

DISTRIBUTION AND SUPPLY OF PLASMA DERIVED FRACTIONATED BLOOD PRODUCTS AND RECOMBINANT PRODUCTS IN NEW ZEALAND

REASON FOR CHANGE: DCR23840 section 5.6 add definition of 'authorised locations' and clarify that stock-holding sites are referred to as Medical Facilities; add reference to eTraceline; other minor changes made throughout.

1. INTRODUCTION

NZBS is responsible for the supply of plasma derived fractionated blood products and equivalent recombinant products throughout New Zealand. CSL Behring is contracted by NZBS to manufacture plasma derived fractionated blood products from volunteer plasma donated in New Zealand and plasma sourced from overseas. NZBS is the agent for CSL products manufactured from New Zealand plasma and acts as the Distributor of the products. This brings a number of responsibilities but NZBS has no formal involvement in the application for registration of new and changed medicines. This role is undertaken solely by CSL.

A small number of plasma derived fractionated and recombinant blood products manufactured overseas are sourced from other New Zealand Distributors.

NZBS fulfils several functions for fractionated blood products and recombinant products:

- **Agent** for CSL products
- **Distributor** for CSL products
- **Wholesaler** for all products
- **Supplier** for all products
- **Dispenser** for some products

It is essential that there are effective systems for these activities to ensure that all statutory compliance requirements are fulfilled. NZBS has been issued with a Wholesaler's Licence by the Ministry of Health to undertake these functions; the licence is renewed on an annual basis subject to their requirements being met.

2. SCOPE

This policy outlines the key responsibilities involved in the distribution, wholesaling and supply of plasma derived fractionated blood products and equivalent recombinant products. In addition, this policy defines the systems for introduction of new or changed medicines into New Zealand.

Systems for the dispensing of blood products are covered separately, refer to 111P001 NZBS Dispensing Policy.

3. DEFINITIONS

Manufacturer	The organisation that manufactures the medicine/product.
Distributor	The organisation that imports the medicine into New Zealand. This involves responsibility for onward distribution to the wholesaler, or, as the wholesaler, to the supplier or retailer.
Wholesaler	The organisation that takes responsibility for 'the effective, safe and efficient handling, storage and distribution of medicines whilst they are moving between their site of manufacture and the retail outlet or end-user'. This is a part of the overall supply chain.

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Supplier	The organisation that takes responsibility for issuing of medicines to registered health professionals for administration to patients under their care. This function is normally undertaken by the Blood Bank within the hospital.
Dispenser	The individual that supplies medicines directly to a patient for self-administration. Medicines are dispensed following receipt of a prescription from a registered health professional (Medical Practitioner or Midwife).
Medicine	A product registered for use in New Zealand. Fractionated blood products are all Prescription Only Medicines.
Sponsor	The organisation that submits requests to Medsafe to register both New and Changed medicines. Where more than one organisation takes responsibility for these activities they become Co-sponsors.
New Medicine	A new registered Medicine in New Zealand.
Changed Medicine	A medicine that is already registered for use but whose manufacturing processes are altered. Changed Medicines can only be distributed following approval from Medsafe.
CSL Product	In this context refers only to product manufactured by CSL Behring on behalf of NZBS from NZBS sourced plasma or in the specific example of Rh(D) immunoglobulin from plasma sourced overseas.
Wholesaler's Licence	Issued by the Ministry of Health to importers, wholesale distributors, manufacturers and packers who have wholesaling functions in their businesses, and who satisfy the Code of GMP section 4.
Adverse Event	Any untoward occurrence associated with the collecting, testing, processing, storage and distribution of blood and blood components that might lead to an adverse reaction in blood recipients or blood donors.
Adverse Reaction	A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.
Serious Adverse Reaction	An adverse reaction which results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or in a congenital anomaly/birth defect.
Unexpected Adverse reaction	An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.
Authorised location	These are known as Facilities in eTraceline, and include both facilities where products are supplied directly from a Blood Bank to a patient, and external stock facilities that are geographically or logistically separate from a Blood Centre or Blood Bank.

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4. POLICY

Plasma derived fractionated blood products and equivalent recombinant products are manufactured in a highly regulated environment. Products are frequently upgraded with the incorporation of new safety or purification steps.

The introduction of new or changed products and subsequent distribution within New Zealand involves the following:

4.1 Submission to Medsafe of the Request to Register a New or Changed Medicine

This is the responsibility of the sponsor, normally the manufacturer. Where the medicine is manufactured outside of Australasia the distributor, or agent, may take on this role. NZBS is not formally involved in this step.

4.2 Registration of New or Changed Medicine

This is the responsibility of the Regulator (Medsafe). Following publication of the registration in the New Zealand Gazette the new or changed medicine can be distributed. NZBS is not formally involved in this process.

CSL Behring provides a quarterly status report to NZBS of all new registrations and changed medicines applications that are submitted to Medsafe for regulatory approval. This report outlines the regulatory status of the medicines, the clinical implications of the submissions and the anticipated effective date of change. Prior to delivery, CSL Behring also provides NZBS with a letter outlining any changes that have clinical implications, copies of changed cartons, labelling, product information leaflets and datasheets.

4.3 Distribution of New or Changed Medicine

NZBS maintains a list of plasma derived fractionated and recombinant products that are approved for distribution. This list also contains recombinant products that are approved for distribution (111D132 List of Fractionated Products and Recombinant Products Approved for Distribution). A product cannot be added to this list or ordered from the manufacturer unless approval has been given by the Chief Medical Officer.

Before NZBS accepts responsibility for the distribution of new or changed medicines an assessment is made of the nature of the new or changed medicine and whether there are any clinical implications for the end-user. If the changes have clinical implications, a communication plan is developed that identifies the required level of notification to those NZBS stakeholders who are affected by the changes. The level of notification is dependent on the nature of the changes to the medicine. Notification includes some or all of the following:

- Potential recipients of a new product are provided with information that outlines the appropriate use, risks and unwanted effects of transfusion. This will usually be in the format of a printed leaflet. In the example of changes to an existing product, changes to an existing leaflet are sometimes required.
- DHB Clinicians and NZBS Clinical Team are provided with notification of the availability of the new or changed product, the indications for use, dose and administration, risks and adverse reactions.

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- NZBS and DHB Blood Banks and NZBS Logistics Departments are provided with information that explains the mechanism for introduction of the new or changed medicine, the documentation that has been changed and an outline of the notification process.
- Changes to approved fractionated blood products are published on the NZBS website.

A decision is made whether the product is interchangeable with any other product and defines the substitution rules and requirements for Informed Consent (See 111P001 NZBS Dispensing Policy).

4.4 Distribution of Non-Registered Medicines

NZBS normally only distributes products that are registered by Medsafe. When such products are not available, consistent with its statutory responsibilities outlined in the New Zealand Public Health and Disability Act 2001 and associated Gazette notices, NZBS arranges supply of non-registered products. Introduction of such products is managed utilising the principles for new medicines outlined in 5.3 above.

NZBS maintains systems for procurement of fractionated products for designated patients following requests from registered medicine practitioners. Products in these categories are distributed in accordance with section 29 of the Medicines Act 1981. Section 29 allows the supply *'by any person to any medical practitioner, on the medical practitioner's request, of any medicine required by that medical practitioner for the treatment of a particular patient currently under that medical practitioner's care.'* A summary of section 29 medicines issued through eTraceline, including fractionated and recombinant blood products, is reported to Medsafe.

4.5 Wholesaling of Fractionated Blood Products

NZBS only wholesales products that are included in 111D132 List of Fractionated Products Approved for Distribution. Systems are maintained to ensure compliance with the New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods Part 4: Wholesaling of Medicines and Medical Devices.

- A dossier of information is maintained for each product
- A Specification checklist (SCL) is developed and maintained to assist the management of inwards goods and product release. This includes review of transportation temperatures to ensure that requirements are met.
- If the product deviates from the specifications, is damaged or defective or in any other way does not meet quality standards, the adverse event is documented as an incident in Q-Pulse, the manufacturer is notified and the reason for the untoward event is investigated. The product cannot be released until the issue is resolved. If supply of the product is delayed by this process, the Chief Medical Officer is notified immediately.

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4.6 Supply of Products to Authorised Facilities and Health Professionals

NZBS supplies fractionated blood products and recombinant products only to authorised facilities and professionals such as DHBs, private hospitals and independent registered healthcare practitioners. Transfusion Medicine Specialists authorise requests for the supply of products only to facilities and individuals who are legally entitled to possess medicines. The authorisation process also includes checks that adequate product transportation, storage and audit trail systems are in place. Authorised stock-holding sites are defined as Medical Facilities in eProgesa / eTraceline. Refer to 111P086 Distribution and Supply of Plasma Derived Fractionated Blood Products and Recombinant Products in NZ for full details on the requirements.

4.7 Supply and Dispensing of New and Changed Products

Systems are maintained at Blood Centre and Blood Bank level to manage the supply of fractionated products within the hospital setting and also to support the dispensing of products to community based patients.

4.8 Adverse Reaction Reporting

All reports of adverse reactions to plasma derived fractionated blood products are managed through the NZBS adverse reaction investigation and reporting process. (111M003 Managing Notifications of Adverse Reactions to Fractionated Blood Products). These reactions are reported to the manufacturers of the products at the same time that they are notified to NZBS.

Manufacturers are notified using NZBS form 111F003 Fractionated Blood Product - Adverse Event Notification, ensuring patient identifiers such as name/address are redacted. On receipt of notification of an adverse reaction manufacturers are to provide an acknowledgement to NZBS and may request further information if required.

CSL Behring– fax a copy of 111F003 to CSL Behring as per 111M003. CSL Behring provides NZBS with a quarterly report of all New Zealand notifications of adverse reactions and this is cross referenced against reports that have been made directly to NZBS.

Baxalta – notify the pharmacovigilance department by emailing 111F003 to APAC.PV.Hub@baxalta.com.

Grifols – notify by emailing 111F003 to Australia_medinfo@grifols.com.

All reports of adverse reactions are regularly reviewed and reported to the Clinical Advisory Group on a regular basis. An annual summary of all adverse reactions is prepared for inclusion in the NZBS Haemovigilance Programme Report.

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4.9 Adverse Event Reporting

All adverse events that occur during the collection, testing, processing, storage and distribution of the plasma derived fractionated blood product are recorded in Q-Pulse, notified to the manufacturer and, investigated. Individual donation withdrawal arising out of the provision of post donation information also falls into this category.

All complaints made by external customers or end-users about an adverse event to a plasma derived fractionated blood product are recorded in accordance with NZBS's Managing Notifications of Adverse Reactions to Fractionated Blood Products as per 111M003, notified to the manufacturer using either the NZBS form 111F003 or their customised forms, investigated and resolved. Product that is returned to NZBS (for CSL Behring products refer to 111D135 CSL Product Complaint Process Flowchart) must be held in quarantine until it has been established whether the manufacturer has requested the return of the product. CSL Behring will provide a customs clearance letter to accompany returned product. If appropriate, action is taken to correct the cause of the complaint or recall defective product so as to minimise the possibility of recurrence of the complaint. An NZBS response letter is sent to the complainant outlining the cause and resolution of the complaint.

CSL Behring Customer Services provides a response letter to the complainant and also provides a quarterly and annual report of customer complaints to NZBS and this is used for cross referencing reports that have been made directly to NZBS.

Adverse Event reporting processes to manufacturers other than CSL Behring have yet to be formally established.

4.10 Plasma Master File

CSL Behring holds a Plasma Master File (PMF) for New Zealand that contains information on plasma from collection to production of the plasma pool that is relevant to the manufacture of the fractionated products. NZBS is required to notify CSL Behring on an annual basis about changes that have been made to the collection or manufacturing process of the source plasma. The PMF information is updated to meet the requirements of the EMEA/CPMP/BWP/3794/03 – Guideline on the Scientific Requirements of a Plasma Master File (PMF) and submitted to TGA for approval on an annual basis.

4.11 Review Process

NZBS reviews systems used for the distribution and supply of fractionated blood products in New Zealand on a regular basis.

5. REFERENCES

- The Medicines Act 1981
- The Medicines Regulations 1984
- The Medicines Amendment Regulations 2011
- The NZ Code of Health and Disability Services Consumers' Rights
- The NZ Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods Part 4: Wholesaling of Medicines and Medical Devices
- EMEA/CPMP/BWP/3794/03 26/02/2004 – Guideline on the Scientific Requirements of a Plasma Master File (PMF)