European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)
COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

DRAFT

NOTE FOR GUIDANCE ON GUIDANCE ON MINIMISING THE RISK OF TRANSMITTING ANIMAL SPONGIFORM ENCEPHALOPATHY AGENTS VIA HUMAN AND VETERINARY MEDICINAL PRODUCTS

AMENDMENTS TO SECTIONS 6.2 AND 6.3

DISCUSSION IN EXPERT GROUP	30 March 2004
DISCUSSION IN THE BWP	May 2004
TRANSMISSION TO CHMP and CVMP	May 2004
RELEASE FOR CONSULTATION	June 2004
DEADLINE FOR COMMENTS	End of August 2004
DISCUSSION IN THE BWP	
TRANSMISSION TO CHMP and CVMP	
ADOPTION BY CHMP	
DATE FOR COMING INTO OPERATION	

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Note:

A TSE expert group was convened at the EMEA on 30 March 2004 to discuss, in the light of a first cases of BSE in the USA and Canada, TSE aspects related to gelatin, bovine blood derivatives and other ruminant materials from GBR III countries.

Based upon the latest scientific information and the outcome of the discussions, the TSE expert group proposed amendments to the wording of sections 6.2 (gelatin) and 6.3 (bovine blood derivatives) of the TSE Note for Guidance.

The proposal from the TSE Expert group was endorsed by the BWP, and subsequently adopted by the CHMP and CVMP for external consultation.

For ease of reference, the changes made to the current text (EMEA/410/01 rev.2) are highlighted.

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6.2 GELATIN

Gelatin is a natural, soluble protein, gelling or non-gelling, obtained by the partial hydrolysis of collagen produced from bones, hides and skins, tendons and sinews of animals.

For gelatin, documentation to demonstrate compliance with this Note for Guidance needs to be provided taking into account the provisions listed in sections 3 to 5. In addition, consideration should be given to the following:

(i) The source material used

Gelatin used in medicinal products can be manufactured from bones or hides.

- *Hides as the starting material*- On the basis of current knowledge, hides used for gelatin production represent a much safer source material as compared to bones. However, it is highly recommended that measures should be put in place to avoid cross-contamination with potentially infected materials during procurement.
- *Bones as the starting material*- Where bones are used to manufacture gelatin, the quality of the starting materials[1] is the primary parameter that will ensure the safety of the final product. Therefore, the following should be applied:
    1. As a first precautionary principle, skulls[2] and spinal cord shall be removed from the collected bones (raw/starting material) from cattle of all ages from all countries.
    2. Additionally, vertebrae shall be removed from the raw/starting materials from cattle of all ages from GBR II and III countries.
    3. Gelatin shall be manufactured using one of the manufacturing methods described below.

~~more stringent production conditions shall be applied (see below). In any case, the removal of skulls and spinal cords from the starting material is considered as a first precautionary measure, which largely affects the safety of the product. As far as practicable, bones should be sourced from countries classified as GBR I and II. Bones from category GBR III countries can be used if the gelatin is manufactured under defined conditions as indicated below and if vertebrae from cattle over 12 months of age are removed from the raw/starting materials.~~

(ii) Manufacturing methods

No specific measures with regard to the processing conditions are required for gelatin produced from hides provided that control measures are put in place to avoid cross-contamination both during the procurement of the hides and during the manufacturing process.

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[1] Regulation (EC) No 1774/2002 of the European Parliament and of the Council laying down health rules concerning animal by-products not intended for human consumption shall apply unless justified. Regarding the manufacturing of gelatin and collagen or import of raw material for such manufacturing for use in pharmaceutical products, only material from animals fit for human consumption shall be used. ~~The use of vertebrae from such animals from category II countries, which according to the risk assessment is safe, shall continue to be allowed.~~

[2] The removal of the entire head from the collected bones is encouraged.

However, where bones are used as the starting material, the mode of manufacture will be the second parameter that will ensure the safety of gelatin. ~~must be taken into account where bones are used as the starting material.~~

- Gelatin can be manufactured only from bones from GBR Category I, II and III countries sourced in accordance with the conditions described in section 6.2. (i), using the acid, alkaline or heat/pressure manufacturing process. ~~An additional alkaline treatment (pH 13, 1 hour) of the bones/ossein may further increase the TSE safety of acid-derived bone gelatin~~
- The manufacturing process shall be taken into consideration when performing the risk assessment as described in Section 4 of this Note for Guidance. Although the alkaline extraction process (prior to the finishing steps) has shown a slightly higher inactivation/removal capacity compared to the acid process, both the acid and the alkaline manufacturing methods to produce the final gelatin have shown similar overall inactivation/removal of TSE infectivity in the gelatin validation experiments. Studies have shown that an additional alkaline treatment (pH 13, 1 hour) of the bones/ossein increases further the TSE inactivation/removal capacity of the acid manufacturing process.
- For a typical alkaline manufacturing process, bones are finely crushed, degreased with hot water and demineralised with diluted hydrochloric acid (at a minimum of 4 % and pH < 1.5) over a period of at least two days to produce the ossein. This is followed by an alkaline treatment with saturated lime solution (pH at least 12.5) for a period of at least 20 days. The gelatin is extracted, washed, filtered and concentrated. A 'flash' heat treatment (sterilisation) step using 138-140 °C for 4 seconds is applied. Bovine bones may also be treated by an acid process. The liming step is then replaced by an acid pre-treatment where the ossein is soaked overnight at pH < 4. In the heat/pressure process, the dried degreased crushed bones are autoclaved with saturated steam at a pressure greater than 3 bar and a minimum temperature of 133°C, for at least 20 minutes, followed by extraction of the protein with hot water. The finishing steps for both the acid and heat/pressure process are similar to the alkaline process.

~~Bones (including vertebrae) for the production of gelatin using acid treatment shall be sourced only from GBR category I or II countries. An additional alkaline treatment (pH 13, 1 hour) of the bones/ossein may further increase the TSE safety of acid-derived bone gelatin~~.

~~For bones sourced from a GBR category III country, the alkaline process shall be applied. However, this manufacturing method is optional for bones coming from GBR category I and II countries.~~

~~- For a typical alkaline manufacturing process, bones are finely crushed, degreased with hot water and demineralised with dilute hydrochloric acid (at a minimum of 4% and pH < 1.5) over a period of at least two days to produce the ossein. This is followed by an alkaline treatment with saturated lime solution (pH at least 12.5) for a period of at least 20 days. The gelatin is extracted, washed, filtered and concentrated. A 'flash' heat treatment (sterilisation) step using 138-140°C for 4 seconds is applied. Bovine hide gelatin can also be produced by the alkaline process. Bovine bones may also be treated by an acid process. The liming step is then replaced by an acid pre-treatment where the ossein is soaked overnight at pH < 4.~~

6.3 BOVINE BLOOD DERIVATIVES

Foetal bovine serum is commonly used in cell cultures. Foetal bovine serum should be obtained from foetuses harvested in abattoirs from healthy dams fit for human consumption and the womb should be completely removed and the foetal blood harvested in dedicated space or area by cardiac puncture into a closed collection system using aseptic technique.

New born calf serum is obtained from calves under 20 days old and calf serum from animals under the age of 12 months. In the case of donor bovine serum, given that it may be derived from animals less than 36 months old, the TSE status of the donor herd shall be well defined and documented. In all cases, serum shall be collected according to specified protocols by personnel trained in these procedures to avoid cross-contamination with higher risk tissues.

For bovine blood derivatives, documentation to demonstrate compliance with this Note for Guidance needs to be provided taking into account the provisions listed in sections 3 to 5. In addition, consideration should be given to the following:

(i) Traceability

Traceability to the slaughterhouse must be assured for each batch of serum or plasma. Slaughterhouses must have available lists of farms from which the animals are originated. If serum is produced from living animals, records must be available for each serum batch which assures the traceability to the farms.

(ii) Geographical origin

Whilst tissue infectivity of BSE in cattle is more restricted than scrapie, as a precautionary measure bovine blood must be sourced from countries classified GBR I and II, unless otherwise justified.

(iii) Stunning methods

If it is sampled from slaughtered animals, the method of slaughter is of importance to assure the safety of the material. It has been demonstrated that stunning by captive bolt stunner with or without pithing as well as by pneumatic stunner, especially if it injects air, can destroy the brain and disseminate brain material into the blood stream. Negligible risk can be expected from a non-penetrative stunner and from electro-narcosis[3]. The stunning methods must therefore be described for the bovine blood collection process.

~~If~~ Where sourcing of blood is ~~allowed~~ from countries where cases of BSE have been detected (GBR III) a non-penetrative stunner shall be used for slaughter animals over 12 months of age.

[3] SSC Opinion on stunning methods and BSE risk (The risk of dissemination of brain particles into the blood and carcass when applying certain stunning methods.) adopted at the meeting on 10-11 January 2002. http://europa.eu.int/comm/food/fs/sc/ssc/out245_en.pdf