



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Human or animal origin therapeutic devices

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TGA Health Safety
Regulation



About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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Human or Animal Origin Devices

This Chapter provides a background to the safety issues associated with therapeutic goods of animal/human origin. It sets out the TGA's guidelines on these goods and provides guidance to sponsors for preparation of submissions for regulatory approval. The guidelines are also applicable to animal/human derived substrates used in the manufacture of therapeutic goods (e.g. enzymes, bovine serum albumin in culture media).

Therapeutic goods of animal/human origin pose a special risk in the fields of medicine and veterinary medicine. Reported incidents of pathogen transmission to humans via these types of therapeutic goods have resulted in a heightened awareness of the need for rules governing tissue selection, harvesting, processing and use.

Documented cases of viral contamination of blood, blood products and vaccines have been associated with reported transmissions of HIV, Hepatitis B and Hepatitis C. Agents implicated in the neurodegenerative spongiform encephalopathies were transferred in cadaveric derived pituitary gland hormonal extracts, dura mater and cornea.

Monoclonal antibodies, recombinant therapeutic proteins (hormones, clotting factors) and gene therapy products (DNA vaccines) may have the potential to provide a path for the transfer of a variety of infectious agents between animal and human or human to human.

Adventitious viral agents present in animal derived ingredients, such as enzymes, foetal calf serum and other growth supplements used in production processes and cell culture, may contaminate the therapeutic good. In the future, therapeutic products may be derived from transgenic animals which may harbour infectious agents (known and unknown).

The medical application of goods derived from human and/or animal tissue is extensive, ranging from implantable therapeutic devices, pharmaceutical products including homoeopathic goods to topical preparations, biological reactants (e.g. enzymes, culture medium) used in the processing of therapeutic goods and those used in the laboratory as *in vitro* diagnostics. Tissues retrieved from a single cadaver donor may be transplanted to many recipients (cornea, cardiac valves, Achilles tendon, skin, cartilage, soft tissue and bone) and therefore, if infective, will place many at risk.

Common zoonotic and pathogenic organisms are traditionally eliminated or reduced by donor screening, raw material selection and during processing by extraction, chemical treatment and sterilisation; the method chosen is based on the active chemical and/or physical properties of the therapeutic good which need to be retained for therapeutic action.

Primary control of potential infectivity in human and animal materials for use in the production of therapeutic goods shall ideally be achieved through donor selection. Screening donors for evidence of transmissible disease is effected by studying the medical/veterinary history, and in the case of human donors the response to an appropriate life style and medical questionnaire by the donor (live donation) or relatives, and in all cases performing specific tests on tissue samples to detect surrogate markers or antigens.

In some cases (e.g. Hepatitis C), the existence of a window period following infection compromises

these safeguards, however new techniques such as nucleic acid amplification may increase the probability of detecting the presence of viruses and other conventional infectious agents during this interval. Further protective steps should be built into the manufacturing protocol to ensure the destruction of any residual infectivity. Human/animal materials contained in therapeutic goods for supply in Australia are subjected to rigorous scrutiny of the controls on selection, screening and processing as an aid in determining the risk of infectious species surviving through to the end product.

Transmissible Spongiform Encephalopathies

Agents thought to be responsible for the infectivity of neurodegenerative diseases of the spongiform encephalopathies, (e.g. Creutzfeldt-Jakob Disease (CJD), bovine spongiform encephalopathy (BSE) kuru, scrapie), are resistant to virtually all forms of conventional sterilisation techniques. These agents, generally argued to be prions (infective protein), are resistant to proteolytic enzymes and saponification in various detergents. They are insensitive to normal autoclaving cycles at 121⁰C, UV-irradiation, treatment with ethylene oxide, freeze-drying, dry heat to at least 200⁰C and chemical sterilants such as formaldehyde and glutaraldehyde.

Transmissibility of the spongiform agents between species has been observed, sheep scrapie to cattle, scrapie/BSE agents to exotic and domestic cats and, in the laboratory, agents of scrapie, BSE and CJD to mice, hamsters and primates. During the last two decades brain extracts from scrapie infected sheep have been tested to determine the physicochemical features, transmissibility and distribution of prions in host tissue.

More recently, with the advent of bovine spongiform encephalopathy and the recognition of transmissible spongiform disease in other species, comparison of the agent and clinical manifestation have been extensively studied. Research, however, has been hampered by the long incubation period of the infectious agent and the lack of diagnostic procedures available for its early detection.

Guidance documents, Pharmacopoeial Monographs and Codes of GMP

Guidance documents have been developed by the major international regulatory agencies to provide tissue selection and manufacturing criteria for minimising the risk of prion and viral contamination of therapeutic products. Pharmacopoeial specifications for some biological products are in the process of being modified to prescribe donor sourcing criteria.

In addition to the guidance provided by the Committee for Proprietary Medicinal Products (CPMP), quality in selection and manufacture of materials is to some extent governed under the Codes of Good Manufacturing Practice in most countries and more comprehensively in Australia under the *Australian Codes of Good Manufacturing Practice for Therapeutic Goods - Human Tissues (September 1995)* and - *Blood and Blood Components (December 1995)*. These two Australian Codes require manufacturers of human materials to select donors according to specified safety criteria, to keep complete records of each donor/donor history, raw material retrieval, processing through to recipient/s, for a period of at least twenty years.

As Guidance documents, Pharmacopoeial monographs and Codes of GMP inevitably lag behind scientific discovery and development of new techniques, it is incumbent upon manufacturers to keep themselves informed of matters relevant to their products.

Australian Requirements for Therapeutic Goods of Biological Origin

There are two levels of import control imposed on therapeutic goods of biological origin proposed for supply in Australia.

- The Australian Quarantine Inspection Service (AQIS) of the Department of Primary Industry and Energy (DPIE) restricts the importation of animal materials to Australia to prevent introduction of exotic diseases into the animal population. For example, the importation of catgut/collagen sutures, which may be administered in the treatment of both animal and human patients, is restricted to those containing material derived only from herds in countries free of BSE (bovine material) or scrapie (ovine, caprine material). Biological goods solely for use in humans generally receive minimal assessment by AQIS for Import Permit issue.

An Import Permit must be obtained from AQIS, Department of Primary Industry & Energy, prior to importing goods containing biological material. Refer Chapter 1.4 *Quarantine Requirements*.

- The TGA requires goods containing animal/human ingredients or materials and those which employed animal/human substrates during manufacture to bring the therapeutic good to its final state to be evaluated for safety, quality and in some cases efficacy to determine eligibility for importation and/or supply in Australia for therapeutic use. Evidence to establish compliance with the following principles and guidelines must be submitted in support of an application for registration or listing.
 - a) compliance with the Therapeutic Goods (Manufacturing Principles)^{2,3,4} as determined under the *Therapeutic Goods Act 1989*;
 - b) freedom of the donor/s (human or animal) from known infectious agents pathogenic to the recipient; and
 - c) adherence to the principles of the following Committee for Proprietary Medicinal Products (CPMP) guidelines (as applicable to the product type):
 - i) *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products - CPMP/BWP/877/96* (attached).
 - ii) *Note for Guidance on Plasma Derived Medicinal Products - CPMP/BWP/269/95* (attached).
 - iii) *Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies Validating the Inactivation and Removal of Viruses - CPMP/BWP/268/95* (attached).
 - d) other product criteria set out by the TGA in the respective publications which provide guidelines for determining the safety and efficacy of therapeutic goods^{5,6,7}.

A questionnaire, *Source Materials and Risk of Infectivity*, must be completed for each type of tissue material. Details can be found in Chapter 2.10 *Animal Origin Devices* and 2.15 *Human Origin Devices*, dealing with devices containing human or animal tissue. The questionnaire is divided into the following sections:

Section A	Source Material and Risk of Infectivity - Human Materials
Section B	Source Material and Risk of Infectivity - Animal Materials
Section B1	Virus control
Section B2	Control agents causing spongiform encephalopathies

to assist applicants to provide the minimum information required for the evaluator to make an assessment of the potential pathogenicity of the product.

Section A	considers factors important in reducing the risk of viral contamination and agents causing prion diseases in products of human origin.
Section B1	deals with the risk factors of potentially pathogenic viral contamination in therapeutic goods derived from animal materials.
Section B2	inquires into the additional steps taken to minimise the infectious agents responsible for the transmission of spongiform encephalopathies in therapeutic goods that are derived from bovine, ovine or caprine materials.

Goods currently exempt from the *Source Materials and Risk of Infectivity* Questionnaire:

- *In vitro* diagnostic goods* of human origin or those for home use or supplied under the Pharmaceutical Benefits Scheme (PBS) which include material of human and/or animal origin (the exemption does not include *in vitro* diagnostic HIV or Hepatitis C kits);
- banked human tissues and blood which undergo primary processing** only;
- the following species and processed substances, used as actives or excipients in the manufacture of products for oral, aural, topical, vaginal and rectal administration, but not necessarily exempted from GMP or AQIS requirements (refer to (d) above). This list of exemptions will be reviewed periodically:
 - Lactose EP
 - Gelatin EP
 - Animal Waxes
 - Casein and caseinates
 - Phosphatidyl choline, lecithin, phospholipids -
except those derived from neural tissue)
 - Cholesterol EP
 - Amino acids
 - Trypsin EP
 - Glycerol and glyceryl esters of fatty acids,
including triglycerides complying with Fasciculum 19, EP 2nd Ed)
 - Stearic acid and metal salts of stearates
 - Stearyl alcohols and their esters
 - Cetyl alcohols and their esters

- Sorbitan esters
- Polyoxyethylene alkyl ethers
- Wool fat BP (Anhydrous Lanoline) and its derivatives
- Hydrous Wool Fat BP (Lanoline) and its derivatives
- Wool alcohols BP
- Materials of insect origin (e.g. shellac, beeswax, silk)
- Materials obtained from marine species (e.g. cod liver oil, squalene, spermaceti)
- Materials of mollusc (e.g. squid, cuttlefish, snail, oyster) origin
- Spiders, crustaceans, centipedes, millipedes, coral, sea cucumbers, starfish
- Sponges, jellyfish, eels, worms, leeches
- Amphibians (e.g. frogs, toad, salamanders)
- Reptiles (e.g. snakes, lizards, crocodiles, turtles)
- Marsupials (e.g. kangaroo, possum)
- Materials of totally synthetic origin, the starting materials for which are not themselves of animal origin
- Any substance which does not contain carbon in its molecular structure



* In vitro diagnostic goods of human origin or those for home use or supplied under the PBS which include material of human and/or animal material, are required to comply with the relevant guidelines specified in Chapter 3.21 *In Vitro Diagnostics*.

** Primary processing - retrieval, cleaning/washing, trimming, segmenting, sterilisation, and transferral to storage solutions (if appropriate) and containers, of human material at a tissue bank complying with the *Australian Code of Good Manufacturing Practice for Therapeutic Goods Human Tissues* or the *Australian Code of Good Manufacturing Practice for Therapeutic Goods Blood and Blood Components*, whichever is relevant.

Fresh viable tissue e.g. liver, kidney, heart for direct donor-recipient transplantation, leather, wool, hides and bristles are excluded therapeutic goods and are therefore not subject to the requirements of the *Therapeutic Goods Act 1989* or these guidelines. The application of this policy is relevant to biological goods of animal/human origin other than those specifically listed as exempt above.

Bibliography

1. Guidelines for the Importation of Biological Products; Australian Quarantine and Inspection Service, Department of Primary Industry, July 1994
2. Australian Code of Good Manufacturing Practice for Therapeutic Goods Human Tissues, Sept 1995
3. Australian Code of Good Manufacturing Practice for Therapeutic Goods Blood and Blood Components, Dec 1995
4. Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 1998
5. DR4, Requirements for the supply of Therapeutic Devices under the Therapeutic Goods Act 1989.

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