

# **REG-59 version 1**

## **Requirements for marketing authorisations of medicinal products in respect of risk of transmitting animal spongiform encephalopathy agents**

This guideline supersedes guideline REG-59 with effect from 28.1.2009.

Transmissible Spongiform Encephalopathies (TSEs) are chronic degenerative nervous diseases characterised by the accumulation of an abnormal isoform of a cellular glycoprotein known as PrP (or prion protein). Transmissible Spongiform Encephalopathies (TSEs) include bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep and goats, chronic wasting disease (CWD) in cervids, transmissible mink encephalopathy (TME) and feline spongiform encephalopathy (FSE). In humans, spongiform encephalopathy includes different forms of Creutzfeldt-Jakob disease (CJD), kuru, Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI). There is a convincing evidence to show that variant form of CJD (vCJD) is caused by the agent which is responsible for BSE in cattle. Therefore, a cautious approach continues to be warranted if biological materials from species naturally affected by TSE diseases, especially bovine species, are used for the manufacture of medicinal products. Since the use of animal-derived materials is unavoidable for the production of some medicinal products and complete elimination of risk at sources is rarely possible, the measures taken to manage the risk of transmitting animal TSEs via medicinal products represent risk minimisation rather than risk elimination.

The State Institute for Drug Control (in co-ordination with the Ministry of Health, the Institute for State Control of Veterinary Immunologicals and Medicaments, and other institutions) takes measures aimed at minimising the risk of transmission of animal spongiform encephalopathies via medicinal products. Decree No. 228/2008 Coll., on marketing authorisations, defining the content of MAA dossier, lays down the requirement for evidencing measures taken in respect of prevention of transmission of animal spongiform encephalopathies: for each manufacturing step the applicant has to prove compliance of used material with the note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal product and relevant Annexes published by the Commission in the EU Official Journal.

The general requirements for taking into account available scientific knowledge (Section 33, par. 1 of Act No. 378/2007 Coll., as amended, hereinafter referred to as the “Act”) and the obligation to minimise as much as possible the adverse effects of pharmaceuticals upon humans (Section 33, par. 3 letter c) of the Act) imply that the manufacturing authorisation holders in the Czech Republic must ensure that all of their products be protected against the risk of TSE transmission also after the manufacturing authorisation has been granted.

Since 1 January 2000, the general monograph of European Pharmacopoeia “6.2.1 Products with risk of transmitting agents of animal spongiform encephalopathies” applies and this monograph determines that manufacture of all materials or products obtained from tissues or secretions of animals susceptible to transmissible spongiform encephalopathies (TSEs) as well as all substances and products in which products obtained from such animals have been used as active ingredients or excipients or substances used in the course of manufacture (e.g. as raw materials or source materials, starting materials or reagents) must comply with the general monograph “5.2.8. Minimisation of the risk of transmitting animal spongiform encephalopathies via medicinal products”. This general monograph is identical to the

Committee for Proprietary Medicinal Products and Committee for Veterinary medicinal Products guideline EMEA/410/01 and is updated following revision of this guideline.

SÚKL Guideline valid from 1.5.2001, specified requirements for products manufactured from tissues of ruminants or products whose manufacture involved the use of materials of bovine origin. At the same time the rules were specified on the grounds of which SUKL verified whether and in what manner marketing authorisation holders/manufacturers ensured safety of their medicinal products against the risk of transmitting TSE. With regard to new scientific knowledge and facts related to ensuring safety of products derived from organs and tissues of ruminants the SUKL Guideline REG-59 should be updated and therefore its new version is published.

All the above mentioned requirements are based also upon guidance documents and requirements set by the European Communities, i.e. Directive 2001/82/EC (veterinary medicinal products) and Directive 2001/83/EC, as amended by Directive 2003/63/EC (human medicinal products), and related guideline of the Committee for Proprietary Medicinal Products (CPMP) and the Committee for Veterinary Medicinal products (CVMP) EMEA/410/01 (February 2001), and its Annexes. The issue of ensuring safety of products derived from organs or tissues of ruminants has been the subject matter of intensive discussions and an ongoing development, which can result in changes of requirements, recommendations and measures within the EU. A list of guidance documents and notifications of the European Medicines Agency (EMA) is attached to this guideline. A current overview is available at website <http://www.emea.europa.eu>.

Marketing authorisation applications shall be supported by the following background documentation:

- Fill in the relevant part of marketing Authorisation Application form 2.6.2 List of materials of animal and/or human origin contained or used in the manufacturing process of the medicinal product. A short list of substances susceptible to the risk of transmitting TSE/BSE is given in Annex 1.
- For each raw material of animal and/or human origin used in the manufacture of a medicinal product, all manufacturers thereof shall be listed. Each change of manufacturer occurring after marketing authorisation has been granted must be treated as a variation to marketing authorisation.
- In Module 3 of the dossier, safety data with respect to the risks of TSE transmission of all used raw materials, and therefore, of the product, shall be evidenced. The proof of safety can be provided in the following manner:
  - Detailed scientific data for the given raw material from the given manufacturer shall be provided (the applicant shall request these from the manufacturer of the raw material), according to requirements set forth in Note for guidance on minimisation of the risk of transmitting animal spongiform encephalopathies via human and veterinary medicinal products and its Annexes ( NfG EMEA 410/01) with particular respect to:
    - the origin of the source material,
    - the type of tissue used,
    - the manufacturing process.
  - Where a valid “Certificate of Suitability to the European Pharmacopoeia TSE monograph Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products” (hereinafter referred to as

“TSE Certificate”), issued by the European Directorate for Quality of Medicines, (EDQM) is available, a copy of the certificate shall be submitted. In this case, other scientific data need not be submitted, unless requested by the Institute additionally. The manufacturer of the raw material shall request the issue of a TSE Certificate from the EDQM; a TSE Certificate can be issued also for such raw material, for which a Ph.Eur. monograph does not exist ([www.pheur.org](http://www.pheur.org));

- A raw material means an active ingredient, an excipient, as well as a material used in the manufacture of an active ingredient or an excipient, or used in the course of manufacture of the medicinal product, which, however, is not contained in the product per se (e.g. bovine serum albumin, enzymes, validation media, culture media including those intended to prepare working cell banks or new master cell banks).

#### Post-Authorisation Changes:

For all authorised medicinal products, compliance with Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products and Annexes thereof must be proved; this applies also to any change in the approved dossier that may have an impact on product safety as regards TSE.

The assessment of data submitted includes evaluation of whether the applicant has demonstrated that the medicinal product is manufactured in compliance with requirements listed in Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products and Annexes thereof, taking into account also the method of administration of the product, daily doses, duration of treatment, intended use and the overall risk/benefit ratio of the product in question.

Technical requirements on ensuring safety of medicinal products are given in the following documents:

Transmissible Spongiform Encephalopathies (TSE) (Animal and Human)-Scientific Guidelines for Human Medicinal Products:

<http://www.emea.europa.eu>

[EMEA/410/01](#) Rev. 2 Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, (Adopted by CPMP/CVMP October 2003)

[EMEA/410/01](#) Rev. 3 Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, (Released for consultation June 2004)

[EMEA/CPMP/BWP/337/02](#) Final Public Report on Risk and Regulatory Assessment of Lactose and other products prepared using Calf Rennet (following a meeting of the Biotechnology Working Party in February 2002)

[EMEA/430600/00](#) Explanatory Note: Gelatin for Use in Pharmaceuticals (an Appendix to the Note for Guidance on Minimising the Risk of transmitting Animal Spongiform...)

[CPMP/BWP/1952/98](#) Position Statement on Polysorbate 80

[CPMP/1163/97](#) Position Paper on Production of Tallow Derivatives for Use in Pharmaceuticals December 97

EMEA/CHMP/BWP/27/04 First Cases of BSE in USA and Canada: Risk Assessment of Ruminant Materials Originating from USA and Canada (July 2004)

[EMEA/22314/02](#) Position Paper on Re-establishment of Working Seeds and Working Cell Banks using TSE compliant materials

[EMEA/CPMP/BWP/476/01](#) Public Statement on the Evaluation of Bovine Spongiform Encephalopathies (BSE) - risk via the use of materials of bovine origin in or during the manufacture of Vaccines

[CPMP/BWP/819/01](#) Questions and Answers on Bovine Spongiform Encephalopathies (BSE) and Vaccines  
See also [EMEA/CPMP/BWP/498/01](#) - Explanatory Note for Medicinal products for Human use on the Scope of the Guideline.

[EMEA/CPMP/BWP/2879/02](#) Revision 1CHMP Position Statement on Creutzfeldt-Jakob disease and Plasma-derived and Urine-derived Medicinal Products

[EMEA/CPMP/5136/03](#) Guideline on the Investigation of Manufacturing Processes for Plasma-Derived Medicinal Products with Regard to VCJD risk

[EMEA/CPMP/BWP/450/01](#) Report from the Expert Workshop on Human TSEs and Medicinal products derived from Human Blood and Plasma (1 December 2000)

[CPMP/BWP/1244/00](#) Report from the Expert Workshop on Human TSEs and Plasma-derived Medicinal Products (15 -16 May 2000)

[CPMP/BWP/257/99](#) EMEA Workshop on Applications to Pharmaceuticals of Assays for Markers of TSE (held on 19-20 January 1999)

### **List of raw materials susceptible to risk of transmitting TSE/BSE**

Material which presents a risk in terms of transmitting TSE/BSE (Transmitting Spongiform Encephalopathy/Bovine Spongiform Encephalopathy), is defined in CPMP and CVMP EMEA/410/01, Rev. 2 - Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Medicinal Products (<http://www.emea.europa.eu>). A detailed list of risky raw materials is not given in this note for guidance because an exhaustive and binding list for practical use cannot be made. Placing on the list depends on manufacturing technology since the same raw material may be obtained from different sources by different methods (processing of animal or vegetable tissue, synthetic manufacture, material used in manufacture was/was not risky in terms of TSE...). However, for your convenience and as a non-binding information we provide below a short list of raw materials which often may be of animal origin and therefore should be under particularly close monitoring from the point of view of BSE/TSE.

Please consider the listing below as provided for your convenience only!!!

Pay special attention to mixtures of raw materials which are marketed under various trade names and check their composition!

Pay special attention also to biotechnologically produced active ingredients because it is highly probable that cultivation media containing TSE risky material were used during their manufacture!

- Gelatine, gelatine capsules hard and soft
- Collagen, elastin – Croguat
- Raw materials obtained by tallow processing
  - Fatty acids – e.g. palmitic, oleic, stearic, arachidine, caprylic acid
  - Fatty acids salts – e.g. stearates, palmitates,..
  - Fatty acid and glycerine esters – triglyceride – e.g. fatty acid esters with Macrogol, Arlatone, adeps solidus (Witepsol)
  - Fatty acids and their esters mixtures – e.g. polysorbates (tween), Some type of cover layer of Opadry (contains polysorbate) Polyols (fatty acids strings), Simethicone/Dimethicone emulsion (emissive components, Antifoam), Dehymuls (emulgator)
  - Glycerol
  - Propylene glycol
  - Soaps
- Raw materials obtained by processing of wool or pelage :
  - Lanoline, wool alcohols - Eucerin
  - Amino acids (pancreatic enzymes can be used when processing wool)
- Milk and raw materials obtained from milk (pancreatic enzymes can be used in milk processing):
  - Lactose, lactic acid, caprylic acid and other milk derivatives
  - Casein, casein hydrolysed by pancreatic enzymes, Casamino Acids, NZ Amine
  - Calf rennet
- Glycosaminoglycans:
  - heparin and its salts,
  - low-molecular heparines (enoxaparine, reviparine, parnaparine, dalteparine, nadroparine, sulodexid, certoparine...)
  - chondroitin sulphate,
  - danaparoid, heparinoid
- Enzymes:
  - pepsin, trypsin, chymotrypsin
  - RNAsa, DNAsa
  - hyaluronidase, amylasa, lipasa
  - enzyme mixture – pancreatine, Primatone, Primagen
  - fibrinolysin (plasmin), thrombin
  - lysozym, mucoproteasa
- Hormones:
  - insulin, glucagon , thyroxin, thyreotropin, somatotropin, somatostatin, corticoids (dexamethazon, hydrocortizon... ),
  - calf thymus extract (thymosin, thymomodulin, thymin, thymostatin, thymostimulin.), follicle-stimulating hormone,....
- Glycoproteins –mucin, transferines
- cholesterol

- phospholipids , pulmonary surfactant
- bovine lipoproteins
- suprarenal extract
- aprotinin
- Calf blood, sheep blood, bovine blood
  - Foetal Bovine serum, Foetal Calf Serum,
  - BSA (bovine serum albumin)
  - Fetuin
  - Hemin, Hemoglobin, Hematin, hematoporphyrin
- Culture media containing raw materials of bovine origin :
  - Pepton (Trypton), Casein-meat Pepton, Chocolate Agar Slants, Bacteriological Meat Extract, Beef Heart Infusion,
  - Blood Meal, Bactocasitone, Bacto Tryptone, Beef Extract, Blood Agar, Caso Bouillon, Charcoal Agar, Lab Lemco
  - Powder, Nutrient Broth, Soytone, Terrific Broth, Thioglycolate Medium, Todd Hewitt Broth, Trypcase Soja bouillon,
  - Trypticase Pepton, Trypticase Soy Broth, Tryptose, TSB Caso Bouillon, and others
- Fel tauri
  - chenodeoxycholic acid, ursodeoxycholic acid, glycocholic acid, cholic acid, deoxycholic acid, dehydrocholic acid and their salts
- Vitamins
- Azelaic acid