



**TSE / BSE**  
**RISK & REGULATIONS IN**  
**PHARMACEUTICALS**

An Overview by Saravananaraja Subramanian



# FOREWORD

- ❖ Risk & Regulations of TSE/BSE in pharmaceuticals are of great importance because of its irreversible fatal effects on human health. Before knowing the risk and regulations of TSE/BSE in pharmaceuticals, it is very much necessary to know what is TSE/BSE, how it affects human, sources of TSE/BSE, the history/discovery and the modus operandi.
- ❖ The objective of the presentation is to provide an overview of the implications of TSE/BSE and to help the reader to understand TSE/BSE in a simple way so as to realize the risk & regulations which can be implied in the day to day quality & regulatory activities.
- ❖ The contents in this presentation is simplified to the possible extent to make things very clear and easy to understand. The compliance to guidelines is necessary when the product/material is at risk of having TSE/BSE. Unless otherwise specified, if the material is not risk, there is no need to meet the requirements of complying to TSE/BSE.
- ❖ In an ever growing need on compliance in the pharmaceutical industry, one must aware of the basic things which I feel is the very first act to be done before proceeding with any operations/activities and therefore the basics of TSE/BSE described in this presentation.

# WHAT IS TSE?

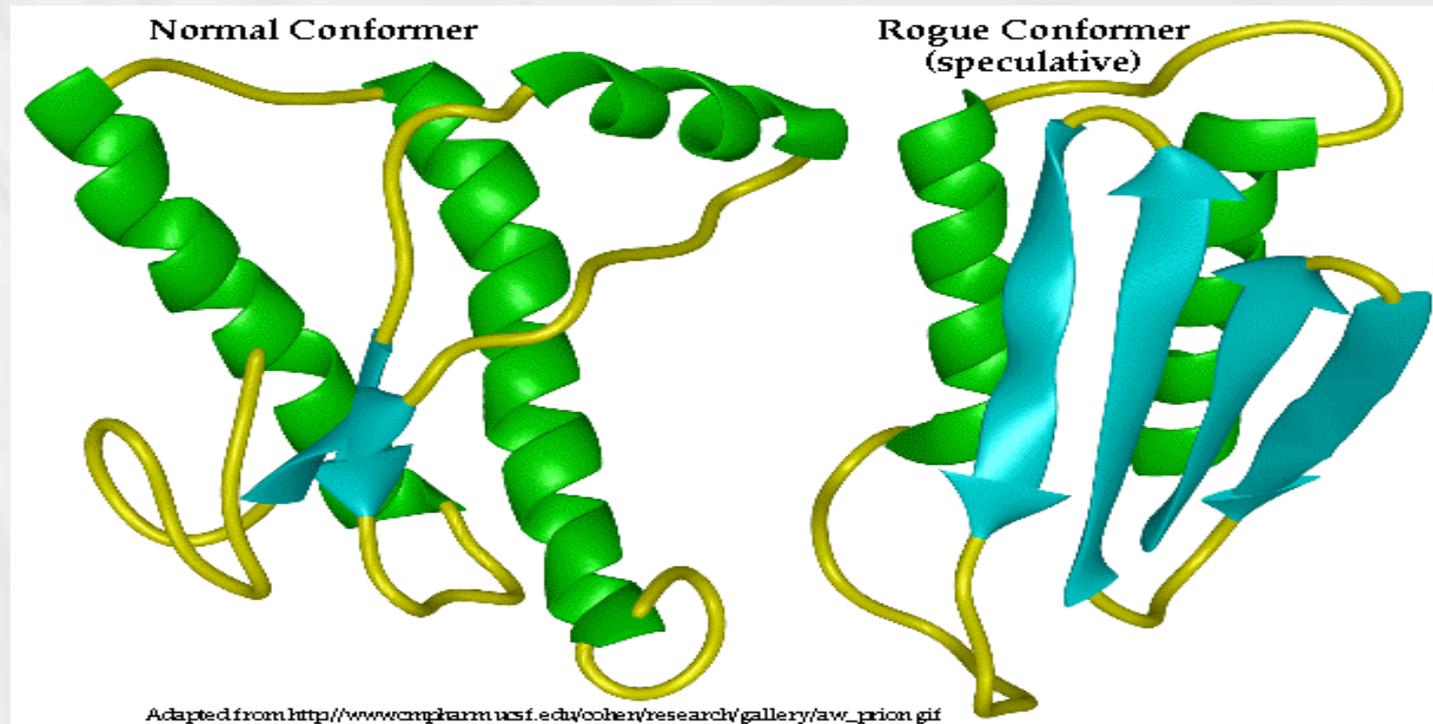
- ❖ TSE – Transmissible Spongiform Encephalopathy – In general, it is a disease. A group of rare degenerative brain disorders characterized by tiny holes that give the brain a "spongy" appearance<sup>1</sup>.
- ❖ It is a rare disease occurs in Humans and Vertebrate animals (Vertebrate = Animals having backbone)
- ❖ TSE = A disease capable of being transmitted by infection and gives the appearance of sponge like tiny holes in the brain. There are many types of Human TSEs.
- ❖ The literal meaning of TSE is as below
  - Transmissible = Capable of being transmitted by infection
  - Spongiform = Sponge like
  - Encephalopathy = Brain Disease[encephalon + pathy = the technical name of brain + Pathy = disease]

# WHAT IS BSE?

- ❖ BSE – Bovine Spongiform Encephalopathy – It is a brain disease that occurs in bovines; generally known as “Mad Cow Disease”
- ❖ It is a rare disease occurs in Vertebrate animals; for example, cow/cattle.
- ❖ BSE = A disease capable of transmitted by infection and gives a appearance of sponge like tiny holes in the brain of bovines.
- ❖ The literal meaning of BSE is as below
  - Bovine = Characteristic of or resembling cows or cattle.
  - Spongiform = Sponge like
  - Encephalopathy = Brain Disease
  - [encephalon + pathy = the technical name of brain + Pathy = disease]

# WHAT IS THE CAUSATIVE AGENT?

- ❖ The causative agent is NOT a bacterium or a virus or a fungus or any plant(s). It is a protein called as Prion, usually present in the body cells of Human and Animals<sup>2</sup>. The structure of the prion protein is given below<sup>3</sup>.



# THE CAUSATIVE AGENT CONTINUES...

Prion have two forms as said below.

- ❖ Prion = proteinaceous infectious particle, named as Prion Proteins [PrP]

## Normal Form

A harmless protein found in the body's cells which is unfolded in structure which does not cause TSE

## Abnormal Form

The protein which is in folded structure and can cause TSE

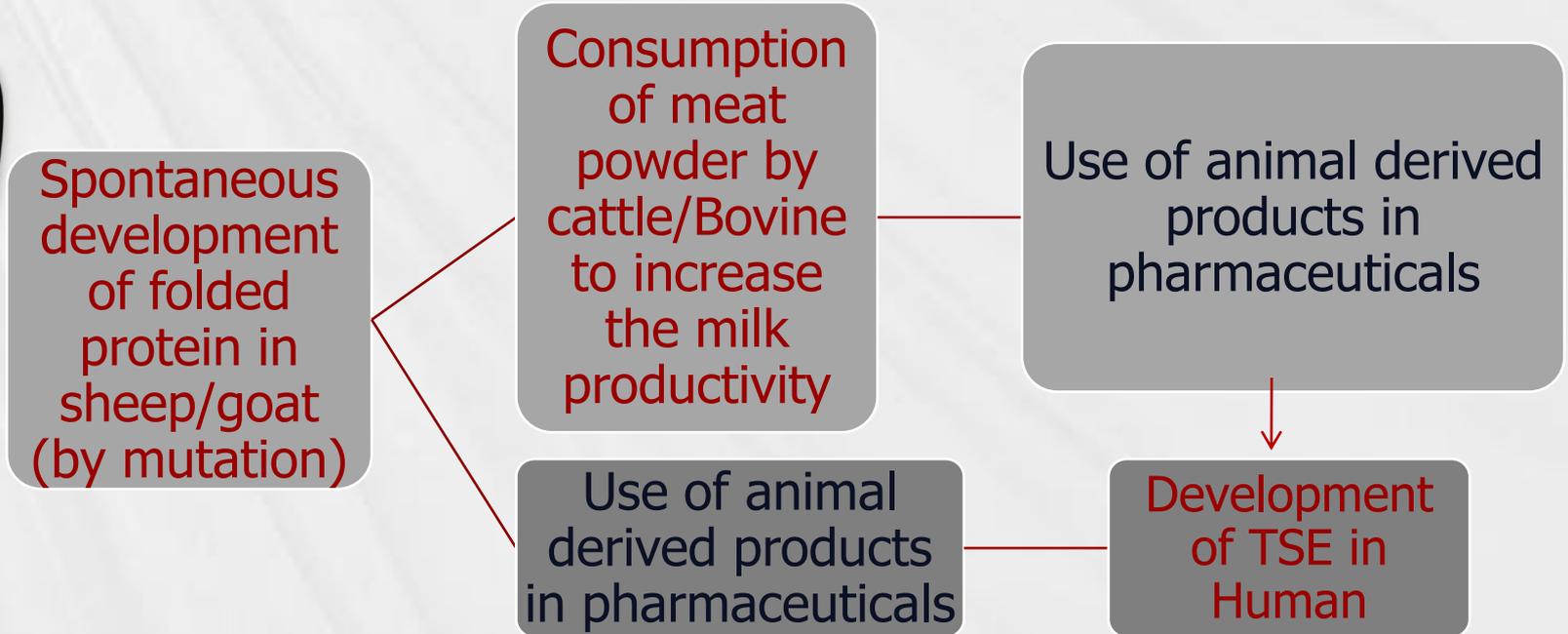
- ❖ Both normal and abnormal prion are identical except the folding in the structure of abnormal proteins. The accumulation of an abnormal isoform of the prion protein in the Central Nervous System causes the diseases. Creutzfeldt-Jakob disease in its sporadic form is the most frequent type of human TSE<sup>4</sup>
- ❖ After the name of the causative agent the disease is also named as prion diseases.
- ❖ Nevertheless, there are some other hypothesis to the cause of the disease like Multi-component theory and Viral theory but protein theory is scientifically proven to certain extent of acceptance by scientists<sup>5</sup>.

# HISTORY / DEVELOPMENT OF TSE/BSE

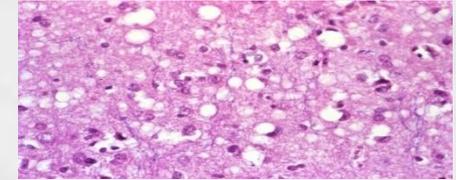
- ❖ “Scrapie”, a disease appeared in sheep/goat having characteristics of a typical TSE/BSE is the pioneer of TSE/BSE diseases. Scrapie was first reported in UK in 1980s. BSE first came to the attention of the scientific community in November 1986 with the appearance in cattle of a newly-recognized form of neurological disease in the United Kingdom (UK)<sup>6</sup>.
- ❖ Though there were no direct scientific proofs on how TSE/BSE evaluated and transmitted to humans, it is believed the prion protein which is naturally present in the sheep/goat mutated spontaneously and developed the disease. It is believed that the meat of the infected sheep was fed to cattle as a dietary supplement to increase the milk production as the meat is a proven source of high proteins, and thus, cattle were infected with spongiform encephalopathy. The evolution of spongiform encephalopathy in humans has no proven evidence. However, it is believed that it might have occurred spontaneously or by the consumption of infected meat of animals likely of a sheep or deer.
- ❖ It is also proved that not only bovine (sheep/goat/cattle) were affected by spongiform encephalopathy but a wide variety of animal like deer, Monkey and even some ovine species have been identified as susceptible to TSE.
- ❖ The first report of risk of TSE to human was reported in October 1997 through Global Alert and Response (GAR) by WHO on a consultation on medicinal and other products in relation to human and animal transmissible spongiform encephalopathies<sup>7</sup>.

# DEVELOPMENT FLOW OF TSE/BSE

- ❖ The flow is based on the information from available literatures and is one the of most- accepted hypothesis by scientists.



# TYPES OF HUMAN TSE



- ❖ There are a number of types<sup>8</sup> of human TSEs reported; one is a sub classification of CJD as described below:
  - Kuru prion
  - Creutzfeldt-Jakob disease (CJD)
  - (New) Variant Creutzfeldt-Jakob disease (vCJD, nvCJD)
  - Gerstmann-Sträussler-Scheinker syndrome (GSS)
  - Fatal familial insomnia (FFI)
  
- ❖ At present, there is no proven specific or effective treatment available for any form of TSE<sup>4</sup>. The image as presented above shows the sponge like appearance of the brain after infection by the prion and it is of the type CJD<sup>9</sup>. To know what happens to human if infected by the protein is really important to understand why the regulations came into existence for pharmaceutical Products.
  
- ❖ Thus, the risk of transmission of products/derivatives form any animals or infected sources into pharmaceutical products has become a significant health concern and all regulatory agencies has published their regulations towards it.

# THE RISK OF TSE/BSE IN PHARMACEUTICALS

- ❖ There is a possible risk of contamination of infected animal derived products in the pharmaceutical finished dosage form for human consumption leads to transmission of TSE/BSE to human beings.
- ❖ In some cases, the Pharmaceutical preparations like Finished Dosage Forms, Active Pharmaceutical Ingredients and their Starting Materials, and Primary Packaging Materials involves the use of products/materials derived from animals. For example, use of proteins, enzymes, amino acids from animals used in the manufacturing of API and API starting materials.
- ❖ The primary packaging materials like gelatins capsules derived from the fat of animals also increases the possibilities of transmission of TSE/BSE.
- ❖ There is a high risk in the case of biotechnological products like serums, blood products and vaccines where the source material is derived from animals and animal derived products.
- ❖ There is also a possible risk of TSE/BSE through the equipments/utilities where in biologically-derived products and/or products of animal origin is handled. For example, Culture media used in reactors for media fill studies.
- ❖ Ideally, the use of such animal derived product/material should be avoided in the pharmaceutical preparation. However, during unavoidable circumstances, the use of such animal derived products is accepted, provided that the manufacturing process and procedures complies to the applicable regulations set by WHO, European Commission and USFDA.

# REGULATIONS TO MINIMIZE THE RISK OF TSE/BSE

- ❖ The most assumed causative agent , i.e. the prion proteins are highly resistant to temperature, and other chemicals. Hence, the complete removal of the infection in animal derived products is merely not possible. Hence, every step and guidance has been proposed to minimize the risk of contamination.
- ❖ Europe is the first which victimized the event of TSE/BSE through Scrapie in the early 1980s. Hence, the regulations also first evaluated from Europe. However, the epidemic was also notified to the world in 1997 by WHO. Thus, WHO also came into the picture in light of making awareness and guidance to the world. USFDA, Canada also published their guidelines.
- ❖ The following guidance and regulatory compliance activities are available at present:
  - ◆ WHO Fact Sheet & Guidelines
  - ◆ USFDA guidelines
  - ◆ EU Guidelines
  - ◆ General Monograph in European Pharmacopeia
  - ◆ Certificate of Suitability for TSE/BSE by EDQM
  - ◆ Canadian Guidelines
- ❖ There are many other guidelines which are dealing with the TSE/BSE for food safety and animal diseases category.

# REGULATIONS TO MINIMIZE THE RISK OF TSE/BSE

- ❖ According to WHO fact sheet #113, Human and veterinary vaccines prepared from bovine materials may carry the risk of transmission of animal TSE agents. The pharmaceutical industry should ideally avoid the use of bovine materials and materials from other animal species in which TSEs naturally occur. If absolutely necessary, bovine materials should be obtained from countries which have a surveillance system for BSE in place and which report either zero or only sporadic cases of BSE. These precautions apply to the manufacture of cosmetics as well<sup>10</sup>.
- ❖ Annex I to European Parliament and council directives for Veterinary 2001/82/EC and for Human medicinal products [2001/83/EC (as amended by commission directive 2003/63/EC)] describes Regulatory compliance through Risk Assessment, Legal Aspects and General Monographs.
- ❖ According to European Pharmacopeia, General Chapter 5.2.8., Risk Assessment indicates "Risk minimization rather than risk elimination" as below  
*The complete elimination of risk at source is rarely possible, appropriate measures and considerations should be taken to manage the risk of transmitting animal TSEs via medicinal products represent the risk minimization rather than the risk elimination.*
- ❖ Because of the well known mad cow disease, a BSE which had killed thousands of cow in UK and in the rest of Europe, the level of concern became high and therefore, Steps have been taken across Europe and EU directives have been made first to control TSE/BSE. In Europe, the note for guidance has been given the force of law by virtue of Annex I to EU directives for regulatory compliance

# REGULATIONS TO MINIMIZE THE RISK...CONTINUES

- ❖ Also, a General Monograph has been placed as a part of European Pharmacopeia and a control has been put in place by regulatory compliance activities through obtaining a Certificate of Suitability of TSE/BSE for pharmaceutical products/materials at risk of TSE.

The general Monograph reads as below:

*The general monograph "Products with risk of transmitting agents of animal spongiform encephalopathies" of European Pharmacopeia is identical to the note for Guidance. The monograph forms the basis for issuing Certificate of Suitability as a procedure for demonstrating TSE compliance for substances and materials used in the manufacture of Human and veterinary medicinal products.*

- ❖ Also, EP has classified a group of animals as "TSE -relevant animal species" (TSE-RAS).

It has been classified that Cattle, Sheep, Goats and animals that are naturally susceptible to TSE agents or susceptible to infection through oral route other than humans and non-human primates are defined as "TSE relevant animal species".

Any product/material derived from TSE-RAS like active substances, excipients, adjuvant, raw and starting materials and reagents used in the production should meet the requirements of the Note for Guidance published by EC.

Example: Bovine Serum, Enzymes

# REGULATIONS TO MINIMIZE THE RISK ...CONTINUES

- ❖ Other sources of TSE/BSE
  - Culture Media (used in reactors for process simulation studies like media fill)
  - Cleaning Agents
  - Softeners
  - Lubricants
  - Any equipment that comes in contact with TSE-RAS
  - Wool derivatives
  - Milk and Milk derivatives
  - Tallow derivatives
  - Collagen
  - Bovine blood derivatives (serums for vaccines)
  - Animal Charcoal
  
- ❖ If any product/material is procured for use in pharmaceutical preparations like dosage forms or APIs or API starting material, the origin of the material must be evaluated whether it originated from any one of the sources as mentioned above. If the product does not originate from any of the above said sources, then, it can be considered that the material is not at risk of transmitting TSE/BSE.
  
- ❖ If the product/material is originated from the above sources, it can be considered that the product/material is at risk and necessary compliance must be ensured as cited in the following slides.

# REGULATIONS TO MINIMIZE THE RISK ...CONTINUES

- ❖ The European community has developed good risk assessment strategies as the complete removal or elimination is not possible for TSE/BSE agents. Also, the TSE/BSE agents are highly resistant to temperature and other procedures of removal, minimizing the risk is the only possibility. As matter of this fact, the European community has developed the following risk assessment strategies. The risk assessment strategies are only applicable if any product/material is used from live or slaughtered animals.
- ❖ In case of unavoidable circumstances, TSE-RAS shall be used in the production for pharmaceutical preparation but it must be fully justified by the applicant and necessary requirement of the note for guidance (EU) should be met. There are no ready diagnostic tool available and the diagnosis is based on the ante and post mortem of infected animal brain. Further, the incubation period is too long ( 4 to 5 years for humans and Onset to a few months for cows) after infection. This does not allow the diagnosis immediately before the use of Animal derived products. Keeping in mind of these challenges of diagnosis, minimizing the risks of transmission heavily depends on the below three parameters.
  - ⊕ The source animals and geographical origin
  - ⊕ Nature of animal material
  - ⊕ Production processes including the quality assurance system
- ❖ The regulation (EC) No 999/2001 describes the rules for the prevention, control and eradication of TSE/BSE. Though, the scope of the guideline excludes medicinal products, the principles for the determination for BSE status shall be taken from this guidance.

# RISK ASSESSMENT STRATEGIES

## ❖ The Source Animals

- ⊕ Animals fit for human consumption following Ante- and post mortem inspection shall only be used for the manufacture of medicinal products
- ⊕ In case of live animals, it should be found healthy after clinical examinations.

## ❖ Geographical Origin

- ⊕ The geographical origin status is established by two agencies. Firstly, the Organization for Internationale des Epizooties (OIE) and secondly, the European Commission Scientific Steering Committee (SCC). According to SCC, the countries have been classified according to the Geographical BSE Risk (GBR). According to SSC GBR classification, the countries are categorized in four levels as below

GBR Level	Presence of one or more cattle clinically or pre-clinically infected with BSE in a geographical region/country
Level - I	Highly unlikely
Level - II	Unlikely but not excluded
Level - III	Likely but not confirmed or confirmed at lower level
Level - IV	Confirmed at higher level

- ❖ Higher level is defined as equal to or more than 100 cases per million adult cattle per year. New Zealand and Australia are the preferred sources of animal origin products of small ruminants.

# RISK ASSESSMENT STRATEGIES CONTINUES

- ❖ BSE negligible risk bovine Herds
  - ⊕ GBR level –I countries have been considered as BSE negligible risk bovine herds as there is a highly unlikely status.
- ❖ Animal Parts, Body Fluids and Secretions as Starting Material
  - ⊕ In a TSE infected animal, different organs and secretions have different levels of infectivity. Based on the infectivity, the tissue have been classified as below.

Category A (Shall not be used, unless justified)	High Infectivity Tissues	(Central Nervous System) CNS and tissues anatomically associated with CNS
Category B (For example, blood)	Lower Infectivity Tissues	Peripheral tissues tested positive for infectivity and/or in at least one form of TSE
Category C (Though the risk is less, it shall be used only upon adequate risk assessment)	Tissues with no detectable infectivity	Tissues tested for infectivity and found no infection

# GBR CLASSIFICATION OF COUNTRIES

- ❖ GBR classification with respect to the risk of TSE/BSE has been conducted by Scientific Steering Committee (SSC) and European Food Safety Authority (EFSA). The outcome of assessment and year of publication reveals the GBR assessment as below<sup>11</sup>.
- ❖ The SSC has classified the GBR level –I countries as follows:

Argentina-2003		Australia-2000		Botswana-2001		Brazil-2003
Chile-2003		Costa Rica-2003		El Salvador-2001		Iceland-2002
Namibia-2001		NewCaledonia-2003		New Zealand-2002		Nicaragua-2001
Norway-2000		Panama-2001		Paraguay-2003		Singapore-2003
Swaziland-2001		Uruguay-2003		Vanuatu-2002		

However, The EFSA at a later stage has classified some of the above countries in GBR level-II & III.

Botswana-2005 – GBR-II		Brazil-2005 – GBR-II		Chile-2005 – GBR-III
Costa Rica-2005 – GBR-II		El Salvador-2005 – GBR-II		Namibia-2005 – GBR-II
Nicaragua-2005 – GBR-II		Norway-2004 – GBR-II		Swaziland-2005 – GBR-II

# GBR CLASSIFICATION OF COUNTRIES

- ❖ The SSC has classified the GBR level –II countries as follows:

Canada-2000 | Columbia -2001 | India-2001 | Kenya-2001  
Mauritius -2001 | Nigeria-2001 | Pakistan-2001 | Sweden-2000  
USA-2000

However, The EFSA at a later stage has classified some of the above countries in GBR level-III like Canada and USA in 2004.

- ❖ The SSC has classified the GBR level –III countries as follows:

Andorra-2002 | Albania-2001 | Austria-2003 | Belarus-2003  
Belgium-2000 | Bulgaria-2002 | Croatia-2002 | Cyprus-2003  
Denmark-2000 | Estonia-2001 | Finland-2002 | Czech Republic-2001  
France-2000 | Germany-2000 | Greece-2002 | Republic of Macedonia-  
2003  
Hungary-2001 | Ireland-2000 | Israel-2002 | Italy-2000  
Latvia-2002 | Lithuania-2003 | Luxembourg-2000 | Malta-2002  
Netherlands-2000 | Poland-2001 | Romania-2001 | San Marino-2002  
Slovenia-2002 | Spain-2000 | Switerland-2001 | Slovak Republic-2001  
Turkey-2002

The EFSA has not classified any countries from GBR level-III to any other level.

# GBR CLASSIFICATION OF COUNTRIES

- ❖ The SSC has classified the GBR level –IV countries in the year 2000 as follows:
  - ⊕ United Kingdom
  - ⊕ Portugal
  
- ❖ Note:
  - ⊕ The GBR assessment done by SSC & EFSA is covering a period 2000 to 2006 only. For current updates, reference shall be made from the website of EFSA.
  
  - ⊕ The risk assessment includes all the EU member states and a few third party countries based on the request by them to European Commission with the aim of establishing a trade relation on bovine and bovine products.
  
  - ⊕ In the year 2003, the responsibility for assessing GBR assessment was transferred from SSC to EFSA and EFSA has reassessed a total 19 countries.
  
  - ⊕ There are only two countries in GBR level –IV

# RISK ASSESSMENT STRATEGIES CONTINUES

## ❖ Cross Contamination

- ⊕ There is potential risk of cross contamination of the different types of tissues while the collection of the desired animal parts. The risk of cross contamination is depend upon on the stunning or slaughtering methods employed.
- ⊕ There is a high risk if penetrative brain stunning method is employed or if the brain or spinal cord is sawed. The risk can be minimized in such a way that there is minimal damage to tissue and cellular components.
- ⊕ Collection of parts such as Skull shall be considered for risk assessment as it is high-infectivity tissue.
- ⊕ For certain cases, the separation/removal of higher infectivity tissues from lower infectivity tissues is very difficult and appropriate procedures must be in place for the collection of such body parts/fluids. The role of stunning/slaughtering methods plays an important role in cross contamination and by applying adequate procedures the risk can be minimized.
- ⊕ The risk of cross contamination, procedures applied for stunning/slaughtering, procedures for collection of parts/fluids, procedures for the separation and removal parts, and measures taken to avoid cross contamination must be detailed in the Marketing Authorization Application (MAA) by the Applicant.

# RISK ASSESSMENT STRATEGIES CONTINUES

## ❖ Age of Animals

- ⊕ The age of animals plays an important role in determining the TSE/BSE status as the incubation period is too long. It is considered sensible to source desired product/material from young animals.

## ❖ Manufacturing Process

- ⊕ Measures taken into account to minimize the risk with respect to Sourcing of raw/starting material and the manufacturing process play an inevitable role in controlling TSE/BSE in pharmaceuticals.
- ⊕ A quality assurance system such as ISO certification, Hazard Analysis Critical Control Point (HACCP) or GMP must be in place for the manufacturing of animal derived products.
- ⊕ The quality system must encompass the basic requirements like Batch Manufacturing system, Cleaning between batches using 20000 ppm chlorine for 1 hour, Self audit, in-process controls, Isolation and Separation by physical means via filtration, steps/stages of manufacturing, dedicated use of equipments, and traceability systems of each batch inputs. The quality system shall also be described in the MAA.
- ⊕ Removal/inactivation studies shall be carried out based on the available identification techniques, spiking studies and possible investigations of removal and inactivation techniques.

# REGULATORY COMPLIANCE

- ❖ The applicant/MAA holder shall consider all the scientific Principles for Minimizing the risk in case use of a TSE-relevant animal species
- ❖ Based on the risk assessment strategies/methods applied by the applicant and if it is found adequate, regulatory compliance is certified by EDQM through Certificate of Suitability. However, the final determination of regulatory compliance rests with the competent authority. The application must encompass (along with other requirements) as below
  - ⊕ All TSE-risk factors considered for the assessment study
  - ⊕ Control measures taken into account
  - ⊕ Risk minimized by applicant
  - ⊕ Risk Various material derived from TSE-RAS
  - ⊕ TSE reduction or inactivation techniques /steps employed
  - ⊕ Justification for the selection of the source
  - ⊕ Justification for the selection of tissues/body parts/fluids
- ❖ The benefit/risk evaluation involves the consideration of route administration, quantity of animal derived products used, daily dose, duration of treatment and intended use of the medicinal product and its clinical benefit. High infectivity tissues and substances derived thereof should not be used in the manufacture of medicinal products and their starting materials, intermediates unless justified. A justification why no other material is used should be described in the application. In an unavoidable circumstances where there is a absolute need, TSE-RAS shall be used from GBR level-I countries only if justified.

# GIST OF TSE/BSE

- ❖ If no animal origin material is used, there is no risk of TSE/BSE. However, a declaration for all raw materials/reagents/Packing materials regarding TSE/BSE-risk-free-status is required.
- ❖ If any animal origin material and/or any material comes in contact with animal origin material is used, risk evaluations of TSE/BSE must be done according to the guidance.
- ❖ In case of mandatory requirement of animal origin material, low infectivity material is preferred.
- ❖ In case of mandatory requirement of animal origin material, it can be produced from GBR Level-I countries.
- ❖ In case of high infectivity material, the need must be justified.
- ❖ If the product is at risk, an expert certificate is required indicating the level of risk and infectivity.
- ❖ For biotechnological products like serums, vaccines and blood products needs a complete verification of TSE/BSE status.
- ❖ Products like enzymes, collagens and gelatin, amino acids the specific conditions as provided in EP general chapter 5.2.8 shall be met

# GIST OF TSE/BSE

- ❖ In case of use of animal origin material, the following shall be verified in general
  - ⊕ Type of tissue/body part/fluid used
  - ⊕ Type of animal from which the material is required (Ruminant/non-ruminant/bovine/ Caprine /Ovine/Porcine)
  - ⊕ Age of animals/health status from which the material is required
  - ⊕ Geographical origin of the animal (Country/Continent)
  - ⊕ A detailed risk assessment and expert certification
  - ⊕ Type of stunning/slaughtering method employed
  - ⊕ Type of certification like ISO, HACCP or GMP of the manufacturer of animal product manufacturer
  - ⊕ Traceability of animal slaughtering source
  - ⊕ Methods of segregation of tissues during slaughtering
  - ⊕ Potential of cross contamination during slaughtering/Packing/handling
  - ⊕ Name, complete address of the supplier
  - ⊕ Prior reduction claims from the manufacturer of animal derived products
  - ⊕ CEP certification of the pharmaceutical product
  - ⊕ Information regarding the Facility of manufacturing animal derived material
  - ⊕ Information regarding Products derived from elk, deer

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  - ❖ United States Pharmacopeia, General Information/<1024> Bovine Serum
  - ❖ Annex I to European Parliament and council directives for Veterinary 2001/82/EC and for Human medicinal products [2001/83/EC (as amended by commission directive 2003/63/EC)]

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