



BI
Biological Industries
Culture of Excellence

Sera



Foetal Bovine Sera (FBS)

Bovine Sera

Other Sera



Introduction

Serum is commonly used as a supplement to basal growth medium in cell culture. The most common type of serum used for cell growth is foetal bovine serum (FBS), also known as foetal calf serum (FCS).

Foetal bovine serum is obtained from foetuses harvested in abattoirs from healthy dams fit for human consumption.

Occasionally, there may be use of other bovine sera, such as newborn calf serum or donor bovine serum. In cell culture, serum provides a wide variety of macromolecular proteins, low molecular weight nutrients, carrier proteins for water - insoluble components, and other compounds necessary for in vitro growth of cells, such as hormones and attachment factors. Serum also adds buffering capacity to the medium and binds or neutralizes toxic components. Attempts to replace serum entirely with serum-free medium have met only with limited success.

The selection of a serum supplement for cell culture applications is primarily dependent on the chemical definition of the basal medium, the type of cell to be grown, and the culture system being employed.

Collection

In the FBS manufacturing process, whole blood is collected aseptically in disposable sterile plastic bags and allowed to clot. Once the serum has been separated from the clot, it is pooled and frozen.

Controlling the initial collection of foetal blood is a crucial factor in the quality of the final serum product. Only raw material that meets our specifications is approved for production.

Handling Serum Products

Using Serum – Although the product has been sterile filtered, aseptic procedures must be followed at all times.

Granules, flocculent material or turbidity may develop after thawing. This particulate matter does not alter the performance of the serum as a supplement for cell culture medium. Repeated freezing/thawing of serum may increase the amount of precipitate and is therefore not recommended. If you do not intend to use an entire bottle of serum aliquot it into usable quantities in sterile containers before freezing a second time.

Wipe the outside of each bottle with a suitable disinfectant solution, before setting it on the work surface. Remove the heat seal and wipe the outside of the cap with the disinfectant solution.

All serum products should be treated as potentially harmful and appropriate care should be taken when handling them.

Raw Materials

Two distinct grades of FBS are available on the world market: USDA-Grade FBS and European-Grade FBS.

USDA-Grade FBS is produced from raw materials originating only from countries certified to be free of both BSE (Bovine Spongiform Encephalopathy) and FMD (Foot and Mouth Disease). This product can be freely imported into any country, and is the product of choice in all countries for manufacturing purposes. Furthermore, only the use of this product allows researchers to send their cells, or the products of their cells, to collaborators in other countries with strict import regulations.

All FBS processed in the Biological Industries plant is USDA-Grade.

Processing

Selected batches of serum raw material are thawed, tested for endotoxins and hemoglobin content and only the accepted material is pooled. The pooled raw material is thoroughly blended under refrigerated conditions and membrane filtered for sterility according to a well validated filtration protocol. Biological Industries processes FBS through a sequence of pre-filters and membrane filters. The filtration step includes the use of three 0.1 micron sterilizing grade membrane filters in series.

After filtration, the serum is dispensed into bottles by an aseptic filling process which has been validated to insure sterility of the final product.

Serum products are produced in a controlled environment (clean rooms) designed to carefully control air pressure and particulate matter.

The manufacturing area is a class 100,000 (ISO 8) environment. The sterile bottles and equipment are stored in a class 10,000 (ISO 7) environment, and the filling room is a class 1000 (ISO 6) environment with class 100 (ISO 5) laminar air flow sterile bench. Clean rooms are monitored on a regular basis for particulate and microbial levels to ensure that the air handling system, cleaning protocols and personnel maintain standards control.

After filling, the final product is quickly frozen to -20°C and held in quarantine until all quality control tests have been completed.

Quality Control

Each lot of FBS is tested to confirm that the serum meets the written specifications. Final product release is done after reviewing all production and quality control records to determine compliance with all established, approved written procedures.

Physical and chemical tests

- Electrophoretic Pattern
- pH
- Osmolality
- Total proteins
- Albumin
- IgG
- Hemoglobin
- Globulins

Biochemicals Tests

The following tests are conducted on each lot of FBS:

- Alanine Transaminase (ALT)
- Alkaline Phosphatase
- Aspartate Aminotransferase (ast)
- Bilirubin – total
- Bilirubin – direct
- Blood Urea Nitrogen (BUN)
- Calcium
- Chloride
- Cholesterol
- Creatinine
- Creatinine Kinase (CK)
- Gamma-Glutamyl Transferase (GGT)
- Glucose
- High Density Lipoproteins (HDL)
- Lactate Dehydrogenase
- Low density Lipoproteins (LDL)
- Phosphorous (Inorganic)
- Potassium
- Sodium
- Triglycerides (TG)
- Uric Acid

Microbiological tests

- **Sterility tests:**
Bacterial and fungal sterility tests according to the current USP
- **Mycoplasma contamination:**
According to the Code of Federal Regulations (CFR), title 9, part 113 (culture method).
- **Viral contaminants:**
According to the protocols described in CFR, title 9, part 113 for Bovine Viral Diarrhea (BVD), Infectious Bovine Rhinotracheitis (IBR) and Parainfluenza type 3 (PI3).
- **Viral antibodies:**
FBS is screened to determine the titer of neutralizing antibodies to BVD, IBR and PI3.
- **Endotoxins:**
The test is performed using the standard Limulus Amebocyte Lysate (LAL) with the kinetic turbidimetric method.

Biological performance (cell growth)

The cell growth tests are designed to check the efficacy of the FBS in promoting cell growth. Cells used are fibroblasts (MRC-5 diploid normal cells), epithelial cells Vero and hybridoma cells. Each test is conducted using the tested serum and a validated control lot. Growth promotion using MRC-5 cells is evaluated through several subculture generations to observe any evidence of cytotoxicity and morphological changes of the cells.

Vero cells (ATCC, CCL 81): plating efficiency.

MRC-5 cells (ATCC, CCL 171): 3 passages test.

Hybridoma cells: cell growth.

Stability

FBS stability at -20°C temperature was evaluated for long periods. The FBS did not lose its performance for 5 years. Storage of FBS at -20°C without defrosting will maintain the quality of the FBS at least until the expiration date stated on the label.

Quality Assurance

The FBS production process is carried out under controlled conditions in a controlled environment. The steam-in-place (SIP) sterilization, filtration for sterility and filling are validated as required for key aseptic processes. A dossier (Device Master Record) exists for serum with all relevant data concerning serum production. The production process from the raw material to the final product in storage, as well as the quality control tests and results, are documented and filed to ensure traceability and control of the process.

Biological Industries' products are manufactured in compliance with the quality management standard ISO 9001:2008 and ISO 13485:2003.

Certifications are available upon request.

In addition, the FBS production process conforms to the In Vitro Diagnostics Directive (IVDD 78/79/EC) of the European Parliament. Therefore, our FBS received the CE mark making it eligible for sale in the European Union for in vitro diagnostics.

A Bovine Spongiform Encephalopathy (BSE) Certificate of Suitability has been issued to Biological Industries by the European Directorate for the Quality of Medicines (EDQM) in accordance with monographs of the European Pharmacopeia.

BlisalsoamemberoftheInternationalSerumIndustryAssociation(ISIA).

All documents and certifications are available upon request.

Foetal Bovine Sera (FBS)

Serum, as a biological material, represents an undefined mixture of components in which composition varies from one lot to the other. Some cell types are sensitive to the variations in serum performance.

Customers are encouraged to evaluate serum samples with their own culture system and cells while we reserve the quantities of the specific lots until customer testing is completed. In this way, the customer may choose the best serum for his own applications.

Biological Industries offers you the following certified sterile Foetal Bovine Serum Products:

Product Name	Catalogue No.	Unit Size	Storage Temp.
Certified Foetal Bovine Serum	04-001-1A	500ml	-20°C
	04-001-1B	100ml	-20°C
Foetal Bovine Serum (FBS) European Grade (South American Origin)	04-007-1A	500ml	-20°C
	04-007-1B	100ml	-20°C
Certified Foetal Bovine Serum Heat Inactivated	04-121-1A	500ml	-20°C
	04-121-1B	100ml	-20°C
Foetal Bovine Serum (FBS) European Grade Heat Inactivated (South American Origin)	04-127-1A	500ml	-20°C
	04-127-1B	100ml	-20°C
Certified Foetal Bovine Serum Qualified for Human Embryonic Stem Cells	04-002-1A	500ml	-20°C
	04-002-1B	100ml	-20°C
Certified Foetal Bovine Serum Qualified for Human Embryonic Stem Cells Heat Inactivated	04-222-1A	500ml	-20°C
	04-222-1B	100ml	-20°C
Certified Foetal Bovine Serum Functionally Tested for use with Tetracycline Regulated Systems	04-005-1A	500ml	-20°C
	04-005-1B	100ml	-20°C
Certified Foetal Bovine Serum Functionally Tested for use with Tetracycline Regulated Systems Heat Inactivated	04-125-1A	500ml	-20°C
	04-125-1B	100ml	-20°C
Certified Foetal Bovine Serum Dialyzed	04-011-1A	500ml	-20°C
	04-011-1B	100ml	-20°C
Certified Foetal Bovine Serum, Charcoal-Stripped	04-201-1A	500ml	-20°C
	04-201-1B	100ml	-20°C
Certified Foetal Bovine Serum (FBS), Qualified for Mesenchymal Cells	04-400-1A	500ml	-20°C
	04-400-1B	100ml	-20°C
Certified Foetal Bovine Serum (FBS), Gama Irradiated	04-111-1A	500ml	-20°C

Heat inactivated FBS

Product Name	Catalogue No.	Unit Size	Storage Temp.
Certified Foetal Bovine Serum Heat Inactivated	04-121-1A	500ml	-20°C
	04-121-1B	100ml	-20°C
Foetal Bovine Serum (FBS) European Grade Heat Inactivated (South American Origen)	04-127-1A	500ml	-20°C
	04-127-1B	100ml	-20°C

Heat inactivation of serum is performed by raising the temperature of the serum to 56°C and maintaining that temperature for 30 minutes. Heat inactivation is the method of choice to destroy complement proteins activity.

FBS qualified for human Embryonic Stem (ES) Cells

Product Name	Catalogue No.	Unit Size	Storage Temp.
Certified Foetal Bovine Serum Qualified for Human Embryonic Stem Cells	04-002-1A	500ml	-20°C
	04-002-1B	100ml	-20°C
Certified Foetal Bovine Serum Qualified for Human Embryonic Stem Cells Heat Inactivated	04-222-1A	500ml	-20°C
	04-222-1B	100ml	-20°C

Embryonic Stem (ES) Cells are pluripotent cells derived from the inner cell mass of the blastocyst. The stem cells can be maintained in vitro for extended periods without loss of their capacity to differentiate to all cell lineages when reimplanted back into a blastocyst. ES cells may differentiate in vitro to a variety of cell types including neuronal, muscle, endothelial and hematopoietic progenitors. General culture conditions are well established and usually require ES cells to be grown on an inactive feeder cell layer or with basement membrane components (Matrigel, Fibronectin, Laminin). When growing ES cells, one of the most important parameters is the maintenance of the cells in the undifferentiated state. Pre-screening of the serum is essential before using it for the culture of ES cells. Various lots of sera are screened for the growth of Human ES cells using MEF's as a feeder layer.

The following parameters are measured for the screening:

- Human ES cells colony morphology
- Plating efficiency
- Differentiation rate: analysis of Human ES cells surface marker expressed on the undifferentiated cells membrane (FACS analysis). The results are used as an indication of the quality of sera for the growth and maintenance of undifferentiated stem cells.

FBS Qualified for Mesenchymal Stem Cells

Product Name	Catalogue No.	Unit Size	Storage Temp.
Certified Foetal Bovine Serum (FBS) Qualified for Mesenchymal Stem Cells	04-400-1A	500ml	-20°C
	04-400-1B	100ml	-20°C

Mesenchymal Stem Cells, also known as MSC's, are another well-characterized population of adult stem cells. These are multipotent stem cells that can differentiate into a variety of cell types and include chondrocytes, myocytes, adipocytes, and, as described recently, betapancreatic islets cells. Although not immortal, they have the ability to expand exponentially in culture while retaining their growth and multilineage potential. Unlike most other Human Adult Stem Cells, MSC's can be obtained in quantities appropriate for clinical applications, making them good candidates for use in tissue repair. The established techniques utilized for the isolation and amplification of MSC's in culture have proven that these types of cells can be maintained and propagated in cell culture for the long-term without losing their viability and their capacity to differentiate. Furthermore, MSC's can take up and keep introduced genes, a phenomenon that may be exploited for the delivery of advantageous molecules to targeted sites.

Perhaps one of the most exciting considerations for Human applications is that MSC's may be derived from a small bone marrow sample from a given patient, expanded in culture and given back to the patient, thus avoiding the typical problems associated with immune rejection of foreign transplanted cells or tissues.

Pre-screening of the serum is an essential procedure before using it for culture of MSC's as Stem Cell Research requires the highest possible serum purity to prevent adverse differentiation. Biological Industries pre-screens multiple FBS batches\lots to eliminate the often time-consuming and costly process of testing and re-testing in order to allow researchers to focus on more important tasks. Various Lots/Batches of Sera are screened for the growth of Mesenchymal Stem Cells.

The following parameters are measured during the screening process:

- MSC Morphology
- Plating Efficiency
- Differentiation Rate

The results are utilized as an indication of the highest purity of the sera that emphasizes maximum expansion of unaltered MSC's, while at the same time, maintaining their unrestricted multiipotency.

FBS - Functionally Tested for use with Tetracycline Regulated Systems

Product Name	Catalogue No.	Unit Size	Storage Temp.
Certified Foetal Bovine Serum Functionally Tested for use with Tetracycline Regulated Systems	04-005-1A	500ml	-20°C
	04-005-1B	100ml	-20°C
Certified Foetal Bovine Serum Functionally Tested for use with Tetracycline Regulated Systems Heat Inactivated	04-125-1A	500ml	-20°C
	04-125-1B	100ml	-20°C

Functionally Tested for use with Tetracycline Regulated Systems FBS that have been pre-tested to ensure that they permit the range of tetracycline-regulated induction with well-characterized Tet lines.

Dialyzed FBS

Product Name	Catalogue No.	Unit Size	Storage Temp.
Certified Foetal Bovine Serum	04-011-1A	500ml	-20°C
Dialyzed	04-011-1B	100ml	-20°C

Most cells grown in culture require a serum component of the growth medium to maintain their proliferative capacity. While whole serum is permissible for routine purposes, studies involving nutritional parameters or incorporation of labeled material require that the constituent under study be removed from the serum. The most commonly used method for removal of these constituents is dialysis of whole serum.

For dialysis by diafiltration, serum is circulated through a hollow-fiber by the concentration method. The filtrate, however, is replaced by the addition of physiological saline to the serum.

Charcoal-stripped FBS

Product Name	Catalogue No.	Unit Size	Storage Temp.
Certified Foetal Bovine Serum	04-201-1A	500ml	-20°C
Charcoal-Stripped	04-201-1B	100ml	-20°C

Charcoal-stripped FBS is used to elucidate the effects of hormones in a variety of in vitro systems. Studies include steroid- receptor binding, steroid regulation of cellular receptors, hormone secretion of various tissues and the function of thyroid hormones. The production procedure includes the use of charcoal and dextran to remove the hormones from the FBS.

Gama irradiated FBS

Product Name	Catalogue No.	Unit Size	Storage Temp.
Certified Foetal Bovine Serum, (FBS) Gama Irradiated	04-111-1A	500ml	-20°C

Gamma irradiation is a process which involves exposing material to high energy gamma photons released by radioisotopes, such as cobalt 60. This energy is transferred from the photons to the products, and is responsible for organism inactivation by ionization of nucleic acid bonds. The irradiation of serum is intended to provide complete assurance of viral inactivation. An extensive validation study has been performed to validate the irradiation process using FBS spiked with several viruses. We have demonstrated that properties and cell culture performance of FBS are not altered by gamma irradiation exposure of 2.5-4 MRad.

Foetal Bovine Sera (FBS) FAQs

- **What is the difference between Foetal Bovine Serum (FBS) and Foetal Calf Serum (FCS)?**
They are the same and describe exactly the same serum product.
- **My FBS contains precipitates. What are they and what should I do?**
The precipitates contain fibrin (clot forming protein) and lipoproteins. This is a normal characteristic and will not affect product performance. To remove the precipitates, centrifuge the serum or simply let it settle to the bottom of the bottle and transfer the serum carefully to another sterile bottle.
- **My FBS arrived partially thawed, what should I do?**
Let the serum defrost completely, swirl the serum bottle gently and then re-freeze the serum. The quality of the serum will not have been affected.
- **How do I heat-inactivate serum?**
Serum heat-inactivation is performed in a waterbath at 56°C for 30 minutes. The water level should be higher than the level of the serum.
Monitor the temperature in a reference bottle containing water at the same volume during the heat inactivation. You must swirl the bottles to mix the serum every 5 minutes during heat inactivation to insure uniform heating. Use a calibrated thermometer only!
- **I have a jellylike fraction on the bottom of the bottle. What is it?**
As a result of improper heat inactivation of the serum (temperature above 56°C, more than 30 minutes), or inactivation without mixing the serum, a protein denaturation caused the jellylike fraction on the bottom of the bottle. Do not use this serum.
- **How should I thaw FBS?**
We recommend thawing the serum at 2-8°C. However, if necessary, you may thaw the serum at room temperature. Swirl the bottles gently to mix the serum during the thawing process.
- **Why is the color of the FBS not exactly the same as with my previous lot?**
The color of FBS is brown to brown-red. It is dependent mainly on the hemoglobin concentration in the specific lot. The color does not affect the FBS performance.
- **Is the FBS raw material free of BSE?**
FBS sold by Biological Industries has always been produced from raw materials originating from countries that are free of BSE according to the OIE (Office International des Epizooties).
- **How can I be certain regarding the country of origin of the raw material that was used to manufacture sterile FBS?**
Ask Biological Industries for a copy of the original raw material veterinary documents.

Bovine Sera

Newborn Calf Sera

Product Name	Catalogue No.	Unit Size	Storage Temp.
Newborn Calf Serum (Less than 10 days)	04-102-1A	500ml	-20°C
	04-102-1B	100ml	-20°C
Newborn Calf Serum Heat Inactivated	04-122-1A	500ml	-20°C
	04-122-1B	100ml	-20°C

Bovine Sera

Product Name	Catalogue No.	Unit Size	Storage Temp.
Adult Bovine Serum	04-003-1A	500ml	-20°C
	04-003-1B	100ml	-20°C
Adult Bovine Serum Heat Inactivated	04-123-1A	500ml	-20°C
	04-123-1B	100ml	-20°C

Other Sera

Product Name	Catalogue No.	Unit Size	Storage Temp.
Donor Horse Serum	04-004-1A	500ml	-20°C
	04-004-1B	100ml	-20°C
Donor Horse Serum Heat Inactivated	04-124-1A	500ml	-20°C
	04-124-1B	100ml	-20°C
Porcine Serum	04-006-1A	500ml	-20°C
	04-006-1B	100ml	-20°C
Rabbit Serum	04-008-1A	500ml	-20°C
	04-008-1B	100ml	-20°C
Donor Goat Serum	04-009-1A	500ml	-20°C
	04-009-1B	100ml	-20°C

Sera



Biological Industries (BI) has been committed for over 30 years to provide optimal and innovative solutions for cell culture practice.

BI manufactures and supplies life science products to biopharmaceutical, academic and government research facilities, as well as to biopharma companies.

Our diverse portfolio of products and services includes all of the following:

- Liquid and powdered cell culture media
- Sterile sera (Foetal Bovine Serum, Newborn Calf serum, Donor horse, etc.)
- Novel serum-free and animal component-free media and supplements
- Products for stem cell culture
- Products for cytogenetics
- Products for mycoplasma detection and treatment
- Disinfectants
- ECM-coated plastic ware
- Products for molecular biology
- Contract manufacturing and custom formulations

The production and the filling processes are according to GMP Quality System guidelines in a cGMP compliant facility. BI products are manufactured in a controlled environment (clean rooms), according to ISO 14644:2001 and EU\GMP annex 1.

The clean rooms are monitored on a regular basis for particulate and microbial levels to ensure that the air handling system, cleaning protocol and personnel maintain standards control.

The production and the preparation area are class 100,000 (ISO 8) environments.

Sterile bottles and equipment are stored in class 10,000 (ISO 7) environment.

The filling room is a class 1,000 (ISO 6) environment with class 100 (ISO 5) laminar air flow sterile bench.

Only properly trained personnel are authorized to perform the product preparation, filtration and filling. The personnel entering the production and filling rooms are gowned as per the gowning procedure of BI Ltd.

In addition, BI Ltd. holds ISO 9001:2008, ISO 13485:2003 and also comply with the legal requirements set in the European IVD Directive 98/79/EC.

We also export our products to 50 countries worldwide, via a network of exclusive distributors. Over the years we have established a reputation for fast delivery, and excellent technical support.

From the outset, the policy of BI has been based on the need to maintain an active Research and Development program in all facets of company activities. The company has its own in-house R&D department, and in addition, we maintain active contact with science-based companies and research institutions in Israel and abroad, including know-how agreements with several such institutions. These ongoing efforts have led to the introduction of a series of serum-free medium products, and a novel product line for stem cell research, as well as many other products for cell culture and molecular biology.



BI
Biological Industries
Culture of Excellence

Biological Industries Israel Beit Haemek Ltd.
Kibbutz Beit Haemek 25115, Israel
T.+972.4.9960595 F.+972.4.9968896
Email: info@bioind.com
www.bioind.com



CGMP
Manufacturing
Facility