

STANDARDIZATION OF FETAL BOVINE SERUM QUALITY ASSESSMENT AND REPORTING DEFINITIONS AND SAMPLE CERTIFICATES INCLUDED

One of the objectives of the International Serum Industry Association is to provide guidance to manufacturers, suppliers, customers and regulatory agencies by standardizing the most critical serum quality and integrity assessment tests, and simplifying their documentation on an appropriate Certificate of Analysis (a suggested form of which is attached). This will assist concerned parties to compare results easily and will assist buyers in determining which bovine serum to purchase.

Based on the results of a 2007 Fetal Bovine Serum 'testing and reporting' survey of 15 member companies, and comparison of those results with the current regulatory requirements of various countries, a proposal for a standardized set of key quality assessment tests, together with their associated specifications and units of measure, was formulated and reviewed at the annual meeting in April 2008. Fetal Bovine Serum is defined as described in Appendix 1.

The proposed standardization would not preclude organizations from performing and reporting optional testing, adopting narrower acceptability ranges, or utilizing a company-specific format for their Certificate of Analysis.

Minimum Testing Standards:

The tests listed below relate to the minimum batch analysis required for final-filtered Fetal Bovine Serum products. The corresponding units of measure, specifications and methodologies should be applied consistently by all ISIA member organizations.

The ranges determined under 'specifications' are to be understood as the broadest range acceptable, and an organization is free to use their own (narrower) acceptability ranges as established via historical values or scientific data, provided that these ranges fall within the specifications listed below. Some of the specifications that were derived from the survey results are extremely broad. For this reason, the chart below also lists recommended, narrower ranges for these respective specifications. A future objective of the ISIA includes narrowing these ranges to the 'recommended' ranges. Currently, these recommended ranges are purely voluntary.

The list of methodologies in the chart below resulted from the survey as well. Per test, an organization may select one or more of the referenced methodologies.

A firm time frame for implementation of this QC standardization will to be determined after an appropriate phase-in period to allow for any needed changes in documentation, training, etc. With the publication of this document ISIA members are encouraged to move towards compliance with this policy.

The ISIA Board of Directors may, at any time, revise, modify or change the foregoing procedures and standards and will notify its members within a reasonable time after any such revision, modification or change is made. If any member needs further clarification with regard to the foregoing, they should contact the CEO of ISIA.

RECOMMENDED TESTS AND SPECIFICATIONS

	Test	Specification	Unit of Measure	Methodology (use at least one)
1.	Bacteria and Fungi/Sterility	Not Detected	N/A	Current edition of USP <71> Current edition of EP Current edition of JP
2.	Mycoplasma	Not Detected	N/A	Barille, MF and Kern, J (1971), P.S.E.M.B. 138,432 9CFR 610.30 or PTC EP
3.	Virus Testing - Cytopathic Agents	Not Detected	N/A	9 CFR Part 113.53 c [113.46, 113.47] EP
4.	Virus Testing - Hemadsorbing Agents	Not Detected	N/A	9 CFR Part 113.53 c [113.46, 113.47] EP
5.	Virus Testing - Bovine Virus Diarrhea	Tested	N/A	9 CFR Part 113.53 c [113.46, 113.47] EP
6.	pH	6.5-8.5 <i>Recommended range: 7-8</i>	N/A	USP<791> Current edition of EP
7.	Osmolality	260-350 <i>Recommended range: 270-330</i>	mOsm/kg	USP<785>
8.	Total Protein	2.5-6 (or 25-60) <i>Recommended range: 3-4.5 (30-45)</i>	gm/dl (or mg/ml)	Biuret Method for the Determination of Total Protein... Fund. Of Clin. Chem, pages 302 – 304 Biuret Method; Doumas et al (1975) Clin Chem 21. 1159
9.	Endotoxin	Test and Record	EU/ml	USP <85> / USP <151> Guidance on validation of LAL test as an end-product endotoxin test... FDA, December 1987 EP
10.	Hemoglobin	Test and Record	gm/dl (or mg/ml)	Fleming, AF and Woolf AJ (1965) Clin. Chem. 12, 67
11.	Electrophoretic Pattern	Normal	N/A	Cellulose Acetate Electrophoresis
12.	Performance Testing	Tested and Acceptable	N/A	Company Specific Method

Standard Certificate of Analysis:

Each lot/batch of final-filtered Fetal Bovine Serum must be subjected to the minimum panel of required product integrity and species identity tests as outlined above before it is released for distribution to the end-user. These tests must be documented and summarized in a Certificate of Analysis that is made available to the customer with each lot/batch purchased.

The Certificate of Analysis must (1) list the name of each quality control test performed; (2) clearly document the test method used; and (3) display the specification or acceptability range for the test, the unit of measure and the result.

Furthermore, the Certificate of Analysis must supply, at a minimum, the following additional information pertaining to the lot/batch:

- Company Name, Address and Contact Information of Supplier
- Product Name, Catalog Number, Lot/Batch Number
- Manufacture Date
- Expiration Date
- Intended Use
- Raw Material Country(ies) of Origin
- Date and (electronic) Signature (QC Department)

ISIA recommends that every participating organization also list the Country of Final Processing, Filtration Data, and Storage Conditions.

Every organization may also list on their Certificates of Analysis additional QC tests performed as well as additional information, depending on their individual requirements, and may also select their own format.

CERTIFICATE OF ANALYSIS

(Example Format)

Organization Name, Address, Contact Information

Product Name:
Catalog Number:
Lot/Batch Number:
Manufacture Date:
Filtration Data:
Expiration Date:
Intended Use:
Country of Raw Material Origin:
Country of Final Processing:
Storage Conditions:

Date and (electronic) Signature:

Test	Method	Units	Specification	Result
Bacteria and Fungi	USP <71>	N/A	Not Detected	Not Detected
Mycoplasma	Barille, MF and Kern, J (1971)	N/A	Not Detected	Not Detected
Virus Testing:				
Cytopathogenic Agents	9 CFR Part 113.53 c [113.46,	N/A	Not Detected	Not Detected
Hemadsorbing Agents	113.47]	N/A	Not Detected	Not Detected
BVD Virus		N/A	Tested	Tested
pH at RT	USP<791>	N/A	6.5 to 8.5	(Result)
Osmolality	USP<785>	mOsm/kg	260-350	(Result)
Endotoxin	USP <85>	EU/ml	Test and Record	(Result)
Hemoglobin	Fleming, AF and Woolf AJ (1965) Clin. Chem. 12, 67	gm/dl	Test and Record	(Result)
Total Protein	Biuret Method; Doumas et al (1975) Clin Chem 21. 1159	gm/dl	2.5 – 6.0	(Result)
Electrophoretic Pattern	Cellulose Acetate Electrophoresis	N/A	Normal	Normal
Performance Testing	Company specific method	N/A	Tested and Acceptable	Tested and Acceptable

Appendix 1

Definitions

Definition of Serum Origin:

We recognize that there could be differences between the serum industry definition of origin and standard trade or WTO definitions or rules about origin. In the best interest of the parties in ISIA we propose specific definitions for the origin of Slaughterhouse Derived Materials and Donor Origin Materials. Furthermore, we endorse the clear separation of batches of serum such that two or more origins of serum are not combined, or at least if they are combined, then both origins appear on the official certification.

Slaughterhouse-Derived Materials - The country where the animals from which the raw blood was collected were slaughtered.

Donor-Derived Materials – The country of birth of the animals and the country of collection designate the origin of donor-derived materials. Members are required to provide birth herd traceability for all Donor Animals. In the event that animals are moved from the country of birth to another country for blood collections, the documents must identify both the country of origin as well as the country where the donor animals resided during the testing and bleeding program. ISIA prefers that farm of origin information be maintained and well documented.

Definition of Serum Type:

1. Fetal Bovine Serum:

Fetal Bovine Serum (FBS) is defined as the liquid fraction of naturally clotted blood (which is therefore depleted of cells, fibrin and clotting factors) derived from normal fetuses (not delivered by birth process) from healthy dams deemed fit for human consumption. It is collected in government-inspected and registered slaughterhouses or abattoirs. There are no deletions, additives or preservatives allowed. Specialized products derived from FBS via deletions, additives or preservatives should be appropriately named to clearly indicate that they are modified FBS, and not FBS in its natural form.

2. Newborn Bovine Calf Serum:

Newborn Bovine Calf Serum (NBCS) is defined as the liquid fraction of naturally clotted blood (which is therefore depleted of cells, fibrin and clotting factors) derived from animals from birth to two weeks of age, deemed fit for human consumption. It is collected in government-inspected and registered slaughterhouses or abattoirs. There are no deletions, additives or preservatives allowed. Specialized products derived from NBCS via deletions, additives or preservatives should be appropriately named to clearly indicate that they are modified NBCS.

3. Bovine Calf Serum:

Calf serum (BCS) is defined as the liquid fraction of naturally clotted blood (which is therefore depleted of cells, fibrin and clotting factors) derived from animals from 2 weeks to 12 months of age, deemed fit for human consumption. It is collected in government-inspected and registered slaughterhouses or abattoirs. There are no deletions, additives or preservatives allowed. Specialized products derived from BCS via deletions, additives or preservatives should be appropriately named to clearly indicate that they are modified BCS.

4. Adult Bovine Serum:

Adult Bovine Serum is defined as the liquid fraction of naturally clotted blood (which is therefore depleted of cells, fibrin and clotting factors) derived from animals greater than 12 months of age, deemed fit for human consumption. It is collected in government-inspected and registered slaughterhouses or abattoirs. There are no deletions, additives or preservatives allowed.

5. Donor Bovine Serum:

Donor Bovine Serum is defined as the liquid fraction of naturally clotted blood (which is therefore depleted of cells, fibrin and clotting factors) derived from healthy, live animals, greater than 12 months of age, from carefully managed and strictly segregated herds. It is collected on government-inspected and registered farms. There are no deletions, additives or preservatives allowed.