SOP Title:	**Certificate of Origin Policy for Raw Materials/Components Used at the BDP**
SOP Number:	**21106**
Revision:	**06**

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1. PURPOSE

This procedure assures the regulatory compliance of Current Good Manufacturing Practices (CGMP) products manufactured at the Biopharmaceutical Development Program (BDP) to Food and Drug Administration (FDA), United States Department of Agriculture (USDA), and European Union/International Council for Harmonization (EU/ICH) requirements pertaining to the use of animal-derived raw materials in the manufacture of drugs and biologics. Animal-derived materials may not be used as raw materials in GMP manufacturing unless appropriate non-animal alternatives cannot be identified. If animal-derived materials must be used, those materials must meet the requirements listed in this SOP.

This SOP defines the procedure to assess whether animal-derived products are present in the raw materials/components used for GMP manufacturing.

2. SCOPE

This procedure is applicable to BDP personnel who develop processes; purchase, specify, test, or release raw materials/components; inventory or assign part numbers to raw materials/ components; or use raw materials/components in a GMP manufacturing process.

3. RESPONSIBILITIES

3.1 Project Scientist / Product/Process Development Staff

- Uses raw materials/components that meet the requirements of this procedure.

3.2 Manufacturing personnel

- Uses raw materials/components that meet the requirements of this procedure.

3.3 BDP personnel

- Obtains and attaches a current COO (as applicable) to the Part Number Request Form for each vendor/manufacturer listed, when establishing part numbers.
- Verifies a COO is on file when submitting a Purchase Request for a raw material/component.

3.4 Quality Assurance (QA)

- Maintains electronic copies of COO in the PN/MS Database.
- Provides quality oversight.
- Verifies that the information presented on a COO is acceptable for use in manufacturing operations, consulting with Regulatory as needed, prior to approving a Part Number Request.

4. DEFINITIONS

- **Certificate of Origin (COO)** – A certificate or letter provided by a raw material manufacturer stating that all components used in the manufacture of a raw material (as defined below) were not derived from animal sources, or alternatively specifying any animal-derived components used in manufacture and satisfactorily addressing the risk associated with the use of those components. A COO is required for chemicals, resins, filters, media, buffers, and cell lines (bacterial, viral, mammalian, human, insect, yeast).

  NOTE: The United States Customs Service (USCS) issues a COO as part of the North American Free Trade Agreement. However, the USCS COO is not acceptable because it does not meet the regulatory requirements of the FDA for animal origin certification.

  NOTE: Some manufacturers/suppliers of raw materials/components may supply a "Certificate of Suitability" (COS) instead of a COO for ruminant materials. This is acceptable documentation if it meets the requirements specified in this SOP.

- **Component** – Anything other than raw materials (Refer to raw materials below) that are used in the manufacturing process at the BDP that contacts the product or has the potential to contact the product.

- **Raw Material** – For the purposes of this procedure, raw materials are defined as chemicals, chromatography resins, filters, media, buffers, and cell lines (bacterial, viral, mammalian, insect, human, yeast) used directly in the manufacture of products that have product contact or have the potential for product contact.

- **Ruminant** – Any cud-chewing hoofed mammal with an even number of toes and a stomach with multiple chambers. Cattle, sheep, goats, deer, camels, and giraffes are some examples of ruminants.

5. PROCEDURE

5.1 Obtaining COOs for a new Raw Material or Component as defined in Section 4 from a Manufacturer.

5.1.1 As part of initiating a Part Number Request, to identify whether the material is of animal origin, the raw material/component manufacturer technical services department or an alternate source of information (e.g., Vendor's website) must be contacted to confirm origin information and request that a COO be provided.

5.1.2 Contact with the raw material/component manufacturer's technical services department may be done in writing, by phone, email, or fax. Most raw material/component manufacturers have a website that contains current COO documentation for downloading or contact information to request a COO.

5.1.3 Explain to the representative that the requested information regarding the origin of the raw material/component will be used to determine if any animal-derived material was used in the manufacture. If no animal-derived material was used in the manufacture of the material, then request that the supplier put this statement in writing on supplier letterhead and send it to the BDP.

5.1.4 If animal-derived material was used, then the country of origin and/or the source of the animal-derived material are requested. The documentation must identify the country of origin and/or the source of the raw material (preferably both).

If the material is bovine or other ruminant derived, the following additional information is requested from the vendor.

- Country of origin.

- The animal species.
- Body fluids, parts, etc., used.
- Procedures used to minimize risk of Transmissible Spongiform Encephalopathy agents.
- Procedures used to inactivate or remove infective agents.

Should the material be human or porcine derived, the minimum testing required is listed in Sections 5.4.2.3 – 5.4.2.4.

5.1.5 Lot-specific certification is not required if lots are prepared identically.

5.1.6 The documentation supplied may be in the form of a letter on company letterhead, a certificate, or e-mail with traceability to the company. The certification or letter must include the identity of a company representative who certifies that the information is correct.

5.1.7 If, after diligent multiple documented attempts, the requested source and/or origin information is not available, a letter stating that the information is not available with a brief explanation is requested from the vendor or may be written by the raw material requestor. The letter must include the identity of a company representative who certifies the source information is not available. This information will be reviewed by the Director of BQA or designee prior to approval of the Part Number Request. A diligent and documented attempt must be made to identify an alternate source for raw materials lacking COO information.

5.1.8 Upon receipt, include the COO with the Part Number Request Form and forward the Part Number Request Form to BQA per **SOP 21902 - Requirements for Establishing Part Numbers and Specifications for BDP Components and Materials**. Should there be any question as to information supplied by the vendor, contact BQA for assistance.

5.1.9 BQA, as part of the approval process for the Part Number Request Form, ensures that a COO is included. BQA Auditing (or Regulatory Affairs as needed) will verify that the information meets the requirements defined in Sections 5.1.4 to 5.1.6 and is acceptable for use, reference Section 5.4.

5.1.10 A copy of the COO and the Part Number with which it is associated is included in the PN/MS database.

5.2 Project/Process Development Stage COO Requirements

5.2.1 The Project Scientist or designee ensures that the raw materials/components used in the development process comply with regulatory requirements and applicable FDA guidance documents. No animal-derived materials may be used unless an appropriate non-animal alternative cannot be identified.

5.2.2 Product-contact raw materials, components, and cell lines must be traceable. Traceability of cell lines, whether generated at a vendor or cultured at the BDP, includes information pertinent to the history of the isolation and propagation of the cells (including growth medium used to culture cells). If, after diligent multiple documented attempts, the requested source and/or origin information is not available, a letter stating that the information is not available with a brief explanation is requested from the vendor or may be written by the raw material requestor. The letter must include the identity of a company representative who certifies the source information is not available. This information will be reviewed by the Director of BQA or designee prior to approval of the Part Number Request. A diligent and documented attempt must be made to identify an alternate source for source materials lacking information.

5.2.3 During the process development stage, use raw materials/components with an existing BDP part number assigned by MMIC if available and appropriate. A listing of these raw materials/components can be found in the PN/MS database.

5.2.4 If a new raw material/component is needed, contact the raw material/component manufacturer technical services department prior to purchasing the raw material/component to confirm that the raw material/component meets the requirements of this procedure (refer to Step 5.1). Such confirmations should be written.

5.2.5 Raw material/component origin information is included in the Technology Transfer Package (Reference **SOP 25103**). Animal-derived materials and the source of the material described are identified in the Technology Transfer Package by Product/Process Development personnel.

5.3 Raw Material Specification Sheet COO Requirements

5.3.1 Part Number/Master Specification Sheets (PN/MS) are established for CGMP materials per **SOP 21903 - Using the Part Number/Master Specification Program to Establish Raw Material Part Numbers and Master Specifications.**

5.3.2 Part Number/Master Specification Sheets contain a requirement for including a COO for "B," "C," or "D" inspection level materials.

5.3.3 The PN/MS will not be approved without a COO (where applicable).

5.4 Acceptance of Raw Materials Certificates of Origin for Use in BDP Manufacturing Operations

5.4.1 QA personnel review the COO to confirm that the material is acceptable. The COO must state that the material is not of ruminant animal origin or animal ruminant origin. If of ruminant origin, it must be from a country listed as a World Organization for Animal Health (OIE) list of member countries with Negligible (or Controlled, see below) Bovine Spongiform Encephalopathy (BSE) Risk **(**https://www.woah.org/en/disease/bovine-spongiform-encephalopathy/#ui-id-2).

5.4.2 Acceptability of raw materials/components based on the origin is judged on the criteria presented below in the order of their priority.

5.4.2.1 Not of animal origin.

5.4.2.2 Animal Ruminant Origin.

5.4.2.2.1 Animal ruminant origin but source is not from a BSE-affected country [Reference: 9 CFR 94.19 https://www.ecfr.gov/cgi-bin/text-idx)] and World Organization for Animal Health (OIE) list of member countries with Negligible BSE Risk **(**https://www.woah.org/en/disease/bovine-spongiform-encephalopathy/#ui-id-2 **)**

5.4.2.2.2 Animal ruminant origin and source is from a BSE-affected country but not from banned parts and tissues (brain, spinal cord, retina, optic nerve, spinal ganglia, trigeminal ganglia, pituitary gland, and dura mater) (Reference: World Organization for Animal Health (OIE) list of member countries with Controlled BSE Risk **(**https://www.woah.org/en/disease/bovine-spongiform-encephalopathy/#ui-id-2 and the World Health Organization **(**https://www.who.int/publications/m/item/who-guidelines-on-transmissible-spongiform-encephalopathies **)** Annex I**.**

5.4.2.3 Human origin: Material must be tested and found to be negative for HIV-1, HIV-2, HBV, HCV, HTLV-1, HTLV-2, or licensed for human use in the US.

5.4.2.4 Porcine origin: Material must be tested and found to be negative for porcine parvovirus, circovirus, and mycoplasma.

5.4.2.5 Other Origin Materials: Use of any raw materials/components to produce Phase I/II clinical material not covered in items 5.4.2.1 – 5.4.2.4 requires review/approval by the Director of Regulatory Compliance and may require FDA review/consultation.

5.4.3 Acceptance of the COO is indicated by QA approval of the Part Number Request.

5.4.4 If the COO is unacceptable, it is returned to the requestor of the part number to request additional clarification/information from the vendor or to identify alternate sources.

6. DOCUMENTATION AND RECORDS

Vendors' COO, COS, and other supporting documentation will be maintained in the PN/MS database.

7. REFERENCES AND RELATED DOCUMENTS

Document Number	Title
21902	Requirements for Establishing Part Numbers and Specifications for BDP Components and Materials
21903	Using the Part Number/Master Specification Program to Establish Raw Material Part Numbers and Master Specifications
25103	Format and Contents of a Technology Transfer Package
N/A	ICH Guideline (Q5D): Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products.
N/A	Letter to Manufacturers of Biological Products dated April 19, 2000, from Kathryn C. Zoon, Ph.D., Director of the Center for Biologics Evaluation and Research/FDA (included as Attachment 1).
N/A	European Commision, Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathies via human and veterinary medicinal products (EMEA/410/01)

Document Number	Title
N/A	European Pharmacopoeia General Chapter 5.2.8 - Minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.
9 CFR 94.19	https://www.ecfr.gov/cgi-bin/text-idx
N/A	World Organization for Animal Health (OIE) list of member countries with Negligible (or Controlled, see below) BSE Risk https://www.woah.org/en/disease/bovine-spongiform-encephalopathy/#ui-id-2
N/A	World Health Organization (https://www.who.int/publications/m/item/who-guidelines-on-transmissible-spongiform-encephalopathies) Annex I

8. ATTACHMENTS

Attachment 1: FDA Letter Concerning Animal Origin Materials

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

APR 1 9 2000

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

TO: Manufacturers of Biological Products

The Food and Drug Administration (FDA) has issued letters (May 3, 1991, December 17, 1993, and May 9, 1996) and a guidance document (September 1997) requesting that materials derived from ruminants which have resided in or originated from countries where Bovine Spongiform Encephalopathy (BSE) has been diagnosed not be used in the manufacture of FDA-regulated products intended for administration to humans. The United States Department of Agriculture (USDA) also issued an interim rule on January 6, 1998, restricting the importation of ruminants, meat and meat products from ruminants, and certain ruminant products and byproducts from all countries of Europe. Because of the serious nature of this issue, the Center for Biologics Evaluation and Research (CBER) believes it critical to update the current recommendations.

CBER strongly recommends that manufacturers take whatever steps are necessary to assure that materials derived from all species of ruminant animals born, raised or slaughtered in countries where BSE is known to exist, or countries where the USDA has been unable to assure FDA that BSE does not exist, are not used in the manufacture of FDA-regulated products intended for administration to humans. The Agency has previously recommended that manufacturers take the following steps to prevent this occurrence:

1. Identify all ruminant-derived materials (e.g., culture medium, transferrin, albumin, enzymes, lipids) used in the manufacture of regulated products. FDA considers the manufacture of biological products to include the preparation of master (including the original cell line) and working cell banks, as well as materials used in fermentation, harvesting, purification and formulation of the products.

2. Document the country of origin and all countries where the live animal source has resided for each ruminant-derived material used in the manufacture of the regulated product. The regulated-product manufacturer should obtain this information from the supplier of the ruminant-derived product. The regulated-product manufacturer should also obtain the appropriate veterinary regulatory inspection certification of slaughter, as required by the country of origin of live animals, from the supplier. Documentation should be maintained for any new or in-process lots of licensed, cleared or approved products; products pending clearance or approval; and investigational products intended to be administered to humans.

3. Maintain traceable records for each lot of ruminant material and each lot of FDA-regulated product manufactured using these materials. These records should be part of the product batch records and available for FDA inspection. Such records should be maintained for products manufactured at foreign as well as domestic facilities.