

### **TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHY (TSE) GUIDELINES FOR MINIMISING THE RISK OF CONTAMINATION IN CHINESE PROPRIETARY MEDICINES, TRADITIONAL MEDICINES & HEALTH SUPPLEMENTS**

The information in this Guidelines shall be updated or revised from time-to-time. For any new, addition, amendments or deletion made to this Guidelines, please refer to the latest version in our website [www.hsa.gov.sg](http://www.hsa.gov.sg).

## 1 Introduction

Transmissible Spongiform Encephalopathy (TSE) includes scrapie in sheep and goats, chronic wasting disease in mule, deer and elk, bovine spongiform encephalopathy (BSE) in cattle, as well as Kuru and Creutzfeldt-Jakob Disease (CJD) in humans. Agents causing these diseases replicate in infected individuals generally without evidence of infection detectable by currently available diagnostic tests. It is believed that these agents may have incubation periods of up to several years before causing observable disease (usually neurological disorder) and eventually death. No means of therapy are known.

BSE was first recognised in the United Kingdom in 1986. A large number of cattle and individual herds have since been affected. BSE is a food borne infection and there is evidence suggesting that the new variant of human Creutzfeldt-Jakob Disease (vCJD) may be caused by the same agent that is responsible for BSE in cattle.

The discovery of vCJD has raised concerns that the BSE agent can be transmitted to man. Caution is therefore warranted if biological materials from species known to be affected by TSE, are used for the manufacture of health products. This guideline provides recommendations that should be followed to minimise the risk of TSE agent contamination in Chinese Proprietary Medicines, Traditional Medicines and Health Supplements. (These groups of products will subsequently be referred to as “these products” in this document.)

## 2 Scope of Guideline

This guideline highlights the various measures that should be taken to minimise the risk of TSE transmission. It applies to all materials of ruminant origin that are used in the preparation of both active (e.g. sheep placenta) and inactive ingredients (e.g. gelatin), and any other reagent that may come into contact with these products during their manufacturing process (e.g. enzymes). For human blood-derived ingredients, please refer to the “Guidelines on licensing and post-licensing control of medicinal products derived from human blood”. This document is subject to regular updates and review as scientific and regulatory developments are made available.

## 3 Documentary Requirements

The risk of transmission of infectious agents can be greatly reduced, by controlling a number of parameters. These parameters include the source of animals, the nature of animal tissue used in manufacturing and the production process. Detailed information as listed in the following paragraphs must be submitted, when requested, to support the safe use of any of these products that contain animal-derived ingredients.

### 3.1 Source of animals

3.1.1 The most satisfactory source of materials is from countries without any reported case of BSE (please refer to the updated statistics for BSE positive countries provided by Office International Des Epizooties (OIE),

<http://www.oie.int/animal-health-in-the-world/official-disease-status/bse/list-of-bse-risk-status>).

- 3.1.2 Materials sourced from countries where a positive number of indigenous cases have occurred would not be acceptable unless there is proper justification.
- 3.1.3 Companies shall be required to hold the necessary documentary proofs to verify the source and to prove that their products are free from the risk of TSE. The documents should be submitted to the Authorities when required.

### **3.2 Nature of animal tissue used in manufacturing**

- 3.2.1 In a BSE-infected animal, different organs and secretions have different levels of infectivity. On the basis of data on natural scrapie, organs, tissues, and fluids have been classified into four main groups bearing different potential risks, as shown below.

a) Category I (High Infectivity): brain, spinal cord, eye

b) Category II (Medium Infectivity): ileum, lymph nodes, proximal colon, spleen, tonsil, dura mater, pineal gland, placenta, cerebrospinal fluid, pituitary, adrenal

c) Category III (Low Infectivity): distal colon, nasal mucosa, peripheral nerves, bone marrow, liver, lung, pancreas, thymus

d) Category IV (No detectable Infectivity): blood clots, faeces, heart, kidney, mammary gland, milk, ovary, saliva, salivary gland, seminal vesicle, serum, skeletal muscle, testis, thyroid, uterus, foetal tissue, bile, bone, cartilaginous tissue, connective tissue, hair, skin, urine

- 3.2.2 The WHO considers milk and milk products safe. Tallow and gelatin are also considered safe by WHO if prepared by a manufacturing process, which has been shown experimentally to minimise the transmission of the transmissible agent and, if prepared from specifically identified tissues, or from cattle without risk of exposure to TSE. These materials, subject to the above requirements, may be used in these products. Companies are to hold such evidence and submit them to the Authority when required to do so.

- 3.2.3 In certain situations there could be cross-contamination of tissues from different categories of infectivity e.g. direct contact between different materials, or the use of penetrative brain stunning as a method of slaughtering the animals.

- 3.2.4 Companies are responsible for providing supporting documents, to the Authority when required, with detailed information on the following:

- Nature and quantity of each animal-derived material:
  - o Used in the manufacturing process (whether or not this is present in the final product); and
  - o Present in the final product formulation.

- Information from the manufacturer to demonstrate that adequate measures have been taken to prevent cross-contamination.

### **3.3 Production process**

- 3.3.1 Controlled sourcing is the most important criterion in achieving acceptable safety of the product due to the documented resistance of TSE agents to most inactivation procedures. The production process, wherever possible, should be designed to take into consideration all available information on methods that are thought to inactivate or remove TSE agents.
- 3.3.2 If claims are made that inactivation of TSE agents occurs during the manufacturing process, relevant information on the process should be submitted when required by the Authority.

### **3.4 Assessment report for the risk of TSE**

- 3.4.1 The supporting documents should include an assessment report on the risk of TSE in relation to the product when required by the Authority.
- 3.4.2 The scope of this report should cover sections 3.1, 3.2 and 3.3 above, as well as the risk factors associated with the route of administration and the maximum recommended dosage (daily dosage and duration of usage) of the product.

### **3.5 Certificate of Suitability**

- 3.5.1 Where applicable, Certificates of Suitability for some animal-derived materials could be obtained from the European Directorate for the Quality of Medicines (EDQM). Companies could use these Certificates of Suitability, in lieu of the documents stipulated under paragraphs 3.1 to 3.4 above, to support the safe use of their products.
- 3.5.2 Applicant may refer to Ph. Eur. and the EDQM website (<http://www.pheur.org>) for more information on TSE and the Certificate of Suitability.

### **3.6 Summary of requirements**

- 3.6.1 For easy reference, a diagrammatic summary of the controls, along with the checklist for documentary requirements is attached as Annexes I and II respectively.

## **4 OTHER REQUIREMENTS**

### **4.1 Compliance with Legal Requirements**

The responsibility is on companies dealing in these products to ensure that their products comply with the relevant legal requirements.

## 4.2 Requirements for Dealers

Companies dealing in these products that contain ingredients derived from animal sources have to be vigilant in the checking of documentation and maintenance of records. Companies that receive reports on possible product contamination by infective agents such as TSE should immediately check their records for any importation or distribution of the product. The dealer for any of these products should put in place a recall plan and a crisis management plan.

## 5 Conclusion

The acceptability of these products containing animal source ingredients, or which as a result of manufacture could contain these materials, will be influenced by a number of factors, including:

- Documented and recorded source of animals
- Nature of animal tissue used in the manufacture
- Production process
- Route of administration
- Quantity of tissue used in these products
- Maximum therapeutic dosage
- Intended use of the products

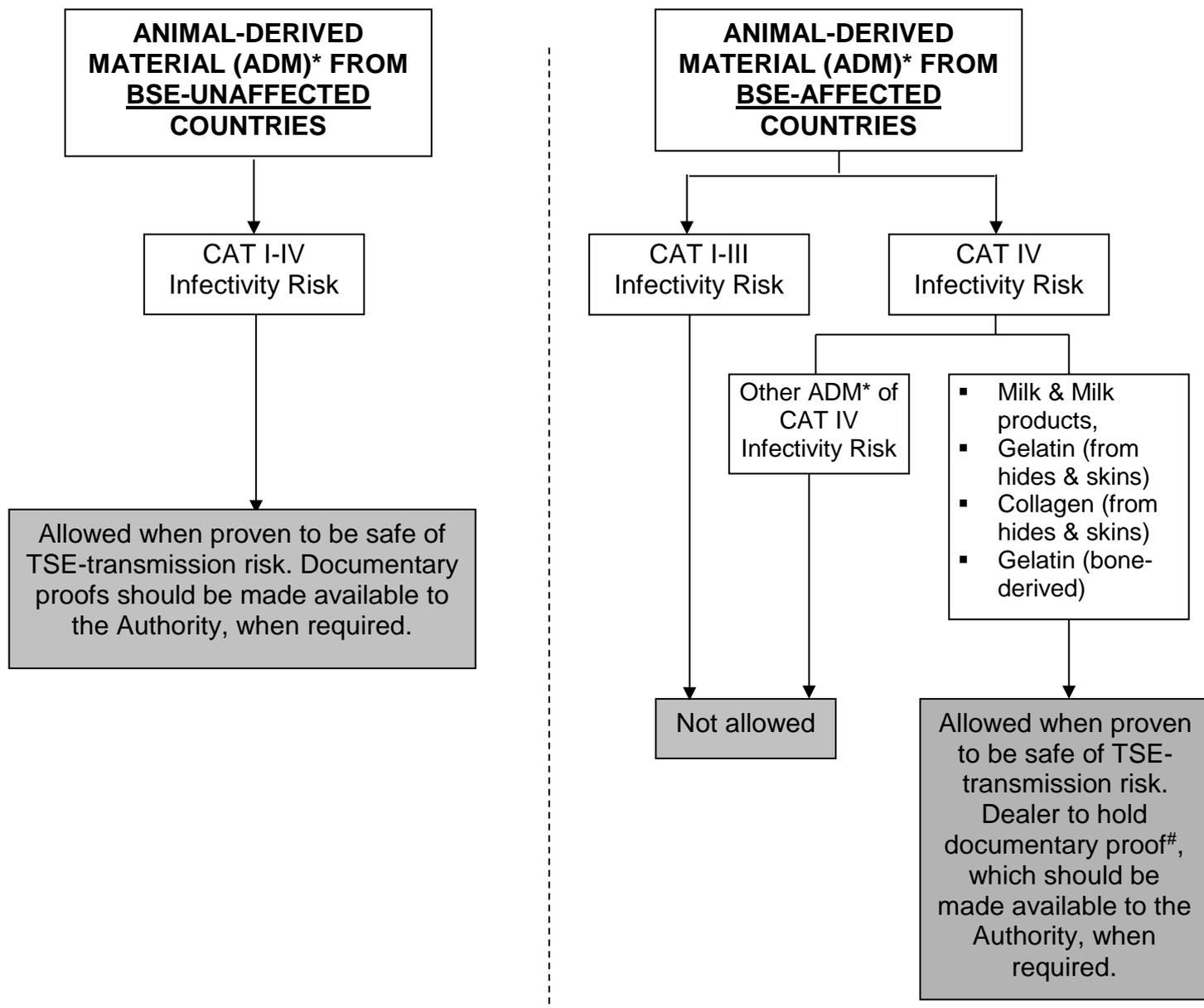
The above guidelines only serve as guidance. Manufacturers and owners are required to observe international best practices at all times and to comply with the requirements of the EU, USA, Australia, Canada, in particular, the requirements set down in the following documents:

- a) CPMP & CVMP's Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, EMEA/410/01
- b) Guidance for Industry – The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use, by US FDA
- c) Ph. Eur. general monograph on “Product with risk of transmitting agents of animal spongiform encephalopathies”

**Updated as of February 2018. The guidance may be updated from time-to-time. For more information on the regulation of health products in Singapore, please refer to the HSA website (<http://www.hsa.gov.sg>).**

ANNEX I

**DIAGRAMMATIC SUMMARY OF CONTROLS**



**#:** As listed in Annex of the “Transmissible Spongiform Encephalopathy (TSE) Guidelines for minimising the risk of contamination in Chinese Proprietary Medicines, Traditional Medicines and Health Supplements”

**\*:** From species known to be affected by TSE e.g. ruminants like sheep, cow etc.

## ANNEX II

## (CHECKLIST)

Ref to Guide	Document	Available? Yes/No Enclosure. No
<b>3</b>	<b><u>Documentary Requirements</u></b>	
<b>3.1</b>	<b>Source of animal*</b>	
3.1.1	<p>Updated notification of BSE cases in the country where each animal material is sourced, where applicable.</p> <p><u>Please note:</u> The onus of responsibility rests on the Company to notify the Authority if there is any reported BSE cases in the country of origin.</p>	
3.1.2	Justification for using animal materials from BSE positive countries (if applicable).	
3.1.3	Documentary proofs issued by the health authorities in the source country to show that the raw materials used are sourced from TSE-free herds.	
<b>3.2</b>	<b>Nature of animal tissue* used in manufacturing</b>	
3.2.2	<p>a. Products containing tallow and gelatin:</p> <ul style="list-style-type: none"> <li>– Evidence to show that the animal-derived materials have been prepared by a manufacturing process, recommended by WHO, shown experimentally to inactivate the transmissible agent and</li> </ul> <p>b. The materials have been prepared from specifically identified tissues, or from cattle without risk of exposure to BSE.</p>	

# HEALTH SCIENCES AUTHORITY

Health Products Regulation Group  
Blood Services Group  
Applied Sciences Group

[www.hsa.gov.sg](http://www.hsa.gov.sg)

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