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January 2014 – Revision 3

Product Origin Information & FAQ

What is the purpose of this Information Sheet?

To provide information and guidance on issues related to the traceability of Sigma-Aldrich products, to country of origination with particular focus on those derived from animal/human tissue.

Introduction

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 repacked for resale. That information is compiled into Certificate of Origin documents, which can be accessed via our web site at www.Sigma-Aldrich.com, Technical Support or by contacting your local representative.

A Sigma-Aldrich Certificate of Origin is intended to provide batch origination, supply chain and if available processing information about a product so customers can perform a risk assessment based upon intended use in their specific application.

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 for the appropriate third-party CEP registration number. The supplier's number will not appear on the Sigma-Aldrich Certificate of Origin document.

Other statements, BSE/TSE risk, proof of health, export affidavit, informed consent may be available upon request.

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

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Frequently Asked Questions (FAQ)

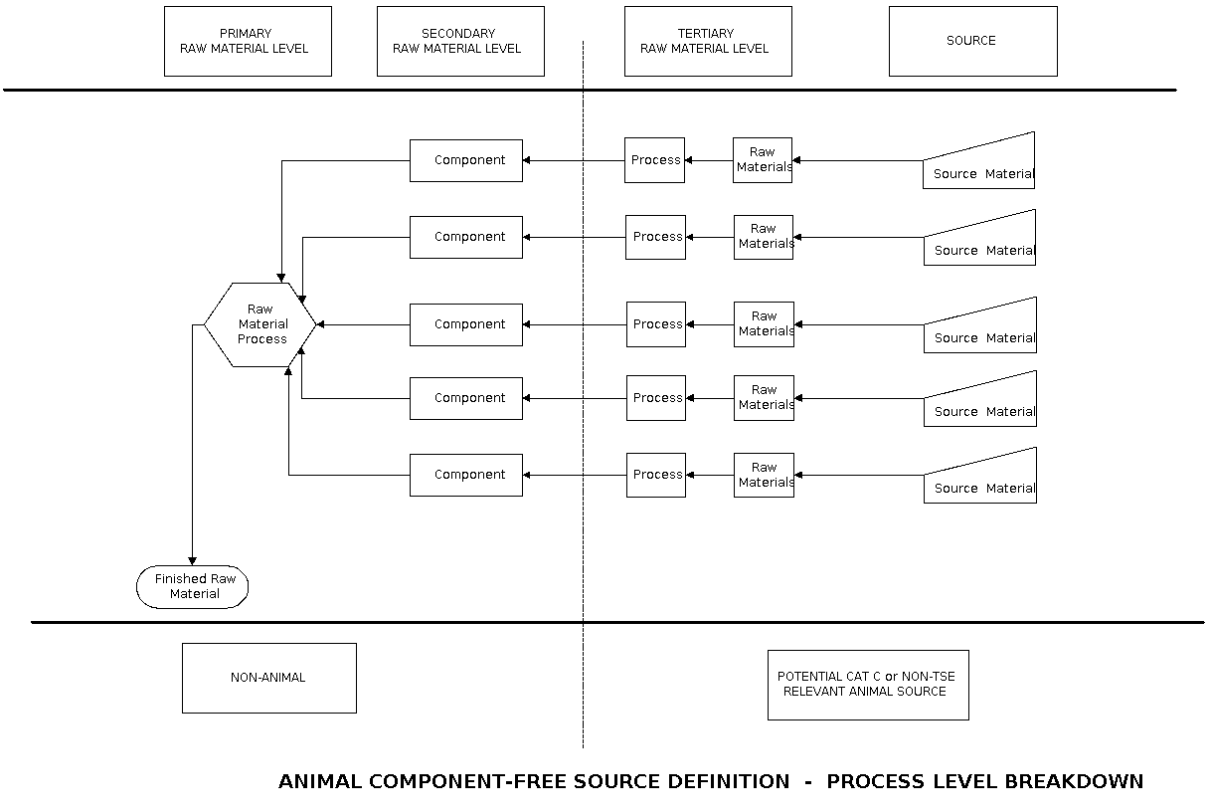
Animal Component Containing (ACC) vs Animal Component Free (ACF), how is that defined?

Animal source materials are primarily a concern with regards to pathogen 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[1]. 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 C as defined by the World Health Organization [3]).

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 C or non-TSE relevant animal species (e.g. pigs and birds), that Sigma-Aldrich products classified as animal component-free pose a negligible risk of transmitting TSE agents.



ANIMAL COMPONENT-FREE SOURCE DEFINITION - PROCESS LEVEL BREAKDOWN

References and Notes

[1]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.

[2]European Medicines Agency. Note for Guidance on Minimizing the Risk of Transmitting Spongiform Encephalopathies via Human and Veterinary Medicinal Products. EMEA/410/01.

[3]World Health organization. WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical products. 2003

Why is TSE/BSE or other pathogens (virus, bacteria) a concern from animal/human tissue?

TSE/BSE (aka Scrapie) is neurodegenerative diseases that 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 and can be re-deposited on other surfaces during processing.
- Prions are resistant to protease treatment, certain chemical agents & heat denaturation.

Other pathogens are also a concern because of similar attributes as Prions, for the potential risk of carry-over into a final purified product.

What can be done to minimize pathogen 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 tissue from countries considered to be least risk for pathogen (see www.oie.int).
  - Certain tissues have a higher risk (i.e. brain, spinal cord) vs. lower risk (i.e. milk, wool) depending upon pathogen.
  - Sourcing tissue from another species not known as a carrier of a certain pathogen, i.e. TSE has not been found in porcine.
  - Sourcing from young animals
- Manufacturing process
  - Exclude presence of any animal or human derived material in production process (raw materials, reagents, contamination of equipment)
  - Dedicated line/equipment, method of tissue collection
  - Cleaning procedures, including control measures put in place in order to minimize the risk of cross-contamination between production batches.

BSE/TSE Relative Infectivity and Risk by Tissue Type

Category	Tissue or Fluid
IA – High Infectivity	**Nervous System:** Brain, Spinal Cord, Spinal and Trigeminal Ganglia, Retina and Optic Nerve, Pituitary Gland, Dura Mater
IB – Lower Infectivity	**Lymphoreticular Tissues:** Spleen, Lymph Nodes, Nicitating Membrane, Thymus, Tonsil **Alimentary Tract:** Esophagus, Fore-stomach (ruminants only), Stomach, Large Intestine, Duodenum, Jejunum, Ileum, Appendix, Colon/caecum, Rectum **Body Fluids:** Cerebrospinal Fluid, Blood, Saliva, Milk, Urine, Feces

	Reproductive Tissues: Placenta, Ovary, Uterus **Other Tissues:** Mammary Gland/Udder, Skin, Adipose Tissue, Heart/Pericardium, Lung, Liver, Kidney, Adrenal, Pancreas, Bone Marrow, Skeletal Muscle, Tongue, Blood Vessels, Salivary Gland, Cornea
IC – Tissues with No Detectable Infectivity	**Reproductive Tissues:** Testes, Prostate/Epididymus/Seminal Vesicle, Semen, Placenta Fluids, Fetus, Embryos **Musculo-Skeletal Tissues:** Bone, Tendon **Other Tissues:** Gingival Tissues, Dental Pulp, Trachea, Thyroid Gland **Body Fluids:** Colostrum, Cord Blood, Sweat, Tears, Nasal Mucous, Bile

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

1. Collecting traceability/processing information

For Sigma-Aldrich products, collecting information from the supply chain, which can include back to the country of manufacturer or in the case of animal/human tissue, abattoir or donor to provide verified information. This supply chain information is presented in a Sigma-Aldrich Certificate of Origin document. 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?
- Materials used during the manufacturing/packaging process?
- 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
  - For animal, Veterinary Health Certificates signed by local country health authority where collection occurred (only applies to inter-country export-import).
  - For human, traceability to individual donor
- 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 employed to minimize risk and would be reported on the Certificate of Origin for that specific product. These can include but are not limited to the following:

- Where feasible, sourcing tissues from low pathogen risk countries.
- 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. For example;
  - 1 N NaOH for $\geq$ 1 hr exposure (per WHO guidelines)
  - $\geq$ 1.6% CIP-100 (Steris Corp.) caustic detergent for $\geq$ 43 ^{o}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 the 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.

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?

- Go to, www.edqm.org to see the current Certificates of Suitability listing with Sigma-Aldrich as holder
- 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 &/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 12 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.

How is Sigma-Aldrich meeting (EC) 1069/2009 requirements?

What is (EC) 1069/2009?

- **REGULATION (EC) No 1069/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 21 October 2009** lays down health rules as regards to animal by-products and derived products not intended for human consumption and repealing Regulation (EC) No 1774/2002 (Animal by-products Regulation). It is the consequence of a long and comprehensive review carried out by the EU Commission to assess the operation of EU-wide controls on animal by-products.

- **The U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS), Veterinary Services (VS)** has created the International Animal Product Export Regulations (IREGS) to provide exporters with our best understanding of importing countries requirements for certain animal-origin products.

    - APHIS regulates veterinary biologics (vaccines, bacterins, antisera, diagnostic kits, and other products of biological origin) to ensure that the veterinary biologics available for the diagnosis, prevention, and treatment of animal diseases are pure, safe, potent, and effective. The primary role of APHIS, VS in the certification of animal products for export, is to provide certification about the animal health status of the region of origin of the product.

    - Annually, Sigma-Aldrich facilities are field inspected by APHIS to be listed as an exporter of animal by-products (not for human consumption) to the EU.

Sigma-Aldrich USDA Site Registrations

Facility Name & Address	APHIS Reference Number	Approval Packages
Sigma-Aldrich Manufacturing LLC Dekalb Facility 3500 Dekalb Street St. Louis, MO 63118 QA Manager : Jeff Heiland	MO-TEC-0004	Intermediate-Chapter 20 Equidae- Chapter 4(A) Other than Equidae- Chapter 4(C) & 4(D)
Sigma-Aldrich Manufacturing LLC Broadway Facility 3506 South Broadway St. Louis, MO 63118 QA Manager: Brandon Clough	MO-TEC-0008	Intermediate-Chapter 20 Other than Equidae- Chapter 4(C) & 4(D)
Sigma-Aldrich Manufacturing LLC Ewing Facility 545 South Ewing Avenue St. Louis, MO 63103 QA Manager: Jeff Heiland	MO-TEC-0009	Intermediate-Chapter 20 Equidae- Chapter 4(A) Other than Equidae- Chapter 4(C) & 4(D)
Sigma-Aldrich Manufacturing LLC Laclede Facility 2909 Laclede Avenue St. Louis, Mo 63103 QA Manager: Jeff Heiland	MO-TEC-0014	Intermediate-Chapter 20
Sigma- Aldrich Manufacturing LLC Cherokee Facility 3300 South Second Street St. Louis, MO63118 QA Manager: Mark Cooley	MO-TEC-0015	Intermediate-Chapter 20
Sigma-Aldrich Co LLC Barton Warehouse 2425 South Second Street St. Louis, MO 63104 QA Manager: Jim Romeo	MO-TEC-0012	Intermediate-Chapter 20 Exporting Warehouse- Chapter 4(C) & 4(D)
Sigma Aldrich Co LLC Spruce Warehouse 3050 Spruce Street St. Louis, MO 63103 QA Manager: Jim Romeo	MO-TEC-0013	Intermediate-Chapter 20 Exporting Warehouse- Chapter 4(C) & 4(D)
Sigma-Aldrich Manufacturing LLC 13804 W. 107th Street Lenexa, Kansas 66215, USA	KS-TEC-0002	Intermediate-Chapter 20 Equidae- Chapter 4(A) Other than Equidae- Chapter 4(C) & 4(D)
Sigma-Aldrich Manufacturing LLC 6000 North Teutonia Avenue Milwaukee, WI 53209	WI-TEC-0008	Intermediate-Chapter 20 Exporting Warehouse- Chapter 4(C) & 4(D)

Relevant Definitions & Abbreviations

Animal (to include Human) –Sigma final packaged product which use component(s) derived from animal material. See next Section for details.

Biologic – Derived from a process involving animal (includes human), plant or microbe.

Bovine Spongiform Encephalopathy (BSE) – Bovine TSE - a form of TSE disease known as "Mad Cow".

Certificate of Origin (C of O) - Sigma-Aldrich created document that provides origination information for a specific batch. The minimum information includes: source type of final product – synthetic, biologic or natural, and the country of origin (manufacturing). If biologic material(s) was used additional information (e.g., genus/species, tissue type(s), country of origin(s) along with processing details (i.e. viral reduction step(s)) can be included.

Certificate of Suitability (CEP) – The European Directorate of Quality Medicines & HealthCare (EDQM) issues this Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP)to the authorized Holder (Sigma Aldrich) when we demonstrate that the raw material complies with the General Chapter (5.2.8) on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathis via Human and Medicinal Products. If Sigma-Aldrich is the authorized holder of a CEP, the reference number of the CEP is indicated on the Certificate of Origin.

Country of Origin (manufacturing) - The country where the final transformational changed/formulation occurred.

Country of Origin (biological source material) - The originating source country of biologic starting material(s) used in the creation of the finished product. This information is presented on the batch level Certificate of Origin. The final product may have been manufactured in a different country.

Component – material used in a manufacturing process, which was not transformed from the original state.

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 Encephalopathy via Human and Medicinal Products.

Fermentation - Any of a group of chemical reactions induced by living or nonliving ferments that split complex organic compounds into relatively simple substances. Final product(s) derived from fermentation contain no components of direct animal origin but could contain at least one component produced from a biological process, which could involve a material(s) of animal origin. If final product derived from fermentation process used a component(s) derived from biological process this information is included on the Certificate of Origin.

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 flavouring/food additive industries".

Pathogen – An agent that causes disease, especially a living microorganism such as a bacterium, virus or fungus.

Prions (PrPsc) – 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.

Process Aid – material used in a manufacturing process, not transformed and typically removed.

Raw Material – material used in a manufacturing process, which was transformed from the original state.

Synthetic - a product produced by a chemical reaction, or series of reactions, antonym to biologic. Therefore a product claimed synthetic on the Certificate of Origin can be considered as **Negligible Risk** for Transmissible Spongiform Encephalopathy (TSE) / Bovine Spongiform Encephalopathy (BSE) per the requirements in EMEA/410/01

Transmissible Spongiform Encephalopathies (TSEs) - central nervous systems disease caused by prions.