge responsibility for ensuring that the goods manufactured consistently meet standards and specifications.

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

3c 04 By means of job descriptions and organisational charts, the areas of responsibility and lines of authority of key personnel should be identifiable. Organisation charts, job descriptions and the names, qualifications and experience of key personnel and their deputies should be available.
3c 09 Where appropriate, operators should be tested for colour-blindness and the results made known to supervisors under whom they work.

3c 10 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.

3c 11 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.

3c 12 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.
Annex 3d

Blood processing centre sanitation and personal hygiene

Note: the following is adapted from the Australian Code of GMP for Therapeutic Goods – Medicinal Products. That Code should be referred to for the original text.

Rationale

3d.01 A high standard of BCC 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 programmes to ensure that the steps have been thought out and, where necessary, validated.

General

3d.02 The BCC, including employee amenity areas, workshops and service rooms, should be clean, dry, sanitary, orderly and free from accumulated waste, dirt and debris.

3d.03 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

3d.04 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, including contract cleaning 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.

3d.05 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.
3d 06 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.

3d 07 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 Quality Assurance in connection with an investigation of the origin(s) of the contamination.

3d 08 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.

Facilities and procedures for personal hygiene

3d 10 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 by at least an air lock. Odour-masking agents should not be used in toilets.

3d 11 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.

3d 12 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.

3d 13 Direct contact between operators’ hands and exposed product should be avoided.

3d 14 A policy regarding the wearing of makeup and jewellery should be established and enforced, as appropriate to the circumstances.

3d 15 Clean working garments appropriate for the work carried out should be worn by all staff.

3d 16 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 or put staff at risk of infection or injury. 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.

3d 17 There should be pre-employment and periodic medical checks, and steps should be taken to see that no person with a disease in a communicable form, or with open lesions on the exposed surface of the body, is engaged in the open manufacture of medicinal products, including venepuncture.

Personnel should be required to report infections and skin lesions, and a defined procedure followed when they are reported.
3d 18 Training relating to BCC sanitation and personal hygiene should be included in staff training programs.

3d 19 Where hazardous or physiologically potent drugs are used the staff should be provided with:

- training and written procedures to ensure the safe handling of these drugs; and

- protective clothing and equipment necessary to implement these procedures.
Annex 3e

Documentation

Note: the following is an extract from the Australian Code of GMP for Therapeutic Goods – Medicinal Products. That Code should be referred to for the original text.

Rationale

3e 01 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.

Kinds of document

3e 02 Manufacturers should have specifications for materials used and products made (including test methods), master documents from which pooled product batch records are derived, standard operating procedures to give directions for recurrent tasks, agreements covering external activities and registers and other records to provide a complete history of each pooled product batch made and the circumstances of its manufacture, in accordance with the following clauses.

Preparation, issue and use of documents

3e 03 Documents should be carefully and logically set out to encourage correct use and be easy to check. Documents should contain all necessary, but no superfluous data. Any headings, items or spaces on a master document that cease to be used should be removed at the earliest opportunity.

3e 04 Each document should indicate or include:

- the user’s company or trading name;
- purpose and title;
- a document identity number which uniquely identifies the document and indicates revision, if any:
  - date of authorisation;
  - date of expiry or review (in the case of standard operating procedures);
- signatures of authorising person(s) and, where different, the signature of the person who prepared the document;
- the distribution list, where copies are distributed (at least on a master copy); and
- page numbers (of number of total pages).

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

The reason for revision should be documented.

3e 05 Issued documents should not be handwritten. Reproduced or computer-printed documents should be clear and legible; in the case of batch documents each must be initialed to indicate a verified issue.

3e 06 Any correction made to a document should be initialed or signed and dated and the correction should permit the reading of the original information. Where appropriate, the reason for the correction should be recorded.

3e 07 Documents which require the entry of data or additional information should:

- provide sufficient space for the entry;
- allow adequate spacing between entries; and
- clearly indicate what is to be entered.
Where any issued document requires the entry of data or additional information, entries should be handwritten clearly and legibly in permanent ink. If a handwritten entry is corrected, the correction should permit reading of the original entry and should be initiated by the person making it.

3e 08 Where documents bear instructions they should be written in the imperative, ie as a direct command, as numbered steps. They should be clear, precise, unambiguous and in plain English that the user can understand. Such documents should be readily available to all concerned with carrying out the instructions.

3e 09 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.

3e 10 Pooled product master batch documents, standard operating procedures and other master documents having a direct bearing on pooled product quality should be authorised by the person responsible for Quality Assurance or that person's delegate as well as by a responsible Production or other relevant Manager.

Storage and retention of documents and records

3e 13 Except where legislation requires longer retention periods, the complete records pertaining to each pooled product 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 20 years after the date of manufacture of the batch.

Records of complaints should be held for a corresponding period.

3e 14 Master documents for batch processing and packaging should be copied and the copies secured against theft, loss, or alteration of information.

3e 15 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 Chapter 2.

3e 16 Paper or film records should be stored in a restricted access area. Records should be protected from tampering or loss.

3e 17 Records may be retained by computer storage, but the procedures and checks in Annex 3I should be followed. Such records should be progressively backed up (eg. daily) and the backup kept at a location remote from the active file.
Essential documents

Starting material:

3e 18 Specifications for blood packs and test material (other than packaging material) should include, where applicable:

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

Notes:

(1) See “Packaging Material” in the glossary: the need for detailed specifications may not apply to “Other Packaging Materials”.

(2) Optional for this document where adequately covered by Standard Names documentation. See also Glossary.

Finished pooled products:

3e 20 Specifications for finished products prepared from pooled blood or plasma should include:

- an agreed name;
- the product code (if any);
- tests and limits for identity, purity, physical and chemical characteristics, assay or potency and (where appropriate) microbiological standards;
- details of, or reference to the test methods to be used by the manufacturer;
- instructions for use or a reference to a product insert or to a user's guide in lieu of the former;
- sampling instructions; and
- the shelf life and storage conditions in relation to the blood pack used.

this code should be that used on the material eg a label code;
- a description of the nature, dimensions and materials of construction of the component;
- quality standards;
- approved label copy (for pre-printed materials);
- bar codes, where applicable, including a reference to the Bar Code Register;
- details of, or references to, tests to be used to determine compliance with the specification;
- approved or certified suppliers (see Note 2);
- sampling plan and sampling instructions or reference to appropriate parts of a standard operating procedure; and
Goods Received Register:

3e 21 A register should be established showing the receipt of blood packs and test material.

The register should include:

- date of receipt;
- Standard Name of material;
- suppliers’ name for material (if different);
- supplier’s batch or lot number(s);
- quantity and number of containers per suppliers’ batch; and
- the Unique Identifying Number(s) allocated.

Standard Names List:

3e 22 A list showing the standard name for each starting material should be established. Standard names should be sufficiently specific to indicate special quality characteristics and be designed to minimise mix-ups. The standard names specified on this list should be used to identify starting materials during storage and manufacture.

Status labels

3e 23 Status labels should include:

- the business name or logo; and
- the words QUARANTINE or HOLD, RELEASED or APPROVED or REJECTED or equivalent terms acceptable to the inspecting authority;

Status labels for starting materials should also include provision for:

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

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

3e 24 REJECT labels should be used only for materials that are unfit for use, those of uncertain status or destined for recovery, re-processing and the like should be designated HC LD, QUARANTINE or the equivalent.

3e 25 The status of any donation should be evident from the visual appearance of its status label.

3e 26 Unless the standard quarantine and release procedure is utilised, a further visually distinct and different standard label should be used for substances used in production but not in the product, eg acids and alkalis for demineraliser regeneration, blue dye for leak testing.
Use of computers

Note: the following is adapted from the Australian Code of GMP for Therapeutic Goods – Medicinal Products 1991. That Code should be referred to for the original text.

3f.01 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.

3f.02 The responsibilities of the key persons in manufacturing and quality departments are not changed by the use of computers.

3f.03 Persons with appropriate expertise should be responsible for the design, introduction and regular review of a computer system.

3f.04 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.

3f.05 Software developed (or changed) after December, 1992, should follow the principles of Australian Standard AS 3563: Software Quality Management System. Changes made prior to December, 1992 may be retrospectively validated; see Glossary.

Where a purchased source code is used or modified, the vendor's attention should be directed to AS 3563. Vendors should be asked to provide written assurance that software development or modification has followed the quality management system of that Standard or of an equivalent system.

A logic flow diagram or schematic for software should be prepared for critical evaluation against system design/requirements/criteria.

3f.06 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.

3f.07 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.

3f.08 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.

3f.09 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.

3f.10 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.

3f.11 The entry of critical data into a computer by an authorised person should require independent verification and release for use by a second authorised person.

3f.12 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, eg names, birthdays, should be
issued and a procedure for regular change of codes should be established.

31.13 The computer system should create a complete record ("audit trail") of all critical entries and amendments to the data base.

31.14 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.

31.15 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 Annex 3e.

31.16 Printed matter produced by computer peripherals should be clearly legible and, in the case of printing onto forms, should be properly registered on the forms.

31.17 Storage of live and master data should be in accordance with Clauses 3e 17 and 3e 14 respectively.

31.18 Records should be available for the following aspects of a computer system validation:

- protocol for validation, whether retrospective or prospective;
- 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; and
- procedure for ongoing evaluation.
Annex 3g

Quality management

Concepts and rationale

3g 01 The management of quality generally has progressed from testing finished product in order to determine whether it meets specifications or not (and if not how to correct it) to an involvement with every aspect of manufacture and testing which will assure senior management that the product will always meet corporate quality criteria, i.e. that the assurance is not conditional upon a favourable test result.

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

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

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

* creating quality systems and procedures;
* authorising key procedures;
* reviewing and challenging specifications and test methods;
* reviewing vendor quality management;
* interacting with product development and manufacturing personnel to validate processes and procedures;
* interacting with processing and engineering personnel in planning for the construction, alteration, renovation, or purchase of premises, plant or equipment;
* interacting with the personnel of other departments concerned with the development of electronic data processing systems, wherever these are concerned with materials or products;
* evaluating Deviation and Fault Reports and complaints;
* improving in-process controls;
* critically examining the environment with a view to minimising product contamination;
* monitoring product stability;
* internal auditing;
* ensuring that goods are produced according to protocols accepted for registration; and
* releasing batches of product for sale on the basis of a certified package of production and laboratory documents.
Quality Control

3g 03 Quality control involves the actual sampling and testing procedures and the actual sampling and testing of starting materials, intermediate products and finished products to verify that they meet specifications before release for further manufacture or use. It includes on-line quality control, though administratively it may be more convenient and philosophically more correct to exert intermediate and in-process controls using Production staff, while Quality Control provides technical support and audit.

Quality Management

3g 04 There should be a comprehensive system for the quality management of all materiel manufactured. There should be a separate department responsible for this system unless other arrangements acceptable to the inspecting authority are made.

Provision for the management of quality should include a laboratory adequately staffed and fully equipped for performing all quality control tests and analyses (including any environmental control tests) required before, during and after manufacture, except where arrangements for contract testing, acceptable to the inspecting authority, are made.

The person in charge of quality assurance should:

- be qualified, authorised and responsible as specified in clause 3c 06;
- be notified promptly of all proposed changes in, and departures from, the donor selection criteria and processing instructions and packaging and labelling instructions for products;
- be notified of all circumstances which may affect the quality of products, whether before or after release;
- ensure that production is compatible with registration protocols; and
- have the final responsibility to management for the testing and release or rejection of all materials and material subject to the quality control system.

Quality Assurance or Quality Control should:

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

Functions and Duties

3g 05 In order to discharge its obligation to ensure that materials released for use or distribution are of satisfactory quality, the quality assurance or quality control department should:

- establish or approve quality control specifications for all materials, for packaging materials in contact with the products and for intermediate materials and other labelling materials where appropriate;
- 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 including CSL material;
- establish or approve written procedures and plans for the sampling of materials, work in progress and materials 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;
- 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;
- sample and test all batches of starting materials, finished products, specified intermediate products and specified packaging materials for compliance.
with their specifications, using the established sampling and test procedures;

- evaluate the stability of all finished material and of starting materials and intermediate material where necessary, and, on the basis of appropriate stability data;

- establish instructions for the storage of material 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 material 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 material (where possible by direct audit) and assign, where appropriate, "approved supplier" or "certified supplier" status;

- Note: Starting material should not be granted "approved supplier" status except in relation to material in sealed containers bearing the manufacturer's original label and batch, lot or equivalent number.

- evaluate and authorise any re-processing or re-working of products or material (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, jointly with Production, an active self-inspection program to determine compliance with GMP requirements.

Certain of the functions shown as * sub-clauses above may be delegated to the specialist area of the BCC.
Annex 3h

Example Document – SOP

STANDARD OPERATING PROCEDURE

Section: . . . General Operating Procedures
Subject: . . . Standard Operating Procedures

1. . . . . . PURPOSE: To describe the method for writing procedures for all general operations.

2. . . . . . SCOPE: All BCC operations.

3. . . . . . RESPONSIBILITY: Key Personnel Accountable for BCC Operations.

4 . . . . . . . PROCESS DESCRIPTION:

4.1 . . . . . A Standard Operating Procedure is the document describing the step-by-step method of performing a job. Standard operating procedures may also be called Basic Operating Procedures, General Operating Procedures or Standard Test Procedures. N.B. It is generally accepted that SOP’s because of their “general” nature should not be designed for individual product-specific application, unless for exceptional circumstances.

Prepare the SOP’s so that they:

4.1.1 use the imperative, are in simple language and not wordy.

4.1.2 convey knowledge.

4.1.3 can be a training aid for operators and an operating guideline.

4.2 Format the SOP in sections, where applicable, as follows:

4.2.1 The name of the BCC, eg Canberra BCC to appear on each page.

4.2.2 The title, “Procedure” to appear on each page.

4.2.3 “Confidential and Proprietary” - This may be needed on each page to ensure confidentiality.

4.2.4 “Page of” - Paginate each page separately, eg Page 2 of 5 denotes that the SOP consists of 5 pages and you are reading page number 2.

4.2.5 “Revision No” - List on each page, original SOP’s are assigned the letters “N/A” for ‘not applicable’. Sequentially letter subsequent revisions (A, B, C, etc).

Author
Date
Checked by
Date
Approved for use by
Date

Annex 3

Code of GMP-Medicinal Products:
Adaptations and extracts
Any alternative sequential system of assigning unique identifying number/alpha codes may be used to identify the current revision copy of the procedure. An exact number of authorised copies should be issued to known locations. If superseded, all obsolete documents must be removed from use and a suitably identified copy keep for archive purposes.

4.2.6 "Effective Date" - Appearing on each page, this indicates the date the procedures in the SOP will be implemented.

4.2.7 "SOP Number" - Place a three digit SOP number on each page to denote the following.

    . . . . 100s General Operating Procedures.
    . . . . 300s Physical Inspection/Measurement Procedures.
    . . . . 400s Manufacturing Procedures.
    . . . . 500s General Raw Material Testing Procedures.
    . . . . 600s General Finished Product Testing Procedures.
    . . . . 700s Process Control Testing Procedures.
    . . . . 800s Equipment Operation, Maintenance, Calibration Procedures.

Complete identification of an S.O.P. should include SOP number and Revision Code.

4.2.8 "Title" - A short, concise description of the procedure.

4.2.9 "Purpose" - This section should answer the question - What aspect of the operation is the SOP trying to teach?

4.2.10 "Scope" - This section should answer the question what operation(s) does this document affect?

4.2.11 "Responsibility" - Describe the individual(s) responsible for adhering to the procedure.

4.2.12 "Other Applicable Documents" - Describe all other documents that could be affected if changes are made to the SOP.

4.2.13 "Equipment" - List all major pieces of equipment by formal name.

4.2.14 "Materials" - List manufacturing materials and critical components or subassemblies.

4.2.15 "Process Set-Up" - Describe the sequential steps taken to prepare a work area for an operation. Includes:

    . . . . 4.2.15 Material and equipment clearance, where applicable.
    . . . . 4.2.15.2 Initial operation or machine startup.
    . . . . 4.2.15.3 Materials staging.

4.2.16 "Process Description" - Describe all key operations performed. Answer where possible the questions:

    . . . . 4.2.16.1 What is to be done?
    . . . . 4.2.16.2 Who's responsible?
    . . . . 4.2.16.3 With What?
    . . . . 4.2.16.4 When?
    . . . . 4.2.16.5 How?
    . . . . 4.2.16.6 Where?
4.2.17 “Process Shutdown” - Describe sequential operations to finish or stop an operation.

4.2.18 “Safety Precautions” - List precautions and equipment that the employee should take while running the operation or working in the area in order to prevent injury to her/himself or others. Also include information concerning potential dangers of which he/she should be aware.

4.2.19 “Illustrations” - Use illustrations to clarify the SOP. Where necessary use diagrams, photographs, examples, forms, lists, etc.

4.2.20 “Author” - The author signs in this space. SOPs may be written by clerks, technicians, supervisors, managers, or any designee approved by the respective department manager. The individual most familiar with the procedure should always assist in writing the SOP.

4.2.21 “Checked By” Signed by a person (not the author) who checked the document for technical content, accuracy, typos, etc.

4.2.21 “End of Document” - Type as the last item of each SOP.

4.2.22 “Approved for use by” - SOPs will be approved by applicable departments before implementation. Designees from each department will be assigned the responsibility for approving finished SOPs. The reviewer's signature (first initial, last name) and date on the finished SOP indicates that the SOP has been checked and accurately describes the procedure to be followed and complies with current Good Manufacturing Practices. Approval signature denotes authorisation for use and should be the same date as the effective date.

N.B. In small BCC operations where appropriate authority rests with the checker the checked by and Approval signature may be actioned by the one signature as an approval signature.

4.3 Prepare SOP's in paragraphic form as follows: 1. 1.1 1.1.1 1.1.1.1 etc, or by numbering clauses sequentially.

4.4 Identify the abbreviations contained in SOPs completely the first time used in the SOP, eg “Standard Operating Procedure(SOP).

4.5 Verify the SOPs against on-site operations on a regular basis, either semi-annually or annually. This verification will also include compliance to this SOP. A record should be made of this verification. This procedure is valid for twelve months after the date of approval for use. To assure this verification step indicate at the end of the S.O.P. a date up to which time the S.O.P. remains current and valid.

5. This procedure is valid for twelve months after the date of Approval for Use.

6. END OF DOCUMENT.
Annex 3i

Sterile Manufacturing Using "Open" Systems

Rationale

3i 01 The manufacture of sterile products requires special care and attention to detail because of the increased hazard to the patient should a product be non-sterile or contaminated.

In order to maximise the probability of success, the compounding, filling and sealing operations are conducted in a clean environment in which the fewest possible pieces of equipment are attended by the fewest possible, suitably clad, operators.

In this environment bulk product formulated from starting materials of lowest practicable biological load is filtered to reduce or eliminate this load and filled (or dried and filled) into clean or sterile containers. Sterilisation is carried out under closely controlled and validated conditions. Additional precautions against contamination are taken with products that are not sterilised in their final containers.

Because these manufacturing processes are susceptible to particulate, pyrogenic and microbiological contamination, the skill, training and attitudes of the personnel involved are critical. Operators must be skilled, disciplined and responsive to supervision. Supervisors must be diligent and dedicated. Managers must communicate goals and provide facilities and systems that preclude or minimise the risk of error.

It is not sufficient that the finished product passes laboratory tests: the whole manufacturing process must be under tight control and the need to quality equipment and validate sterilising processes (see Glossary) assumes singular importance, not least because of the limitations of official tests for "sterility".

Part 2 of the Australian Code of GMP for Therapeutic Goods – Medicinal Products sets out provisions relating to the manufacture of products which are, or which are intended to be, sterile in finished dosage or usage forms. These provisions supplement those of Part 1 and both parts are intended to be applied in their entirety.

Detailed provisions relating to sterility testing and ethylene oxide sterilisation of therapeutic goods are set out in its Appendices C and E respectively.

If a BCC uses anything other than closed bag systems for the collection or processing of blood then the provisions of Part 2 of the above Code of GMP should apply.
Annex 3j

REFERENCED AND RECOMMENDED STANDARDS AND PUBLICATIONS

Standards and Publications cited in the Code

Australian Standards - published by Standards Australia 80 Arthur Street, North Sydney

AS 3666-1989 Air-handling and water systems of buildings - Microbial control ISBN O 7262 5531 9

AS 3787.1-1990 General requirements of single-use, sterile, plastised PVC Blood Packs

AS 3864-1991 Medical refrigeration equipment - for the storage of blood and blood products, and containers for the transport of blood and blood products.

AS 3900/ISO 9000 Quality Systems Guide to Selection and Use

National Association of Testing Authorities 688 Pacific Highway, Chatswood NSW

Microbiological Testing: Laboratory Accommodation Guidelines.

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

Other references


- Blood and Its Products, Red Cross Blood Bank, RCBB, Victoria 1987/ISSN 1030-3472

- Code of Practice for the Clinical Use of Cell Separators, UK DHSS, HMSO 1977


Annex 3 Code of GMP-Medicinal Products: adaptions and extracts page 41


• Guidelines for Blood Donors, NBTC, May, 1991, (c/o Australian Red Cross Society, Blood Transfusion Service, Kavanagh Street, South Melbourne, Victoria 3205) ISBN 0 909896 42.9

• Malaria Risk in International Travel, WHO, Geneva, 1986

• Requirements for Biological Substances No. 1 (General Requirements for Manufacturing Establishments and Control Laboratories, WHO Technical Report Series No. 323, 1966).


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 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

Annex 3k

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 Annex 3g.

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

AIR LOCK: An enclosed space with two or more doors (only one of which is opened at any one time), which is interposed between two or more rooms (e.g. of differing class of cleanliness), for the purpose of controlling the airflow between those rooms when they need to be entered. An air lock may be designed for and used by either people or goods; in the latter case it may also be termed a "pass-through hatch". An air lock may also be the "anteroom" to a "clean room" in which sterile goods are processed.

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 form a 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, e.g. granulations, may be combined by mixing to form a single batch. However, where the bulk batch is divided into lots for different sterilisation or lyophilisation cycles, or 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 also 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).

CLEAN AREA: A suite of rooms with defined environmental control of particulate and microbial contamination, used in such a way as to minimise the introduction, generation and retention of contaminants within it.

CLOSED SYSTEM: A system, (such as a multiple pack assembly), where the registered assembly is manufactured under clean conditions, sealed to the external environment and sterilised by an approved method. Apart from the act of blood collection, where a needle is exposed and enters the donor's arm, the integrity of this assembly must not in any way be breached. Accidental breaching renders the unit unusable.

When a 'sterile docking device' is used to join two packs it can be regarded as a closed system providing that it has been shown that the process of joining and sealing the two packs does not lead to the possibility of microbial contamination of the products in either pack.

See also "open system".

COMPENDIAL: Included in an official compendium such as British Pharmacopoeia.

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

CRITICAL LABELS: a label which identifies a product, such as a blood group label if used to control release for supply.

DEDICATED FACILITY: A room or suite of rooms with attendant equipment and services, including air handling used only for the manufacture of one product or a closely related group of products. Equipment may be similarly "dedicated".

"F:" The lethality of a saturated steam sterilising process, expressed in terms of the equivalent time in minutes at a temperature of 121°C delivered by that process to the product in its final containers with reference to micro-organisms possessing a Z-value of 10. The Z-value is the change in temperature required to alter the D-value by a factor of 10, where the D-value is the time required to reduce the number of viable micro-organisms originally present by a factor of 10. See also USPXXI, page 1349.

IMPERATIVE: (in relation to documents): A positive manner of expression, eg "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.

OPEN SYSTEM: A system which has been breached but where every effort is made to maintain sterility by using sterilised materials and operating in a clean environment, e.g. a procedure where the transfer container is not integrally attached to the blood pack and the blood pack is breached after collection.

Components prepared in an open system should be Manufactured in a Class 3 500 clean room under a Class 3,5 laminar flow hood (see Annex 3i and the current Australian Code of GMP for Therapeutic Goods - Medicinal Products) and monitored for sterility following methods outlined in Appendix C, Australian Code of GMP for Therapeutic Goods - Medicinal Products.

Note: different coagulants may have different effects on cells stored at ambient versus 10°C. It is the responsibility of each BCCD to document these.

See also "closed system".

OPTICAL BAR CODE: A series of marks on preprinted packaging material that may be read by an optical scanning device. By arranging unique markings, each different or altered preprinted material may be distinguished and verified at scanning.

PACKAGING MATERIEL: Any materiel 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 material may be distinguished:

- packaging materials which come in contact with the product (often called 'primary packaging materials');
- printed packaging materials (carrying product labelling); and
- 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 in or with the pharmaceutical industry.

**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 detective 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.

**REGISTERED**: A therapeutic good registered (in some cases only listing is required) on the Australian Register of Therapeutic Goods (ARTG).

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

**SESSION RECORD**: A record which indicates names of donors attending a session together with other details where relevant, such as staff, batches of blood bags used and so on.

**SENSITIVITY** is a term defining the limit of detectable specific reactions using reagents or test systems. The document specifies levels of sensitivity which must be achieved.

**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. Specificity is a term defining the ability of a reagent or
test system to react selectively. In practical terms, it represents the absence of false positive reactions.

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 MATERIEL: Any material employed in manufacture and which may contact or be included in the finished product, including packaging material. 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 material that are not packaging material are sometimes known as chemical starting materials or raw materials or ingredients, although not all such material 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 (eg 'Quarantine', 'On Test', 'Released', 'Restricted Use', 'Hold', 'Rejected', 'To be Cleaned').

STERILE: Free from viable micro-organisms.

STERILISATION: (1) A process intended to produce sterile goods. (2) Reduction of the probability of the presence of viable micro-organisms to an acceptable extent. Sterilisation is effected by moist or dry heat, by treatment with a gaseous sterilant such as ethylene oxide, by irradiation with ionising radiation or, where such processes are inapplicable to solutions, by filtration.

STERILITY: The concept of the complete absence of living micro-organisms.

UNIQUE IDENTIFYING NUMBER: See Batch Number.

VALIDATION - GENERAL: Validation of a manufacturing method is a part of a Quality Assurance programme and consists of those steps which are taken in advance to ensure that the product will be of the quality required for its intended use and that tests used in monitoring will accurately reflect the quality of the product. 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.

VISUAL BAR CODE: A series of marks, printed at the edge of packing materials such as unit cartons, that may be visually inspected to detect 'foreign' packages.

WORKING STANDARD is a preparation prepared nationally or locally containing a known or agreed concentration of the activity being measured and it should be assayed with each group of tests to establish the sensitivity or calibration of the unknown tests in the group.

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

The Act and Regulations should always be consulted for the exact wording and context.

"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;
(b) a place (whether enclosed or built upon or not);
(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;
(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;

"therapeutic devices" means therapeutic goods other than goods that are represented to achieve, or are likely to be taken to achieve, any of the principal purposes of their use as a result of chemical action within or upon the body of a person or animal, but does not include therapeutic goods declared by the Secretary, by order published in the Gazette, not to be therapeutic devices;

Therapeutic goods which are not therapeutic devices are referred to as "drugs" in the Regulations to the Act.

Persons exempt from the requirement to have a manufacturing licence includes persons who operate blood collection centres except those that supply plasma for the manufacture of blood components.
Annex 4

General specifications for labelling, storage and transportation of blood and blood products

Rationale

These operating procedures provide guidance only. Further specific definition is required by individual BCCs. The guidance given in this Chapter sets out the minimum requirements for labelling, storage and transportation of materiel, i.e. raw materials, intermediate and finished products at any facility involved in the collection, separation or processing of blood, blood products or plasma fractions.

Labelling

4001 The design and use of labels should comply with specifications set out in appropriate sections of the:

- British and European Pharmacopoeias;
- Part A, section 8, of the revised Requirements for Biological Substances No. 1 (General Requirements for Manufacturing Establishments and Control Laboratories); and
- No. 323 of the WHO Technical Report Series should also be followed, together with the additional recommendations in Part D.9 of the revised Requirement for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives, WHO 1988

Note:

- the use wherever possible of bar codes and bar code readers is recommended.
- specific guidelines on labels for single donor and small pool products, plasma derivatives and reagents for blood group serology are given, where appropriate, in the relevant section of these guidelines and in the RCBTS document “Blood Products – Proper Names and Definitions”. See also Annex 6.

Storage

Procedures

4002 Written procedures for the storage of materiel should be established and followed.

These should include at least the following:

- designated storage areas - definition of the designated storage areas including the conditions which should be achieved, the status of materiel to be stored in each area and the persons authorised as requiring access to each area;
- housekeeping - a procedure for regular verification of the cleanliness and good order of all storage areas;
- quarantine - a procedure for the quarantine of materiel before release by the designated person;
- stacking - specific directions on stacking units of stock such that storage does not jeopardise the identity, integrity or quality of individual units;
- stock control - a procedure for stock control allowing batch differentiaton and rotation of stocks; and
- storage validation - a procedure for validating the conditions of storage achieved in any given storage area.
Operation

4003 Storage areas should provide adequate space, suitable lighting, and be arranged and equipped to allow dry, clean and orderly placement of stored material under controlled conditions of temperature and humidity.

4004 Storage areas should provide for suitable and effective separation of quarantined and released material. There should be clear demarcation in the storage of similar materials.

4005 Segregated areas should also be available for rejected or returned material.

Note: see also Annex 3a.

Recommended Storage Conditions (and expiry dates).

4006 At all stages of the manufacturing process, material should be stored at temperatures and under conditions shown to be adequate to prevent contamination by the proliferation of microorganisms and to preserve biological activity as appropriate.

4007 Expiry dates should be assigned to material as appropriate, indicating the maximum period of storage under a given set of conditions.

Transportation

General considerations

4008 Blood and blood products should be transported under conditions as similar as possible to the recommended conditions of storage. Transit times should be minimised, and on receipt material should be transferred to storage under the recommended conditions, unless for immediate use.

Procedures

4009 Written procedures for the transportation of material and products should be established and followed. These should include at least the following:

- definition of the approved systems of transportation, and of the conditions it is required to be maintained in each case;
- specific directions on the packing of material such that transportation does not jeopardise identity, integrity or quality;
- procedures for identifying the contents of a given vehicle load by a system of consignment notes;
- procedures for validating the condition of storage achieved during transportation; and
- procedures for the regular verification of the cleanliness and good order of all vehicles and containers used for the transport of materials and products.

Operations

4010 Material should be transported both within and between sites by means which ensure the following:

- identity is maintained;
- status (quarantined, released or rejected) is maintained;
- integrity is maintained; and
- material is not adversely affected by the conditions of storage during transportation.
Annex 5

Accredited donors of red cells for Rh immunisation

Rationale

5001 Accredited donors are a special panel of donors who, because they have been tested in detail on a very regular basis, can be relied upon to provide extremely safe blood components which are very valuable for the immunisation and boosting of Rh negative donors for the collection of high titre plasma for the production of anti-Rh (D) immunoglobulin.

Accreditation

The donor should comply with the following.

OPTIONAL

5002 The donor should have made either 100 plasmapheresis donations or 25 whole blood donations.

MANDATORY

5003 The donor must have donated blood or plasma on at least three occasions during the last two years and have blood samples tested at intervals of not greater than three months for one year.

All samples must be negative for:

- anti-HBc;
- HBsAg;
- HIV 1 and 2 antibody;
- Hepatitis C antibody;
- HTLV-1 antibody; and
- syphilis

5004 A test for HIV antigen must be performed at the end of the accreditation period and at the time any donation is made for the purpose of immunisation, and found negative.

5005 On each occasion the donor must have serum values within the normal range for: total protein, albumin, alanine aminotransferase, gammaglutamyl transpeptidase and aspartate transaminase.

5006 The donor must meet normal donor selection criteria given in Chapter 5 of the Code of Good Manufacturing Practice For Therapeutic Goods - Blood and Blood Products.

5007 The donor must not have been transfused or injected with blood, tissue or any components other than autologous since 1977.

5008 The donor must not have had acupuncture, ear piercing, or tattooing since the start of regular sampling.

5009 In addition to the full red cell typing done by the BCC concerned, red cells from the accredited donors should be grouped for all clinically relevant red blood cell antigens.
The use of accredited red cells for immunisation/boosting of volunteers.

5010 Reconstituted frozen red blood cells from an accredited donor should be used for immunisation/boosting of donors for the production of anti-Rh immune plasma.

5011 The frozen red cells should be stored for at least six months before being used for immunisation/boosting, to enable repeat testing of the donor to determine, as far as possible, if there had been any change in accredited status since the time of red blood cell donation.

5012 Before the red blood cells are used for immunisation/boosting (ie at the end of the six months period of frozen storage) the donor must again meet the criteria for accreditation, including a negative HIV antigen test.

5013 Every attempt should be made to ensure that the donor maintains the accredited status for at least three and six months after the donor's red blood cells have been used for Rh immunisation/boosting.

5014 Donors, for whom continuing accreditation is likely to be required, should be fully tested every three months.
# Blood and Blood Products – Proper Names and definitions

<table>
<thead>
<tr>
<th>Proper Name</th>
<th>Barcode*</th>
<th>Definition Of Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin Whole Blood</td>
<td>a0001103b</td>
<td>Whole blood collected into heparin anticoagulant.</td>
</tr>
<tr>
<td>CP2DA Whole Blood</td>
<td>a0001703b</td>
<td>Whole blood collected into Citrate Phosphate Double Dextrose Adenine anticoagulant.</td>
</tr>
<tr>
<td>CP2D Whole Blood</td>
<td>a0001803b</td>
<td>Whole blood collected into Citrate Phosphate Double Dextrose anticoagulant.</td>
</tr>
<tr>
<td>CPD Whole Blood</td>
<td>a0001503b</td>
<td>Whole blood collected into Citrate Phosphate Dextrose anticoagulant.</td>
</tr>
<tr>
<td>Whole Blood Autologous</td>
<td>a0001973b</td>
<td>Whole blood collected into anticoagulant for autologous use.</td>
</tr>
<tr>
<td>Whole Blood Directed</td>
<td>a0001983b</td>
<td>Whole blood collected into anticoagulant for directed use.</td>
</tr>
<tr>
<td>Red Blood Cells Packed</td>
<td>a0040903b</td>
<td>Centrifuged or sedimented whole blood from which approximately two thirds of the plasma has been removed.</td>
</tr>
<tr>
<td>AS-2 Red Blood Cells</td>
<td>a0042203b</td>
<td>Red blood cells to which has been added a buffered electrolyte and sugar solution containing adenine (Tuta).</td>
</tr>
<tr>
<td>AS-1 Red Blood Cells</td>
<td>a0042103b</td>
<td>As above (Fenwal Pack).</td>
</tr>
<tr>
<td>AS-5 Red Blood Cells</td>
<td>a0042503b</td>
<td>As above (Terumo Pack).</td>
</tr>
</tbody>
</table>

*Barcodes - the reader should note that there may be state to state variations.
## Blood and blood products – proper names and definitions

<table>
<thead>
<tr>
<th>Proper Name</th>
<th>Barcode</th>
<th>Definition of product</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS Red Blood Cells Paediatric</td>
<td>a0042913b</td>
<td>As above but divided into several volumes.</td>
</tr>
<tr>
<td>AS Red Blood Cells Autologous</td>
<td>a0042973b</td>
<td>As above but for autologous use only.</td>
</tr>
<tr>
<td>AS Red Blood Cells Directed</td>
<td>a0042983b</td>
<td>As above but for directed use only.</td>
</tr>
<tr>
<td>AS Red Blood Cells Buffy Coat Poor</td>
<td>a0046903b</td>
<td>Red blood cells from which the buffy coat has been removed and to which has been added a buffered electrolyte and sugar solution containing adenine.</td>
</tr>
<tr>
<td>AS Red Blood Cells Leucocyte Poor Filtered</td>
<td>a0043903b</td>
<td>Red blood cells from which leucocytes have been removed by filtering and to which has been added a buffered electrolyte and sugar solution containing adenine.</td>
</tr>
<tr>
<td>Red Blood Cells Leucocyte Poor Filtered and Washed</td>
<td>a0048903b</td>
<td>Red blood cells from which leucocytes have been removed by filtering and then washed with a compatible solution.</td>
</tr>
<tr>
<td>Red Blood Cells Washed</td>
<td>a0049903b</td>
<td>Red blood cells which have been washed with a compatible solution.</td>
</tr>
<tr>
<td>Red Blood Cells Frozen</td>
<td>a0062003b</td>
<td>Red blood cells frozen after the addition of a cryoprotectant.</td>
</tr>
<tr>
<td>Red Blood Cells Deglycerolised</td>
<td>a0064003b</td>
<td>Red blood cells which have been stored frozen and subsequently thawed and deglycerolised.</td>
</tr>
<tr>
<td>Platelets</td>
<td>a0120003b</td>
<td>Platelets prepared by centrifugation of whole blood and suspended in plasma.</td>
</tr>
<tr>
<td>PS Platelets</td>
<td>a0120803b</td>
<td>Platelets prepared by centrifugation of whole blood and suspended in plasma-free medium.</td>
</tr>
</tbody>
</table>

*Barcodes - the reader should note that there may be state to state variations.*
# Blood and blood products – proper names and definitions

<table>
<thead>
<tr>
<th>Proper Name</th>
<th>Barcode*</th>
<th>Definition of product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Apheresis</td>
<td>a0123003b</td>
<td>Platelets prepared by apheresis and suspended in plasma.</td>
</tr>
<tr>
<td>PS Platelets Apheresis</td>
<td>a00123803b</td>
<td>Platelets prepared by apheresis and suspended in plasma-free medium.</td>
</tr>
<tr>
<td>Buffy Coat</td>
<td>a0163003b</td>
<td>Buffy coat separated from whole blood.</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>a0164103b</td>
<td>Granulocytes collected by apheresis.</td>
</tr>
<tr>
<td>Fresh Frozen Plasma</td>
<td>a0182003b</td>
<td>Plasma separated from whole blood and frozen within 8 hours of blood collection.</td>
</tr>
<tr>
<td>Fresh Frozen Plasma Paediatric</td>
<td>a0182013b</td>
<td>As above but divided into several smaller volumes before freezing.</td>
</tr>
<tr>
<td>Fresh Frozen Plasma Apheresis</td>
<td>a0182103b</td>
<td>Plasma collected by apheresis and frozen within 8 hours of collection.</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>a0101003b</td>
<td>The cold insoluble portion of plasma processed from frozen plasma previously frozen within 8 hours of blood collection.</td>
</tr>
<tr>
<td>Fresh Frozen Plasma Cryoprecipitate Depleted</td>
<td>a0184003b</td>
<td>Residual plasma refrozen after the removal of cryoprecipitate.</td>
</tr>
<tr>
<td>Plasma Autologous</td>
<td>a0185073b</td>
<td>Plasma separated from whole blood for autologous use only.</td>
</tr>
</tbody>
</table>

*Barcodes - the reader should note that there may be state to state variations.*
## Blood and blood products – for laboratory use

<table>
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<tr>
<th>Proper Name</th>
<th>Barcode*</th>
<th>Definition Of Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotted Whole Blood</td>
<td>a0001003b</td>
<td>Whole blood without anticoagulant.</td>
</tr>
<tr>
<td>Serum</td>
<td>a0000003b</td>
<td>Serum obtained from clotted whole blood.</td>
</tr>
<tr>
<td>Red Blood Cells NOT for Transfusion</td>
<td>a0040993b</td>
<td>Red blood cells not suitable for transfusion due to medical restriction.</td>
</tr>
</tbody>
</table>

*Barcodes - the reader should note that there may be state to state variations.*
Plasma for further manufacture at a fractionation centre

<table>
<thead>
<tr>
<th>Proper Name</th>
<th>Barcode</th>
<th>Definition of product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh Frozen Plasma for AHF</td>
<td>a0198003b</td>
<td>Plasma prepared by centrifugation of whole blood, frozen within 24 hours of collection and suitable for manufacture of coagulation factors, SPPS, NSA and immunoglobulins.</td>
</tr>
<tr>
<td>Fresh Frozen Plasma for AHF</td>
<td>a0198103b</td>
<td>As above but collected by apheresis.</td>
</tr>
<tr>
<td>Apheresis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovered Plasma</td>
<td>a0195003b</td>
<td>Plasma separated from whole blood up to 5 days after the expiration time of the whole blood and suitable for the manufacture of SPPS, NSA and immunoglobulins.</td>
</tr>
<tr>
<td>Recovered Plasma Apheresis</td>
<td>a0195103b</td>
<td>As above but collected by apheresis.</td>
</tr>
</tbody>
</table>

*Barcodes - the reader should note that there may be state to state variations.*
## Plasma for manufacture to specific immunoglobulins

<table>
<thead>
<tr>
<th>Proper Name</th>
<th>Barcode*</th>
<th>Definition of product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered Plasma CMV</td>
<td>a0195913b</td>
<td>Plasma containing high titre antibody to cytomegalovirus.</td>
</tr>
<tr>
<td>Recovered Plasma Hepatitis B</td>
<td>a0195923b</td>
<td>Plasma containing high titre antibody to Hepatitis B</td>
</tr>
<tr>
<td>Recovered Plasma Rh (D)</td>
<td>a0195933b</td>
<td>Plasma containing antibody to Rh (D).</td>
</tr>
<tr>
<td>Recovered Plasma Tetanus</td>
<td>a0195943b</td>
<td>Plasma containing high titre antibody to tetanus.</td>
</tr>
<tr>
<td>Recovered Plasma Zoster</td>
<td>a0195953b</td>
<td>Plasma containing antibody to Herpes Zoster.</td>
</tr>
<tr>
<td>Fresh Frozen Plasma for AHF</td>
<td>a0198943b</td>
<td>Fresh Frozen Plasma for AHF containing high titre antibody to tetanus.</td>
</tr>
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</table>

*Barcodes - the reader should note that there may be state to state variations.*
Annex 7

**Standards Required**

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<th>Parameter</th>
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<td>HBsAg</td>
<td>Weak positive control</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>National working standard</td>
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<tr>
<td>anti-HIV</td>
<td>National working standard</td>
</tr>
<tr>
<td>anti-HCV</td>
<td>National working standard</td>
</tr>
<tr>
<td>anti-Syphils</td>
<td>National working standard</td>
</tr>
<tr>
<td>anti-CMV</td>
<td>National working standard</td>
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