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BIOTECHNOLOGY WORKING PARTY

FIRST CASES OF BSE IN USA AND CANADA:

RISK ASSESSMENT OF RUMINANT MATERIALS ORIGINATING FROM USA AND CANADA

Executive summary

1. This risk assessment considered the implications of the first Canadian and US BSE[1] case on medicinal products that contain, or use during their manufacture, ruminant materials of Canadian or US origin.

2. This combined Canadian-USA risk assessment has been prepared by the BWP in July 2004 in anticipation of the possible reclassification of Canada and USA by the European Food Safety Authority (EFSA) from GBR II to GBR III countries.

3. The primary aim of this assessment was to evaluate if these BSE cases would create a *public health risk*, i.e. if they would render some of the authorised medicinal products unsafe with regard to TSE. The second aim of this risk assessment was to evaluate what the implications will be for *regulatory compliance* with the TSE Note for Guidance[i], which is a legal requirement in the EU.

4. The risk assessment is based on three complementary criteria given in the TSE Note for Guidance: country of origin, type of tissue and manufacturing process (including quality assurance system and traceability).

5. From a public health perspective the reclassification of Canada and USA (to GBR III[ii]) does not change significantly the BSE risk of bovine blood and blood derivatives, gelatin or other ruminant materials.

6. Regulatory compliance issues have been identified for some materials, i.e. acid bone gelatin, adult bovine serum and bovine blood derivatives of US or Canadian origin. Discussions are taking place with manufacturers, the European Commission and EDQM to resolve them without causing an undue shortage of these materials.

1. Background information

On 20 May 2003, the Canadian Government confirmed the first Canadian case of Bovine Spongiform Encephalopathy (BSE) in an eight year old cow. The Canadian Food Inspection Agency (CFIA) confirmed that all of the animals from the case farm or from other farms that were associated with the feed investigation (in total approx. 1500 cattle) were negative when tested post-mortem for BSE. For more information, the website of the CFIA can be consulted[iii].

[1] Abbreviations used throughout this paper:
- BSE: Bovine Spongiform Encephalopathy
- TSE: Transmissible spongiform encephalopathy
- GBR: Geographical BSE risk
- SRM: Specified Risk Material
- EFSA: European Food Safety Authority
- EDQM: European Directorate for the Quality of Medicines

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On 23 December 2003, the US Department of Agriculture (USDA) confirmed the first US case of BSE in a six and half year old cow. The index cow (BSE cow) was a non-ambulatory dairy cow and was slaughtered on 9 December 2003. Brain tissue was tested (as part of the routine BSE surveillance programme) and on 22 December preliminary test results were positive for BSE. All meat from the group of 20 animals slaughtered on 9 December 2003 was recalled by the USDA Food Safety and Inspection Service (FSIS). Products rendered from the BSE cow (tallow, meat and bone meal) have not left the rendering plants (i.e. placed on a voluntary hold). For more information, the website of the USDA can be consulted[iv].

Following the announcement of these two cases, the Biotechnology Working Party (BWP) of the Committee for Proprietary Medicinal Products (CPMP)[v] has performed a risk assessment, considering the implications of these BSE cases on medicinal products that contain, or use during their manufacture, ruminant materials of Canadian or USA origin. These risk assessments were considered by the CPMP and the Committee for Veterinary Medicinal Products (CVMP) at their meetings of September 2003 (Canadian risk assessment) and February 2004 (USA risk assessment).

This combined Canadian-USA public risk assessment has been prepared by the BWP in July 2004, based upon the confidential risk assessment reports of September 2003 and February 2004, in anticipation of the possible reclassification of both countries by the EFSA from GBR II to GBR III.

2. General considerations

2.1. Risk Assessment - Aim and Limitations

This risk assessment considered the implications of the Canadian and US BSE cases on medicinal products that contain, or use during their manufacture, ruminant materials of Canadian or US origin. The primary aim of this assessment was to evaluate if these BSE cases would create a public health risk, i.e. if they would render some of the authorised medicinal products unsafe with regard to TSE[vi]. The second aim of this risk assessment was to evaluate what the implications will be in terms of regulatory compliance with the TSE Note for Guidance (which is a legal requirement in the EU) for bovine derived materials of US or Canadian origin.

The risk assessment is based on three complementary criteria given in the TSE Note for Guidance: country of origin, type of tissue and manufacturing process (including quality assurance system and traceability).

The focus of the risk assessment is mainly on bovine blood and blood derivatives from Canadian/US cattle and gelatin produced from Canadian/US bones, insofar as additional precautionary measures (processing conditions, source material selection or slaughtering techniques) have to be applied if these source materials are obtained from a GBR III country.

2.2. Reclassification of Canada and USA as a GBR III country

Canada and USA are currently classified as a GBR II country, which means that the '*Presence of BSE cases unlikely but not excluded*'. The first indigenous BSE case could result in the reclassification of USA and Canada as a GBR III country: '*Presence of BSE cases likely but not confirmed, or confirmed at a lower level'* and the EFSA is currently reviewing the GBR classification of Canada and USA.

The following factors have been taken into consideration in this risk assessment:

1. Canada has an active surveillance system for BSE (which proved to be effective). This BSE surveillance programme was implemented in 1992 and requests the testing of all animals with clinical signs that could be compatible with BSE. At random testing of mature animals without clinical signs of BSE is also performed as part of the surveillance programme: in 2002 19,990 cattle were tested.
2. USA has a limited active surveillance system for BSE. This BSE surveillance programme was implemented over 10 years ago: the USDA surveillance program condemns and tests any cows displaying signs of neurological problems at slaughter. The USA has tested 20,000 cattle in each of the last two years; the testing of healthy animals for human consumption is, however, very limited;

3. Since 1997, Canada and USA have a ban on the feeding of ruminant proteins (meat and bone meal) to ruminants.

4. For the Canadian risk assessment:

   - Canada is considering the expansion of this feed ban to all mammalian species and also the elimination of SRMs from all animal feeds in Canada.

   - The CFIA has conducted a thorough investigation of the origin of this first BSE case and no additional cases of BSE have been detected in any of the animals, which are linked or may be linked to this first BSE cow.

   - The BSE animal was considered unfit for human consumption at slaughter and consequently none of the animal parts entered the food chain. However, the carcass of this animal was rendered into meat and bone meal and tallow.

5. For the USA risk assessment:

   - As one of the additional precautions after the first BSE case, the USA has banned the use of Specified Risk Materials[vii] (SRMs) from the human food chain. Additional measures have been taken related to banning of non-ambulatory (downer) animals from the human food chain, product holding, advanced meat recovery, stunning method and mechanically separated meat[viii]. These new rules came into effect on 12 January 2004;

   - The USDA has conducted a thorough investigation of the origin of this first BSE case and no additional cases of BSE have been detected in the birth cohort of the index cow or in its offspring.

   - The index cow was imported from Canada in 2001. With its age of 6.5 years, it was born before the meat and bone meal ban came into operation in Canada and the USA.

6. It is very unlikely that any part of the Canadian or US BSE cow was used to prepare ruminant material for use in the pharmaceutical industry. It has been confirmed that none of the products rendered from the US BSE cow (tallow) have left the rendering plant.

7. There is no indication that blood was collected from these animals for use in the pharmaceutical industry.

These factors indicate that Canada and USA have taken additional, necessary steps to protect public health. The additional measures taken by the US in January 2004 should provide additional safeguards to minimise the risk of BSE infected materials entering the human food chain[ix].

3. Risk assessment of bovine serum and bovine blood derivatives

Introduction

A TSE risk assessment of all bovine serum and bovine blood derivatives has been performed in the past, either by the EDQM (when issuing TSE certificates), or by Licensing Authorities (as part of Marketing Authorisation applications or variations). The outcome of these risk assessments was that bovine serum and blood derivatives, when manufactured in accordance with the TSE Note for Guidance, do not pose a risk of transmission of TSE.

Risk assessment after the first BSE cases in Canada and USA

a. Public health viewpoint

The following factors have been considered when conducting this assessment:

1. All actions taken by Canada and USA to ensure the protection of public health following their first BSE case have been listed in Section 2.2 of this report. The additional measures should provide further safeguards to minimise the risk that BSE infected materials enter into the human food chain.

2. BSE infectivity has never been detected in bovine blood and, if present, must be of very low titre.

3. Additional criteria guarantee the BSE safety of bovine serum and blood products for use in the manufacture of medicinal products: age of the animals, sourcing from healthy animals/animals fit for human consumption and measures in place to avoid cross contamination with higher risk tissues. Cross contamination is linked to the slaughtering method: some stunning methods might disseminate brain particles into the blood (see point 5 below)

4. The following factors are unchanged since the previous risk assessments:

   - Measures to prevent cross-contamination with high-risk tissues
   - Manufacturing process[x] (including QA systems, audit etc)

5. The use of air-stunning as a slaughtering method has been prohibited in USA. Theoretically this further limits the risk of dissemination of brain material into the blood stream. However, as air-stunning was seldom used in the past, this new requirement will in practise not contribute greatly to the reduction of possible infectivity of the blood. The stunning technique used will not influence the TSE safety of the following types of bovine serum used by manufacturers of medical products:

   - foetal bovine serum, which is used frequently during the manufacture of viral vaccines and recombinant proteins,
   - calf serum (from animals less than 12 months, no BSE infectivity detected in brain of cattle below the age of 12 months) and
   - donor bovine serum (from live animals).

Based on the available information and in view of the factors listed above, it can be concluded that the **reclassification of Canada and USA (to GBR III) does not change the level of BSE risk of bovine serum and blood derivatives significantly**. From a public health perspective, the risk assessment for bovine serum and blood derivatives as performed previously is still valid[xi].

b. Regulatory perspective

The requirement to use non-penetrative stunning if sourcing is performed in GBR III countries has been inscribed in Rev. 2 of the TSE Note for Guidance. Manufacturers of bovine serum (other than foetal bovine serum, calf serum and donor bovine serum) and blood derivatives of Canadian or US origin will be asked to investigate and confirm that this requirement is complied with.

4. Risk assessment of gelatin

Introduction

Bovine gelatin can be made from either bones or hides:

- *Hide gelatin* is not considered further in this chapter: on the basis of current knowledge, hides used for gelatin production represent a much safer source material compared to bones. The only requirement is that measures are in place to avoid cross-contamination with potentially infected materials during procurement. This can be achieved using normal slaughtering techniques.
- *Bone gelatin* is considered in detail in this risk assessment because:
  - it is generally accepted that cross contamination of the bones (Cat. C tissue) with high risk material (Cat. A material, mainly vertebral bones being contaminated with residual spinal cord material) is difficult to avoid,
  - vertebrae may not be removed from all countries of origin during the bone collection (as this is linked to the specific slaughtering and meat processing techniques),
  - the gelatin manufacturing process[xii] has been validated for TSE inactivation/removal and the validation experiments show a substantial reduction of TSE infectivity via the manufacturing process. However, these log reduction values are not considered sufficient to rely solely on the manufacturing method to assure TSE safety of gelatin.

The safety of bone gelatin depends on two parameters: the safety of the starting materials and the validated removal/inactivation of the TSE agent via the production process. As part of the legal requirement to demonstrate TSE compliance, a risk assessment has been performed in the past for gelatin used in or during the manufacture of medicinal products. In most cases, TSE certificates of suitability from the EDQM have been used to demonstrate TSE compliance; in a few cases, scientific information on the countries of origin, the types of tissues used and the manufacturing process have been provided directly to the EU competent authorities as part of the application dossier. Currently, all gelatins used in medicinal products are manufactured in compliance with the TSE Note for Guidance.

The TSE Expert Group has recently considered new data on the inactivation/removal of TSE infectivity during gelatin manufacture:

- The removal of high risk tissues from the source materials is considered to be of paramount importance. Therefore, to increase the overall safety level, the removal of vertebrae for bones from cattle of all ages and from GBR II and III countries should be obligatory. (Currently, there is no requirement for the removal of vertebrae from GBR II countries and the removal of vertebrae from GBR III sourced animals applies for animals over 12 months old only).
- The validation experiments, which were well conducted and convincing, showing a cumulative removal of 5 to 6 logs of infectivity during the manufacturing process.
- With these stricter sourcing criteria, and taking into consideration the updated validation data, both the acid and the alkaline extraction processes, as well as the heat-pressure processes, could be used for bones from GBR II and III countries if sourced as described above. (Currently GBR III sourced bones cannot be used in the acid process for gelatin manufacture.)

Risk assessment after the first BSE cases in Canada and USA

a. Public health concerns

The following factors were considered:

- It has been confirmed by the Gelatin Manufacturers of Europe (GME) that skulls, spinal cord and vertebrae are removed from all bones imported from GBR II and III countries (including Canada and USA).
- One of the additional regulations put in place in the US to further enhance safeguards against BSE is the removal of Specified Risk Materials, which include skull, spinal cord and vertebrae, from cattle over 30 months from the human food chain.
- The amount of BSE infectivity, if present, in the vertebral column (from incomplete removal of spinal cord) and in the dorsal root ganglia in animals below the age of 30 months is low.
- The manufacturing process of gelatin (acid and alkaline) reduces TSE infectivity with at least 5 logs.

In view of all points listed above, it is considered that the **reclassification of Canada/USA (to GBR III) does not change the level of BSE risk of any gelatin (acid or alkaline) made from Canadian or US bones**.

b. Regulatory perspective

Whereas the direct public health impact on gelatins is negligible, the situation from a regulatory perspective is different.

As vertebrae are removed from the starting materials, there is no regulatory issue for alkaline bone gelatin (the current Note for Guidance allows production of gelatin from bones from GBR III countries using the alkaline manufacturing process). The current TSE Note for Guidance, however, does not allow the production of acid bone gelatin from GBR III sourced bones, and therefore acid gelatin from US/Canadian bones might cause a regulatory problem.

It is the view of the TSE experts, that, provided the starting materials are free of skulls, spinal cord and vertebrae, and taking into consideration the new data of the gelatin validation studies, both the alkaline and the acid process can be used for the production of gelatin from bones from GBR III countries. An amendment to the TSE Note for Guidance in this respect is being proposed.

5. Risk assessment of other ruminant materials of Canadian / US origin (other than blood derivatives and gelatin)

Introduction

Most other tissues used in the manufacture of ruminant derived materials for use in medicinal products are Category C tissues (Tissues with no detectable infectivity)[xiii]. These tissues include, but are not limited to:

- Adipose fat tissue (tallow) for the production of tallow derivatives,
- Milk for the production of milk-derivatives and culture media,
- Meat (muscle tissue), bile, connective tissue and skin, used in the production of peptone.

Materials from Category B tissues (Lower infectivity tissues) are used in only a few cases, namely:

- Pancreas for the production of insulin and enzymes,
- Spleen and liver extracts for the production of some culture media,
- Enzymes extracted from bovine intestines,
- Ruminant materials extract from lungs.

For most of the materials derived from Cat. B tissues, the EDQM has issued TSE certificates.

For some of the materials (e.g. tallow derivatives), the manufacturing process will contribute to the removal and/or inactivation of TSE infectivity (if present). For other materials such as milk derivatives, peptone, insulin and extracts from organs, the manufacturing process will have no or only a limited contribution to the removal of TSE infectivity.

All of these other ruminant materials of US/Canadian origin currently used in, or in the manufacture of, medicinal products have been assessed for TSE compliance and have been found acceptable. For many materials, TSE certificates of suitability have been issued, which provide reassurance that all criteria of the TSE Note for Guidance have been taken into consideration. For other materials, such as milk derivatives, a formal risk assessment has been conducted by the BWP/CPMP[xiv], indicating that no TSE risk is associated with the use of such materials.

Risk assessment after the first BSE cases in Canada / USA

a. Public heath viewpoint

The following factors have been considered when conducting this assessment:

1. All actions taken by Canada/USA to ensure the protection of public health following their first BSE case have been reviewed in Section 2.2 of this report.
2. The following factors are unchanged since the previous risk assessments:
    a. Infectivity level of ruminant tissue used;
    b. Measures to prevent cross-contamination with high-risk tissues. The obligatory removal from the food chain of SRMs will further reduce the cross contamination risk (i.e. greater awareness of what are high risk tissues might indirectly reduce cross contamination of low risk tissues)
    c. Manufacturing process (including QA systems, audit etc)
3. For ruminant materials derived from **Category C tissues** of Canadian/US origin, taking into account points 1. and 2. above and taking into account the contribution of the manufacturing process for products such as tallow derivatives, it can be concluded that such materials (of Canadian/US origin) do not cause any concern with regard to TSE safety.

4. A limited number of ruminant materials are derived from **Category B tissues**. Considering:

   - that the contribution of factors such as the manufacturing process, the QA systems and the measures to prevent cross contamination are unchanged since the previous risk assessment,
   - that the tissue infectivity has not changed since the previous risk assessment,
   - that actions have been taken by Canada/USA to ensure the protection of public health,
   - that TSE certificates have been available for many years for most of these materials (which provides assurance that all criteria of the TSE Note for Guidance have been taken into consideration),

   it can be concluded that the TSE risk of such materials of Canadian/US origin has not changed substantially since the risk assessment conducted previously. Therefore, despite the notification of the first BSE cases in USA/Canada, the use of these products remains acceptable.

In view of the above factors it can be concluded that the reclassification of Canada and USA (to GBR III) does not change the level of BSE risk of ruminant materials significantly.

b. Regulatory viewpoint

There are no specific requirements for the sourcing of Category B or C tissues (other than blood and bones for gelatin, which are dealt with separately) from GBR III countries.

[i] Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products. EMEA/410/01-rev 2 of October 2003, published in the Official Journal of the European Union (OJ 2004/C 24/03 p. 6 of 28.1.2004)

[ii] Geographical BSE Risk (GBR), as defined in Regulation (EC) No 999/2001 of the European Parliament and Council (OJ L 147 p. 1 of 31.5.2001)

[iii] http://www.inspection.gc.ca/english/anima/heasan/disemala/bseesb/bseesbindexe.shtml

[iv] http://www.usda.gov/

[v] Now the Committee for Human Medicinal Products (CHMP)

[vi] TSE: Transmissible spongiform encephalopathy. Group of neurodegenerative diseases including BSE (Bovine spongiform encephalopathy, BSE) in cattle and Scrapie (in sheep).

[vii] Regarding the SRM definition in USA: The tissues banned are identical as in Europe [Regulations (EC) No. 999/2001 (human food) and (EC) No. 1774/2002 (animal by-product not intended for human consumption)]. However, the age of the cattle from which SRM have to be removed is very different: 12 months in Europe versus 30 months in the USA.

[viii] USDA News release (‘*Veneman announces additional protection measures to guard against BSE’*) of 30 December 2003.

[ix] ‘Food chain’ with the meaning of food and other human uses, such as pharmaceuticals.

[x] There is no information on the efficacy of the manufacturing steps in the preparation of bovine serum with respect to the removal or inactivation of the TSE agents, but this removal/inactivation capacity, if present, is expected to be limited. Manufacturing processes during the preparation of other blood derivatives might contribute to the removal of TSE infectivity, but these have not been validated and should not be taken into consideration in the risk assessment.

[xi] The CPMP *position 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* (EMEA/CPMP/BWP/476/01) of 28 February 2001 (http://www.emea.eu.int/pdfs/human/press/pus/047601en.pdf) remains valid as well.

[xii] Gelatin manufacturing process: Bone gelatin can be made using an acid or an alkaline process. 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. For gelatin made using the acid process, the liming step is replaced by an acid pre-treatment where the ossein is soaked overnight at pH < 4.

[xiii] See Section 3.3 of Rev. 2 of the TSE Note for Guidance. This classification is based upon the WHO tissue classification (February 2003).

[xiv] http://www.emea.eu.int/pdfs/human/bwp/033702en.pdf