



**Australian Government**  
**Department of Health**  
Therapeutic Goods Administration

# Guidance 10: Adventitious agent safety of medicines

(Previously ARGPM Appendix 10: Ingredients  
of human or animal origin)

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**TGA** Health Safety  
Regulation

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# Contents

<b>Introduction</b>	<b>4</b>
<b>10.1 What is involved in adventitious agent safety</b>	<b>4</b>
<b>10.2 Information about adventitious agent safety in an application for ARTG entry</b>	<b>5</b>
10.2.1 For applications to register a medicine on the ARTG	5
10.2.2 For applications to list a medicine	5
<b>10.3 Testing cell banks for mycoplasma and viruses</b>	<b>6</b>
<b>10.4 Evaluation of materials of animal origin for adventitious agent safety</b>	<b>7</b>
10.4.1 Viral and mycoplasma safety for all materials of animal origin	7
10.4.2 Transmissible spongiform encephalopathy safety for materials of ruminant origin	7
10.4.3 Specific requirements for materials of bovine serum and porcine trypsin	8
10.4.3.1 Bovine serum	8
10.4.3.2 Porcine trypsin	8
<b>10.5 Evaluation of materials of human origin for adventitious agent safety</b>	<b>9</b>
10.5.1 Relates to applications to register a medicine	9
10.5.2 Viral and mycoplasma safety for materials of human origin	9
10.5.3 TSE safety requirements for materials of human origin	9
10.5.4 Specific requirements for human plasma-derived ingredients that are used as excipients	10
<b>10.6 Viral validation studies and risk assessments for adventitious agent safety</b>	<b>11</b>
10.6.1 Relates to applications to register a medicine	11
10.6.2 Viral validation studies	11
10.6.3 Viral risk assessment for retroviruses	11

## Introduction

This guidance is for sponsors of all medicines that contain, or are manufactured using [materials of animal or human origin](#).

It provides guidance on the information required in applications to:

- register or list a medicine on the [Australian Register of Therapeutic Goods \(ARTG\)](#) to demonstrate their safety with regard to [adventitious agents](#)
- vary the details of a registered prescription medicine.

This guidance does not address safety issues for sterility, or for endotoxin, chemical or other types of contamination.

## 10.1 What is involved in adventitious agent safety

Adventitious agent safety involves viral and mycoplasma safety, and TSE safety:

- testing of cell banks for mycoplasma, and endogenous and exogenous viruses
- evaluation of materials of animal origin, such as media components, materials used as part of a chromatography matrix and excipients
- evaluation of materials of human origin, such as human serum albumin
- viral validation studies and viral risk assessment
- TSE risk assessment.

## 10.2 Information about adventitious agent safety in an application for ARTG entry

### 10.2.1 For applications to register a medicine on the ARTG

Include the information outlined in this guidance in Module 3, Section 3.2.A.2, 'Adventitious agent safety evaluation' of the [Common Technical Document \(CTD\)](#).

### 10.2.2 For applications to list a medicine

- Refer to European Pharmacopoeia (Ph. Eur.) - 5.2.8, 'Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products'.
- Complete and submit the [Pre-clearance application for animal-derived ingredients form](#) to obtain a pre-clearance number.
- Complete the necessary fields in the [eBusiness listed medicines online application form](#) (such as ingredient, country of origin, animal, animal part and preparation, and the pre-clearance number for the ingredient).

#### Related information and guidance

- [British Pharmacopoeia](#) (BP) 2012 - Appendix XXIIB, 'Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products'.
- Ph. Eur. - 5.2.8, 'Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products'.
- European Directorate for the Quality of Medicines & HealthCare (EDQM) certificate, if available.
- TGA's [Approach to minimising the risk of exposure to TSEs through medicines and medical devices](#).



## 10.3 Testing cell banks for mycoplasma and viruses

Provide information that cell banks have been tested for mycoplasma and viruses in accordance with the following guidelines:

- [Note for guidance on quality of biotechnological products: derivation and characterisation of cell substrates used for production of biotechnological/biological products \(CPMP/ICH/294/95\)](#)
- [Note for guidance on quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin \(CPMP/ICH/295/95\)](#)

Provide test protocols and study reports to the TGA for assessment.

## 10.4 Evaluation of materials of animal origin for adventitious agent safety

The following guidance relates to applications to register a medicine.

### 10.4.1 Viral and mycoplasma safety for all materials of animal origin

Provide the following information for each material of animal origin that is contained in, or used in the manufacture of the medicine:

- tissue and species of origin
- evidence that the material is from animals slaughtered in a government-approved slaughterhouse
- evidence of ante-mortem and post-mortem (if applicable) inspection and an assurance that the materials come from healthy animals that are fit for human consumption
- details of the manufacturing process, such as a flow chart
- details of the measures taken to prevent cross-contamination with tissues from other species.

### 10.4.2 Transmissible spongiform encephalopathy safety for materials of ruminant origin

In addition to the viral and mycoplasma safety requirements listed above:

- provide the following information for each material of ruminant origin that is contained in, or used in the manufacture of the medicine:
  - country or countries of origin
  - details of measures taken to prevent cross-contamination of Category IC tissue with higher infectivity (Category IA or Category IB) tissues.



#### Related information and guidance

- Ph. Eur. - 5.2.8, 'Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products'

### 10.4.3 Specific requirements for materials of bovine serum and porcine trypsin

In addition to the viral and mycoplasma safety requirements for materials of animal origin and the specific requirements for materials of ruminant origin (if relevant), the following materials of animal origin require additional information in Module 3, Section 3.2.A.2 of the CTD.

#### 10.4.3.1 Bovine serum

Bovine serum includes:

- adult bovine serum
- fetal bovine serum
- newborn calf serum.

Provide a certificate of analysis that indicates that the bovine serum tested negative for the following adventitious agents:

- **Bacteria**
  - Mycoplasma
- **Viruses**
  - bluetongue and related orbiviruses
  - bovine adenovirus
  - bovine parvovirus
  - bovine respiratory syncytial virus
  - bovine viral diarrhoeal virus
  - infectious bovine rhinotracheitis virus
  - parainfluenza-3 virus
  - rabies virus
  - reovirus 3.

#### 10.4.3.2 Porcine trypsin

Provide evidence that the suppliers of porcine trypsin have implemented measures to ensure adventitious agent safety.



#### Related information and guidance

- Note for guidance on the use of bovine serum in the manufacture of human biological medicinal products (CPMP/BWP/1793/02)



## 10.5 Evaluation of materials of human origin for adventitious agent safety

### 10.5.1 Relates to applications to register a medicine

Provide the requested information in Module 3, Section 3.2.A.2 of the [CTD](#).

### 10.5.2 Viral and mycoplasma safety for materials of human origin

Provide the following information for each material of human origin that is contained in, or used in the manufacture of the medicine:

- donor questionnaire
- results of viral marker testing for individual donations, including details of the kits and test methods used. At a minimum, provide results for human immunodeficiency virus, hepatitis B virus and hepatitis C virus
- full details of the manufacturing process.

### 10.5.3 TSE safety requirements for materials of human origin

In addition to the viral and mycoplasma safety requirements, provide the following information for TSE safety assessment:

- country or countries of origin
- assurance that the donors have not:
  - resided in the United Kingdom for a cumulative period of six months or more between 1980 and 1996
  - received a blood transfusion or injection of blood or blood products in the United Kingdom from 1980 onwards (as specified in [Therapeutic Goods Order No. 102 – Standards for blood and blood components](#) [TGO 102]).



#### Related information and guidance

- [Position statement on CJD and plasma-derived and urine-derived medicinal products \(EMA/CHMP/BWP/303353/2010\)](#)
  - (Section 9.2.5) minimising TSE risk for albumin used as an excipient
  - (Section 9.3) urine-derived products
- [Therapeutic goods that contain or are produced from human blood or plasma](#)

## 10.5.4 Specific requirements for human plasma-derived ingredients that are used as excipients

In addition to the viral, mycoplasma and TSE safety requirements for materials of human origin, provide the following information for these human plasma-derived ingredients:

- [plasma master file \(PMF\)](#)
- assurance of compliance with [TGO 102](#) and [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)
- details of the full manufacturing process
- results of viral validation studies and viral risk assessment for the viral markers
- results of TSE validation studies and TSE safety assessment.

Adventitious agent safety does not need to be assessed separately if the human serum albumin is registered as a primary product in the ARTG.

Provide the ARTG number and details of the approved PMF.

If the human serum albumin is registered as a primary product with another regulatory agency, adventitious agent safety may have already been demonstrated. In this case, provide an assurance that the plasma donors who contributed to the manufacture of the albumin comply with TGO 102 and TGO 88.



### Related information and guidance

- [Therapeutic goods that contain or are produced from human blood or plasma](#)

## **10.6 Viral validation studies and risk assessments for adventitious agent safety**

### **10.6.1 Relates to applications to register a medicine**

Provide the requested information in Module 3, Section 3.2.A.2 of the CTD.

### **10.6.2 Viral validation studies**

Relates to medicines manufactured by biotechnology and medicines derived from plasma.

Provide viral validation study report, and protocols that have been carried out in accordance with:

- Virus validation studies: The design, contribution and interpretation of studies validating the inactivation and removal of viruses (pp. 295 - 309 of Rules 1998 (3A) - 3AB8a)
- 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)

### **10.6.3 Viral risk assessment for retroviruses**

Provide details of calculations for estimation of retroviral particles in biotechnological medicines carried out in accordance with the following guideline:

- 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)

## Version history

<b>Version</b>	<b>Description of change</b>	<b>Author</b>	<b>Effective date</b>
V1.0	Original publication	Office of Medicines Authorisation	09/08/2013
V1.1	Changed references to TGO 81 to TGO 102	Scientific Evaluation Branch	05/04/2019

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