

ema 5

Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products

EU perspectives

JH Trouvin
CPMP,
Biotechnology working party
EMA London

ema 5

- EU guideline: the three criteria
- Additional measures
 - Cross contamination
 - Traceability
 - Quality assurance system
- Discussion
 - Geographical criterion
 - Assessment factors
- Conclusion

ema 5

Transmissible spongiform encephalopathies (TSE)

- Scrapie in sheep and goats
- Chronic wasting disease (CWD) in mule deer and elk
- Transmissible Mink encephalopathy (TME)
- Bovine spongiform encephalopathy (BSE) in cattle
- Kuru, Creutzfeldt-Jakob disease (CJD) in human

ema 5

EU guideline:
Minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products

- First issue in 1991, revisions in 1997, 1999
- TSE risk and measures to minimising the risk of transmission via medicinal products
- Covers materials of animal origin, particularly those of ruminant origin
- Material used as
 - Active substances
 - Excipients
 - Raw or source materials and reagents used in production of medicinal products

ema 5

Scope

- To request detailed information on starting materials of animal origin taking into account:
 - The source of the animals (geographical origin)
 - The nature of the animal tissue
 - The production processes
- Scientific evaluation undertaken against these criteria and taking into account the nature of the specific product concerned

ema 5

Source of animals

- Careful selection of source material is the most important criterion
 - The most satisfactory source is from countries which have not reported cases of BSE
 - Materials may also be sourced from countries where a low number of indigenous cases have occurred
 - Source material should not be used from countries where there is a high incidence of BSE
 - Source material from well monitored herds may provide an extra safety margin
- OIE criteria to be used for assessing the BSE status of a country

ema (5)

Animal tissues (I)

- ★
- ★
- ★
- ★
- ★

- In a TSE infected animal, different organs and secretions have different level of infectivity
- WHO classification

ema (5)

Animal tissues (II)

- ★
- ★
- ★
- ★
- ★

- Level of infectivity, depending on the tissue, organ and secretion
 - Category I: High infectivity (*brain*)
 - Category II: Medium infectivity (*Ileum, proximal colon, spleen*)
 - Category III: Low infectivity (*bone marrow, liver, pancreas*)
 - Category IV: No detectable infectivity (*milk, skeletal muscle, skin, bone*)
- WHO classification is a worst case scenario for BSE: distribution in infected cattle appears to be more restricted

ema (5)

Animal tissues (III)

- ★
- ★
- ★
- ★
- ★

- Cross contamination
 - the risk will be dependent on several complementary factors including
 - The level of contamination during collection
 - Precautions adopted to avoid contamination during collection
 - e.g.*fetal blood is collected without contamination from other maternal or fetal tissues including placenta, amniotic and allantoic fluids...* (EU guideline)

ema (5)

Age of animals

- ★
- ★
- ★
- ★
- ★

- As the accumulation of TSE infectivity occurs over an incubation period of several years sourcing from young animals may be prudent

ema (5)

Manufacturing Process(es)

- ★
- ★
- ★
- ★
- ★

- Manufacture of the starting materials
 - Harsh processes are feasible e.g. tallow derivatives
- Manufacture of the medicinal product
 - Vaccines are not made of bovine-derived material
 - Bovine-derived material are in-process reagents the content of which is reduced significantly during manufacture

ema (5)

Discussion

- ★
- ★
- ★
- ★
- ★

- The risk of transmission can be greatly reduced by controlling a number of parameters together including:
 - source of animals
 - nature of animal tissue used
 - age of animal
 - production process(es)

ema

5

Discussion Geographical criterion (I)



- BSE risk assessment and management measures often based on the incidence of clinical BSE cases
- Incidence, however, depends heavily on the quality and effectiveness of the country surveillance system
- European concept of Geographical BSE Risk (GBR)
- This is only one of the criterion taken into account in risk assessment

ema

5

Discussion Geographical criterion (II)



- GBR classes:
 - I highly unlikely
 - II unlikely but not excluded
 - III likely but not confirmed or confirmed at lower level
 - IV confirmed at a higher level

ema

5

Discussion Geographical criterion (III)



- Geographical origin is not an absolute parameter
 - Evolution of the BSE status
 - Traceability
- Assurance given by the geographical origin alone is not enough

ema

5

Discussion Assessment Factors (I)



- Multi-parameter evaluation
- Each criterion contributes to the overall safety assessment
- No single approach alone will necessarily establish the safety of a product
- the three approaches are used in a complementary way to minimise the risk of contamination

ema

5

Discussion Assessment Factors (II)



- The acceptability of a particular medicinal product, will be influenced by a number of factors, including
 - Documented and recorded source of animals
 - Nature of animal tissue used in manufacture
 - Production process(es) - further reduces the risk
 - Quantity of tissue used in the medicinal products
- Route of administration
- Maximum therapeutic dosage
- Intended use of the product

ema

5

Discussion Assessment Factors (III)



- ..marketing authorisation holder should avoid the use of ruminant material wherever possible..
- ..the preferred option should be to avoid the use of material derived from animals known to be susceptible to TSEs
- Importance of the quality assurance system
 - the trace-ability system
 - audit of the providers
 - producers "responsible for the selection and justification of adequate measures"

Conclusion



- All concerned medicinal products have been reviewed in Europe using the EU guideline criteria
- Risk assessment involves the evaluation of a number of factors and should not be reduced to the geographical origin alone
- Scientifically-based evaluation is necessary to accommodate any evolution of the worldwide TSE situation