GONE VIRAL
Infectious Diseases Testing on Therapeutic Goods and its Regulatory Complications

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The Therapeutic Goods Administration (TGA)

The TGA was established in 1990 to safeguard and enhance the health of the Australian Community through effective and timely regulation of therapeutic goods

Legislation
Therapeutic Goods Act 1989
Therapeutic Goods Regulations 1990
Therapeutic Goods (Medical Devices) Regulations 2002
About the TGA

- A division of the Department of Health & Ageing
- A partner in Australia’s National Medicines Policy
- 700 staff including scientists, medical officers and pharmacists
- Budget approximately A$120m per annum
- Full cost recovery from industry fees and charges

Therapeutic use means use in or in connection with:
- preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury influencing, inhibiting or modifying a physiological process
- testing the susceptibility of persons to a disease or ailment influencing, controlling or preventing conception
- testing for pregnancy replacement or modification of parts of the anatomy
TGA structure
Biologicals and Biological Medicines

**Biological Medicines**

Recombinant peptides and proteins, blood, plasma-derived products (IVIg, clotting factors), monoclonal antibodies, anti-venoms

Generally, approval of the finished product (batch manufacturing)

**Biologicals**

Human cell and tissue based therapies

E.g. Musculoskeletal and ocular tissue, chondrocytes, mesenchymal stem cells

Generally, approval of manufacturing process (individual product manufacture)

Few international standards
The Biologicals Framework

• The *Therapeutic Goods Act 1989* was written in terms of medicines and devices.

• May 2011 the TGA introduced a regulatory framework for human cell- and tissue-based therapeutic goods, or ‘biologicals’

• Established subsequent to recommendations endorsed by all Australian Health Ministers and based on extensive industry and stakeholder consultation taking into account international practice.

• To provide:
  – greater regulatory certainty for the use of cell and tissue therapy products
  – a more flexible framework to respond to changes in technology
  – a move to the adoption of a risk based approach to regulation
Biologicals Framework

What’s in & what’s out

Not regulated by the TGA
- Assisted reproductive technologies (in vitro fertilisation)
- Fresh viable organs
- Fresh hematopoietic progenitor cells (bone marrow transplants)
- Cells and tissues made by a medical practitioner for a single patient under the care of that medical practitioner

Regulated as biologicals
- Human stem cells
- Tissue-based products (skin, bone, ocular, cardiovascular)
- Cell-based products (genetically modified, in vitro cell expansion/depletion)
- Combined cell and tissue products (collagen matrices for localised cell delivery)

Regulated, but not as biologicals
- Biological prescription medicines (vaccines, plasma derivatives)
- Animal tissue products (xenotransplantation)
- Labile blood and blood components
- Haematopoietic progenitor cells (non-fresh transplants)
Regulation of Therapeutic Goods

Blood and Blood Components

Blood, blood components and plasma derivatives are regulated under the Therapeutic Goods Act 1989

**Fresh Blood Components**
- Whole Blood
- Red Cell Components
- Clinical Fresh Frozen Plasma
- Platelet concentrates
- Cryoprecipitate
- Leucocytes

**Plasma Derivatives**
- Albumin
- Intravenous Immunoglobulins
- Hyperimmune Immunoglobulins
- Plasma Derived Coagulation Factors
- Serpin Derivatives

**Blood Products**
Blood and Blood Components

Standards

- Therapeutic Goods Order No. 81 Standards for Blood and Blood Components
- 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
- Australian code of good manufacturing practice for human blood and blood components, human tissues and human cellular therapy products

must meet the requirements of the Council of Europe document 'Guide to the preparation, use and quality assurance of blood components' 14th edition, and must only be manufactured from blood that tests negative for HIV-1 and HCV using Nucleic Acid Amplification Technology.
Blood activity in Australia 2011-12 *

▲ Processing
Tonnes of plasma collected:  502
Collection centres:       1,136
Processing and distribution centres:  13

▲ Donations
No of donors:    > 570,000
Plasmapheresis donors:  > 70,000
Blood donations:  > 1,300,000

▲ Issuing
Units of RBC:     801,295
Units of Platelets: 134,149

*NBA Annual report 2011-12
Three principles protecting from transmission of pathogens

**Donor selection**
- Fast implementation
- Unknown/unexpected agents?

**Testing**
- Sensitive/specific
- Reliable

**Inactivation/removal**
- Effective against many unknown/unexpected viruses
- Reliable

**Limitations**
- Donors with unknown risk
- Reliability of application?
- Availability of plasma/plasma products
- No detection of unknown pathogens
- Limit of detection
- Feasibility without damage to product
- Resistant and small non-enveloped viruses?
Testing

Blood and blood components are tested from three aspects:

1. Screening for transfusion-transmitted viral infections in order to minimise the risk of transmission of viral infections and ABO, Rh (D) grouping (mandatory testing)
2. Quality control testing to monitor the critical processes (non-mandatory testing)
3. Bacterial contamination screening to ensure the microbiological safety of the blood and blood components

Quality Assurance Programs (QAP) which monitor the efficacy and accuracy of the test systems
External quality controls for mandatory screening methodology.
Control of Equipment
Mandatory testing samples are tested for the following:

- Anti-HIV 1/2
- Anti-HCV
- HBsAg
- Anti-HTLV I/II
- HCV RNA
- HIV-1 RNA
- HBV DNA
- Anti-treponemal (Syphilis) testing

- ABO blood group
- Rh (D) blood group
- Red Cell Antibody Screen
Testing

Window Period

The time period between actual infection and the appearance of detectable viral markers (antibody/antigen/nucleic acid) is termed the assay ‘window period’ (WP). The WP duration varies for different viruses, viral markers and assays.
Hepatitis B Virus
Virologic/Serologic Profile

HBV DNA Copies/mL vs. Days

HBV DNA - Purple
HBsAg - Orange
Anti-HBs - Blue
Anti-HBc - Green

S/CO vs. Days

S/CO - 0 to 40

Days - 0 to 130

“Stramer Transfusion 2005, 45 vol 8 cover”
HIV WP

McDonough et al. Infusionsther Transfusionsmed 1998;25:164
NAT Reduces Window of Detection\textsuperscript{1,2}

<table>
<thead>
<tr>
<th></th>
<th>Days of Infection to Procleix Ab or Ag Detection</th>
<th>Reduction of Window by NAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>HCV</td>
<td>23</td>
<td>82</td>
</tr>
<tr>
<td>HBV</td>
<td>34</td>
<td>59</td>
</tr>
</tbody>
</table>

2. Package Insert for the PROCLEIX® HIV-1/HCV Assay, #IN0076.1
Testing

Viral residual transfusion risk estimates (median point estimates)

Australian data

HIV 1 in 20,046,000 (7,943,000– 28,211,000)

HBV 1 in 9,872,000 (4,477,000– 19,478,000)

HCV 1 in 2,263,000 (533,000– 5,894,000)
TGA Evaluation responsibilities

**IVD** (Office of Device Authorisation; ODA)
Test kit reviewed for design and full validation of the test method per manufacturers claims (NRL)

**BSS** (Office of Scientific Evaluation; OSE)
Is the test kit appropriate for use e.g. validated for use on pooled vs non-pooled samples (sensitivity); cadaveric vs fresh samples (intended use)
Test must be performed in a lab with GMP licence/clearance
Is sample transport and storage appropriate and validated

**OMQ** (Office of Manufacturing Quality; OMQ)
Review protocol and verification data for testing lab
Review of equipment used in assay and storage of samples
Review appropriate storage of test kit
Competency and training of staff performing test
Evaluation

Generally, the protocol is not assessed in detail but:

Protocol may be reviewed to ensure conditions, standards and samples used are representative of the manufacturing process

Close out on any deviations are considered when reviewing results

Focus on results and acceptance criteria

Detailed Requirements can be found:

AS ISO/IEC 17025 – 2005
General requirements for the competence of testing and calibration laboratories

AS ISO 15189 – 2013
Medical laboratories – Requirements for quality and competence

NATA Technical Note 17 – 2012
Guidelines for the validation and verification of quantitative and qualitative test methods
Evaluation

- Detailed review of all processes validations
- Validation of analytical methods, including infectious disease testing
- Validation of any product and sample transport
- Review quality of critical materials (includes raw materials)
- Review to latest guidelines and standards
Evaluation example

Presentation in accordance to guideline, acceptance criteria and summary of results
Access to raw data may be requested
For controls acceptance range usually set by kit manufacturer

<table>
<thead>
<tr>
<th>2) Kit Control Testing</th>
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<tbody>
<tr>
<td><strong>Assay</strong></td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Ferritin</td>
</tr>
<tr>
<td>Ferritin</td>
</tr>
<tr>
<td>Ferritin</td>
</tr>
<tr>
<td>Anti-HBs</td>
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<tr>
<td>Anti-HBs</td>
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<tr>
<td>Anti-HBs</td>
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</tbody>
</table>
### Evaluation example

<table>
<thead>
<tr>
<th>Sample ID</th>
<th>Assay</th>
<th>Historical Interpretation (from existing Analyser)</th>
<th>PQ Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0054001</td>
<td>Anti-HBc</td>
<td>Non-reactive</td>
<td>Non-Reactive</td>
</tr>
<tr>
<td>0054002</td>
<td>Anti-HBc</td>
<td>Non-reactive</td>
<td>Non-Reactive</td>
</tr>
<tr>
<td>0054011</td>
<td>Anti-HBc</td>
<td>Reactive</td>
<td>Reactive</td>
</tr>
<tr>
<td>0054012</td>
<td>Anti-HBc</td>
<td>Reactive</td>
<td>Reactive</td>
</tr>
<tr>
<td>0054013</td>
<td>Anti-HBc</td>
<td>Reactive</td>
<td>Reactive</td>
</tr>
</tbody>
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Description of cut-off values and raw data requested by evaluator
To allow comparison of detection methods actual values measured need to be compared (%CV between test results the crucial determinant)
Transmissible spongiform encephalopathies (TSEs)

There is no commercial test available. Blood collectors and fractionators rely on the Donor Questionnaire.

The blood supply is protected through a decision by all Australian Health Ministers to defer blood donations from anyone who lived in Britain for a cumulative period of six months or more between 1980 and 1996 or who received a blood transfusion in Britain from 1980 onwards, irrespective of their length of stay.

TGA TSE policy (under review at present)
Supplementary requirements for therapeutic goods for minimising the risk of transmitting Transmissible Spongiform Encephalopathies (TSEs)*
Cadaveric Testing

Limited Availability of Licensed Donor Screening Tests Labelled for Use with Cadaveric Blood Specimens
Any change to the intended use of a commercial kit to adopt it for cadaveric testing would require a full validation

Guidance

FDA
‘Recommendations for Obtaining a Labelling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)’

NATIONAL PATHOLOGY ACCREDITATION ADVISORY COUNCIL NPAAC
‘REQUIREMENTS FOR THE DEVELOPMENT AND USE OF IN-HOUSE IN VITRO DIAGNOSTIC DEVICES (IVDs)’
IVD Medical Devices Regulation Basics

In vitro diagnostic medical devices (IVDs) are, in general, pathology tests and related instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or in making decisions concerning clinical management. IVDs are typically used in diagnostic laboratories, at the point of care, and in the home.

A new regulatory framework commenced on 1 July 2010 that ensures all IVDs will undergo a level of regulatory scrutiny that is commensurate with the risks associated with their use.
IVD Medical Devices Regulation Basics

The consultation on:

**Proposed amendments to the new regulatory framework for In Vitro Diagnostic medical devices (IVDs)**
closed on 7 June 2013.


For any questions, clarifications or advice please feel free to contact

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A Questionnaire will be distributed to Laboratories in August, please take some of your time and respond.
Emerging and re-emerging infectious agents

Direct Impact Australia

**Dengue** (Flaviviridae, pos. Sense RNA)
**Ross River** (Togaviridae, pos RNA)
**Murray Valley Encephalitis** (Flaviviridae, pos. Sense RNA)
**Japanese Encephalities** (Flaviviridae, pos. Sense RNA)
**Kunjin (WNV)** (Flaviviridae, RNA)
**Barmah Forest** (Togaviridae, pos RNA)
**Nipec (Bat Lyssa Virus)** (Paramyxoviridae, neg. sense RNA)
**Hendra** (Paramyxoviridae, neg. Sense RNA)
**Malaria** (Plasmodium)
**Leishmania** (Trypanosomatid protozoa)

Unknown infectious Agents
Thank You