APPENDIX 9 *GUIDELINE ON THE REGISTRATION OF HUMAN THERAPEUTIC PRODUCTS CONTAINING MATERIALS OF ANIMAL ORIGIN*

Therapeutic products containing animal-derived components carry the potential risk of Transmissible Spongiform Encephalophathy (TSE) and/or may harbour and support the growth of adventitious agents. The safety of these products is assured through the requirements as described in this appendix along with the main guidance document.

Transmissible Spongiform Encephalopathy (TSE)

Transmissible Spongiform Encephalopathy (TSE) is a group of degenerative brain diseases that includes Bovine Spongiform Encephalopathy (BSE) in cattle, scrapie in sheep and goats, Chronic Wasting Disease (CWD) in deer, and Kuru Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD) in humans. Agents causing these diseases replicate in infected individuals generally without evidence of infection detectable by currently available diagnostic tests. There is evidence to show that these agents may have incubation periods of up to several years before causing observable disease, usually neurological disorders, and eventually death. There is currently no treatment or vaccine for the disease.

BSE is a food-borne infection characterised by the presence of prion proteins in nervous tissue. The subsequent spongy degeneration of the brain results in severe and fatal neurological signs and symptoms. There is evidence suggesting that the variant form of Creutzfeldt-Jakob disease (vCJD) in humans 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 humans. Therefore, caution is warranted if biological materials from animals known to be affected by TSE are used in the manufacture of therapeutic products.

1 SCOPE

This guideline[1] is applicable to all therapeutic products that employ materials derived from animals in the manufacture of the drug product. It applies to all materials of animal origin that are used in the preparation of active substances (e.g. insulin), excipients and adjuvants (e.g. gelatin), as well as raw/starting materials (e.g. seed lots, cell banks) and reagents used in production (e.g. bovine serum albumin, enzymes, culture media) of the therapeutic product. This guideline is also applicable to any other animal-derived materials that may come into direct contact with the equipment used in the manufacture of the therapeutic product, or that come into contact with the therapeutic product and therefore have the potential for contamination.

2 DOCUMENTARY REQUIREMENTS

Applications for therapeutic products containing animal-derived materials will be evaluated on the products' quality, safety and efficacy. Documents with detailed information must be submitted to support the registration of all therapeutic products that contain animal-derived ingredients.

For milk and certain milk derivatives such as lactose, in light of the current scientific knowledge and irrespective of geographical origin, these excipients are generally considered non-infectious. As such, a declaration from the supplier of the excipient(s) stating that the milk is sourced from healthy cows fit for human consumption and that no other potentially infectious ruminant materials, with the exception of calf rennet, were used in the preparation of such derivatives (e.g. pancreatic enzyme digests of casein) would suffice. This declaration is to be submitted in CTD section 3.2.P.4.5.

Milk derivatives produced using other processes or rennet derived from other ruminant species must demonstrate compliance with the relevant international guidelines.

[1] Adapted from CPMP-CVMP NfG on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMA/410/01 Rev. 3)

The checklists in Annex 1 serve as a guide to the documents required to support the application. The documentary requirements are further described below in sections 1.1, 1.2 and 1.3. The relevant checklist(s) in Annex 1 is to be completed and submitted in CTD section 3.2.P.4.5 with the supporting documents submitted in ICH CTD section 3.2.A.2 or ACTD section Q.A.2.

Information on the use of animal-derived materials must be captured in section 4.3b of PRISM in the following format: [animal species & tissue/ fluid type, material] – [purpose] – [source country; where applicable].

e.g. Bovine hide, gelatin – excipient (capsule shell) – USA
*e.g. Bovine milk, lactose – excipient**
*e.g. Avian feathers, L-cysteine- manufacturing process (media component) ***
*e.g. Lac bug resin, shellac – excipient (printing ink) ***

**For milk and milk-derivatives (e.g. lactose), it is not required to specify the source country.*
*** For non TSE-relevant species, it is only required to provide information on the source country if the animal-derived material is of mammalian or avian origin, and used as the drug substance, excipient and/ or adjuvant.*

As far as possible, information on the residual amount of animal-derived materials present in the drug product should be clearly stated as follows in CTD section 3.2.P.4.5 and product labels, where applicable:

e.g. Foetal bovine serum (residual) ≤ 0.350 mcg/mL

2.1 Products Containing TSE-Relevant Animal-Derived Materials WITH a Valid TSE Risk Evaluation Certificate of Suitability (CEP)

Preference is accorded to animal-derived materials that have been awarded Certificates of Suitability by the European Directorate for the Quality of Medicines

& Healthcare (EDQM). Applicants may refer to the European Pharmacopoeia and the EDQM website for more information on TSE and the Certificate of Suitability.

The supporting documents to be submitted include:

(a) A valid TSE Risk Evaluation Certificate of Suitability (CEP) and any other supporting information;

(b) A certificate of analysis for each animal-derived material used; and

(c) The purpose of each animal-derived material used.

2.2 Products Containing TSE-Relevant Animal-Derived Materials WITHOUT a Valid TSE Risk Evaluation Certificate of Suitability (CEP)

The use of animal-derived materials that have NOT been awarded Certificates of Suitability by the EDQM may be acceptable, subject to a TSE risk assessment.

The supporting documents to be submitted include:

(a) A brief description of the following:

(i) Rationale for using animal-derived materials

The rationale for using animal-derived materials instead of that with a non-animal origin should be given.

(ii) Information on all countries which the animals were sourced from

A compulsory notification of BSE cases in the country of origin and a compulsory clinical and laboratory verification of suspected cases are required for product applications.

The most satisfactory source of materials is countries without any reported cases of BSE. The assessment of a country's BSE status is based on the following:

- World Organisation for Animal Health (OIE) classification; and
- Opinions of the Scientific Steering Committee of the European Commission

As far as possible, animal-derived materials should be sourced from countries with a negligible BSE risk, in accordance with the Terrestrial Animal Health Code (Chapter 11.4) of the World Organisation for Animal Health (OIE).

(iii) The nature of animal material used and measures taken to minimise BSE risk

a. A declaration on the nature (tissue/ fluid type) of the animal tissue used should be submitted.

In a TSE-infected animal, different organs and secretions have different levels of infectivity. According to the EMA Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Product, tissues and fluids are classified into the three main categories as follows:

- Category IA (High Infectivity): brain, spinal cord, retina, optic nerve, spinal ganglia, trigeminal ganglia, pituitary gland and dura mater.

- Category IB (Lower Infectivity): peripheral nerves, autonomic ganglia, spleen, lymph nodes, tonsils, nictitating membrane, thymus, oesophagus, forestomach, stomach/abomasum, duodenum, jejunum, ileum, appendix, colon/ caecum, rectum, placenta, ovary, uterus, mammary gland/ udder, skin, adipose

tissue, heart/ pericardium, lung, liver, kidney, adrenal, pancreas, bone marrow, skeletal muscle, tongue, blood vessels, nasal mucosa, salivary gland, cornea, blood, cerebrospinal fluid, saliva, milk, urine, faeces.

- Category IC (No Detectable Infectivity): semen, placenta fluids, prostate/ epididymis/ seminal vesicle, foetus, embryo, bone, tendon, gingival tissues, dental pulp, trachea, thyroid gland, colostrum, cord blood, sweat, tears, nasal mucus, bile

Specific considerations:

- Gelatin may be extracted from the hide and/or bones of cattle. Gelatin extracted from hide has a lower risk than gelatin extracted from bones. When bones are used to manufacture gelatin, skulls and spinal cord should be removed from the collected bones independent of the age or the country of origin of the cattle. Hide gelatin offers little opportunity for cross-contamination with potentially infective tissue (e.g. brain, spinal cord and ganglia). Thus, it is recommended to collect bovine bones for processing into gelatin only from BSE-free countries or from countries with a low prevalence of BSE. Gelatin should be manufactured using the acid, alkaline or heat/ pressure manufacturing process.

- Materials derived from ruminant tallow, such as triglycerides, glycerol, sorbitan esters and polysorbate, or amino acids of ruminant origin (even if higher-risk tissues were not completely eliminated) are considered highly unlikely to remain infectious by the time the final reagent has been produced, as long as they were manufactured under the conditions at least as rigorous as those specified in EMA's Note for Guidance.

b. 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 brain stunning (penetrative or non-penetrative) as a method of slaughtering the animals or if the brain and/ or spinal cord is sawed.

In such cases, procedures used in collecting the intended animal tissues/organs and the measures in place to avoid cross-contamination with a higher risk material must also be described in detail.

(b) Detailed Assessment Report on the risk of TSE

(i) The scope of this report should include, but is not limited to, the risk factors associated with the route of administration, quantity of animal material used, maximum therapeutic dosage (daily dosage and duration of treatment) and the intended use of the drug product and its clinical benefits. The presence of a species barrier should also be considered.

(ii) Production process steps for inactivation of TSE agents

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.

If claims are made that the inactivation of TSE agents occurs during the manufacturing process, then relevant information on the process should be submitted for evaluation.

The production process should also include the quality assurance system in place to ensure product consistency and traceability.

(c) Certificate of analysis for each animal-derived material used.

(d) Purpose of each animal-derived material used

2.3 Products Containing Non TSE-Relevant Animal-Derived Materials

The use of animal materials derived from non TSE-relevant animal species (e.g. pigs, birds, fish, etc.) in therapeutic products is to be supported by the following documents:

a) Information on all countries which the animals were sourced from*;

b) Declaration on the nature of the animal tissue and/or fluid used;

c) Relevant information to demonstrate that the manufacturing process is capable of inactivating adventitious agents, where applicable;

d) Certificate of analysis for each animal-derived material used; and

e) Purpose of each animal-derived material used.

** Information on source countries is only required if the animal-derived material is of mammalian or avian origin and used as the drug substance, excipient and/ or adjuvant.*

3 RESPONSIBILITY OF PRODUCT REGISTRANT

The product registrant is responsible for ensuring that the product imported for local sale and supply is identical, in all aspects, to that approved by the licensing authority. The product registrant should notify HSA of any variations and obtain approval from HSA before implementing the variation, if applicable (for example, change of source materials for manufacturing).

4 CONCLUSION

The acceptability of a therapeutic product containing animal-derived ingredients, or which as a result of the manufacturing process, 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 the therapeutic product;
- Maximum therapeutic dosage;
- Intended use of the product; and/or
- Presence of a species barrier.

The above information only serves as a guide. Pharmaceutical manufacturers and product owners are required to observe international best practices at all times and to comply with current international guidelines.

5 REFERENCES

(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 Rev. 3 – July 2011).

(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 "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products".

(d) Guidelines on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with regard to vCJD risk (EMEA/BWP/5136/03).

(e) CPMP/BWP/337/02/Public/Final, Risk and regulatory assessment of lactose and other products prepared using calf rennet.

(f) EMA/CHMP/BWP/457920/2012 rev 1 Guidance on the use of Bovine Serum in the manufacture of human biological medicinal products.

(g) Terrestrial Animal Health Code, World Organisation for Animal Health (OIE).

(h) Use of Materials Derived from Cattle in Medical Products Intended for Use in Humans and Drugs Intended for Use in Ruminants; Unified Agenda 0910-AF54 (Spring 2011)

(i) Transmissible Spongiform Encephalopathies- TGA Approach to Minimising the Risk of Exposure (version 2.0, April 2014)

(j) Guidance for Industry – Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt–Jakob Disease (CJD) and Variant Creutzfeldt-Jacob Disease (vCJD) by Blood and Blood Products. U.S. FDA, Department of Health and Human Services, Center for Biologics Evaluation and Research, May 2010.