# DRAFT NEW MONOGRAPH FOR COMMENTS

This draft new monograph contain text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to further revisions prior to publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Comments received after the last date will not be considered by the IPC before finalizing the monograph.

**Please send any comments you may have on this draft document to** lab.ipc@gov.in/ biologics-ipc@gov.in **before the last date for comments.**

## Document History and Schedule for the Adoption Process

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**BOVINE SERUM**

DEFINITION

The liquid fraction of clotted blood obtained from the ox (*Bos taurus* L.) and from which cells, fibrin, and clotting factors have been removed.

Different types of bovine serum are used:

- *adult bovine serum* obtained at slaughter from cattle that are declared fit for human consumption;
- *calf serum* obtained at slaughter from animals, fit for human consumption, before the age of 12months;
- *new-born calf serum* obtained at slaughter from animals before the age of 20 days;
- *foetal bovine serum obtained from normal foetuses from dams fit for human consumption;*
- *donor bovine serum* obtained by repeated bleeding of donor animals from controlled donor herds.

*This monograph provides guidelines for the production, sourcing, quality and safety of Bovine Serum. Various measures should be applied during the production of bovine serum aimed at obtaining a product that is acceptable regards to its quality and safety. The NRA should approve the source(s) of bovine serum. The manufacturer is responsible for ensuring the quality and safety of bovine serum used in the manufacturing of biologicals. Importantly, the manufacturer mandatorily provides the declaration about the TSE and BSE-free serum being used in the manufacturing process. Neither single measure, nor the combination of measures outlined below can guarantee complete viral safety but they rather reduce the risk involved in the use of serum in the manufacture of medicinal products. It is therefore necessary for the manufacturer of a medicinal product to take account of this when choosing the serum for a particular use by making a risk assessment.*

PRODUCTION

All stages of serum production are submitted to a suitable quality management system.

Traceability of serum is maintained from the final container to the abattoir of origin (for blood collected from slaughtered animals) or to the herd of origin (for blood collected from donor animals).

Further guarantee of the safety and quality of serum shall be ensured by the use of a controlled donor herd. Where serum is obtained from such a herd, the animals are subjected to regular veterinary examination to ascertain their health status. Animals introduced into the herd are traceable as regards source, breeding and rearing history. The introduction of animals into the herd follows specified procedures, including defined quarantine measures. During the quarantine period the animals are observed and tested to establish that they are free from all agents and antibodies from which the donor herd is claimed to be free. It may be necessary to test the animals in quarantine for freedom from additional agents, depending on factors such as information available on their breeding and rearing history. It is recommended that animals in the herd should not be vaccinated against bovine viral diarrhea virus (BVDV). Tests are carried out for any agent and/or antibody from which the herd is claimed to be free of BVDV

Serum is obtained by separation of the serum from blood cells and clot under conditions designed to minimise microbial contamination. Serum from a number of animals is pooled and a batch number is allocated to the pool. Appropriate steps are taken to ensure homogeneity of the harvested material, intermediate pools and the final batch. Pooled serum is aseptically mixed and filtered through 0.2 µ or lesser pore size filters. The filtration process should be validated to ensure the sterility of the serum; a triple filtration through 0.1µ filtered serum resulted in significant removal/ elimination of Mycoplasma using a validated procedure, the filtered serum shall be aseptically filled into sterile containers and hermetically closed with an appropriate/ approved closure system.
Before further processing, the serum is tested for sterility. General and specific tests for viral contaminants are carried out as described below.

A step or steps for virus inactivation/removal are applied to serum intended for the production of biologicals. Unless otherwise justified and authorised for a particular medicinal product, a step or steps

for virus inactivation/removal are applied to serum intended for production of human and non-immunological veterinary medicinal products.

*INACTIVATION*

The inactivation procedure applied is validated with respect to a suitable representative range of viruses covering different types (enveloped, non-enveloped, DNA, RNA viruses). The optimal choice of relevant and model viruses depends strongly on the specific inactivation/removal procedure; representative viruses with different degrees of resistance to the type of treatment must be included. The inactivation procedure should not affect quality and stability of the serum and should not lead to generation of undesired product(s). Bovine viral diarrhea virus must be included in the viruses used for validation. Serum free from antibodies against bovine viral diarrhea virus is used in part or all of the validation studies.

For bovine serum intended for use in immunological veterinary medicinal products, for inactivation by gamma irradiation a minimum dose of 30 kGy is applied, unless otherwise justified and authorised.

Critical parameters for the method of virus inactivation/removal are established and the parameters used in the validation study are strictly adhered to during subsequent application of the procedures to each batch of serum.

For inactivation by gamma irradiation, critical parameters include:

- the temperature;
- packaging configuration;
- distribution of dosimeters to assess the effective dose received by the product whatever its position;
- the minimum and maximum dose received.

QUALITY CONTROL TESTS APPLIED TO EACHBATCH

A suitable sample size for each batch is established. Specific tests for viral contaminants are validated with respect to sensitivity and specificity. The cell cultures used for general tests for viral contaminants are shown to be sensitive to a suitable range of potential contaminants. Control cells used in the tests are cultivated, where relevant, with a bovine serum controlled and inactivated as described in this monograph.

Serum free from antibodies to bovine viral diarrhoea virus is required for validation of the effect of antibodies on the detection limits for bovine viral diarrhoea virus.

**Tests carried out on the batch prior to treatment**

The following tests are carried out on the serum (before any virus inactivation/removal steps, where applicable).

*Tests for toxicity-cell growth:*

Appropriate cell line(s) should be used for testing each batch of serum for cell growth. The cell line chosen may depend on the intended use of the serum. These tests should be performed using the final batch of serum after any viral inactivation step or other processing.

*Tests for viral contaminants.*

General tests supplemented by specific tests are carried out.

*General tests*. Validated tests are carried out by inoculation of the serum on at least 2 distinct cell lines, one of which is of bovine origin. The cell lines used are suitable for detecting haemadsorbing viruses such as bovine parainfluenza virus 3 and cytopathic agents such as bovine herpesvirus 1.

*Specific tests for viral contaminants (if not detected by general tests), where relevant in view of the country of origin of the serum* :

bluetongue virus, bovine adenovirus, bovine parvovirus, bovine respiratory syncytial virus, bovine viral diarrhoea virus, rabies virus and reovirus, bovine parainfluenza virus type etc.

Depending on the country of origin, specific tests for other viruses may be needed. The animal health status of countries is defined by the 'Office International des Epizooties' (OIE).

For serum to be subjected to a virus inactivation/removal procedure, if evidence of viral contamination is found in any of the tests described above, the serum is acceptable only if the virus is identified and shown to be present in an amount that has been shown in a validation study to be effectively inactivated.

For serum that is not to be subjected to a virus inactivation/removal procedure, if evidence of viral contamination is found in any of the tests described above, the serum is not acceptable.

A test for bovine viral diarrhoea virus antibodies is carried out; an acceptance criterion for the titre is established taking account of the risk assessment.

*Composition*. The content of a suitable selection of the following components is determined and shown to be within the expected range for the type of serum: cholesterol, α-, β- and γ-globulin, albumin, creatinine, bilirubin, glucose, serum aspartate transaminase (SAST, formerly SGOT - serum glutamic-oxaloacetic transaminase), serum alanine transaminase (SALT, formerly SGPT - glutamic-pyruvic transaminase), phosphorus, potassium, calcium, sodium and pH.

**Tests carried out on the batch post-treatment**

If bovine viral diarrhoea virus was detected before virus inactivation/removal, the following test for bovine viral diarrhoea virus is carried out after virus inactivation/removal.

*Test for bovine viral diarrhoea virus*. A validated test for bovine viral diarrhoea virus is carried out, for example by inoculation into susceptible cell cultures, followed by not fewer than 3 subcultures and detection by immunostaining. No evidence of the presence of bovine viral diarrhoea virus is found.

IDENTIFICATION

A. The electrophoretic pattern corresponds to that for serum and is consistent with the type (foetal or other) of bovine serum.
B. Bovine origin is confirmed by a suitable immunochemical method (*2.2.14*).

TESTS

**Osmolality** (*2.4.23*). 280 mosmol/kg to 365 mosmol/kg for foetal bovine serum and 240 mosmol/kg to 340 mosmol/kg for other types.

**Total protein** (*2.3.49*). 30 mg/ml to 45 mg/ml for foetal bovine serum and minimum 35 mg/ml for other types.

**Haemoglobin**. maximum 4 mg/ml, determined by a validated method, such as spectrophotometry.

**Bacterial endotoxins** (*2.2.3*). less than 10 IU/ml for donor bovine serum, less than 25 IU/ml for foetal bovine serum, less than 100 IU/ml for other types.

**Sterility** (*2.2.11*). It complies with the test. Use 10 ml for each medium.

**Mycoplasmas** (2.7.4). It complies with the test.

STORAGE

Frozen at − 10° or below.

LABELLING

The label states:

- the type of serum;
- where applicable, that the serum has been inactivated and the inactivation method;
- where the serum has been inactivated by gamma irradiation, the target minimum dose of the irradiation procedure.