IPFA Workshop Session 7: REGULATORY CONSIDERATIONS

TGA regulation of local manufacturers of plasma derivatives – CSL Behring Australia's overview

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"*Technological, regulatory and organisational tools to produce plasma for fractionation*"

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TGA regulation of Plasma for Fractionation

- Company history and overview
- Overview of the Australian Therapeutic Goods Administration's (TGA) regulation of blood product manufacturers and plasma processed in an Australian facility
- Legal requirements for manufacturers
- Plasma Master File (PMF) concept & contents
  - Assurance of ongoing plasma safety & quality
  - Applicability for domestic and export supply
- TGA evaluation and approval process, variations, fees

CSL Company Overview & History

Where it all began – Melbourne, 1916

Images of the Parkville site in Melbourne

- CSL was formed as a government-owned entity in 1916 to serve & protect Australia.
- Now a global public company that remains proudly Australian.

CSL staff packing Spanish flu ‘vaccine’ at the height of the 1919 pandemic.

CSL Limited

- Headquarters: Melbourne, Australia
- 14,335 employees in over 30 countries
- A century of experience in the development and manufacture of vaccines and plasma protein biotherapies
- CSL's businesses:
  - CSL Behring
    - CSL Plasma
  - Seqirus
  - CSL R&D

Innovation and new product development for unmet medical needs continue to drive CSL's growth.

CSL Behring Manufacturing Sites

Each manufacturing site is a **Center of Excellence** for the production of core products

	Bern Switzerland	**Melbourne Australia**	**Kankakee USA**	**Marburg Germany**
				
Core products	**Immunoglobulins** IVIG, SCIG	**Toll Manufacturing**	**A1PI**	**Coagulation factors**
Niche/ specialty products	*Albumin, Anti-D, CMV, Pastes*	*IVIg, SCIg, FVIII, FIX, PCC, Albumin*	*Coagulation factors, Albumin, Pastes*	*Hyperimmunes, Specialty products, Pastes*

Description of CSL Behring (Australia) plasma product business:

- Domestic **toll** plasma fractionation for Australia
- **Export only toll** manufacture of plasma products for:
  - New Zealand
  - Hong Kong
  - Malaysia
  - Singapore and
  - Taiwan
- Other non-toll business

Workflow for Plasma Approval

Plasma Supplier

- Inspected, Qualified/certified, PIC/S Guide
- Human Plasma for Fractionation, Ph.Eur./BP monograph (0853)

TGA

- Plasma Master File (PMF) approval if manufactured in Australia, TGA Act, EMA Guideline for PMFs
- MAA approval (submitted concurrently with PMF for initial approval)
- Export Listing

Regulatory Authority (Other)

- MAA approval in country of product supply (where applicable)
- PMF approval

Background on TGA's regulation of therapeutic goods containing human blood or plasma

- **Australia:** signatory to a World Health Organization (WHO) policy on self-sufficiency
- **Policy aim:** therapeutic goods containing human blood or plasma for supply in Australia to be manufactured from blood or plasma from Australian donors
- **National Blood Authority (NBA):** manages the supply of these products
- **TGA:** international standards and guidelines to minimise the risk of transmitting infectious diseases
- **Sponsors:**
  - submit a PMF to support an application on Australian Register of Therapeutic Goods
  - update the PMF annually to ensure continued product safety and quality

Legal Requirements: Manufacturers who fractionate Australian and overseas sourced plasma

- Condition of local manufacturer's Licence to Manufacture (Therapeutic Goods Act, Section 36 (*Manufacturing Principles*)[1]
- Manufacturers must submit a separate PMF for plasma from each different overseas source
- Only overseas-sourced plasma with a TGA-approved PMF can be fractionated in the same facility as Australian plasma
- These requirements, together with good manufacturing practice (GMP), ensure the safety and quality of products are not compromised

[1]Determination No. 1 2013 MP1/2013 Australian Government Department of Health and Ageing, Therapeutic Goods Administration).

Relevant Guidelines & Standards for Plasma for Fractionation:

- Guideline on plasma-derived medicinal products **(EMA/CHMP/BWP/706271/2010)**
- Guideline on the Scientific Data Requirements for a Plasma Master File (PMF) **(CHMP/BWP/3794/03)** Rev 1.0 including Annex 1 to Guideline (as adopted by the TGA and the EMA)
- Guideline on Epidemiological Data on Blood Transmissible Infections (**EMA/CHMP/BWP/548524/2008)**.
- European Pharmacopoeia (Ph. Eur.) & British Pharmacopoeia (BP) monograph *'Human plasma for fractionation*' (0853) which is a Standard under subs. 3(1) of the Act
- In addition to the requirements of the standard monograph, the plasma used for fractionation must comply with Therapeutic Goods Order No. 81 - Blood and blood components (**TGO 81**) and the
- Therapeutic Goods Order No. 88 - Standards for donor selection, testing and minimising infectious disease transmission via therapeutic goods that are human blood and blood components, human tissues and human cellular therapy products (**TGO 88**) with regard to donor exclusion and screening requirements, particularly exclusion criteria for variant Creutzfeldt-Jakob disease (vCJD)
  - TGOs require the following in the PMF:
    - a statement identifying the countries of origin of the plasma
    - an assurance that the individual donors had not resided in the United Kingdom for a cumulative period of six months or more between 1980 and 1996, or received a blood transfusion in the United Kingdom from 1980 onwards
    - an assurance that donations had been screened using nucleic acid amplification technology for human immunodeficiency virus (HIV) and hepatitis C virus (HCV)

Description of the Plasma Master File (PMF):

- A stand-alone document
  - Separate but supportive of Product Registration
- Detailed scientific information on
  - Human plasma used as a starting and/or raw material from collection centre to fractionation pool
  - Quality & Safety aspects of plasma used for the manufacture of therapeutic derivatives/products

PMF – Content acc. to CHMP/BWP/3794/03, Rev 1.0[1]

- **Summary of Changes**
- **General information**
  - A plasma-derived products list
  - A safety strategy/general risk assessment/general logistics
- **Technical information section**
  - Information on collection establishments & centres

    Eg. List of centre address details, inspection/audit status
  - Information on testing centres

    Eg. Address, Inspection/audit status, participation in proficiency studies

[1]*CHMP Notes for Guidance on the Scientific Data Requirements for a Plasma Master File (PMF) (CHMP/BWP/3794/03) Rev 1.0* including Annex 1 to Guideline (as adopted by TGA and EMA)

PMF – content acc. to CHMP/BWP/3794/03, Rev 1.0 continued

- **Characteristics of donations**
  - Whole blood (FFP or recovered), Plasmapheresis, hyperimmunes
- **Epidemiology data[1]**
  - Incidence data: Data measuring of the risk of developing some new condition within a specified period of time.
  - Prevalence data: Data measuring the total number of cases of the disease in the population at a given time.

- **Donor selection/exclusion criteria**
  - Compliance with Ph.Eur., CHMP guidance, CoE recommendations, WHO + local requirements

[1]*Compliance with Guideline on Epidemiological Data on Blood Transmissible Infections EMA/CHMP/BWP/548524/2008.*

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PMF – content acc. to CHMP/BWP/3794/03, Rev 1.0 continued

- **Post collection information**
  - System in place to trace path of any donation from collection centre to product & vice versa
- **Plasma Quality & Safety**
  - EP “Plasma for Fractionation” compliance
  - Testing & Test Methods (Plasma supplier & CSL)
    - Single donations, mini-pools, large pools
    - Validation; Proficiency Studies
- **Blood bags & anticoagulant solutions**
- **Storage & Transport conditions**
- **Inventory Hold period & procedure**
- **Characterisation of plasma pool**
- **Contracts & Conditions, quality specifications**
- **PMF Annexes**

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PMF Annexes

Annex A	List of Plasma-Derived Products (internal & external)
Annex I	Checklist on the annual update
Annex II	Information on blood/plasma collection centres
Annex III	Information on laboratories performing testing of donations and plasma pools
Annex IV	Information on storage establishments
Annex V	Information on organisations involved in transport
Annex VI	Logistics including flowcharts
Annex VII	Epidemiology data, First time donors, Repeat tested donors
Annex VIII	Information on Testing (serology and testing); validation reports
Annex IX	Information on blood bags and bottles
Annex X	Quality and Delivery requirements

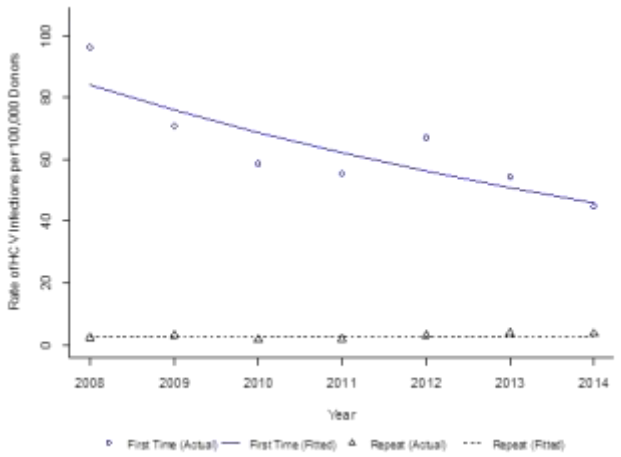
Additional European/TGA requirements:

1. Review of Positive Cases

- Results of the number of positive donations that have been identified per viral marker by NAT (Nucleic Acid Amplification Technique) testing at the fractionation pool including mini-pool testing should be provided in PMF annually for each batch of product

2. Assessment of trend

- An epidemiological assessment of trend over time must be conducted to identify any overall trends in the rates of infectious markers in the donor population.
- Trend calculated for HIV, HCV, HBV in accordance with epidata
  - At least 3 data points (years of epidata) are required
  - A comparison is made with the data provided from the preceding year of reporting



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3. Overall Viral Risk Assessment

- Factors taken into account in determining viral risk assessment include:
  - Donor epidemiology data (HIV, HCV, HBV),
  - Screening tests ie. assay detection limit
  - Virus Load based on theoretical window period data
  - Virus inactivation/removal over process ie. Validated viral reduction factor
  - Plasma pool size
  - Donation volume
  - Inter-donational interval
  - Product yield, number of vials of final product

TGA's Evaluation/Approval process: PMF classifications[1]

For administration purposes, TGA has grouped PMFs into 2 categories:

- **Type I PMFs** - information to support products registered for supply to the Australian market.
  - No annual fees, expiry date or statutory time frame for evaluation
  - Submitted annually eg. AU PMF

- **Type II PMFs** - information on overseas sourced plasma fractionated for export to foreign markets (required to be submitted acc. to TGA Act)
  - Fees charged based on number of pages, ~ 60 wd evaluation timeframe
  - Approval granted for 1 year only ie expiry date provided, submitted annually
    - Eg. NZ, SG, HK, MY, TW PMFs

[1]*TGA Guidance 9: Therapeutic goods that contain or are produced from human blood or plasma*

TGA Fee Structure for Type II PMFs[1]

Evaluation fees - per submission	Pages (number)	Fee (AU $)
PMF	1 - 10	1,235
PMF	11 - 50	10,600
PMF	51 - 100	23,700
PMF	101 - 1000	31,900
PMF	1001 - 3000	49,700
PMF	3001 - 4000	66,200
PMF	>4,000	80,700

[1] TGA Fees & Charges From 1 January 2016 v1.2, Dec 2015

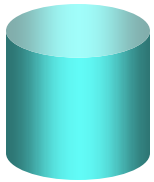
TGA's requirements for PMF Variations

- Major Variations requiring **TGA approval before implementation**:
  - Viral reduction step affecting risk calculation
  - Plasma country of origin; new plasma organisation
  - Tests and site of viral testing of manufacturing plasma pool
  - Manufacturing pool size or number of donations per pool
  - Donor selection/exclusion criteria
  - Hold times or quarantine period for plasma
- TGA approval of PMF variation : 45 working days

CSL Behring Australia

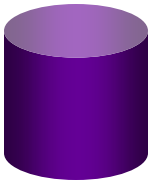
Integrated Safety System: Plasma Products

The Four Pillars of the Safety System



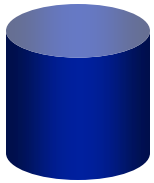
PLASMA SELECTION

- Donor Suitability
- Plasma Testing
- Inventory Hold
- Unit Verification
  - Lookbacks & traceability



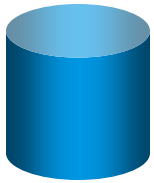
MANUFACTURING

- Plasma Pool Testing
- Fractionation
- Virus Inactivation and Elimination
- Batch-to-Batch Segregation
- Virus Validation Studies



QUALITY CONTROL

- Final Approval
- Batch Release



MONITORING

- Pharmaco-vigilance
- Traceability
- Post-donation Information

Thank-you!