

Review of CVMP & CHMP guidelines applying to the assessment of bovine serum in human and veterinary medicinal products

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In the EU....

...there is **no authorization procedure for bovine serum** for use in human medicinal products or veterinary medicinal products.

The suitability of bovine serum is evaluated during authorisation of the medicinal product.

Europe

- **Ph. Eur. Monograph on bovine sera**
→previous presentation today
- EMEA/CVMP/743/00-Rev.2 (2006) Requirements and controls applied to bovine serum used in the production of immunological veterinary medicinal products – **declared obsolete**
- CPMP/BWP/1793/02
Guideline on the use of bovine serum in the manufacture of human biological medicinal products
- EMA/410/01 rev.3 (2011) Guideline on Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products

USA

9CFR113.53: requirements for ingredients of animal origin used for production of biologics

Includes:

- 113.46; detection of cytopathogenic and/or hemadsorbing agents
- 113.47: Detection of extraneous viruses by fluorescent antibody techniques

USP <1024> Bovine Serum



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 May 2013
EMA/CHMP/BWP/457920/2012 rev 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the use of bovine serum in the manufacture of human biological medicinal products

The original guideline (CPMP/BWP/1793/02) was adopted by CPMP in July 2003 and came into operation in October 2003. This revision affects mainly Sections 7.3.3 and 7.3.4 where the testing requirements for BVDV and anti-BVDV antibodies have been revised to be in accordance with the requirements applied for the production of immunological veterinary medicinal products (EMA/CVMP/743/00-rev 2.)

Virus detection using *in vitro* cell cultures

Ph. Eur: *Validated tests are carried out by inoculation of the serum on at least 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.*

EMA CHMP: *... at least two distinct cell lines, one of which should be of bovine origin, and should be validated and in compliance with appropriate guidelines. The cell lines chosen should be capable of detecting haemadsorbing viruses such as parainfluenza virus 3 and cytopathic agents such as infectious bovine rhinotracheitis virus (IBRV). Control cells should be cultivated with a serum previously shown to be free of virus contamination.*

US 9CFR/USP: *...cultivation of detector cells in cell culture media supplemented with 15% test serum for at least 21 days. Cells are subcultured at least twice during this period, usually 7 and 14 days post inoculation. At the conclusion of the last subculture (after a total of at least 21 days of incubation), cells are examined for general signs of virus amplification. The following end points are used for general virus detection: microscopic cell examination for cytopathogenic agents such as infectious bovine rhinotracheitis virus, cell staining and microscopic examination for inclusion bodies, and hemadsorption test to detect hemadsorbing agents such as PI-3*

Required Tests for specific viruses

Virus	Ph. Eur	EMA CHMP	US 9CFR	USP
BTV	yes	yes*	yes	yes
BAdV	yes	yes	yes	yes
BPV	yes	yes	yes	yes
BRSV	yes	yes	yes	yes
BVDV	yes	yes	yes	yes
RabiesV	yes	yes	yes	yes
ReoV	yes	Yes (Reo 3)	yes	yes

* *BTV and related orbiviruses*

Bluetonguevirus (BTV), Bov. Adenovirus (BAdV) , Bovine parvovirus (BPV) , Bovine respiratory syncytial virus (BRSV), , bovine viral diarrhoea virus (BVDV) , rabies virus (RabiesV) , reovirus (ReoV).

Testing on more Viruses?

Ph. Eur: *Depending on the country of origin, specific tests for other viruses may be needed.*

EMA CHMP: *Tests for specific viruses will depend on: (1) the ability of the general test(s) to detect specific viruses (2) the current epidemiological situation in the country of origin*
Section.

...Serum suppliers and users should also be aware of emerging bovine viruses....

...bovine polyoma virus (BPyV) is a common contaminant of bovine serum (→presentation next day)

USP: *The serum end user is responsible for determining whether full 9 CFR testing is sufficient, and if other specific viral agents should be tested for. Examples of specific viruses not covered by the current virus testing guide may include akabane, bovine herpesvirus 1 (BHV-1), Parainfluenza-3 virus (PI-3), bovine leukemia, bovine rotavirus, bovine circovirus, bovine polyomavirus, coronavirus, torovirus, bovine enterovirus, bovine astrovirus, foot-and-mouth disease virus (FMDV), and rinderpest. Appendix 2 provides a general description of some of these viruses as well as the ones for which testing is required. A serum end user's thorough risk analysis should determine the scope of testing and serum treatment options*

→ The geographic origin of bovine serum must be defined...

EMA CHMP Guideline

7.3.4. Detection of anti-BVDV antibodies

Revised wording:

Anti-BVDV antibodies in bovine serum may mask the detection of BVDV in an infectious virus assay. Therefore, a validated test should be employed to detect such antibodies and an assessment made of their impact on the partial or complete neutralisation of any infectious BVDV virus that may be present in the serum, and of their impact on virus detection, and on the validation of the viral inactivation process. An impact on virus detection may be particularly critical in the case of residual infectivity potentially remaining after inactivation treatment. The assessment should therefore take into account the estimated residual virus in the product (virus burden before inactivation treatment vs. virus clearance by inactivation treatment).

The original CHMP-Guideline required that the inhibition of BVDV growth by antibodies (Serum inhibitory test) was not more than $2 \log_{10}$. However, many batches are found with higher inhibition (antibody levels).

Virus Inactivation:

Ph. Eur: *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.*

EMA CHMP: *Due to the risk of viral contamination associated with the use of bovine serum, it is strongly recommended, in addition to direct testing for viruses, to inactivate the serum by a validated and efficacious treatment. The use of non-inactivated serum should be justified*

USP: *...Serum treatment by **gamma irradiation** is very common and one of the most effective methods of virus inactivation. The most frequently used minimum dose is 25 kilograys (kGy). Some countries specify higher dose requirements (>30 kGy) for imported serum.*

.. Serum manufacturers may use UV treatment to inactivate viruses, mycoplasma, and bacteria, but manufacturers must validate the process to demonstrate its effectivity

... Heat inactivation may also inactivate viruses, mycoplasma, and bacteria. Heat inactivation provides significantly less assurance of virus inactivation than does irradiation.

Current EU-Regulations on TSE risk from Bovine Blood/Serum for medicinal products

EMA

EMA/410/01 rev.3 (2011) Guideline
Minimising the risk of transmitting animal
spongiform encephalopathy agents via
human and veterinary medicinal products



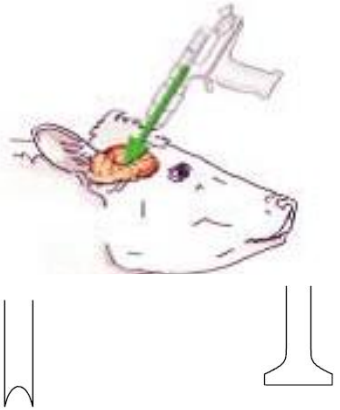
Ph. Eur.

General chapter 5.2.8 "Minimising the risk of
transmitting animal spongiform encephalopathy
agents via medicinal products" and of the new
monograph on "Products with risk of transmitting
agents of animal spongiform encephalopathies
(1483)"

Identical text from EMA-Guideline and Ph. Eur.

Infectivity was **never** detected in blood from BSE- infected cattle

In the EMEA-Guideline/Ph. Eur., the use of Bovine Serum (FBS, Newborn calf Serum) or bovine blood derivatives (e.g. bovine serum albumin, bovine aprotinin etc.) **never has been restricted** to countries with negligible BSE risk (e.g. Australia, New Zealand)



Penetrating captive bolt

Non penetrating captive bolt

Brain tissue fragments or elevated levels of a marker protein for brain tissue were detected in venous blood samples from 4% (95% confidence interval, 1.6 to 9.8%) of cattle stunned by penetrating captive bolt gun and from 2% (95% confidence interval, 0.6 to 7%) of those stunned by nonpenetrating captive bolt gun [Coore](#) et al., J. Food Prot. 2005. 68:882-884.

EFSA 2004

1. *Significantly higher risk level should be allocated to penetrating captive bolt stunning (without pithing) than as given in the SSC Opinion.*
2. *Significantly higher risk level should be allocated to non-penetrating stunning than as given in the SSC Opinion*
3. *CNS material artificially injected in jugular vein could be detected in aortic blood, which would indicate passage of emboli through the lung's capillary bed.*

[Report of the EFSA Working Group on BSE risk from dissemination of brain particles in blood and carcass. Question N° EFSA-Q-2003-122 . October 2004]

No bovine blood Geographical origin with „Cat C – Risk“

Product	Foetal bovine serum	Donor calf serum	Adult bovine donor Serum	Calf serum	Adult bovine serum/plasma	Adult bovine serum/plasma	Adult bovine serum derivative	Adult bovine serum derivative
Geographical origin of cattle	A and B (GBR I - III)	A and B (GBR I - III)	A and B ^a (GBR I - III)	A and B ^a (GBR I - III)	A (GBR I)	B (GBR II - III)	A (GBR I)	B (GBR II - III)
Age of cattle	unborn	<1 year	< 36 mo	<1 year	no limit	< 21 mo ^b	no limit	< 30 mo
Slaughtering/ cross contamination of blood with CNS material	No risk of cross contamination			Risk of cross contamination				
Demonstration of prion reduction during manufacture	NO			NO				

^a: When sourced from Category B countries, cattle should be from well defined and documented herds.

^b: A higher age may be allowed if cross contamination of blood with CNS material can be clearly ruled out (e.g. halal slaughter).

^c: Demonstration of prion reduction may not be required if cross contamination of blood with CNS material can be clearly ruled out (e.g. halal slaughter).

Revision necessary? (→ next presentation)

TSE-Certification has been established at EDQM

<https://www.edqm.eu/en/background-legal-framework>

EDQM certification covers

- Origin of cattle
- Control of age
- Manufacture related to prion reduction
- Nature of animal tissue minimising cross contamination
- Traceability
- Quality system

EDQM **TSE**-Certification does not include evaluation of viral safety

Thank you for the attention!