JULY 2022

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

The information in these Guidelines may be updated from time-to-time. For the latest version of the Guidelines, please refer to our website at www.hsa.gov.sg.

Content: **Page**

1. Introduction

1.1 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. There is currently no treatment or vaccine against it.

1.2 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.

1.3 The discovery of vCJD has raised concerns that the agent causing BSE 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, Health Supplements and Traditional Medicines. (These groups of products will subsequently be referred to as “these products” in this guideline.)

2. Scope

2.1 These guidelines highlight the various measures that should be taken to minimise the risk of TSE transmission. They apply to all materials of ruminant origin that are used in the preparation of both active ingredients that contribute to a product’s intended function (e.g. sheep placenta) and inactive or formulation ingredients that do not contribute to the intended function of the product (e.g. gelatin), and any other materials that may come into contact with these products during their manufacturing process (e.g. enzymes, processing aids, and solvents). These guidelines are subject to regular updates and review as scientific and regulatory developments are made available.

3. Documentary Requirements

3.1 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. When requested, detailed information as listed in the following paragraphs must be submitted, to support the safe use of products that contain animal-derived ingredients.

A. Source of animals

3.2 The safest 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), Official Disease Status - WOAH - World Organisation for Animal Health.

3.3 Materials sourced from countries where a positive number of indigenous cases have occurred would not be acceptable unless there is clear justification.

3.4 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. These documents should be submitted to HSA when required.

B. Types of animal tissue used in manufacturing

3.5 The WHO has categorised the levels of infectivity of different organs and secretions of BSE-infected animals into 3 categories of infectivity. More details are available in the Guidance notes published by WHO: "WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies" (updated 2010) WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies.

a) High infectivity (Category IA): brain, spinal cord, retina, optic nerves, spinal ganglia, pituitary gland, and dura mater.

b) Lower infectivity (Category IB): peripheral nerves, spleen, lymph nodes, thymus, oesophagus, stomach, colon, rectum, placenta, ovary, uterus, mammary gland, liver, kidney, lung, adrenal gland, pancreas, blood vessels, salivary gland, cornea, bone marrow, CSF, blood, saliva, milk, urine, and faeces.

c) Tissues with no detectable infectivity (Category IC): testis, prostate, semen, placental fluid, foetus, embryos, bone, tendon, dental pulp, trachea, thyroid gland, colostrum, sweat, tears, and bile.

3.6 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 specific 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 HSA when required to do so.

3.7 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. Measures to prevent and/or reduce cross contamination of materials in Categories IA, IB and IC should be taken into consideration when sourcing raw materials.

3.8 Companies are responsible for providing supporting documents to HSA when required, with detailed information on the following:

- Nature of each animal-derived material:
    - Used in the manufacturing process (regardless of whether it is present in the final product); and
    - Present in the final product formulation.
- Information from the manufacturer to demonstrate that adequate measures have been taken to prevent cross-contamination.

C. Production Process

3.9 The production process, wherever possible, should be designed to take into consideration all available information on methods that could inactivate or remove TSE agents, as this would augment the safety provided by controlled sourcing.

3.10 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 HSA.

D. Assessment Report for the Risk of TSE

3.11 The supporting documents should include an assessment report on the risk of TSE in relation to the product when required by HSA.

3.12 The scope of this report should cover sections 3.A, 3.B and 3.C as described 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.

E. Certificate of Suitability

3.13 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.A to 3.D above, to support the safe use of their products.

3.14 Please refer to Ph. Eur. and the EDQM website http://www.pheur.org for more information on TSE and the Certificate of Suitability.

F. Summary of Requirements

3.15 For easy reference, a diagrammatic summary of the controls, along with the checklist for documentary requirements are found in Annex 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. A recall plan and a crisis management plan should be put in place when dealing in these products.

5. Summary of Requirements

5.1 The acceptability of these products containing animal-sourced ingredients, or which as a result of manufacture could contain these materials, will be determined by a number of factors, including documented:

- Source of animals
- Nature of animal tissue used
- Production process
- Route of administration
- Quantity of tissue used
- Maximum therapeutic dosage
- Intended use

5.2 These guidelines serve only as guidance. Manufacturers, product owners and importers 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:

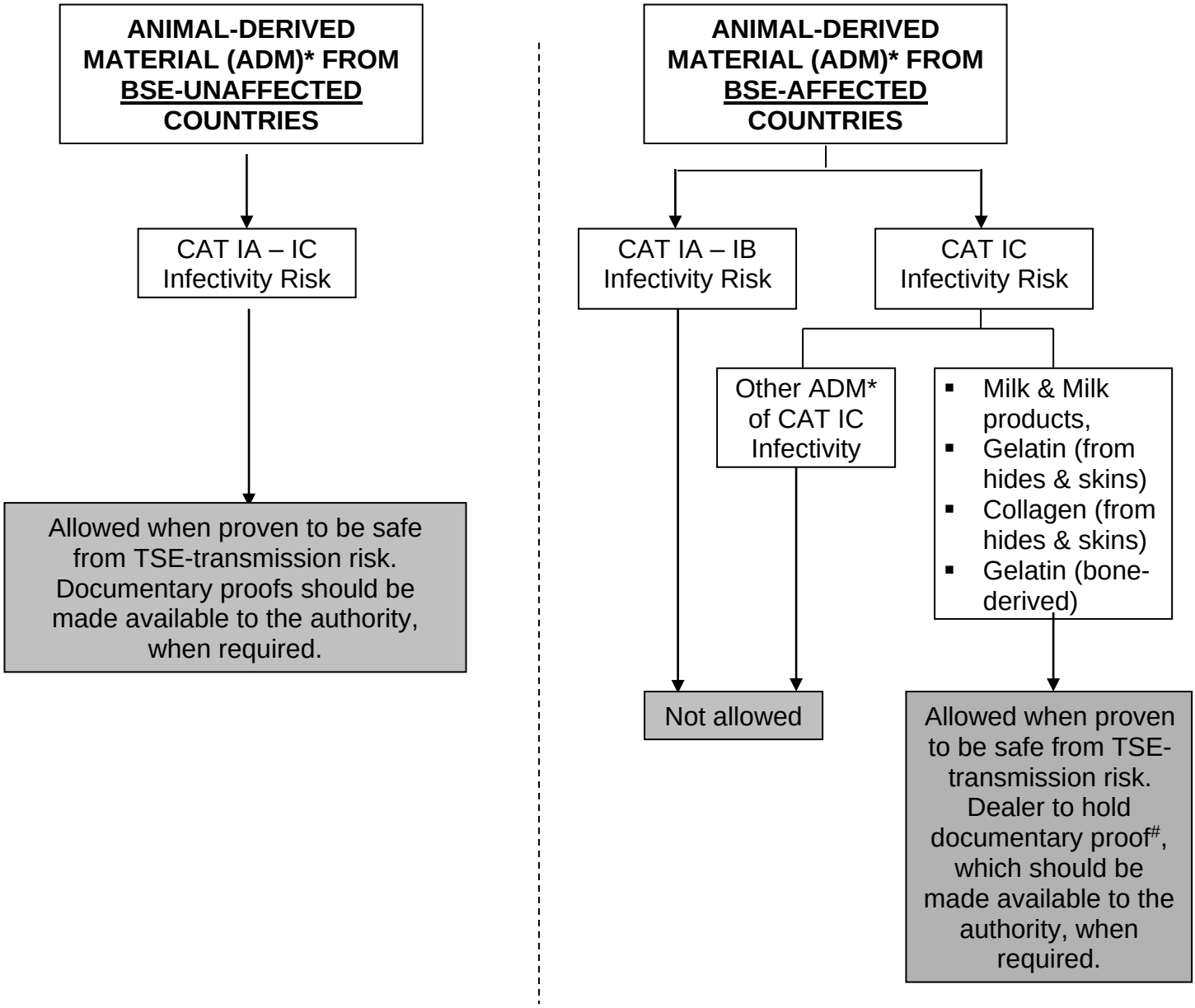
a) CPMP & CVMP's Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, EMEA/410/01

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"

6. ANNEX I

DIAGRAMMATIC SUMMARY OF CONTROLS



 # As listed in Annex II of these guidelines

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

7. ANNEX II

CHECKLIST FOR SELF-ASSESSMENT

Ref to Guide	Document	Available? Yes/No Enclosure number
3	**Documentary Requirements**	
A.	**Source of animal**	
	Updated notification of BSE cases in the country where each animal material is sourced, where applicable. Please note: The onus rests on the company to notify HSA if there are any reported BSE cases in the country of origin.	
	Justification for using animal materials from BSE positive countries (if applicable).	
	Documentary proof issued by the health authorities in the source country to show that the raw materials used are sourced from TSE-free herds.	
B.	**Type of animal tissue used in manufacturing**	
	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.	
	The materials have been prepared from specifically identified tissues, or from cattle without risk of exposure to BSE.	
	Considerations have been taken to reduce cross contamination between different tissues when sourcing, storing, and processing the raw materials.	
C	**Manufacturing process(es)**	
	Evidence to show that TSE inactivation/reduction methods have been considered when developing the manufacturing methods.	
	Documentary proof from manufacturers on the inactivation of TSE agents during the manufacturing process of the product.	

8. References

8.1 ASEAN Guidelines for Minimising the Risk of Transmissible Spongiform Encephalopathies in Health Supplements

8.2 ASEAN Guidelines for Minimising the Risk of Transmissible Spongiform Encephalopathies in Traditional Medicines

Contact information
Complementary Health Products Branch
Medicinal Products Pre-Market Cluster
Health Products Regulation Group
Health Sciences Authority

11 Biopolis Way
Singapore 136667
www.hsa.gov.sg
Email: hsa_chp@hsa.gov.sg