

# Chapter 8

## Regulation of plasma products

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The global plasma products industry is one of the most heavily regulated sectors within pharmaceutical manufacture. The World Health Organization (WHO) has observed that this is because all medicines regulators have faced ‘serious and complex challenges at a scientific, technological and regulatory level to ensure that these biological products are of good quality, safety and efficacy’.<sup>1</sup>

The manufacturing paradigm for plasma products, like all biological products derived from human or animal tissue, differs significantly from that applicable to synthetically derived medicines. The manufacture of conventional medicines using chemically consistent raw materials and standard manufacturing techniques can produce generic bio-equivalent products. The manufacture of plasma products, in comparison, entails inherent variability in the following areas:

- **Source material:** Each batch of starting plasma may contain thousands of plasma units from donors that have been pooled for processing. Each plasma starting pool will contain a different protein profile, which is manufactured, through intermediate product stages, to produce a suite of final products that must conform with approved specifications unique to each product.
- **Risk factors:** The manufacture of plasma products, like all blood products, carries the risk of transmission of blood-borne pathogens (including bacteria, viruses and prions). This has been a tangible, not theoretical, risk, evident in the past transmission of hepatitis C and the Human Immunodeficiency Virus (HIV) through the blood supply, including through plasma products, prior to the introduction of specific screening tests and other safety measures in the 1980s and 1990s. Although the risk of viral transmission has decreased considerably over the past 20 years, the recognition that Transmissible Spongiform Encephalopathies (TSEs), including variant Creutzfeldt-Jakob disease (vCJD), could be transmitted by transfusion has sharpened the focus on regulatory requirements for addressing emerging pathogens. There is significant focus by manufacturers and regulators on the requisite measures to apply throughout the manufacturing chain so as to provide assurance of the safety and quality of the final products.
- **Manufacturing process:** Although common manufacturing steps are employed by fractionators, there are no standard universal manufacturing procedures for specific final products. Each fractionator adopts unique manufacturing procedures in order to maximise the yield, safety, quality and clinical efficacy of final products. Each manufacturing process requires individual assessment by regulators.
- **Final products:** The diversity of fractionation processes may mean differential clinical efficacy for different brands of the same product. Because different brands of the same product may have slightly different clinical properties and side effects, regulators require each product brand to be trialled in the clinical setting prior to marketing approval.

The issues identified here are fundamental to the safety, quality and efficacy of plasma products. Because of the global consolidation of plasma product manufacturers and an increasingly global market for these goods (see Chapter 3), the regulatory response has also shifted towards international harmonisation of standards. The WHO, while stating that individual countries should develop national regulations for plasma products, asserts that these should be based on current international standards and that national regulators should 'actively participate in initiatives towards international harmonisation of regulation'.<sup>2</sup> Australia has played a key role in this process of regulatory harmonisation.

This chapter provides an overview of the Australian regulatory framework implemented by the Therapeutic Goods Administration (TGA). The key issue of the regulatory oversight of overseas-manufactured plasma products, and whether this oversight should be strengthened if a toll fractionation model were adopted for Australia, is specifically addressed. This chapter also describes the international model for regulation of the safety and quality of plasma products, and looks at why some regulatory approaches are specific to Australia.

### The Australian regulatory framework

The Therapeutic Goods Administration is part of the Australian Government Department of Health and Ageing, with responsibility for administering the *Therapeutic Goods Act 1989* (Cwlth) (hereafter 'the Act'). The TGA's key objectives in the regulation of therapeutic goods in Australia are to ensure that these goods:

- meet appropriate standards of safety, quality and efficacy
- are made available to the community in a timely manner.

The TGA currently regulates over 50 000 therapeutic goods, including prescription and non-prescription medicines, medical devices, blood, and blood and tissue products. The number of goods regulated by the TGA is continually increasing, as new therapies evolve, as new applications for existing therapeutic goods are found, and as international markets continue to expand. Manufacturing techniques are also changing and improving with the advent of new technologies. In 2004–05, the TGA assessed over 11 000 applications for product registration, listing or inclusion on the Australian Register of Therapeutic Goods (ARTG), and for variations to existing registrations or listings, and tested a total of 2861 samples of 1254 products, as part of post-market surveillance.

Plasma for fractionation and plasma products have been regulated by the TGA since its inception in 1991. This includes:

- plasma products derived from plasma collected and fractionated in Australia for use in Australia
- plasma products derived from plasma collected and fractionated overseas for use in Australia
- plasma products derived from overseas-sourced plasma fractionated in Australia for use overseas.

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<sup>2</sup> World Health Organization, *Ensuring the Quality and Safety of Plasma Derived Medicinal Products*, <[http://www.who.int/bloodproducts/publications/en/Infosheet\\_plasma\\_derived.pdf](http://www.who.int/bloodproducts/publications/en/Infosheet_plasma_derived.pdf)>.

## **Review of Australia's Plasma Fractionation Arrangements**

The Australian and New Zealand governments have commenced a consultation process to establish a joint regulatory agency. This would see a new authority that would replace both the TGA and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe). Legislation to establish the Australia New Zealand Therapeutic Products Authority (ANZ/TPA) is expected to be introduced into Parliament in 2007. While no practical changes to the content of current regulations for plasma products are planned as part of the proposed establishment of a trans-Tasman therapeutic products agency, it is likely that under the new authority plasma products would be regulated within a discrete biologicals framework.

Plasma products in Australia are currently regulated as registered medicines. This results in their being subject to an intensive level of pre- and post-market scrutiny. The existing TGA regulatory model for plasma products includes:

- establishing standards and guidelines for the safety and quality of products
- pre-market product assessment before registration of a product on the ARTG and marketing approval in Australia
- licensing of domestic manufacturers, and certification of overseas manufacturers of the plasma products supplied in the Australian market
- controls on advertising and promotion
- post-market surveillance mechanisms, including Good Manufacturing Practice (GMP) audits, monitoring of adverse events, sampling and analysis of products, and recalls of defective products
- administrative and criminal penalties and sanctions for breaches of the Act
- special arrangements for the supply of products not approved for general marketing, including through the Special Access Scheme and for clinical trials.

The key elements of this framework are pre-market product assessment against relevant standards and guidelines for registration on the ARTG; manufacturer licensing (for Australian manufacturers) and certification of overseas manufacturers (either by the TGA or by an accepted overseas regulator); post-market product and manufacturer surveillance; and enforcement of compliance following breaches. Some plasma products, however (like other therapeutic products), can be supplied in Australia as unregistered products, with their supply being considered on a case-by-case basis under the Special Access Scheme.

### **Registration of plasma products**

The Therapeutic Goods Administration undertakes a comprehensive assessment of the safety, quality and efficacy of all domestic and imported plasma products before they can be registered on the Australian Register of Therapeutic Goods and approved for supply in the Australian market.

The TGA has access to independent expert advisory committees. These include the Therapeutic Goods Committee (which provides advice on standards), the Australian Drug Evaluation Committee (ADEC) (which provides advice on product safety,

quality and efficacy) and the Adverse Drug Reactions Advisory Committee (which reviews adverse drug reactions).

The ADEC is composed mainly of practising specialist clinicians drawn from outside the TGA. The ADEC provides the TGA with expert advice on any issues that have arisen during the evaluation process of a product, and recommends to the TGA whether the product should be included in the ARTG.

The broad framework for the registration of all high-risk medicines, which includes plasma products, is outlined in the Australian Regulatory Guidelines for Prescription Medicines (June 2004). These guidelines describe:

- the Australian data requirements for applications for product registration
- the evaluation and decision-making process undertaken by the TGA on each application.

The Australian data requirements for product registration cover:

- **administrative information**, including product labelling and packaging, and evidence of manufacturer licensing or certification against GMP standards
- **product quality data**, including chemical, pharmaceutical and biological studies
- **product safety data**, including preclinical, pharmacological and toxicological studies
- **clinical data**, demonstrating clinical efficacy and capacity to meet therapeutic claims, through clinical studies.

Applications for product registration are submitted to the TGA by an Australian product sponsor. The sponsor is responsible for the accuracy of all data submitted and for complying with all post-approval conditions specified by the TGA. These areas of obligation include responsibility for notifying the TGA of any change in product registration details or manufacturing process that may affect the safety, quality or clinical data previously submitted; and post-market responsibilities in relation to registered products. In essence the Australian sponsor is legally responsible for any unauthorised change in product registration details and for meeting many of the requirements imposed by the Act. A sponsor must be an Australian resident or an Australian incorporated body responsible for the manufacture, import or export of the product, or who has the product manufactured or imported on its behalf.

One critical issue raised with the Review has been the importance of confidence in the TGA in terms of the evaluation of the safety, quality and efficacy of domestic and imported plasma products. All products supplied in Australia, regardless of origin, are assessed against the same standards and guidelines for product registration.

## Review of Australia's Plasma Fractionation Arrangements

The Australian Regulatory Guidelines for Prescription Medicines make it clear that:

- Applications for product registration must comply with statutory standards established by Therapeutic Goods Orders made under the Act and monographs in the British Pharmacopoeia.<sup>3</sup> Australia applies the standards of the European Pharmacopoeia by adoption of the British Pharmacopoeia.<sup>4</sup> The Pharmacopoeia sets minimum mandatory standards for the manufacture and quality of pharmaceuticals for human and veterinary use. Specific monographs for final products include standards for: the definition of active substances; specification of the origin and quality of source materials (this includes standards for blood donor selection and screening; in respect of donors, Australia also has specific requirements in its own Therapeutic Goods Orders<sup>5</sup>); specifications for in-process testing and final product release testing, specific reference tests and assays for the purity and potency of products, and measuring residual impurities and permitted limits of impurities. The Pharmacopoeia includes specific monographs on human plasma for fractionation, and for individual plasma derived products.<sup>6</sup>
- Applications for product registration should comply with the European Union (EU) guidelines adopted in Australia by the TGA.<sup>7</sup> Following consultation with the Australian pharmaceutical industry, the TGA adopts specific guidelines published by the European Medicines Agency (EMA), to ensure that Australia's technical data requirements for product registration are closely aligned with those in the EU. While the EU guidelines are not legally binding, sponsors must provide justification for any data that does not conform with requirements in a guideline.

The key EMA blood and plasma guidelines adopted in Australia are: the Note for Guidance on Plasma-Derived Medicinal Products,<sup>8</sup> the Guideline on Assessing the Risk for Virus Transmission,<sup>9</sup> the Guideline on the Scientific Data Requirements for a Plasma Master File,<sup>10</sup> and the Guideline on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with Regard to vCJD Risk.<sup>11</sup>

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3 Sections 3(1) and 10 of the Therapeutic Goods Act provide that where the Minister has not determined a specific standard to apply to a therapeutic product under a Therapeutic Goods Order, then standards established in relevant monographs of the British Pharmacopoeia will apply. Current standards for plasma products are set by the British Pharmacopoeia 2005, which is harmonised with the European Pharmacopoeia 2005.

4 The TGA is an observer on several expert groups that advise the European Pharmacopoeia Commission on the maintenance and development of the product monographs that make up the European Pharmacopoeia. Since 1997 the TGA has been an observer on a specialist group concerned with plasma and related products.

5 *Therapeutic Goods Order No. 74: Standards for Blood Components*, Therapeutic Goods Administration, Canberra, 2006, <<http://www.tga.gov.au/docs/html/tgo/tgo74.htm>>.

6 For a list of the European Pharmacopoeia monographs for plasma derived products, see Committee for Proprietary Medicinal Products, *Note for Guidance on Plasma-Derived Medicinal Products*, revision 3 [CPMP/BWP/269/95 rev. 3], European Medicines Agency, London, 2001, pp. 19–20 (Annexes I and II), <<http://www.emea.eu.int/pdfs/human/bwp/026995en.pdf>>.

7 See Therapeutic Goods Administration, *European Union Guidelines Adopted in Australia*, Therapeutic Goods Administration, Canberra, 2006, <[http://www.tga.gov.au/docs/html/euguide/euad\\_app.htm](http://www.tga.gov.au/docs/html/euguide/euad_app.htm)>.

8 Committee for Proprietary Medicinal Products, *Note for Guidance on Plasma-Derived Medicinal Products*, revision 3 [CPMP/BWP/269/95 rev. 3], <<http://www.emea.eu.int/pdfs/human/bwp/026995en.pdf>>.

9 Committee for Medicinal Products for Human Use, *Guideline on Assessing the Risk for Virus Transmission* [CPMP/BWP/5180/03], European Medicines Agency, London, 2004, <<http://www.emea.eu.int/pdfs/human/bwp/518003en.pdf>> (also adopted as new Chapter 6 in the Note for Guidance on Plasma-Derived Medicinal Products (see note 6 above)).

10 Committee for Medicinal Products for Human Use, *Guideline on the Scientific Data Requirements for a Plasma Master File (PMF)*, revision 1 [EMA/CPMP/BWP/3794/03R.ev. 1], European Medicines Agency, London, 2006, <<http://www.emea.europa.eu/pdfs/human/bwp/379403en.pdf>>.

11 Committee for Medicinal Products for Human Use, *Guideline on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with Regard to vCJD Risk* [CPMP/BWP/5136/03], European Medicines Agency, London, 2004, <<http://www.emea.eu.int/pdfs/human/bwp/513603en.pdf>>.

## Review of Australia's Plasma Fractionation Arrangements

Adoption of these guidelines has ensured provision to the TGA of extensive data relevant to the safety and quality of plasma products, including:

- quality assurance of the starting plasma – through annual updates of the sponsor's Plasma Master File covering donor selection, screening of donations, audits of collection centres, systems for tracing donors to finished products, storage and transport of donations
- quality assurance of the manufacturing process – through testing and control of intermediate products, specification, quality control and validation of the purification and viral-inactivation and removal processes.

Assessment of product registration data essentially occurs at a fixed point in time. Although the data provided in the application process address the quality assurance and control systems built into the manufacturing process, the post-market surveillance system provides for risk-based review of these systems through the monitoring of adverse events; periodic product safety updates; product testing; annual reviews of plasma master files; and GMP surveillance audits.

One issue for attention relates to the certification of product batch release by an appropriately qualified person. At present, sponsors are not required to certify that each batch of products for supply in Australia meets product registration specifications. This is already a requirement in the EU and the United States.

The TGA has experienced some difficulties in resolving issues related to product quality with representatives of sponsors in Australia when these representatives do not have a technical understanding of the product involved. The TGA will shortly enter into formal consultation with industry on the proposal that all batches of imported medicines should be released for supply only after an appropriately qualified person has certified that the batch meets required specifications for quality and safety. It is agreed that it is important to ensure that an appropriately qualified person is responsible for certification of batch release.

A second issue relates to the TGA's capacity to independently test products. The TGA employs a risk-based program of targeted testing of products in the marketplace to ensure compliance with specifications and registration data. The TGA has occasionally found problems with batches of products that have passed testing by the manufacturers. The Review supports independent testing by the TGA. The extent of this testing would vary depending on the risk posed by the product and TGA experience of the particular manufacturer. In the EU, there is a system of Official Medicines Control Laboratories that test all batches of plasma products prior to release in Europe. The regulatory agencies of North America, which include the Food and Drug Administration (FDA) and Health Canada, test products on a risk management basis that is more targeted. It is anticipated that the presence of a qualified person representing the sponsor will assist the TGA in the establishment of a similar program for plasma derivatives in the Australian market.

### **Licensing and certification of manufacturers**

The regulation of manufacturers in Australia is an essential part of the TGA's regulatory framework. The aim is to ensure that medicines are manufactured in accordance with standards of GMP, in order to 'build in' safety, quality and efficacy.

## Review of Australia's Plasma Fractionation Arrangements

The current Australian Code of Good Manufacturing Practice for Medicinal Products (the Code of GMP) was introduced in August 2002.<sup>12</sup> It is based on the 2002 Guide to Good Manufacturing Practice for Medicinal Products published by the Pharmaceutical Inspection Cooperation Scheme (the PIC Scheme) and is a key element in the movement towards international harmonisation of therapeutic goods regulation. The PIC Scheme Guide provides an international benchmark for certification of medicine manufacturers.

The Australian Code of GMP is extracted from the PIC Scheme Guide and is the mandatory standard for the regulation of medicine manufacturers in Australia. The Code provides a standard framework for assessing compliance with quality management requirements in: the manufacture of medicines; standards for premises and equipment; personnel; documentation; production and quality control; contract manufacture; complaints handling; product recall; and self-inspection.

Australian manufacturers are assessed by the TGA against the Code of GMP before being issued a manufacturing licence. The TGA subsequently undertakes (scheduled) announced and (risk-based) unannounced audits to assess whether a domestic manufacturer remains compliant with the Code. Generally, scheduled audits are conducted every two years. A licence is perpetual, subject to satisfactory audit outcomes, regular re-audits being conducted, and payment of an annual licence charge. Licences can be suspended or revoked if audit outcomes are very unsatisfactory.

Some of the key issues assessed in GMP audits of plasma fractionators are:

- **critical process steps:** control of plasma starting pools, virus inactivation and removal, and aseptic processing
- **prevention of contamination and cross-contamination in manufacture:** handling and segregation of materials, qualification of critical equipment, cleaning and sanitation of facility and equipment
- **process consistency:** process validation and quality control.

Overseas manufacturers of medicines supplied in the Australian market are outside the licensing jurisdiction of the Therapeutic Goods Act. However, under the Act, the TGA must be satisfied that 'if a step in the manufacture of the goods has been carried out outside Australia ... the manufacturing and quality control procedures used in the manufacture of the goods are acceptable'.<sup>13</sup>

Overseas manufacturers are certified by the TGA as part of the pre-market product assessment and post-market approval conditions placed on Australian sponsors in the product registration process. Certification is provided by:

- TGA acceptance of a certificate of GMP compliance issued by an overseas regulator with which Australia has a Mutual Recognition Agreement (MRA) or other accepted agreement; or by
- TGA certification of GMP compliance on the basis of an on-site audit of the overseas manufacturer, when there is no other acceptable information available.

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12 Therapeutic Goods Administration, *Australian Code of Good Manufacturing Practice for Medicinal Products*, Therapeutic Goods Administration, Canberra, 2002, <<http://www.tga.gov.au/docs/pdf/gmpcodau.pdf>>.

13 *Therapeutic Goods Act 1989* (Cwlth), s. 25(1)(g); see also ss. 25(2), 26(1)(g), 26(2).

The TGA accepts certificates of GMP compliance through Mutual Recognition Agreements. MRAs are legal instruments between Australia and one or more countries. Prior to entering an MRA, each signatory is expected to assess the GMP standards and audit procedures adopted in the other countries, in order to establish regulatory equivalence. Other agreements, such as Memoranda of Understanding (MOUs) or 'cooperative agreements', provide for exchange of information between signatories but do not impose an obligation to accept certificates of GMP compliance, generally because GMP regulatory equivalence has not been formally established for signatory countries. The TGA has recently introduced a process of conducting thorough 'desk audits' to assess the GMP reports for non-MRA countries.

Australia is currently signatory to four MRAs for GMP assessments of medicines: (1) the European Union MRA (known as the EC MRA), coupled with the European Free Trade Association MRA (EFTA MRA), and bilateral MRAs with (2) New Zealand, (3) Canada (specifically excludes from its scope medicines derived from human blood or plasma) and (4) Singapore. Since 1993 Australia has had an MOU on GMP for medicines with Japan, and has also had a cooperative information-sharing agreement with the United States, which expired in October 2005. This agreement, on GMP for pharmaceutical products, is currently in the process of being renewed.

The EC MRA was entered with the European Community and covers the 15 countries that were members of the EC when the MRA came into effect.<sup>14</sup> The status of the 10 new members of the EU with regard to the MRA is under review while the TGA is negotiating to establish GMP regulatory equivalence.<sup>15</sup> A key provision of the EC MRA is that, although parties should generally accept the certificates of GMP compliance provided by other member countries, individual members have a limited capacity, in exceptional circumstances, to conduct GMP audits of manufacturers in the other jurisdictions. The TGA has used this provision on one occasion. For this to occur, however, the TGA must notify the European Commission, outlining very strong reasons. In such a case, the Australian product sponsor must agree to pay for the audit.

The relevant European regulators for the overseas fractionators with facilities in Europe at this time are shown in table 8.1.

The EFTA MRA was negotiated on terms almost identical to the EC MRA. It extends the regime of the EC MRA to include Norway, Liechtenstein and Iceland. The Pharmaceutical Inspection Convention (PIC) agreement, which applies to Australia and Switzerland, differs from the EC MRA in that members do not have the right to undertake their own GMP audits in exceptional circumstances. Under Swiss law, Swissmedic (the national regulator) must lead any audit involving another national regulatory authority.

The Pharmaceutical Inspection Cooperation Scheme (the PIC Scheme) was established to promote harmonised GMP standards and guidance documents; to promote consistent training and auditing practices across regulatory authorities; and

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<sup>14</sup> These were: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain, Sweden and the United Kingdom.

<sup>15</sup> Ten new members joined the EU as of 1 May 2004: Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, the Slovak Republic and Slovenia.

**Table 8.1** European medicines regulators

Fractionator	Regulators
Baxter	<ul style="list-style-type: none"> <li>• Austria – Ministry for Health and Women</li> <li>• Belgium – Directoraat Generaal Geneesmiddelen (DGG) / Direction Générale Médicaments (DGM)</li> </ul>
BPL	<ul style="list-style-type: none"> <li>• United Kingdom – Medicines and Healthcare Products Regulatory Agency (MHRA)</li> </ul>
CSL Behring	<ul style="list-style-type: none"> <li>• Germany – Paul-Ehrlich-Institut</li> <li>• Switzerland – Swiss Agency for Therapeutic Products (Swissmedic)</li> </ul>
LFB	<ul style="list-style-type: none"> <li>• France – Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) (French Health Products Safety Agency)</li> </ul>
Octapharma	<ul style="list-style-type: none"> <li>• Austria – Ministry for Health and Women</li> <li>• France – Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) (French Health Products Safety Agency)</li> <li>• Germany – Paul-Ehrlich-Institut</li> <li>• Sweden – Medical Products Agency / National Board of Health and Welfare</li> </ul>
Sanquin	<ul style="list-style-type: none"> <li>• Netherlands – Netherlands Medicines Inspectorate (Ministry)</li> <li>• Belgium – Directoraat Generaal Geneesmiddelen (DGG) / Direction Générale Médicaments (DGM)</li> </ul>

to undertake peer assessment of audit practices.<sup>16</sup> The PIC Scheme is not a GMP regulatory equivalence scheme.

The frequency of GMP audits is comparable for Australian and overseas manufacturers covered by GMP agreements. The TGA has noted that the frequency of scheduled audits in Australia, generally conducted every two years, is consistent with the PIC Scheme standard.

With regard to the conduct of unannounced audits, the Review has considered the implications of current differences between the situation for domestic manufacturers and the situation for overseas manufacturers. Unannounced audits in Australia are one component of GMP regulatory practice. Several factors can trigger an unannounced audit (including tip-offs, issues associated with sample testing, a manufacturer's GMP

<sup>16</sup> For the PIC Scheme, see *Pharmaceutical Inspection Convention/Pharmaceutical Inspection Cooperation Scheme*, <<http://www.picscheme.org>>. The PIC Scheme is a cooperative arrangement between 28 participating countries: Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Malaysia, the Netherlands, Norway, Poland, Portugal, Romania, Singapore, the Slovak Republic, Spain, Sweden, Switzerland and the United Kingdom.

audit track record, and product recalls). Over the last five years, fewer than 5% of GMP audits in Australia were unannounced.

The situation is different for overseas manufacturers. Under the MRAs to which it is a signatory, Australia has very limited capacity to conduct its own GMP audits, but can request that the relevant local regulator undertake an unscheduled audit. Where the TGA is able to conduct overseas audits under the MRAs, in practice all such audits are announced in advance, because product sponsors must agree to pay for the audits.

As of 31 October 2005, legislation has been in place within the EU countries so that unannounced inspections can be undertaken when necessary. In some EU countries (e.g. Portugal and the United Kingdom) some audits are unannounced, but attitudes to such inspections vary widely within the EU. If the TGA were to rely upon the MRAs in their current form, then unannounced audits may well be achievable overseas. The more pertinent issue is whether Australia should clarify with MRA partners its role in these audits, particularly if a toll fractionation model were implemented for Australia, giving rise to a strong national interest in the conduct of GMP audits. This issue is discussed later in the chapter.

The Act provides strong civil and criminal penalties and sanctions for Australian sponsors and manufacturers who fail to comply with product and manufacturing standards.

### Ensuring safety and quality of plasma products

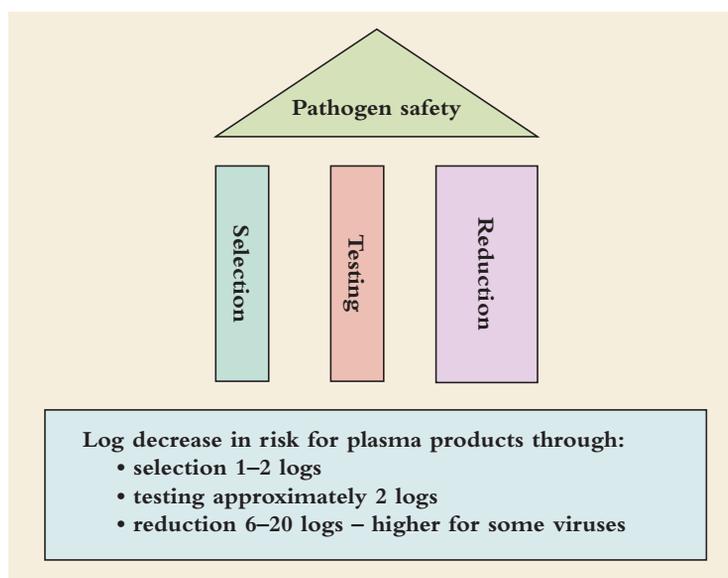
The safety of blood and blood products has been a recurring theme internationally over the last 25 years. The transmission of hepatitis C and HIV through fresh blood products and plasma derived products in the mid 1980s was a major catalyst for the push towards international harmonisation of medicines regulation.

While strong regulatory consistency has been achieved between Australia and the EU, there are still some areas where countries have adopted unique regulatory requirements. This section describes the pathogen 'safety tripod' adopted internationally and some of the measures that are specific to Australia.

Figure 8.1 shows the pathogen safety tripod and the relative contribution of each leg towards the reduction of risk of transmission of blood-borne viruses. The figure sets out reduction factors that are normally expressed on a logarithmic scale. The reason is to imply that, although residual virus infectivity will never be reduced to absolute zero, it may be greatly reduced to a negligible level.<sup>17</sup> While selection of donors and testing of donations each reduce the theoretical risk of transmission approximately 10–100 fold, the third leg of virus inactivation and removal reduces the risk of transmitting a virus approximately another one hundred million fold. This illustrates that the manufacturing process itself plays a central role in ensuring the safety of final products. In combination these three steps significantly reduce the risk of transmission of most current known viruses via plasma products.

<sup>17</sup> See International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Note for Guidance on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*, [CPMP/ICH/295/95], European Medicines Agency, London, 1997, p. 10, <<http://www.emea.europa.eu/pdfs/human/ich/029595en.pdf>>.

**Fig. 8.1** Pathogen safety tripod



Source: Adapted from information in: Thomas R. Kreil, 'Differences between Blood and Plasma: Emerging Pathogens and the Safety of Blood Products – What to Do, or Not, and Why?', *eSource* (June 2006), p. 2, <<http://www.esourcemagazine.org/content/view/39/32/>>.

The more recent challenge to the plasma products sector has been the recognition that Transmissible Spongiform Encephalopathies, including variant Creutzfeldt-Jakob disease, could be transmitted by transfusion. While there is currently no evidence that vCJD or other prion diseases could be transmitted through plasma products, national regulators have uniformly adopted a precautionary approach to reviewing the safety tripod measures.

Prion proteins are normally present in many organs and tissues (including the brain, spinal cord and eyes) of healthy humans and animals. The prion diseases are caused by an abnormal folding and accumulation of prion proteins, which progressively damages the brain. The TSE diseases – fatal degenerative diseases that affect both humans and animals – include Creutzfeldt-Jakob disease (CJD) in humans, bovine spongiform encephalopathy (BSE), or 'mad cow disease', in cattle, and scrapie in sheep. Classical CJD occurs in approximately one person per million of the population per year and it mainly affects older people.

In 1996, variant Creutzfeldt-Jakob disease was first identified in a younger cohort of patients in the United Kingdom, exhibiting a number of distinctive features when compared with classical CJD. Over 150 cases of vCJD have since been identified worldwide, mostly in the United Kingdom but with significant numbers appearing in France. There is strong evidence that vCJD is causally linked to BSE,<sup>18</sup> the likelihood being that infection occurs as a result of eating BSE-contaminated beef

<sup>18</sup> See R. G. Will, M. Zeidler, G. E. Stewart, M. A. Macleod, J. W. Ironside, S. N. Cousens, J. Mackenzie, K. Estibeiro, A. J. E. Green & R. S. G. Knight, 'Diagnosis of New Variant Creutzfeldt-Jakob Disease', *Annals of Neurology*, vol. 47, no. 5 (May 2000), pp. 575–82.

products. Recent reports strongly suggest that the transmission of vCJD has occurred by blood transfusion from apparently healthy donors, prior to their development of vCJD. As of 2006, there have been three overseas reports of possible transmission of vCJD through the use of fresh blood products.<sup>19</sup>

**Donor selection**

Before potential blood or plasma donors can donate they are initially screened. The purpose of this screening is to determine whether a person is in good health, in order to safeguard both his or her health and the health of recipients. Collection centres implement protocols in line with requirements in the European Pharmacopoeia, assessing a donor’s medical history, general health and relevant lifestyle.

The assessment of each donor is carried out by a suitably qualified person working under the supervision of a physician. The assessment involves an interview, a questionnaire and further direct questions if necessary. The screening process also involves the provision of educational materials to all donors. This material explains the donation process, the transmission of blood-borne infections, and the donor’s responsibility in the prevention of such transmission.

The potential transmission of TSEs through the blood supply has led to many countries introducing donor deferral measures as part of the donor selection process,

**Table 8.2** Period of UK residency requiring donor deferral, by country

	UK residency: cumulative period during 1980–96
Austria	6 months
Canada	6 months
Czech Republic	6 months
Finland	6 months
France	6 months
Germany	6 months
Greece	6 months
Ireland	5 years
Italy	6 months
New Zealand	6 months
Spain	12 months
Switzerland	6 months
United States	3 months

<sup>19</sup> See C. A. Llewelyn, P. E. Hewitt, R. S. G. Knight, K. Amar, S. N. Cousins, J. Mackenzie & R. G. Will, ‘Possible Transmission of Variant Creutzfeldt-Jakob Disease by Blood Transfusion’, *Lancet*, vol. 363, no. 9407 (7 February 2004), pp. 417–21; A. H. Peden, M. W. Head, D. L. Ritchie, J. E. Bell & J. W. Ironside, ‘Preclinical vCJD after Blood Transfusion in a PRNP Codon 129 Heterozygous Patient’, *Lancet*, vol. 364, no. 9433 (7 August 2004), pp. 527–9; and ‘New Case of Transfusion-Associated vCJD in the United Kingdom’, *Eurosurveillance*, vol. 11, no. 2 (2006), <<http://www.eurosurveillance.org/ew/2006/060209.asp#references>>.

## Review of Australia's Plasma Fractionation Arrangements

in particular with regard to the donation of blood and plasma that could be affected by a donor's having lived in the United Kingdom for an extended period.<sup>20</sup> In Australia, persons who have spent six months or more in the United Kingdom between 1980 and 1996 are not permitted to donate blood. Table 8.2 sets out the practice in other countries in regard to deferring donors who lived in the United Kingdom during the period considered to represent the greatest risk.

### Testing

Following collection, all donations are tested for relevant infectious disease markers. In-vitro diagnostic (IVD) tests are regulated in Australia, the EU and North America. The tests must meet sensitivity and specificity requirements prior to obtaining regulatory approval. In Australia, IVD test performance is monitored through laboratories' participation in external quality assurance schemes.

Current tests used for infectious disease screening of blood and plasma donations are based on the detection of a relevant antigen and/or antibody, and gene sequences. As required by the British Pharmacopoeia, plasma donations are tested for infectious disease markers at two stages: the individual donation and the first manufacturing plasma pool. Each donation is tested for antibodies against human immunodeficiency viruses 1 and 2 (HIV-1 and HIV-2), for hepatitis B surface antigen (HBsAg) and for antibodies against hepatitis C (HCV). The first manufacturing plasma pool is tested for HIV antibodies and HBsAg, and is also tested for HCV, using nucleic acid amplification technology. In addition to the requirements of the British Pharmacopoeia, the Therapeutic Goods Administration requires that donations are tested for HIV-1 and HCV using nucleic acid amplification technology. If a repeat positive result is found for any of these tests, the donation or pool must not be used.

### Pathogen inactivation and removal

Inactivation and removal of infectious agents is the third and final stage of the pathogen safety tripod. Inactivation and removal processes target viral and prion-based agents.

The EMEA Note for Guidance on Plasma-Derived Medicinal Products states that the fractionation and purification process adopted by manufacturers of plasma products can contribute to the removal of viruses, quite separately from dedicated viral-inactivation and removal steps. This capability is quite specific to the type of manufacturing process employed. The two principal fractionation techniques are:

- **Cold-ethanol fractionation** (often referred to as Cohn fractionation). This involves the addition of varying concentrations of ethanol to cooled plasma; this process, together with variations in salt and pH, precipitates protein fractions. The fractions are further purified into individual plasma products. Cold-ethanol

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<sup>20</sup> In addition to restrictions on former UK residents, in August 2006 the US Food and Drug Administration (FDA) adopted a draft guidance policy in which a donor deferral recommendation is made to collection establishments in respect of individuals who have received a transfusion of blood or blood components in France since 1980 (Center for Biologics Evaluation and Research, *Guidance for Industry: Amendment (Donor Deferral for Transfusion in France since 1980) to 'Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products' - Draft Guidance*, US Food and Drug Administration, Rockville, MD, 2006, <<http://www.fda.gov/cber/gilns/cjdfrance.htm>>). In Canada, potential donors who have spent a cumulative total of six months or more in France between 1980 and 1996 are deferred from donating blood or plasma (see Health Canada, *Health Canada Issues Precautionary Directive for Deferral of Blood and Plasma Donors Who Have Spent Extended Periods of Time in France*, media release, 31 August 2000, Health Canada, Ottawa, <[http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2000/2000\\_85\\_e.html](http://www.hc-sc.gc.ca/ahc-asc/media/nr-cp/2000/2000_85_e.html)>).

fractionation has been employed since the beginning of the plasma products industry in the 1940s and continues to be the predominant methodology used by fractionators around the world. Several variants of cold-ethanol fractionation are employed by manufacturers, chiefly the Cohn-Oncley process in the United States and the Kistler-Nitschmann process in Europe. Cold-ethanol fractionation is well established, and products manufactured using this method have a long history of safety and efficacy.

- **Chromatography** is a process by which the components of a mixture – in this case, plasma – are separated according to size, charge, or other chemical properties, via interaction with a solid medium such as a gel. The chemical properties of the gel provide the basis for the separation. Chromatographic techniques are increasingly being used in plasma fractionation, because higher yields and greater purity can be achieved, less damage is caused to the plasma proteins, and potentially a larger range of proteins can be extracted from the starting plasma. Many products manufactured by CSL Bioplasma at its Broadmeadows plant are purified predominantly by chromatographic techniques. Other manufacturers of plasma derivatives do not have the same reliance on chromatography as CSL Bioplasma. In general, other fractionators have introduced one or more chromatography stages at the end of cold-ethanol manufacturing processes following viral-inactivation procedures.

The European Medicines Agency (EMA) recommends use of two distinct inactivation/removal steps, which are designed to complement each other in their mode of action. At least one of these steps should be effective against non-enveloped viruses. The EMA recognises that ‘designing steps which will complement each other and also be effective against a wide range of viruses including enveloped and non-enveloped viruses of diverse physico-chemical characteristics, is not a straightforward task’.<sup>21</sup>

The TGA requires a minimum of two effective viral-inactivation steps in the manufacturing process. These dual inactivation steps must target both:

- enveloped viruses (such as hepatitis B and C, HIV-1 and HIV-2, and West Nile Virus) and
- non-enveloped viruses (such as hepatitis A and parvovirus B19).

The viral-inactivation procedures used by plasma fractionators vary between products but may include solvent detergent, dry heat, pasteurisation, viral filtration and low pH incubation. Table 8.3 provides an overview of the various viral-inactivation and elimination methods.

Enveloped viruses are generally easier to inactivate than non-enveloped viruses, because enveloped viruses can be inactivated through solvent detergent processes and a number of heat treatment processes.

It is arguable that the most effective of the viral-elimination processes for non-enveloped viruses is nanofiltration. Nanofiltration is a filtration process that can remove small particles such as a virus. However, nanofiltration is not appropriate for all plasma products. For example, nanofiltration for the removal of non-enveloped

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21 Committee for Proprietary Medicinal Products, *Note for Guidance on Plasma-Derived Medicinal Products*, revision 3 [CPMP/BWP/269/95 rev. 3], p. 15, <<http://www.emea.eu.int/pdfs/human/bwp/026995en.pdf>>.

**Table 8.3** Viral-inactivation and elimination methods

Treatment	Advantages	Points to consider
Solvent detergent	<ul style="list-style-type: none"> <li>Extremely efficient against enveloped viruses</li> <li>Relatively simple equipment</li> <li>Non-denaturing effect on proteins</li> <li>High recovery of protein functional activity</li> </ul>	<ul style="list-style-type: none"> <li>Requires a subsequent manufacturing step to eliminate the solvent detergent agents</li> <li>Not effective against non-lipid-enveloped viruses (e.g. parvovirus or hepatitis A virus)</li> </ul>
Pasteurisation	<ul style="list-style-type: none"> <li>Potential to inactivate enveloped and non-lipid-enveloped viruses, including hepatitis A virus</li> <li>Relatively simple equipment</li> </ul>	<ul style="list-style-type: none"> <li>Protein stabilisers may protect viruses</li> <li>Does not inactivate parvovirus</li> <li>Low recovery of fragile coagulation factors</li> <li>Potential generation of neoantigens</li> </ul>
Vapour-heat	<ul style="list-style-type: none"> <li>May inactivate enveloped and non-lipid-enveloped viruses, including hepatitis A virus</li> </ul>	<ul style="list-style-type: none"> <li>Possible risk of transmission of hepatitis C virus and hepatitis G virus</li> <li>Does not inactivate parvovirus</li> </ul>
Terminal dry-heat	<ul style="list-style-type: none"> <li>May inactivate enveloped and non-lipid-enveloped viruses, including hepatitis A virus</li> <li>Treatment applied on the final container</li> </ul>	<ul style="list-style-type: none"> <li>Does not inactivate parvovirus</li> <li>10–20% loss of coagulation factor activity</li> <li>Requires strict control of residual moisture content</li> </ul>
Acid pH	<ul style="list-style-type: none"> <li>Effective against enveloped viruses</li> <li>Relatively simple equipment</li> </ul>	<ul style="list-style-type: none"> <li>Restricted to IgG</li> <li>Limited efficacy against non-lipid-enveloped viruses</li> </ul>
Nanofiltration on 15 nm membranes	<ul style="list-style-type: none"> <li>Elimination of viruses based on size-exclusion effect</li> <li>Eliminates all major viruses, including hepatitis A virus and parvovirus</li> <li>May possibly eliminate prions</li> <li>Filter's integrity and removal capacity is validated after use</li> <li>High recovery of protein activity</li> <li>Non-denaturing for proteins</li> <li>Risks of downstream contamination are limited when filtration is performed prior to aseptic filling</li> <li>Filters are commercially available; no royalties</li> </ul>	<ul style="list-style-type: none"> <li>Non-applicable to high molecular weight protein concentrate (without significant protein loss)</li> </ul>
Nanofiltration on 35 nm membranes	<ul style="list-style-type: none"> <li>Similar to 15 nm membranes</li> <li>Applicable to some Factor VIII and von Willebrand factor concentrates</li> </ul>	<ul style="list-style-type: none"> <li>Elimination of small viruses not total</li> </ul>

Source: Derived from information in: A. Farrugia, *Guide for the Assessment of Clotting Factor Concentrates for the Treatment of Hemophilia*, World Federation of Hemophilia, Montreal, 2003, p. 8, also available online at <[http://www.wfh.org/2/docs/Publications/Safety\\_and\\_Supply/GuideClottingFactor\\_Eng.pdf](http://www.wfh.org/2/docs/Publications/Safety_and_Supply/GuideClottingFactor_Eng.pdf)>.<sup>22</sup>

<sup>22</sup> Farrugia table adapted from: F. Ala, T. Burnouf & M. M. El-Nageh, *Plasma Fractionation Programmes for Developing Countries: Technical Aspects and Infrastructural Requirements*, WHO Regional Publications, Eastern Mediterranean Series, no. 22, World Health Organization, Alexandria, 1999; and T. Burnouf & M. Radosevich, 'Reducing the Risk of Infection from Plasma Products: Specific Preventative Strategies', *Blood Reviews*, vol. 14, no. 2 (June 2000), pp. 94–110.

viruses cannot be used in the case of Factor VIII plasma products, because Factor VIII is such a large protein that it may also be removed by the nanofiltration process.

In the cleaning undertaken between batches of plasma, harsh chemical and physical treatments are used to eliminate prions from the equipment used in fractionation. These treatments cannot be used on the gels employed in chromatographic fractionation. This is because the gels are made up of polymerised sugars, and similar substances, that cannot withstand these processes. Other processes are used to clean gels; these treatments are effective for the inactivation of viruses but less effective for the inactivation of prions.

The TGA introduced segregation of Australian plasma as a regulatory requirement because of the risk of prion contamination from multiple plasma sources. Given that CSL Bioplasma fractionates plasma from a number of countries, including countries with a BSE status inferior to that of Australia, the TGA considered that the application of segregation as a precautionary measure based on scientific uncertainty around prion infectivity was justified. Due to the particular manufacturing procedures used predominantly by CSL Bioplasma at its Broadmeadows plant (i.e. chromatography and not cold-ethanol fractionation), segregation in this instance has meant using separate chromatography columns for fractionating Australian plasma. This use of separate equipment provides an effective barrier between plasma starting pools from different sources, to negate the potential risk of prions being transferred from one pool to another during processing. The segregation measures adopted at different fractionation plants (all of which typically fractionate plasma from multiple countries) are not necessarily identical, and measures to minimise risk are determined with reference to the production technology in use at a particular facility.

It is generally thought that the risk of transmission of vCJD by plasma products is low because the manufacturing processes (particularly those involving cold-ethanol fractionation) remove prions to a significant extent from the fractions that are separated to obtain therapeutic products.<sup>23</sup> However, there is a level of uncertainty, because science has yet to develop a testing procedure that is sensitive enough to detect prions in donor blood and therefore able to accurately test the effectiveness of prion inactivation. In addition, although none of the patients exposed to plasma products sourced from potentially contaminated plasma have developed prion disease, the incubation periods are such that low-titre inocula, as would occur with plasma products, may have transmitted as yet undetected disease. It is partly because of these uncertainties that current regulatory practice around the world is to recall any plasma product made from a plasma pool containing a donation from a person who subsequently develops vCJD, regardless of the theoretical extent to which the production process may have rendered the final product non-infectious. It should be acknowledged that under these circumstances most of the product would have been used by the time the donor became ill.

The TGA uses international best-practice guidelines, and the advice of the Australian National Health and Medical Research Council (NHMRC) Transmissible

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<sup>23</sup> For a comparison of fractionation techniques in this respect, see P. R. Foster, A. G. Welch, C. McLean, B. D. Griffin, J. C. Hardy, A. Bartley, S. MacDonald & A. C. Bailey, 'Studies on the Removal of Abnormal Prion Protein by Processes Used in the Manufacture of Human Plasma Products', *Vox Sanguinis*, vol. 78, no. 2 (March 2000), pp. 86–95.

## Review of Australia's Plasma Fractionation Arrangements

Spongiform Encephalopathies Advisory Committee (TSEAC),<sup>24</sup> in minimising any risk of prion transmission through plasma products. Each plasma product on the Australian market is assessed for this risk regardless of its origin. As mentioned in Chapter 6, the TGA recently introduced a policy that has created a restricted donor pool for the production of the plasma derived Factor VIII product Biostate. Biostate is principally used to treat people with haemophilia A who have developed inhibitors to recombinant clotting factors, and people with von Willebrand's disease. There have been no reported cases of vCJD in recipients of plasma products. The consensus of expert opinion, however, is that people with haemophilia and von Willebrand's disease who require treatment with plasma products are under a higher theoretical risk than recipients of other products because of their lifelong reliance on these products to maintain their health.

TSEAC's risk assessment found that although the theoretical risks of vCJD transmission were very small and that Biostate has an excellent safety record with no cases of transmission of pathogens, further precautions should be taken to reduce that already small risk. While many Factor VIII purification methods clear prions to a large extent,<sup>25</sup> the manufacturing process used by CSL to manufacture Biostate was judged by TSEAC to result in a small residual risk.<sup>26</sup> TSEAC's requirements for prion clearance guide the TGA in its approval of plasma products, whereby an overseas product<sup>27</sup> has been approved which has a prion clearance reflective of TSEAC's advice.<sup>28</sup>

Following the increased access to government-funded recombinant Factor VIII and the consequent reduction in demand for Biostate, it was possible to introduce a new precautionary measure to further reduce the theoretical risk. A plasma collection policy was introduced in June 2005 and came into full effect after 1 April 2006 to ensure that plasma used in the production of Biostate was sourced from donors who had not lived or travelled outside Australia and New Zealand since 1980.<sup>29</sup> Such donors have an extremely low risk of being exposed to vCJD because there have been no confirmed cases of BSE or vCJD in either country. Through this measure an additional level of protection against the theoretical risk of prion transmission is available to protect people who receive Biostate.

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24 As opposed to the FDA's TSEAC, which is charged with providing similar advice to the FDA; see <<http://www.fda.gov/cber/advisory/tse/tsechart.htm>>.

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25 T. Kriel, 'Industry TSE Clearance Studies for Plasma-Derived Factor VIII', presentation, September 2006, <[http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4240S1\\_7\\_files/frame.htm](http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4240S1_7_files/frame.htm)>

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26 S. Caris, 'New Donor Requirements for Plasma Derived Factor VIII in Australia', *National Haemophilia*, no. 153, March 2006, p. 6, <<http://www.haemophilia.org.au/sitebuilder/knowledge/files/254/nhno153march2006pg1-10.pdf>>.

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27 Australian Register of Therapeutic Goods entry for Octanate, <<http://www.tgasime.health.gov.au/SIME/ARTG/ARTGPublicWeb.nsf/MEDpublic?SearchView&Query=octanate&start=1&searchOrder=4&searchMax=1000&searchWV=0&searchFuzzy=0>>.

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28 A. Neisser-Svae, et al., 'Prion Protein Removal during Manufacturing of High-Purity VWF/FVIII Concentrates', *Haemophilia*, vol. 12 (suppl. 2), 2006, p. 20, 05 PO 122.

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29 Caris, 'New Donor Requirements for Plasma Derived Factor VIII in Australia'.

## Regulatory issues arising with toll fractionation

In the event that Australian governments agree to an option for future fractionation arrangements that results in the overseas processing of Australian plasma, either (a) new products would need to be registered on the Australian Register of Therapeutic Goods, or (b) variations in registration details of products already on the ARTG would be required, given the change in the use of Australian plasma in their manufacture for supply to this country.

Under a toll fractionation model, the Therapeutic Goods Administration would continue to monitor safety, quality and efficacy through the product registration process, and then on an ongoing basis through post-market surveillance via the monitoring of adverse reactions; periodic product safety updates; product testing; annual reviews of plasma master files; and GMP surveillance audits. There are six issues that may need resolution:

1. product registration
2. compliance with European provisions regarding eligibility criteria for donors
3. GMP auditing in MRA countries
4. GMP auditing in non-MRA countries
5. costs of overseas audits
6. contractual provisions.

Two important considerations in regard to the overseas fractionation of Australian plasma are: whether there is equivalence of manufacturing requirements between Australia and the countries where manufacturing takes place; and whether the regulatory authorities in those countries will monitor compliance with manufacturing standards to a level that satisfies the TGA for the purposes of meeting the provisions of the Therapeutic Goods Act. These issues arise for toll fractionation particularly because the plasma products made under toll fractionation arrangements would be supplied to the Australian market only, rather than for use in the country of manufacture. Also, the regulator in the country of manufacture may exercise a different level of oversight for products for export only, as distinct from products for the home market.

### Product registration

The TGA currently places specific requirements on the domestic fractionator in relation to the manufacturing process, through the Manufacturing Principles. Currently, the Manufacturing Principles include the provision that any fractionation plant that is used to process Australian plasma into products for use in Australia shall not be used to process any plasma collected outside of Australia unless the TGA is satisfied that the overseas-sourced plasma will not contaminate Australian product with blood-borne pathogens. The Manufacturing Principles specify that the TGA is to do this by evaluation of the Plasma Master File of the overseas-sourced plasma and consideration of the fractionation plant's processes.

While the Manufacturing Principles do not apply outside Australia's jurisdiction, under Section 25 of the Act the TGA is required, when evaluating applications of overseas-manufactured products, to take into account whether 'the manufacturing and quality control procedures used in the manufacture of the goods are acceptable'.

### **Compliance with European provisions regarding eligibility criteria for donors**

Directive 2004/33/EC issued by the European Commission currently requires that blood and blood components imported from third countries, including starting plasma for fractionation, must be sourced from a donor pool that meets EU eligibility criteria for donors of whole blood and blood components. Australian recovered plasma would technically be rendered noncompliant with the Directive because its minimum haemoglobin levels for whole blood donors are lower than those of the EU. The TGA has been in contact with the EMEA on this matter. The intent of the provisions for haemoglobin levels is to protect donor health and have no bearing on the safety and quality of starting plasma and finished products. The European Commission and the EMEA are aware of this issue. It is the TGA's understanding that, in the event that Australian plasma were fractionated in Europe, shipments would not be impeded on the basis of this potential breach that currently exists under the Directive.

In the event that Australia moves to a tender process for future fractionation contracts, negotiations between Australian and European regulatory agencies would need to be held to identify and resolve any regulatory requirements that do not apply to the safety and quality of plasma and finished products but could nonetheless have the effect of impeding the shipment or processing of Australian plasma at a manufacturing facility in Europe. It could be a requirement for tenderers to demonstrate that there were no such impediments in their country.

### **GMP auditing in MRA countries**

The MRAs covering plasma derived products with the European Union, and the PIC agreement with Switzerland, are most pertinent, as these include countries with fractionation plants. Some of the key elements of the EC/EFTA MRAs and PIC agreement for the purposes of this discussion are:

- GMP inspections of overseas fractionation plants are carried out by an overseas regulator in accordance with their GMP requirements, which are agreed to be equivalent to those of Australia.
- The TGA can request the overseas regulator to carry out an inspection to certify that the manufacturer is appropriately authorised to manufacture the products, is regularly inspected and complies with the national GMP requirements of the overseas regulator. Certificates are generally issued within 30 days; however, this may be extended to 60 days in exceptional circumstances. Each regulator is obliged to recognise the conclusions of the audits.
- The TGA can request an inspection report of the last inspection of the manufacturing site. Where the last inspection is more than two years old or where there is a particular need to inspect the site, an up-to-date and detailed report may be requested. A report may comprise a Site Master File and a narrative report describing the most recent audit and any GMP deficiencies, or it may respond to specific queries by the TGA. However, the details in the inspection reports can be quite variable. The same timing for delivery of inspection reports applies as described above. Each regulator is obliged to recognise the conclusions of the audits.

- Under the EC/EFTA MRAs the TGA may conduct an audit of an overseas manufacturer but only in exceptional circumstances. It must identify its reasons for doing so to the overseas regulator and the overseas regulator may join the inspection. Costs may be recovered by the TGA from the Australian sponsor in such circumstances.
- The overseas regulator must communicate to the TGA with appropriate urgency a suspension or withdrawal of product based on noncompliance with the GMP and which could affect the protection of public health.<sup>30</sup>

The current provisions in the EC/EFTA MRAs permit the TGA to conduct an audit in exceptional circumstances. In Switzerland the local regulator must lead the audit. If Australia were to move to overseas toll fractionation this might be considered to be a previously unanticipated circumstance requiring an increased ability for the TGA to conduct joint audits with regulators in MRA countries. This is because plasma products are considered high-risk, the products would be for the Australian market only, and because Australia would be completely reliant for its supply of plasma products on manufacturing sites outside Australian jurisdiction, in contrast to the current arrangements. The Australia–EC/EFTA MRAs could be renegotiated to enable joint inspections by the TGA and designated EC/EFTA GMP Inspectorates of manufacturers of high-risk products, such as fractionated products, in appropriate circumstances. This would maintain Australia's commitment to regulatory harmonisation while enabling the TGA to have input into the scope and depth of the audit. It is noted that a joint audit program would require ongoing negotiations with the relevant European regulatory authorities. Amendments tend to take a long time to negotiate and implement, and would need to involve a detailed examination of how these amendments would operate in practice.

### **GMP auditing in non-MRA countries**

The only non-MRA country with any major commercial fractionators that could undertake toll fractionation of Australian plasma is the United States. The Review undertook liaison with the Food and Drug Administration (FDA) to ascertain the regulatory issues that would arise from toll fractionation in the United States.

The United States Federal *Food, Drug, and Cosmetic Act* (the FDC Act) specifies provisions for the importation of components, including plasma, that are used in the manufacture of therapeutic goods (e.g. drugs) when the finished drug products are to be exported rather than distributed in the United States. This is referred to as 'Import for Export' (IFE). Blood, blood components, and plasma have special requirements under the IFE provisions. If a company were fractionating plasma imported from Australia at a plant in the United States, the company would need FDA permission under the plasma-specific IFE provisions of the FDC Act to import shipments of plasma and would also need to comply with the export provisions of the FDC Act to export finished products to Australia. While neither the imported plasma nor the exported finished products would require FDA-approved biologics licences, a number of the IFE provisions are directed at promoting the safety and quality of products so as not to present a health risk to the country of export under such arrangements.<sup>31</sup>

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<sup>30</sup> See *Guide to the MRAs in Operation* [EMEA/MRA/22/03 Final], European Medicines Agency, London, 2003, <<http://www.emea.europa.eu/inspections/docs/0002203en.pdf>>. This guide published by the EMEA relates to the MRAs between the EU and the respective parties to agreements and is dated 8 May 2003.

<sup>31</sup> See, for example, the requirements in Section 802 of the Federal *Food, Drug and Cosmetic Act*.

## Review of Australia's Plasma Fractionation Arrangements

The scope of regulatory oversight by the FDA for a toll fractionation arrangement would depend on the facts and circumstances of each particular arrangement.<sup>32</sup> For example, if the IFE arrangement involved a US licensed manufacturer, the FDA would inspect, according to its standard policies and procedures, the facilities, including areas and systems involving IFE manufacturing. (This could be either a comprehensive or a streamlined evaluation, depending on the level of inspectional coverage that is deemed appropriate according to perceived risk.) The Review was also interested in whether, if regulatory breaches relating to production for the United States market resulted in the FDA revoking or suspending a fractionator's licence, this would automatically result in suspension of toll fractionation activities at the plant. While a US licence is not necessary for IFE arrangements to exist, action taken by the FDA would be based on the FDA's assessment of the particular circumstances and factors leading to the revocation or suspension of a licence. In practice, the FDA would notify relevant foreign regulators of action against a plant and a formal cooperation agreement between the FDA and the TGA could potentially specify how this could take place.

With regard to whether the TGA could conduct unannounced inspections of facilities in the United States, there are no FDA policies or procedures that require or recommend the TGA to pre-announce an inspection to the company. Conversely, FDA regulations do not require manufacturers to allow such inspections. Provisions in the contract with the fractionator could be employed to facilitate auditing of a US plant by the TGA (contractual provisions are discussed in greater detail below).

Such an understanding could be memorialised in an Agency-to-Agency arrangement. As noted above, the information-sharing agreement between the TGA and the FDA has expired and the agencies are in the process of reviewing it.

### Costs of overseas audits

Undertaking an overseas audit of a toll fractionation facility is costly. It is estimated by the TGA that an audit could cost approximately A\$100 000. The TGA will establish a schedule of fees specifically for plasma products. Given the high cost of overseas audits, the TGA should consider the need to amend the Therapeutic Goods Regulations so that fees may be imposed on a sponsor to recover the costs of GMP auditing by the TGA. This would arguably be best undertaken through amendments to the regulations imposing a fee on the sponsor, but it should be noted that the MRAs also address the issue of costs of inspections and any amendments to the regulations would need to take this into account.

It is noted that an overemphasis on frequent and/or unannounced site audits may bring risks of disruption to production and that any special, or unscheduled, audits should be justified by an assessment of product risk.

### Contractual provisions

When used in conjunction with other mechanisms, such as regulatory provisions and risk management strategies, contractual provisions in supply contracts between Australian product sponsors and the National Blood Authority (NBA) could be a

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<sup>32</sup> The FDA has issued a draft Guidance for Industry document on Exports and Imports under the FDA Export Reform and Enhancement Act of 1996 which, when finalised, will explain the basic requirements and procedures for exporting and importing biologicals and other therapeutic goods, including those that may not be sold or distributed in the United States: <<http://www.fda.gov/oc/guidance/frexport.html>>.

## Review of Australia's Plasma Fractionation Arrangements

useful mechanism for reinforcing the roles and responsibilities of the parties, and of third parties such as the TGA, in relation to ensuring the safety, quality and efficacy of plasma products. By way of example, the Plasma Products Agreement with CSL Limited includes a number of provisions that reinforce CSL's obligations under the Therapeutic Goods Act and provide for remedial action if a unit of product does not meet the standards for safety, quality and efficacy, or any other requirements, associated with the product's registration or listing. It must be noted, however, that, as will be discussed in Chapter 9, legal and practical impediments may be encountered in enforcing a contract involving a manufacturer in another country. It must also be noted that major risks arising from an overseas toll fractionation process, such as threats to the security of supply of plasma and finished products during transportation phases, need to be addressed by mechanisms other than the regulatory framework for the safety, quality and efficacy of products. This issue is also discussed further in Chapter 9.

The Review considers that should Australia adopt an overseas toll fractionation arrangement there are a number of provisions that should be included in a supply contract with an Australian sponsor in relation to the provision of fractionation services by an overseas fractionator. These would include:

- requiring that the company comply with all Therapeutic Goods Act requirements and other relevant Australian laws; and/or
- performance standards designed to ascertain and measure certain aspects of quality control; and/or
- requiring the company to have, maintain and implement an approved risk management plan, which properly deals with the risks associated with ensuring safe, high-quality products (i.e. identifies those risks, the likelihood of occurrence, the impact of occurrence, and strategies to minimise the likelihood or impact of occurrence).

The contract provisions on compliance with the Act will rely on the TGA's regulatory monitoring regime (including activities by overseas regulators, as part of international agreements). The TGA would need to report noncompliance to the NBA so that the NBA could implement or ensure the implementation of appropriate contractual protections (these could include change in payments, withdrawal of a product, supply planning changes).

The contract could also require the company to ensure that it does not enter into any subcontract (in connection with the contract to fractionate Australian plasma) without first complying with certain conditions and NBA approval and Therapeutic Goods Act compliance.

In addition to imposing quality requirements, the contract would also need to include:

- reporting mechanisms (to be adhered to by the sponsor and/or the manufacturer) with regard to TGA requirements/performance measures
- provision for audits of the manufacturing process to be conducted and for access to relevant premises
- undertakings about:
  - who is to conduct the overseas audits (TGA or an equivalent overseas regulator),
  - how often and how they are to be conducted, and who is to bear the cost

## Review of Australia's Plasma Fractionation Arrangements

- contractual remedies for failure to permit the conduct of audits, such as:
  - (a) the ability for the Commonwealth to terminate the contract; and/or
  - (b) reduction in/suspension of payments if the manufacturer does not permit and facilitate auditing; and/or
  - (c) provision for the conduct of tests of the products received in Australia, pursuant to TGA requirements. The contract would need to specify who would conduct such tests, who pays for the conduct of the tests, and the consequences of a product failing any such test.

## Conclusion

Plasma products are biologicals that carry an inherent risk of pathogen transmission. They are regulated as high-risk medicines by the Therapeutic Goods Administration. The TGA regulates the safety, quality and efficacy of domestic and imported plasma products in the Australian market.

The infectious disease safety of plasma products is ensured through donor selection and testing of starting plasma, followed by inactivation and removal of pathogens during the fractionation process. This third step has the greatest effect upon the safety of finished plasma products. In well-regulated environments, plasma products have a long record of safety and for over ten years there have been no international reports that plasma derivatives have transmitted a blood-borne pathogen.

Through the product registration process, the TGA requires acceptable evidence of manufacturing processes and quality control to be demonstrated and maintained. If a toll fractionation model were adopted in Australia, the TGA would apply the same standards as are applied to locally manufactured products.

To ensure the continued supply of high-quality products, the Review considers independent testing of plasma products by the TGA is appropriate.

A key policy issue in considering the feasibility of overseas toll fractionation of Australian plasma is the ability to ensure satisfactory oversight of manufacturing. In terms of post-market surveillance in the case of MRA countries, it would be desirable for the TGA to have a greater scope to conduct and instigate audits of fractionators supplying Australia from plants in these countries. Australia would need to give strong consideration to whether the TGA's current ability to undertake audits of manufacturing sites within an MRA partner's territory would remain adequate. A reappraisal of these provisions could be warranted in order to permit joint inspections by the TGA and counterpart organisations of manufacturers of high-risk therapeutic goods such as fractionated plasma products. The possibility of renegotiating relevant sections of MRAs must take into account, however, the scale of such a task and the need for any such initiatives to be sensitive to the element of reciprocity in MRAs.

For countries where there is no MRA in place, there may be fewer impediments to Australian authorities conducting audits within the terms of existing formal arrangements. However, a greater amount of work by the TGA rather than its counterparts in inspecting overseas facilities would be likely. The costs and resources

## Review of Australia's Plasma Fractionation Arrangements

associated with regulating the fractionation of Australian plasma overseas would need to be addressed for both MRA and non-MRA countries.

In the event that Australian plasma is fractionated overseas, there must be a strong emphasis on contractual provisions between the NBA and the product supplier to reinforce appropriate regulatory oversight by the TGA, together with recognised overseas regulatory agencies as may be required under any applicable international agreements. The role of the TGA in relation to oversight of GMP compliance, including the cost and conduct of GMP audits of relevant manufacturing sites, would need to be confirmed.



*Rove McManus, from the TV show Rove Live, seen here donating blood.  
The Herald & Weekly Times Photographic Collection.*