International Serum Industry Association	Doc. No.: STD-GUI-001	Rev.: 001	Effective Date: May 27, 2002

TITLE: ISIA Certificate of Analysis Guidance Document

1.0 PURPOSE

This document is intended to provide guidance on what should be reported on a Certificate of Analysis (CoA) for finished Fetal Bovine Serum (FBS).

2.0 SCOPE

A CoA should include a core set of quality-driven tests, using industry standardized testing methodologies and units of measure. It may include other testing at the manufacturer's discretion but should avoid any unsubstantiated or potentially misleading terms or claims. Serum manufacturers are strongly encouraged to report their test methods, utilize the methods outlined below and employ the indicated units of measure. This enables customers to make informed, reliable, scientifically and quality- driven comparisons between batches of serum supplied by and across serum manufacturers. This document is not intended to standardize CoA format.

3.0 IN THIS PROCEDURE

4.0 ROLES AND RESPONSIBILITIES

Role	Responsible for
Board of Directors	Approving Document
ISIA Staff	Managing Document
Standardization Team	Maintaining technical information in this document

5.0 REFERENCE

Document Title
<90> FBS – Quality Attributes and Functionality Tests; <1024> Bovine serum, USP 43-NF 38
01/2008:2262 Bovine Serum, Ph. Eur. 10th Edition
Cheever, M et al. A Method for Differentiating Fetal Bovine Serum from Newborn Calf Serum, BioProcessing Journal, Vol 16 (2017)

6.0 SAFETY PRECAUTIONS / REQUIREMENTS

N/A

7.0 DEFINITIONS / ABBREVIATIONS / ACRONYMS

Term	Definition
CoA	The Certificate of Analysis (CoA) is an official document signed by an authorized representative with the responsibility and authority to verify the accuracy of the reported results. The CoA provides an overview of the test results obtained from a product or material. It also includes the assessment of compliance with the determined specification. (EU GMP Guide Part I)
USP	The United States Pharmacopoeia (USP) is an independent, scientific nonprofit organization focused on building trust in the supply of safe, quality medicines. USP is working to strengthen the global supply chain so that the medicines people rely on for health are available when needed and work as expected.
EP/Ph. Eur.	The European Pharmacopoeia (EP/Ph. Eur.) is a single reference work for the quality control of medicines. The official standards it contains provide a scientific basis for quality control during the entire life cycle of a product. These standards are legally binding – as laid down in the Council of Europe Convention on the Elaboration of a European Pharmacopoeia and in EU and national pharmaceutical legislation. EP quality standards become mandatory on the same date in all States that are parties to the convention.
JP	The Japanese Pharmacopoeia is the official pharmacopoeia of Japan. It is published by the Pharmaceuticals and Medical Devices Agency.
Manufacturing Steps	The steps required to turn raw material into a finished product. Please see the flow chart “Processing of Fetal Bovine Serum” located on the ISIA website.
Validation	The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. (ICH Validation of Analytical Procedures: Text and Methodology, November 2005)

9.0 PROCEDURE

9.1 Contents of a CoA

9.1.1 What it should contain/Information Required:

9.1.1.1 General information on the COA – Company data, should include:

- FBS

- Product/catalog number
- Lot/batch number
- Expiration date
- Filtration size
- Manufacture date
- Lot size
- May also include:
  - Company product name and/or Trademarked name

9.1.1.2 Batch/Lot Data

- Country of Collection – Country where blood was collected. If blood was collected in multiple countries, all countries should be listed in descending order of percentage present. The process of collecting blood, separating, and pooling of the serum is considered substantial transformation.
- Country of Manufacturing – Country where filtration, bottling and labeling occurred. These steps are not considered substantial transformation.
- Country of origin required for regulatory requirements
- Country of Further Treatment (optional) – Country where any other steps not listed above occurred. These steps are not considered substantial transformation. If steps are taken that are considered Further Treatment and a new CoA is not generated, appropriate documentation (i.e. Gamma Irradiation documentation) that references both the treatment and the lot that has been further treated should be made available to the end-user/customer.

9.1.1.3 Batch Analysis – Key tests pertinent to the overall quality of the product - either indisputable or considered industry standard. Test methods, test results, test result units, including monograph(s), as appropriate, should be reported.

9.1.1.4 The following recommended CoA **content** is developed from standards set forth by USP, EP, JP, as well as industry best practices. **Alternative methods that have been fully validated and deliver comparable results to the standards set forth will be considered acceptable.**

- pH – Represents the acidity or alkalinity of a sample.

- Osmolality – Represents the concentration of solutes in serum.
- Total Protein - Represents the amount of protein contained in serum.
- Endotoxin - Endotoxin is a type of pyrogen and is a component of the exterior cell wall of Gram-negative bacteria, like E. coli.
- Hemoglobin – Represents the hemoglobin from lysed red blood cells. Levels of hemoglobin reflect the handling of blood during collection and prior to separation of serum from the blood.
- Bacterial and Fungal Sterility - Provides assurance that bacteria and fungi has been removed during manufacturing to provide a product suitable for cell culture applications.
- Mycoplasma - Common contaminant of wet environments. May cause cell culture contamination that is difficult to diagnose.
- Virus Testing – Cytopathic Agents - Cytopathic effect or cytopathogenic effect (CPE) refers to structural changes in host cells that are caused by viral infection. The infecting virus causes lysis of the host cell or when the cell dies without lysis due to an inability to reproduce.
- Virus Testing – Hemadsorbing Agents - The phenomenon of hemadsorption is dependent upon selective attachment of erythrocytes onto the monolayer surface of tissue culture cells. It is demonstrated by addition of erythrocytes to a tissue culture system in which propagation of a hemagglutinin-producing virus has occurred.
- Virus Testing – Bovine Viral Diarrhea Virus – A virus of concern for international trade. **Cell line utilized should be disclosed.**
- IgG – Measurement of the amount of IgG antibodies in serum. In bovines, antibodies do not cross the placental membrane from mother to calf. IgG levels in fetal serum are low.
- GGT - Measurement of the amount of Gamma-Glutamyl Transferase (GGT) – a liver enzyme – in serum. Levels in fetal serum are very low.
- Performance Testing (optional) – Should be based on a commonly used cell line and/or end-user cells. Cell lines should be disclosed on the CoA.
- Serum Origin Confirmation (optional) – Tests for verification

of a stated country of collection. Geographic testing performed must be validated.

9.1.1.5 Footer Data

- Company address and company contact information
- Quality or authorized signature

9.1.2 What it could contain:

9.1.2.1 Other testing that the manufacturer believes may be of use or interest to their customers. Any such data is subject to the same stipulations regarding methods and reported units.

9.1.2.2 Serum may be processed in a registered facility under cGMP. Companies who are registered with and are audited by a competent authority may state compliance with cGMP's for the facility, not the serum. Animal Serum is not a product that is registered with, nor regulated by, the FDA.

9.1.3 What it should not contain:

9.1.3.1 Statements that cannot be substantiated or are misleading (e.g., USDA Approved or EU Approved or FDA Approved)

9.1.3.2 Marketing statements (not product name) that are meaningless, subjective, or exaggerated (e.g., 'Super Serum').

9.1.3.3 The use of groupings of countries by a region (e.g. South America)

10.0 APPENDIX – CoA Sample Content/Data

APPENDIX – CoA Sample Content/Data

Header Data (order not dictated)

Company Name
Product Name/Catalog Number
Batch/Lot Number
Date of Manufacture
Intended use
Expiration Date
Filtration Size
Lot Size
Storage Conditions

Batch Data

Country of Collection
Country of Manufacturing
Country of Further Treatment (OPTIONAL)

Batch Analysis

Test Name	Recommended Test Method[b]	Unit of Measure
pH	USP<791> or EP 2.2.3	N/A
Osmolality	USP<785> or EP 2.2.35	mOsmol/kg of H_2O
Total Protein	Biuret manual, automated (chem analyzer), EP 2.5.33, or USP<1057>	g/dL
Endotoxin	USP <85>, EP 2.6.14, JP 4.01	EU/mL
Hemoglobin	USP<90>	mg/dL
Bacteria and Fungi/Sterility	USP<71> or EP 2.6.1	N/A
Mycoplasma	USP<63> or EP 2.6.7	N/A
Virus Testing – Cytopathic Agents	9CFR 113.46	N/A
Virus Testing – Hemadsorbing Agents	9CFR 113.46	N/A
Virus Testing – Report all relevant viruses as dictated by prescribed regulations	9CFR 113.53 and 113.47 or EMA/CHMP/BWP/457920/2012 r1	N/A
Virus Testing[a] – Bovine Viral Diarrhea Virus	9CFR 113.53 and 113.47 or EMA/CHMP/BWP/457920/2012 r1 ***Report cell line utilized***	N/A
IgG	ELISA	µg/mL
GGT	Chem Analyzer	IU/L
Performance Testing (OPTIONAL)	Report Cell line utilized	N/A
Serum Origin Confirmation (OPTIONAL)	Validated Trace Element analysis	N/A

[a]ISIA recommends the use of a Bovine Turbinate cell line.
[b]Alternative test methods which have been fully validated and deliver comparable results are considered acceptable.

REVISION HISTORY				
Revision	**DCR Number**	**Effective Date**	**Change Description**	**Originator**