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Ref: Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (Doc. Ref. EMEA/410/01 – Rev.4, 21 February 2008)

To Responsible Person(s):

PDA is pleased to provide comments on the revised TSE note for guidance. Our comments were prepared by an expert committee with practical experience in the area of TSE's and their risks to medicinal products. In our regulatory consultations, PDA restricts commentary to scientific and technical issues. Where appropriate we offer recommendations to make the guidance more useful to all parties. Our comments are presented in the standard EMEA table format, followed by several scientific citations.

If you have any questions please contact me, or my colleague James Lyda (lyda@pda.org), who did the staff work with our committee.

With very best regards,

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cc: J. Lyda, R. Levy, R. Dana, H. Willkommen

Attachment

Note: Scientific literature references cited below are listed in detail at the end of this table.

#	Page	Section	Comment and rationale	Proposed change (if applicable)
1	All	Entire document	The OIE member country classification list (i.e., "Bovine Spongiform Encephalopathy Status of Members") references "negligible BSE risk" "controlled BSE risk" and "undetermined BSE risk." For clarity, and consistency with the current classification it is recommended to remove (throughout the guideline) the reference to categories of countries, e.g. Category A, Category B, Category C, and instead use the terminology in the OIE list. Introducing a new classification and terminology would create confusion and difficulty in correlating between the different categorization requirements.	Replace all references in the guideline to Category A, B and C countries with the terminology used in the OIE list, i.e. *'negligible BSE risk', 'controlled BSE risk' and 'undetermined BSE risk'*
2	2/29	Table of Contents	TOC does not reference section "6.9 Peptones".	Add new section *6.9 Peptones* to TOC.
3	3/29	Scientific Background	This section lists the TSEs of animals but fails to mention atypical BSE and atypical scrapie. There is evidence that the L type of atypical BSE may be more pathogenic to humans than classical BSE (Baron et. al., 2007; Beringue et. al. 2007; Comoy 2006). Atypical scrapie is mentioned on page 10 but only in reference to the establishment of closed flocks and genetics. It is not mentioned that atypical scrapie may be a sporadic disease and thus not preventable on a flock or country level.	We suggest that the guidance specify that these precautions be taken for atypical BSE as well as classical BSE, recognizing that revisions may have to be made as new information becomes available.
4	4/29	Scientific Background	There is evidence for significant transmission of scrapie to both sheep and goats in Italy via a vaccine for M. agalactiae (Caramelli et al. 2001).	Including this example in the text: second paragraph, p. 4, would make this section more complete. It also should be noted that neither of the outbreaks were the result of commercially prepared vaccine.

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5	6/29	2. Scope of the Note for Guidance…"	In regard to raw materials produced with animal derived starting or raw materials, it should be clarified in the guideline the level of analysis that is required. For instance, if a culture medium contains rec. insulin and this insulin is made with peptone as a culture additive, the analysis should then include this peptone, but should not go deeper into the raw materials that have been used.	Add the following paragraph after the bullet points in the material section: *The analysis of compliance of the raw and starting materials and reagents should consider materials and reagents that are directly and indirectly used. Raw and starting materials of indirect use means those raw and starting materials which are used to produce the raw and starting materials used in production of the medicinal product It is not necessary to conduct the analysis further back in the process.*
6	8/29	3.2.1.1. bovine material First sentence:	The country classification list for negligible and controlled BSE risk (i.e., "Bovine Spongiform Encephalopathy Status of Members") is not easy to locate from the OIE home page.	Provide in footnote 6 the direct link to the OIE status list of member countries, (http://www.oie.int/eng/Status/BSE/en_BSE_free.htm) and to the OIE Terrestrial Code 11.6.
7	Multi-ple	Footnote 12, 15, 24, 25	The links referenced in these footnotes are not the locations currently in use.	Replace the links with the correct ones, for instance: http://ec.europa.eu/food/fs/sc/ssc/out56_en.html
8	10/29	Footnote 13	The text in this footnote is a key part of the risk management approach for TSE, and should not be relegated to a footnote.	Move the following text from the footnote to the section above where it is referenced, "*If materials from 'TSE-relevant animal species' have to be used, consideration should be given to use materials of the lowest category of risk."* Then, delete Footnote 13.
9	13/29	3.5 Manufacturing process	**Removal/Inactivation validation:** The first sentence of this paragraph 'Validation studies of removal/inactivation procedures for TSE are difficult to interpret' might be too strong in the light of the extensive number of TSE removal studies that have been performed successfully on human plasma products.	The first two sentences of this paragraph should be amended to read as follows: *When validating removal/inactivation procedures for TSEs it is necessary to take into consideration a number of significant variables: the nature of the spiked material…*

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10	13/29	3.5 Manufacturing process	**Removal/Inactivation validation:** The last sentence of this paragraph states, '…if claims are made for the safety of the product with respect to TSEs … they must be substantiated by appropriate studies.' It is appropriate to include here the reference to the CPMP/BWP/5136/03 guideline. (Reference to this guideline is already included at present as footnote 21 on page 18.)	Add, in addition to footnote 21, page 18, a reference to the CPMP/BWP/5136/03 guideline at the end of this paragraph.
11	15/29 and 16/29	6.1. Collagen and 6.2. Gelatin	In both paragraphs it is explained that hides are safer raw materials than bones, but the wording in the two paragraphs differs, i.e., Collagen, *'…might be a safer raw material'* vs. Gelatin, *'...a much safer source material…'.* For clarity, similar wording should be used in both sections as they both relate to the nature of the raw material, and not the intended use.	Please provide clarification and use the same wording in both Section 6.1 and 6.2.
12	16/29	6.2. Gelatin (i) The source material used	**Hides as starting material:** For clarity, it should be clearly stated that material can be sourced independent of the age and the origin of the cattle.	This should be added as 2. sentence in this paragraph: *Hides can be sourced independent of the age and the origin of the cattle.*
13	16/29	6.2. Gelatin (1) The source material used	**Bones as starting material, point 2:** It is expressed that vertebrae must be removed from cattle >30 months old if bones of Cat. B (OIE controlled risk) countries are used. In the interest of clarity it should be added in brackets after Category B *(GBR II and III)*. The addition of GBR categories is in line with the reporting in Table 1.	Revise text to read, "Vertebrae shall be removed from the raw/starting materials from cattle over 30 month from countries of controlled BSE risk *(GBR II and III)*"

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14	17/29	6.3 Bovine blood derivatives	**Bovine blood derivatives, 3. Paragraph, last sentence:** It is written that in addition to the provision given above the following (i) to (v) should be considered. Because this sentence Is written in the direct context of blood derivatives it could be read that the following points need not to be considered in the case of fetal or bovine serum used for production of medicinal products. This cannot be the intention because (i) Traceability, (ii) Geographical origin etc. are also applicable to FBS and bovine serum.	A new paragraph should begin with the last sentence of the third paragraph and should be read as follows: *In addition to the provisions above, consideration should be given to the following:* *(i) Traceability…….*
15	18/29	6.3 (iii) Stunning methods	The section on stunning methods (pg 18/29) outlines potential avenues for CNS contamination by essentially all methods of stunning. While PDA does not take a position on stunning methods, the wording in this section appears open to a wide range of interpretation, including the position that there are no stunning methods which can be acceptable. <u>Special Note</u>: It is our understanding that significant quantities of bovine serum and other blood products are sourced from the USA. Further, we understand that stunning by means of captive bolt is the USA standard. Considering those points, the reduction of the maximum age requirement from 30 to 21 months in controlled risk countries seems impractical, as it is likely to severely limit the amount of product which could be obtained from the USA, thus resulting in shortages of some products.	It is recommended that the section on stunning include references back to page 11, or include actual wording from page 11, in that both the stunning methods and the methods to eliminate or reduce cross contamination should be detailed.
16	18/29	6.3 (iv) Age		

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17	18/29	6.3 (v) Reduction of TSE agents during manufacture	In the interest of clarity, and because the sub-titles cover also blood, the text should clearly express that this chapter is applicable for blood derivatives where the manufacturing process can have some capacity for removal of the TSE agent.	Change the wording of the first sentence to the following: *For blood derivatives*, the capacity of the manufacturing process…
18	20/29	6.6 Milk and milk derivatives	The statement regarding milk is no longer accurate for scrapie. Scrapie infectivity of milk/colostrum has been shown in two recent studies. (Konold et.al., 2008; Lacroux et al., 2008)	The statement in 6.6 should be amended accordingly.
19	22/29	Peptones	It has been shown that mechanical methods of harvesting muscle tissue from bones have resulted in widespread dissemination of nervous tissues throughout meat products.	We suggest that skeletal muscle harvested by any mechanical methods in countries of 'controlled or undetermined BSE risk' should not be used for production of peptone.
20	21/29	Footnote 23	In the interest of clarity the link in footnote 23 should be amended so that a direct access to the document is possible.	Insert the direct link to the risk assessment mentioned: http://www.emea.europa.eu/pdfs/human/press/pus/057102.pdf

References

Baron T, Bencsik A, Biacabe A-G, Morignat E, Bessen RA. Phenotypic similarity of transmissible mink encephalopathy in cattle and L-type bovine spongiform encephalopathy in mouse model. Emerg Infect Dis Volume 13, Number 12, December 2007. Available from http://www.cdc.gov/EID/content/13/12/1887.htm

Béringue V, Andréoletti O, Le Dur A, Essalmani R, Vilotte JL, Lacroux C, et al. A bovine prion acquires an epidemic BSE strain-like phenotype upon interspecies transmission. J Neurosci. 2007; 27:6965–71.

Caramelli M., Ru G., Casalone C., Bozzetta E., Acutis P.L., Calella A. & Forloni G. (2001). – Evidence for the transmission of scrapie to sheep and goats from a vaccine against *Mycoplasma agalactiae. Vet. Rec.*, 148, 531-536.

Comoy E.,Transmission of bovine amyloidotic spongiform encephalopathy (BASE) to the primate. Prion 2006. Strategies, advances and trends towards protection of society; Torino, Italy; 2006 Oct 3–6.

Konold T, Moore SJ, Bellworthy SJ, Simmons HA (2008) Evidence of scrapie transmission via milk. BMC Vet Res 4: 14.

Lacroux, C. Simon., Benestad, SL., Maillet, S. Mathey, J. et al., 2008. Prions in Milk from Ewes Incubating Natural Scrapie. PloS Pathog. 4 (12):e1000238.doi:10,1371/journal.ppat.1000238.