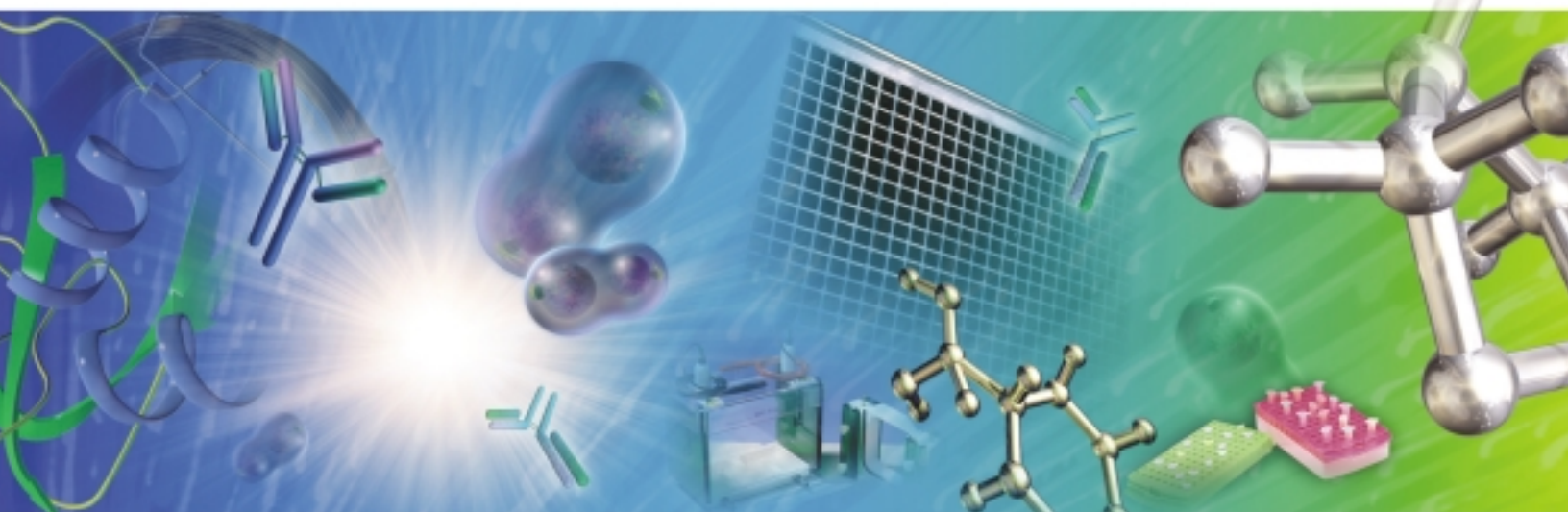


# Certificate of Origin Policy *(TSE/BSE)*



## *Frequently Asked Questions (FAQ)*



**SIGMA-ALDRICH**



## **Table of Contents**

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What is the purpose of this Policy and FAQ .....	2
Policy Statement: What is Sigma-Aldrich response to “TSE-BSE free requests”? .....	2
Why is TSE/BSE a concern?.....	3
What can be done to minimize this risk? .....	3
What is Sigma-Aldrich doing to support this Risk Management approach? .....	4
What current products does Sigma-Aldrich have registered with the EDQM? .....	5
When does Sigma-Aldrich submit a new CEP dossier to the EDQM? .....	5
Why does Sigma-Aldrich not register more products with the EDQM?.....	5
For products that are marketed as Animal Component-Free, how is that defined? .....	6
References and Notes .....	6
Relevant Definitions and Abbreviations .....	7



## ***Certificate of Origin Policy (TSE/BSE)***

### **What is the purpose of this Policy and FAQ?**

To provide information and guidance on issues related to the origination-traceability of Sigma-Aldrich products, particularly those from animal source.

### **Policy Statement**

Sigma-Aldrich recognizes that product traceability is an important requirement for our customers. To meet this requirement, we actively engage our suppliers to provide source and processing information for raw materials used in manufacturing and for materials purchased for resale. That information is compiled into Certificate of Origin documents, which can be accessed via our Web site at [sigma-aldrich.com](http://sigma-aldrich.com), Technical Support, or by contacting your local representative.

A Sigma-Aldrich Certificate of Origin provides batch origin or source information about a product so customers can perform a TSE/BSE risk assessment based upon its intended use in their specific application.

Product-specific validated removal studies have not been conducted for the majority of catalog-offered items. Statements to confirm that a product is "free of TSE/BSE" are not scientifically possible; consequently, Sigma-Aldrich cannot guarantee that our products are free of TSE or BSE materials. However, we will provide data that allow our customers to evaluate and minimize risk when using our products in their production processes.

If Sigma-Aldrich holds a Certificate of Suitability (CEP) for a manufactured product, the CEP registration number will be reported on the Certificate of Origin. If a supplier of Sigma-Aldrich holds the Certificate of Suitability for a purchased product, the information can be located at [www.edqm.org](http://www.edqm.org) for the appropriate third-party CEP registration number. The supplier's number will not appear on the Sigma-Aldrich Certificate of Origin document.

To accommodate our customers' needs, we will make every reasonable effort to obtain Certificate of Origin information. We encourage customers with TSE compliance requirements to contact us within 1 year of purchase to increase the opportunity for obtaining the needed information.

**Sigma-Aldrich Quality and Compliance Management, August 3rd, 2005.**

## Frequently Asked Questions (FAQ)

### Why is TSE/BSE a concern?

The neurodegenerative diseases are caused by a Prion (PrPsc). This Prion (PrPsc) is an infectious protein without DNA or RNA. The host precursor of this infectious protein is a non-infectious agent, which is present in all animal species (including man). While transmission mechanisms of this Prion (within a single species or from one species to another species) are not well known, the transmission minimization of those Prions through pharmaceutical products is a major concern.

### Prion (PrPsc) Background Information

- Prions are chemicals, like endotoxin
- Prions are not living organisms
- Presence of Prions is not easily demonstrated with a diagnostic test (current available testing is very limited, only done at certain laboratories on the actual tissue not on extracted final products, e.g., enzyme)
- Prions adhere very tenaciously to surfaces—making them hard to remove; they can be re-deposited on other surfaces during processing.
- Prions are resistant to protease treatment, certain chemical agents, and heat denaturation.

### What can be done to minimize this risk?

Risk Assessment is considered an acceptable means to demonstrate that the presence of PrPsc is minimized. Per EMEA/410/01, "...the measures taken to manage the risk of transmitting animal TSEs via medicinal products represent risk minimization rather than risk elimination. Consequently, the basis for regulatory compliance should be based on a risk assessment, taking into consideration all pertinent factors..."

- Sourcing
  - Sourcing animals from countries considered to be least risk (i.e., GBR I)
  - Certain tissues have a higher risk (i.e., brain, spinal cord) vs. lower risk (i.e., milk, wool)
- Manufacturing process
  - Exclude presence of any animal or human-derived material in production process (raw materials, reagents, contamination of equipment)
  - Dedicated line/equipment, slaughtering without brain penetration

Category	Tissue or Fluid
<b>A – High Infectivity</b>	<b>Nervous System:</b> Brain, skull, vertebral column, spinal and trigeminal ganglia, retina and optic nerve, Pituitary Gland, dura mater <b>Alimentary Tract:</b> Small Intestine (duodenum, jejunem, ileum) including intestinal mucosa. <b>Lymphoreticular Tissues:</b> Tonsils
<b>B – Lower Infectivity</b>	<b>Lymphoreticular Tissues:</b> Spleen, Lymph nodes, Nictating Membrane, Thymus <b>Alimentary Tract:</b> Esophagus, Fore-stomach (ruminants only), stomach, large intestine <b>Body Fluids:</b> Cerebrospinal Fluid, Blood <b>Other Tissues:</b> Lungs, Liver, Kidney, Adrenal, Pancreas, Bone Marrow, Blood Vessels, Olfactory Mucosa, Gingival Tissue, Salivary Gland, Cornea
<b>C – Tissues with No Detected Infectivity</b>	<b>Reproductive Tissues:</b> Testes, Prostate/Epididymus/Seminal Vesicle, Semen, Ovary, Uterus, Placenta Fluids, Fetus, Embryos <b>Musculo-Skeletal Tissues:</b> Bones, Skeletal Muscle, Tongue, Heart (Pericardium), Tendon <b>Body Fluids:</b> Milk, Colostrum, Cord Blood, Saliva, Sweat, Tears, Nasal Mucous, Urine, Feces

## **What is Sigma-Aldrich doing to support this Risk Management approach?**

### **1. Collecting Traceability/Processing Information**

For Sigma-Aldrich catalog-listed products, we are collecting information from our suppliers and internal manufacturing sites to provide verified source and manufacturing information. This collected information is presented in a Sigma-Aldrich Certificate of Origin document by batch. This information can include, but is not limited to, the following:

- Is product Synthetic, Biological (i.e., animal, plant, human), or from a non-living Natural source?
- Were only Synthetic materials used during the manufacturing/packaging process?
- If product is Biologic or if Biologic-sourced material was used in the manufacturing process;
  - Species (i.e., Bovine, Porcine)
  - Tissue (i.e, Brain, Lung, Blood)
  - Country where the animal originated and tissue was collected
  - Feeding and Slaughter method
- Means for controlling cross contamination (i.e., dedicated equipment, recognized cleaning/sanitization process)
- Quality Management Systems (i.e., ISO, cGMP)

### **2. Manufacturing Process**

For internal manufactured items derived from animal source or where animal source is used in processing, site-specific activities are being employed to minimize risk and would be reported on the Certificate of Origin for that specific product/batch. These can include, but are not limited to, the following:

- Where feasible, sourcing tissues from low-risk GBR I countries (i.e., New Zealand)
- Where feasible, using manufacturing process absent of human/animal-sourced material
- Where possible, dedicated equipment or segregated areas/lines
- For non-dedicated equipment, employing cleaning/sanitization procedures to minimize cross contamination
  - 1 N NaOH for  $\geq 1$  hr exposure (per WHO guidelines)
  - $\geq 1.6\%$  CIP-100 (Steris Corp.) caustic detergent for  $\geq 43$  °C for  $\geq 15$ -minute exposure period  
Fichet, G. et al., **Novel methods for disinfection of prion-contaminated medical devices.** Lancet, vol. **364** (9433) p. 521–526. (2004).

**3. For a few selected products, Sigma-Aldrich is the holder of Certificates of Suitability for TSE risk.**

**Purpose of Certificates of Suitability (CEP)**

CEP's are recognized by 34 signatory states of the European Pharmacopoeia Convention and by the European Union. Other countries have also chosen to recognize them. CEP can be used by the manufacturers of pharmaceutical products in their applications for marketing authorization to demonstrate the compliance of the substance used with the monographs of the European Pharmacopoeia and Directives 2001/83/EC and 2001/82/EC.

**What does the procedure include?**

The EDQM must be sent a full dossier describing in detail the manufacturing method of the substance and the impurities that are associated with it, and/or the countries of origin, the type of animal tissues and the quality assurance, so that the reference to the European Pharmacopoeia can be validated. The dossier is processed according to a procedure that guarantees its confidentiality and it is assessed by independent experts whose impartiality is guaranteed by their status and a confidentiality agreement.

**Who is the procedure for?**

Manufacturers, whatever their location in the world, (or the duly authorized representatives of these manufacturers) of substances, obtained by synthesis, extraction or fermentation, and substances concerned by TSE risk. Suppliers of any substances with TSE risk used in the production or preparation of medicinal products can apply for a certificate concerning the evaluation of the reduction of TSE risk according to the general monograph. This certificate can then be used by manufacturers of medicinal products in their marketing authorizations for demonstration of compliance with Directives 2001/83/EC and 2001/82/EC.

**What current products does Sigma-Aldrich have registered with the EDQM?**

- 31 CEP's for 46 products, i.e., enzymes, serum (Ref: [www.edqm.org](http://www.edqm.org))
- Sigma-Aldrich and SAFC-JRH Biosciences brands
- Contact your Sigma-Aldrich representative for details

**When does Sigma-Aldrich submit a new CEP dossier to the EDQM?**

- Most catalog-offered products do not warrant consideration for submission, however
- Where a product has the potential higher TSE risk due to source i.e. Bovine-Category A tissue, Sigma-Aldrich will consider pursuing a CEP submission with the EDQM in conjunction with the requesting customer's business and/or regulatory requirements. Contact your Sigma-Aldrich representative for details.

**Why does Sigma-Aldrich not register more products with the EDQM?**

- Majority of offered products are intended for research use only
- Expensive: requires fees for initial submission, each revision, and renewal
- Dossier includes: specifications, written analytical methods, defined manufacturing process, impurities, inactivation steps, cleaning/sanitization process, any validation, dedicated equipment, etc.
- Very long submission process: average 20 months and requires continuous monitoring for any changes (raw material, site, production process)
- If monograph revised, affected product will need to be reviewed to determine compliance with new requirements



## Certificate of Origin Policy (TSE/BSE)

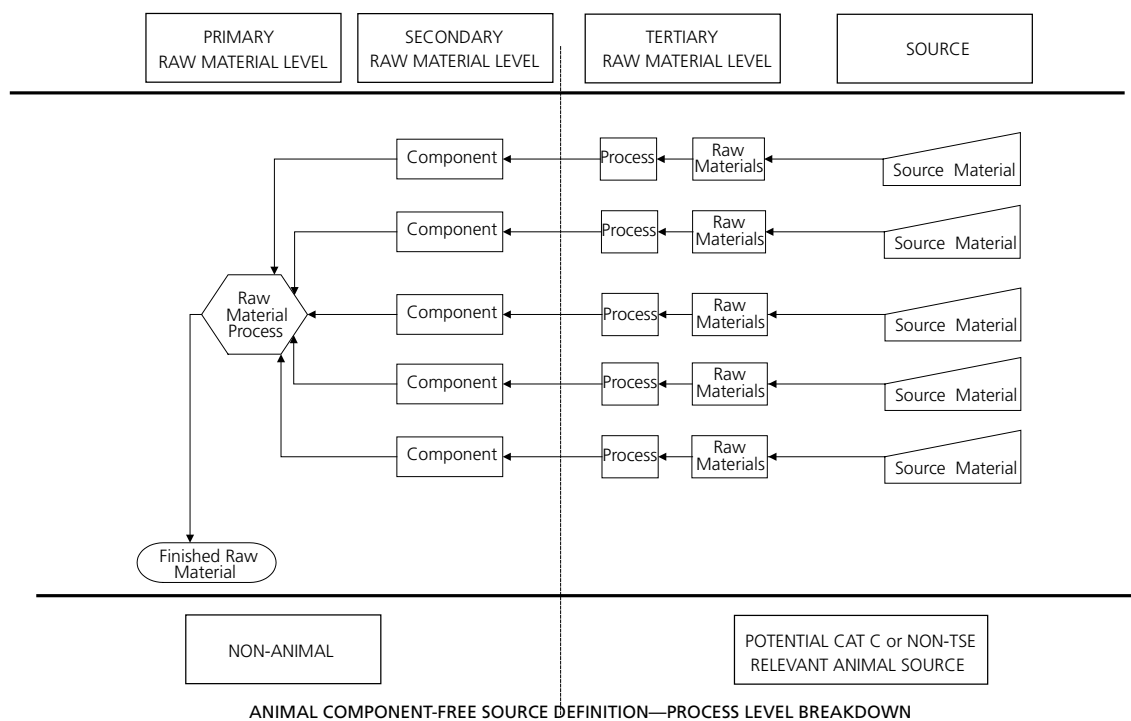
### For products that are marketed as Animal Component-Free, how is that defined?

Animal source materials are primarily a concern with regard to Transmissible Spongiform Encephalopathy (TSE) and viral contamination. Products manufactured by Sigma-Aldrich and classified as animal component-free will not contain or use in the manufacturing process, any primary raw materials derived directly from bovine or other animal tissues<sup>1</sup>. This applies to all aspects of product manufacturing.

Secondary raw materials are defined as non-animal, but may be derived from processes which include tertiary level materials from animal components classified as very low risk (Category IV as defined by the European Medicines Agency<sup>2</sup> or Category C as defined by the World Health Organization<sup>3</sup>).

Based on the positions of the European Medicines Agency and the World Health Organization, Sigma-Aldrich extends the definition of animal component-free to include tertiary materials, which are of "no detected infectivity," i.e., Category C tissues.

We conclude that since none of the raw materials used in the manufacture are derived directly from bovine or any other animal tissues, and any secondary or tertiary level raw material will be sourced from either synthetic or Category IV/C or non-TSE relevant animal species (e.g., pigs and birds), Sigma-Aldrich products classified as animal component-free pose a negligible risk of transmitting TSE agents.



### References and Notes

<sup>1</sup>Primary raw materials manufactured utilizing fermentation processes where the culture medium contains no high infectivity tissues (brain, spinal chord, eye) will be classed as non-animal.

<sup>2</sup>European Medicines Agency. Note for Guidance on Minimizing the Risk of Transmitting Spongiform Encephalopathies via Human and Veterinary Medicinal Products. EMEA/410/01 Rev. 2. July 2004

<sup>3</sup>World Health Organization. WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical products. 2003

## Relevant Definitions and Abbreviations

**Animal**—Components directly derived from animals, does not include components that use animal components in its manufacturing process as nutrients or in enzymatic reactions.

**Animal Component-Free**—See definition on page 6.

**Biologic**—Produced from animal, plant, human, or, microbial sources

**Bovine Spongiform Encephalopathy (BSE)**—Bovine TSE, a form of the disease known as “Mad Cow.”

**Certificate of Origin (C of O)**—Sigma-Aldrich created document that provides origin information to the raw materials used in a specific batch. If biologic material was used, more in-depth information is included (e.g., species, tissue, country of origin, and processing details).

**Certificate of Suitability to the European Pharmacopoeia (CoS) CEP**—The EDQM issues this certificate to the authorized Holder. Includes those plant(s) where final product is manufactured. Must be updated every five years or after any significant modification of the manufacturing procedure. The country(ies) of raw material's and product's origin or the nature of the tissues used may alter the risk of TSE or changes to the specifications of the monograph. Ref: <http://www.edqm.org>

**Country of Origin**—The originating source country of the primary biological raw materials used in the creation of the finished good batch. This information is present in an internally created document called a Certificate of Origin.

**Country of Origin (manufacturing)**—The country where the final product batch was produced/formulated. This Country of Origin is reported on the finished good's package label for import/export purposes.

**Creutzfeldt-Jakob disease (CJD)**—Naturally occurring human form TSE.

**European Directorate for the Quality of Medicines (EDQM)**—Has the responsibility for the creation of European Pharmacopoeia (PhEur) reference monographs including General Chapter (5.2.8) on Minimizing, the Risk of Transmitting Animal Spongiform Encephalopathis via Human, and Medicinal Products.

**European Medicines Agency (EMA)**—Directives including guidance related to TSE/BSE. Ref: <http://www.emea.eu.int>

**Fermentation**—Any of a group of chemical reactions induced by living or nonliving ferments that split complex organic compounds into relatively simple substances.

**Geographical BSE Risk (GBR)**—As defined by the European Scientific Steering Committee under the direction of the European Food Safety Agency (EFSA). A designation of GBR I indicate those countries deemed to be free of BSE, while the highest risk countries for the presence of BSE are rated GBR IV. GBR I examples: New Zealand and Australia. The USA was GBR II until single case in Dec. 2003, re-classified as GBR III. Ref: <http://www.efsa.eu.int>

**Natural**—Produced by nature, non-living (e.g., salts, minerals, crude oil fractions). “NOTE: Not to be confused with the commonly used term “natural” in flavoring/food additive industries.”





## ***Certificate of Origin Policy (TSE/BSE)***

**Plant**—A vegetable; an organized living being, generally without feeling and voluntary motion, and having, when complete, a root, stem, and leaves, though consisting sometimes only of a single leafy expansion, or a series of cellules, or even a single cellule. Can be used as an animal source replacement with recombinant technology.

**Prions (PrP<sup>sc</sup>)**—Infectious proteins that have been identified as the causative agents for a group of CNS (central nervous system) diseases known as Transmissible Spongiform Encephalopathies (TSEs). Also known as Chronic Wasting Disease in deer and elk, Scrapie in sheep and goats, BSE in cows.

**Synthetic**—Produced by synthesis, at the final step (organic and inorganic).

**Variant Creutzfeldt-Jakob disease (vCJD)**—Human form of TSE believed to be contracted from exposure to BSE risk material.