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Questions and answers on Bovine Spongiform Encephalopathies (BSE) and vaccines

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Questions and answers on Bovine Spongiform Encephalopathies (BSE) and vaccines

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1. Introduction (background)

Since recognition of BSE in the 1980's, the use of bovine material in the manufacture of medicinal products, including many vaccines, prompted action by European and National regulatory authorities to assure the continued safety of the products. The appearance of new variant Creutzfeldt-Jakob Disease (vCJD) and its association with BSE, underlined the importance of the measures taken and increased concern regarding any potential risk associated with use of bovine material.

2. Scope

This is an update of the information in the 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[1] and the Questions and Answers on Bovine Spongiform Encephalopathies (BSE) and Vaccines[2]. The public statement and Q&A were intended to provide an assessment of the risk due to BSE of the use of bovine materials in vaccines when they were drafted in 2001. Since 2001, understanding of the risks associated with BSE has progressed significantly and a routine review of EMA guidelines identified this document as requiring updating. It includes information on the use of bovine derived materials in vaccine manufacture. Risk assessment of other TSE-susceptible animal species is covered in the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products[3] and the use of materials of human origin is reviewed in the CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products[4].

3. Summary

Any bovine-derived material used in the manufacture of a vaccine is regulated according to the mandatory TSE guideline which has been continuously updated in the light of scientific knowledge. The guideline dictates that a risk assessment is performed during development and authorisation of all medicinal products. The risk assessment involves controlling the geographical source of the animals used, the nature of the tissue used (risk of infectivity) and the method of production. Safe geographical sourcing of animals is based on the latest Organisation Internationale des Epizooties classification[5] of countries according to their BSE status. The safety of the tissue used for processing is ensured by categorisation according to the WHO tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies[6]. Finally, production methods are assessed for their ability to inactivate or remove the agent responsible for BSE. The CHMP and regulatory authorities within

[1] 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
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003717.pdf
[2] Questions and &Answers on Bovine Spongiform Encephalopathies (BSE) and Vaccines
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/09/WC500003715.pdf
[3] Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003700.pdf. First adopted in 1991 and entered into force in 1992
[4] CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products
http://www.ema.europa.eu/docs/en_GB/document_library/Position_statement/2011/06/WC500108071.pdf
[5] OIE List of Bovine Spongiform Encephalopathy Risk Status of Member Countries
http://www.oie.int/animal-health-in-the-world/official-disease-status/bse/list-of-bse-risk-status/
[6] WHO Tables on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies. Updated 2010.
http://www.who.int/bloodproducts/tablestissueinfectivity.pdf

member states of the European Union undertake benefit/risk assessments before any vaccine is authorised. The final benefit/risk decision includes the BSE risk assessment discussed above.

The CHMP and its experts historically conducted a review on the use of bovine material in the manufacture of vaccines licensed within the EU to ensure that the sourcing of animals and of tissues used up to that point in time was according to the TSE guideline. Subsequently, the assessment of all new products includes an assessment of the BSE risk in line with the TSE guideline.

Based on the above measures being taken, the CHMP considers that the risk of BSE contamination of vaccines used within the EU is extremely low. Nevertheless, in order to provide the highest level of assurance, manufacturers have replaced materials of bovine origin, wherever possible.

There is no evidence to date that any vaccines have been contaminated with the agent which causes BSE. Taking into consideration the measures already employed to ensure the safety of vaccines with respect to BSE, the EMA concludes there is a very high level of assurance against the risk of BSE contamination and therefore reiterates the benefits of vaccination. There is no evidence to relate vaccines to the development of vCJD. Consequently, on the basis of current scientific evidence and of measures being taken to avoid any possible contamination of vaccines with BSE, the EMA is of the view that appropriate measures are in place to protect public health.

4. Questions and answers on Bovine Spongiform Encephalopathy (BSE) and variant CJD

What is BSE?

BSE (Bovine Spongiform Encephalopathy) is a disease of cattle which is sometimes known as Mad Cow disease. BSE belongs to a group of diseases called TSEs (Transmissible Spongiform Encephalopathies). BSE was recognised for the first time in 1986 in the UK. A similar disease in sheep, called scrapie, has been recognised for over two centuries. Due to the eradication measures, this epidemic has declined worldwide and as of 2017, there are only a few cases reported annually[7]. In the UK, where the most cases have been reported, the incidence of BSE has decreased from 37,280 in 1992 at the height of the epidemic, to 0 cases in 2016.

All TSE diseases are associated with the appearance of tiny particles in brain and nerve cells. These particles consist of an abnormal form of prion protein and are responsible for TSE diseases (see “What are prions” below).

The most obvious symptoms of TSE diseases are in co-ordination of movements and mental deterioration. Once a TSE disease becomes established, it becomes progressively more serious.

TSEs are said to be ‘transmissible’, because if certain tissues of an affected animal are given by injection or by mouth to other animals, the disease may be passed on to them. Brain and spinal cord are the tissues which are the highest risk in this respect.

How did the outbreak appear in animals?

The outbreak probably started as a result of feeding of animal derived meat-and-bone meal to cattle. There is strong evidence and general agreement that the outbreak was then amplified by the continued feeding of meat-and bone meal prepared from infected cattle.

[7] http://www.oie.int/animal-health-in-the-world/bse-specific-data/number-of-cases-in-the-united-kingdom/

Does this kind of diseases occur in humans?

Yes, but these human diseases are very rare. They include classical (or sporadic) Creutzfeldt-Jakob Disease (CJD/sCJD), variant CJD (vCJD), Kuru (transmission via cannibalism in Papua New Guinea) and fatal familial insomnia. Classical CJD has been well studied for more than 70 years and occurs sporadically worldwide at a rate of about 1 case per 1 million people and is not linked to BSE.

Can BSE be transmitted to humans?

In 1996, the first cases of a variant of Creutzfeldt-Jacob Disease (vCJD) were reported in the UK (Lancet, 1996, 347: 921-925). There is strong scientific evidence indicating that vCJD and BSE are caused by the same infectious prion agent and strong epidemiological and experimental scientific evidence for the association between the ingestion of BSE contaminated food and vCJD. Experts believe that certain types of meat (mechanically recovered meat which at that time contained high risk tissues) or certain high risk tissues (brain) used in the preparation of industrial minced meat could have played a major role in spreading the human form of TSE (vCJD).

Emergence of variant CJD (vCJD) was noted in the UK in 1996 and a total number of 178 definite or probable cases have been reported so far in the UK[8]. Although the number of cases has been in decline in the UK since 2001, isolated cases of vCJD are still being identified in the UK as in other countries.

Further information can be found in the CHMP position statement on Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products.

vCJD generally affects younger people (average age of onset: 28 years) than classical CJD and the clinical symptoms are different.

What are prions?

Prions are proteins that are found in all animal species and in humans. Abnormal forms of prion protein are found in TSEs such as BSE, scrapie and all forms of CJD. Abnormal forms of prion proteins are closely associated with the spread of the disease. Unlike other infectious particles such as bacteria or viruses, prions do not carry any genetic material. Prions are extremely difficult to destroy: they are resistant to elevated temperatures and standard chemical conditions which would normally kill bacteria and viruses.

How do prions cause BSE?

Spongiform encephalopathies (also known as prion diseases) are degenerative neurological disorders characterised by the presence of massive amounts of modified (structurally abnormal) prion proteins. For an unknown reason, the normal protein can be transformed into a different conformation, by contact with a modified prion protein. This can happen mainly in the brain where a cascade of progressive degeneration may start. It is thought that the ingestion of a critical amount of this modified protein could trigger the disease.

There is no diagnostic test available yet to identify the disease prior to the start of clinical symptoms and the development of a characteristic neurological pattern. However, for detecting BSE in slaughtered animals, diagnostic tests are available and in use.

[8] http://www.cjd.ed.ac.uk/data-and-reports/variant-cjd-cases-worldwide

No medicinal product is available to combat the disease, and no vaccine has been developed to protect animals or people.

Why is the risk of BSE transmission being raised in relation to vaccines for human use?

Material of animal origin, including bovine derived materials, is used in the manufacture of some vaccines.

However, the European Medicines Agency (EMA) has been advised by a panel of international experts that the risk of BSE contamination of vaccines used in the EU is extremely low. There are no indications that vCJD is linked to the use of vaccines, and it is felt that the risk posed by the use of bovine material is very remote as substantiated by the experience to date.

5. Vaccines and risk of BSE transmission

5.1. Questions and answers on bovine materials used in the manufacture of vaccines

What are vaccines and how do vaccines work?

Vaccines are medicinal products, which are given to protect individuals against viral or bacterial infections. Some contain small amounts of inactivated viruses or bacteria, while others may contain micro-organisms which, although alive, no longer cause disease (live attenuated vaccines). Vaccines may also be composed of purified fractions of these micro-organisms or of components derived from recombinant DNA technology. Vaccines act by stimulating the body's own defences (the immune system), so that when he or she comes in contact with the relevant virus or bacterium, he/she will be protected against infection. Tetanus vaccine is an example of a bacterial vaccine and measles vaccine is an example of a viral vaccine.

How are vaccines manufactured?

Vaccines are made by growing cultures of these viruses or bacteria, or cells which have undergone recombinant manipulation, under controlled conditions. Some vaccines are then inactivated by chemical treatment. Other vaccines are attenuated (live, but no longer able to cause the disease). Bacteria require complex culture media for their growth. Viruses need to grow in cells and these cells also require complex culture media. Recombinant cells can be either bacterial, insect or mammalian and have similar complex nutritional needs. The culture media provide numerous nutritious elements and growth factors, sometimes obtained from materials of animal origin, such as serum, milk and milk derivatives, gelatin, meat extract or extracts from other muscular tissues ("peptones").

After the processes of bacterial fermentation, viral growth in cell cultures or growth of recombinant cells are completed, there is a purification process reducing these growth supplements to trace amounts.

The bacterial or viral components of the vaccine are then diluted to the desired strength and prepared into a finished product. Vaccines are presented in vials or pre-filled syringes containing the desired bacterial, viral or recombinant components together with ingredients such as stabilisers. After production, vaccines are given in defined doses which are proven to be safe and effective in clinical trials.

Are any materials of bovine origin used in the manufacture of vaccines?

Bovine derived materials are used at some stages in the manufacture of some, but not of all vaccines. These bovine materials are one source of nutrients and growth factors for the growth of bacteria or for the cells used to grow viruses. These elements are essentially provided from materials of animal origin.

Generally they are used only in the early stages of the manufacturing process of the vaccine component(s), and then they are reduced to trace amounts during the further purification and dilution steps.

In other cases, highly processed derivatives of a bovine material are used, e.g. as a stabiliser of the finished product. For example polysorbates, (which are manufactured using very high temperature and extreme chemical conditions which have been shown to inactivate prions) are used in a small number of vaccines.

Manufacturers of vaccines strictly control the quality of the materials derived from animals by obtaining them only from known, well controlled sources with systems in place to ensure the materials do not pose a risk of contamination with BSE, and by only sourcing the materials from animals which are fit for human consumption (see "How safe is the bovine material used in the manufacture of vaccines?" below).

Is it possible to replace bovine materials used in the manufacture of vaccines with non-animal materials?

Over the past years there have been many attempts to find a way to replace growth media containing bovine derived materials by plant-derived or more synthetic media. This has often been successful. However, not all attempts have succeeded in providing bacteria, viruses or cells with all the nutrients present in the bovine material. In many cases, it has been possible to replace most or all of the animal materials used during the production of vaccines. Researchers continue their efforts to eliminate materials of animal origin in the manufacturing process.

Manufacturers were encouraged to re-establish their Working Seed/Cell Banks (WSB/WCB) if they contained material where not all of the relevant information was available to demonstrate compliance with the TSE Note for Guidance, even if there were no demonstrable TSE risks associated with their use. The new WSB/WCB should be prepared using material for which all relevant information is available[9]. As a general precautionary measure, manufacturers of medicinal products are encouraged not to use materials of bovine origin at all, if possible.

How safe is the bovine material used in the manufacture of vaccines?

Gelatin

Gelatin is extracted from different tissues (usually from skin and bone) from different animal species (usually from cattle and pig). It is used directly in medicinal products, for example in capsules. Gelatin is not made from a high risk material like brain or spinal cord, but it cannot be excluded that a small amount of high risk material could be a contaminant in bones from which gelatin is extracted. BSE infectivity has never been detected in bovine skin[3].

The production of gelatin from bones involves grinding, degreasing, heating followed by a hydrochloric acid bath for several days. The gelatin may then be further treated with strong alkali or acid. In addition there is a heat sterilisation step at a minimum of 133°C or 138°C. These processes have been shown to have high capacity to reduce or eliminate any contaminating BSE prions.

[9] Re-establishment of Working Seeds and Working Cell Banks using TSE compliant materials EMEA/22314/02 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003702.pdf

Bovine serum

Bovine serum is very rich in vitamins, growth factors and other components necessary to grow the cells needed for viral vaccine production. The following measures are taken into account to ensure the safety of serum regarding the risk of transmission of contamination with BSE:

- Bovine serum is obtained only from countries with a negligible or controlled BSE risk
- Bovine serum is obtained only from animals which are fit for human consumption.
- Each batch of serum or plasma is traceable to the slaughterhouse to ensure that material of unknown quality/TSE risk does not enter the supply chain. Methods of animal stunning and slaughter are controlled to reduce/avoid the risk of cross-contamination of blood with high risk tissues such as brain.
- The maximum age of cattle at slaughter is strictly limited
- The presence of the BSE prion has not been conclusively detected in the blood of cattle which are sick or incubating the disease[3].

Milk and milk derivatives (for example lactose)

- Bovine milk has always been considered as non-infectious, regardless of the country of origin. Within the limits of experimental testing, BSE prion has not been detected in the milk of cattle which are sick or incubating the disease[9].
- Lactose is a natural sugar present in milk. Milk used for lactose production must be collected under the same conditions as milk for human consumption. This ensures that milk comes from healthy animals, controlled by veterinary welfare systems.

Meat extracts

Meat extracts are mainly derived from muscular tissues. All of the tissues from which meat extracts are derived are classified in the no or low risk categories by the WHO[3] and high risk material is excluded. This material is collected from countries with a negligible or controlled BSE risk. Taking these criteria into consideration, meat extracts do not represent a risk of BSE transmission.

Polysorbate (Tallow derivatives)

Tallow derivatives are prepared from tallow (fat) which is derived from animal fat tissue. The tallow starting material is prepared by separating it from the protein fraction. It has been shown that BSE infectivity (experimentally added to the animal fat tissue) is never found in the tallow fraction, but can be found in the protein fraction (which is not used in the manufacture of tallow derivatives). Tallow derivatives are made from tallow starting material by very high temperature and extreme chemical treatment. Tallow derivatives are extremely unlikely to pose any risk of transmitting BSE. Examples of tallow derivatives are stearates (used in many tablets) and polysorbate (occasionally used to stabilise vaccines). In most cases, animal-derived polysorbate has been replaced by plant-derived polysorbate.

5.2. Questions and answers on vaccines and the measures taken to prevent the transmission of BSE

What measures are applied to vaccines to prevent BSE infection?

All medicinal products, including vaccines, have been thoroughly evaluated before they are authorised to be marketed. To receive this authorisation to market their product, a pharmaceutical company has to describe in detail (in a dossier) the results of all the studies demonstrating the quality, safety and efficacy of the medicinal product. The dossier also documents the method of production and control of each component of the medicinal product and all factors concerning the risk of BSE transmission are presented. The dossier is evaluated by the relevant National Authorities or the EMA, taking into account all existing guidelines and legal texts. It is only when a dossier is complete and fully satisfactory that a marketing authorisation for a medicinal product is granted.

For all bovine materials used in the manufacture of vaccines (and all other medicinal products) an assessment is made of the risk of BSE contamination. This is carried out in accordance to the European *Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*. This legally mandatory guideline was first applied in 1991, and has been regularly updated since. Factors taken into special account are:

- The country of origin of the animals used,
- The nature of the tissue used (for example, brain is considered the highest risk, serum and muscle tissue are of the lowest risk),
- Information on traceability (origin and follow-up of herds, type of feed, etc.),
- Whether the manufacturing processes of both the materials of bovine origin and the vaccine could reduce or destroy any BSE, if it were to be present.

Therefore, safety related to the risk of transmitting BSE is assessed by taking into account not only the geographical origin of animals but also their feeding, their age at slaughter, technique of slaughter and carving, nature of tissues used, as well as manufacturing processes which must comply with European guidelines, directives and recommendations. It is the assessment of all these criteria, which ensures the freedom of a medicinal product from contamination with the agent that causes BSE before it is authorised and marketed.

In June 2000, the European Medicines Agency (EMA) conducted a review of the safety of all vaccines (including those which were licensed prior to the introduction of the *Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*) on the EU market with respect to BSE contamination and concluded that all vaccines are indeed safe. Therefore, all vaccines authorised to date, have been reviewed for safety with respect to BSE, against the above criteria.

5.3. Questions and answers on the evidence that vaccines do not transmit BSE.

What evidence is there that vaccines were not the cause of the vCJD cases in the UK?

The majority of vCJD cases occurred in the UK between 1996 and 2005. The same vaccines that were given to these people in the UK in their early life were also used in other countries at the same time. No vCJD cases occurred in these other countries despite administration of identical vaccines, from the same manufacturers and using identical materials.

Furthermore, most vCJD patients from the height of the epidemic were vaccinated prior to the occurrence of BSE in British herds (most vaccines are given in the first two years of life). Thus, the vaccines used to immunise children who developed vCJD in later life had been produced in the years

before the BSE epidemic and so the agent that causes BSE could not have been present in the doses of vaccine given to these children.

What is the experts' opinion on the safety of vaccines with respect to BSE?

Vaccines have played, and continue to play, a crucial role in the prevention and eradication of viral infectious diseases, such as measles, mumps, rubella, polio and smallpox, and of bacterial infectious diseases such as diphtheria, tetanus and pertussis. Vaccines currently in use have an excellent safety record. A reduction in use of vaccines is likely to result in the spread of damaging or fatal diseases.

In 2001, the European Medicines Agency (EMA) was advised by a panel of international experts that the risk of BSE contamination of vaccines used in the EU is vanishingly small. To date there are no indications that vCJD is linked to the use of any vaccines, and that the risk posed by the use of bovine materials is very remote as substantiated by the experience to date.

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