REG-59 version 2 Requirements for marketing authorisations of medicinal products in respect of risk of transmitting animal spongiform encephalopathy agents

This guideline supersedes guideline REG-59 version 1 with effect from 2nd January 2026.

The guideline is issued on the basis of and in accordance with the provisions of Part 1 of Decree No. 228/2008 Coll. The guideline is legally binding.

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 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 in 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 (hereinafter referred to as the "Institute" or "SÚKL") 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 (**EMA/410/01** Rev. 3 Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, (Legal effective date 1.7.2004)).

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 "**01/2008:1483** Products with risk of transmitting agents of animal spongiform encephalopathies" applies, which was updated in 2008, 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 (CHMP) and Committee for Veterinary medicinal Products (CVMP) guideline „Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMA/410/01) and is updated following revision of this guideline.

The guideline of the Institute has been valid from 1.5.2001 and 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 the Institute 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 guideline REG-59 should be updated therefore updated version 1, valid from 28.1.2009, was published and its new version 2 is published now.

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 EMA/410/01 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 available at website http://www.ema.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.
- 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 minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products and its Annexes (EMA/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 a raw material, for which a Ph.Eur. monograph does not exist (see www.edqm.eu).
    - 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 its 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 its 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.

All technical requirements on ensuring safety of medicinal products are given on the website of the European Medicines Agency (EMA): https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/biological-guidelines/biologicals-finished-product