

Bovine Serum

Proportionate Risk Approach

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Objectives

- As the global association of serum producers/suppliers, we do believe that it's our duty, to give a maximal support, to our member's clients
=> YOU
- The purpose of this presentation is to inspire producers of medicinal products, using serum in production processes, to prepare the serum related risk assessment of the MAA (Market Approval Application)

NOTE: as Europe is known to be one of the higher regulated regions, we use some EU reference documents.



Principles of ICH Q9



23 January 2025
EMA/CHMP/ICH/24235/2006 Corr.2
Committee for Medicinal Products for Human Use

ICH guideline Q9 (R1) on quality risk management

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Proportionate risk - Principles of ICH Q9

- It is commonly understood that risk is defined as the **combination** of the **probability** of occurrence of **harm** and the **severity of that harm**.
- Two primary principles of quality risk management are:
 1. The evaluation of the risk to quality should be **based** on **scientific knowledge** and ultimately link to the **protection** of the **patient**. (Note: **Risk** to quality includes situations where **product availability** may be impacted, leading to potential patient harm.)
 2. The level of **effort**, **formality** and **documentation** of the quality risk management process should be **commensurate^(*)** with the **level of risk**.

(*) “in proportion with”

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PROPORTIONATE RISK

Do enough to reduce the risk—no more, no less.



PROPORTIONATE RISK

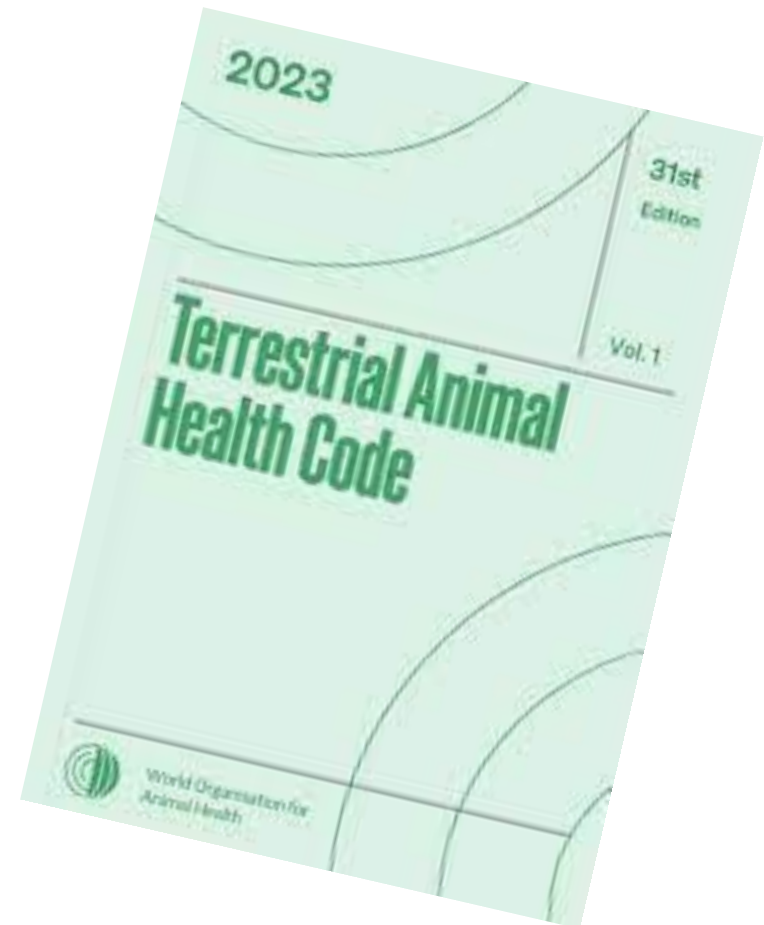
Take action that is proportionate to the risk.
Do enough to reduce the risk—not too little, not too much.

Serum Proportionate Risk Assessment **BSE**



World Organisation
for Animal Health
Founded as OIE

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Serum Proportionate Risk Assessment

Article 11.4.2.

Safe commodities

When authorising the importation or transit of the following *commodities* derived from **bovines**, *Veterinary Authorities* should not require any conditions related to BSE, regardless of the BSE risk posed by the bovine population of the *exporting country, zone or compartment*:

- 1) *milk and milk products*;
- 2) *semen and in vivo* derived bovine embryos collected and handled in accordance with the relevant chapters of the *Terrestrial Code*;
- 3) *hides and skins*;
- 4) *gelatine and collagen*;
- 5) *tallow with maximum level of insoluble impurities of 0.15% in weight and derivatives made from this tallow*;
- 6) *dicalcium phosphate (with no trace of protein or fat)*;
- 7) **fetal blood**.

Other *commodities* of bovines can be traded safely if in accordance with the relevant articles of this chapter.

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Serum Proportionate Risk Assessment

BSE CEP to be adapted for FBS

Certification of Substances Department

Certificate of suitability

1 *Name of the substance:*

2 **FOETAL BOVINE SERUM**

17 After examination of the information provided on the origin of raw material(s) and type of tissue(s)

18 used and on the manufacturing process for this substance on the site(s) of production mentioned

19 above, we certify that the substance **FOETAL BOVINE SERUM** meets the criteria described in the

20 current version of the monograph Products with risk of transmitting agents of animal spongiform

21 encephalopathies no. 1483 of the European Pharmacopoeia, current edition including supplements.

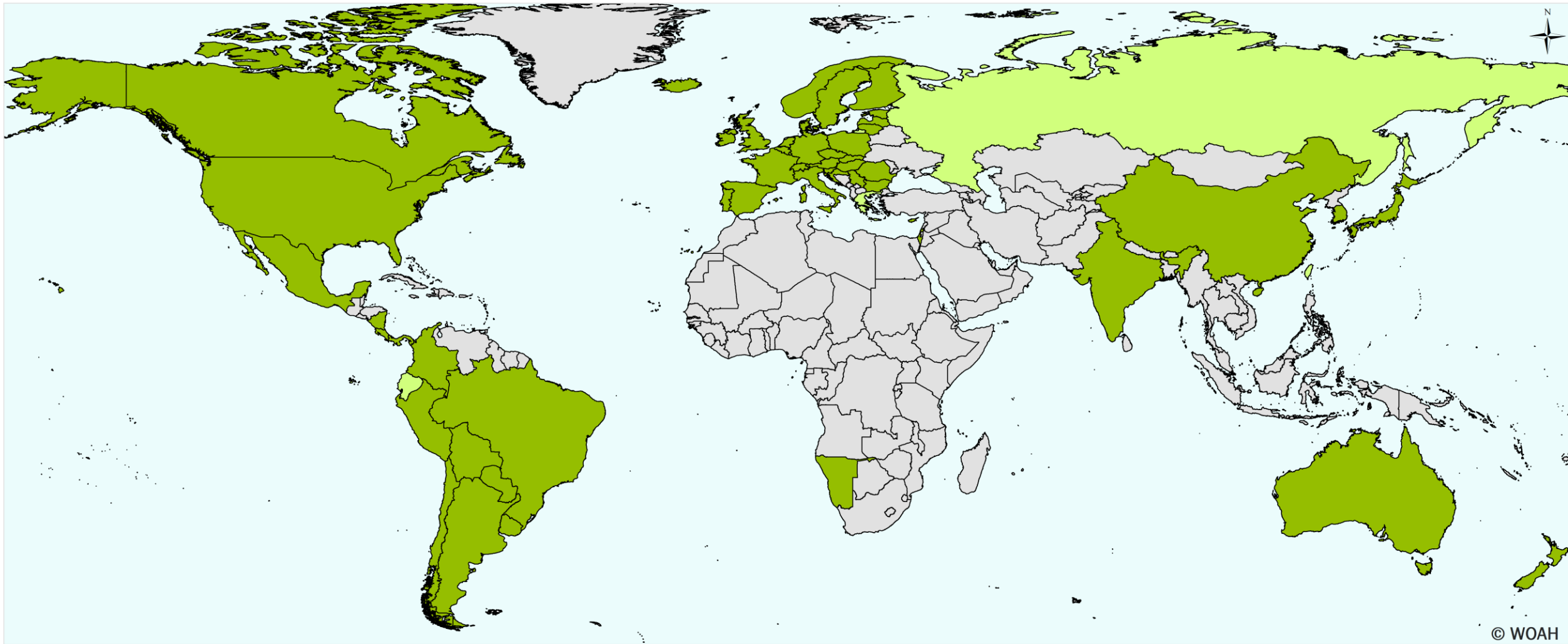


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WOAH Members' official BSE risk status map

Last update June 2025



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-  Members and zones recognised as having a negligible BSE risk status
-  Members and zones recognised as having a controlled BSE risk status
-  Countries and zones without an official BSE risk status

Serum Proportionate Risk Assessment

Starting point **Viruses of interest**

5.2.5. Management of extraneous agents in IVMPs

EUROPEAN PHARMACOPOEIA 11.0



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BOVINE	
Viral agents	Bacterial agents
Akabane virus	<i>Brucella</i> spp.
Alcelaphine herpesvirus	<i>Chlamydia</i> spp.
Bluetongue virus	<i>Coxiella burnetii</i>
Borna disease virus	<i>Leptospira</i> spp.
Bovine adenovirus	
Bovine coronavirus	
Bovine enterovirus	
Bovine ephemeral fever virus	
Bovine herpesvirus BHV-1 (IBR)	
Bovine leukaemia virus	
Bovine papillomavirus	
Bovine papular stomatitis virus	
Bovine parainfluenza virus 3	
Bovine parvovirus	
Bovine polyomavirus	
Bovine respiratory syncytial virus	
Bovine rhinovirus	
Bovine viral diarrhoea virus	
Cache Valley virus	
Cowpox virus	
Endogenous retrovirus (replication competent)	
Epizootic haemorrhagic disease virus	
Foot-and-mouth disease virus	
Jena virus (Norwalk-like)	
Lumpy skin disease virus	
Ovine herpesvirus 2 (malignant catarrhal fever virus, European type)	
Pseudocowpox virus	

BOVINE	
Viral agents	Bacterial agents
Rabies virus	
Reovirus	
Rift Valley fever virus	
Rinderpest virus	
Rotavirus	
Schmallenberg virus	
Swine herpesvirus 1	
Tick-borne encephalitis virus	
Vesicular stomatitis virus	
Wesselsbron virus	



Serum Proportionate Risk Assessment

Step-by-step reduction of the list for FBS

- 1) Veterinary inspection at the farms and in the slaughterhouses => fit for human and animal consumption.
- 2) The impact of the placenta barrier.
- 3) Traceability => does the virus appear at the source?
- 4) Compliance by testing => Is the test relevant?
- 5) The power of gamma irradiation
- 6) Strategic testing on the remaining viruses

Serum Proportionate Risk Assessment (1)

Veterinary inspections – farm & slaughterhouse

- Fit for human and animal consumption => blood collection is allowed.



- Fetuses are inspected rigorously for health status, prior to blood collection. In case of a minor doubt, the animal is discarded.
- Reduction number of viruses on the list (1)

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Serum Proportionate Risk Assessment (2)

The placenta barrier

EUROPEAN PHARMACOPOEIA 11.0 **5.2.5. Management of extraneous agents in IVMPs**

PROPORTIONAL RISK => PERCEIVED RISK VERSUS OBJECTIVE RISK

BOVINE

Viral agents		is bovine foetus susceptible ?	FBS risk	Family	Resistance to gamma-irradiation
1	Akabane virus	Yes, the bovine fetus is highly susceptible, especially in early gestation - Congenital defects (arthrogryposis, hydranencephaly) - Abortion or stillbirths.		Bunyaviridae	Low
2	Alcelaphine herpesvirus	No clear evidence of fetal susceptibility in cattle.		Herpesviridae	Low
3	Bluetongue virus	Limited in cattle, but possible. Transplacental infection: Can occur , especially with some BTV strains (e.g., BTV-8) or modified live vaccines. Effects (rare): Abortion. Fetal malformations (hydranencephaly, porencephaly).		Reoviridae	Moderate

- Reduction number of viruses on the list (2)

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Serum Proportionate Risk Assessment (3)

Traceability

- Traceability to slaughterhouse [EP2262](#) = region where blood was collected.



- WOA [sanitary status](#) in that region => WAHIS: World Animal Health Information System.
- Reduction number of viruses on the list (3)



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for Animal Health

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Serum Proportionate Risk Assessment (4)

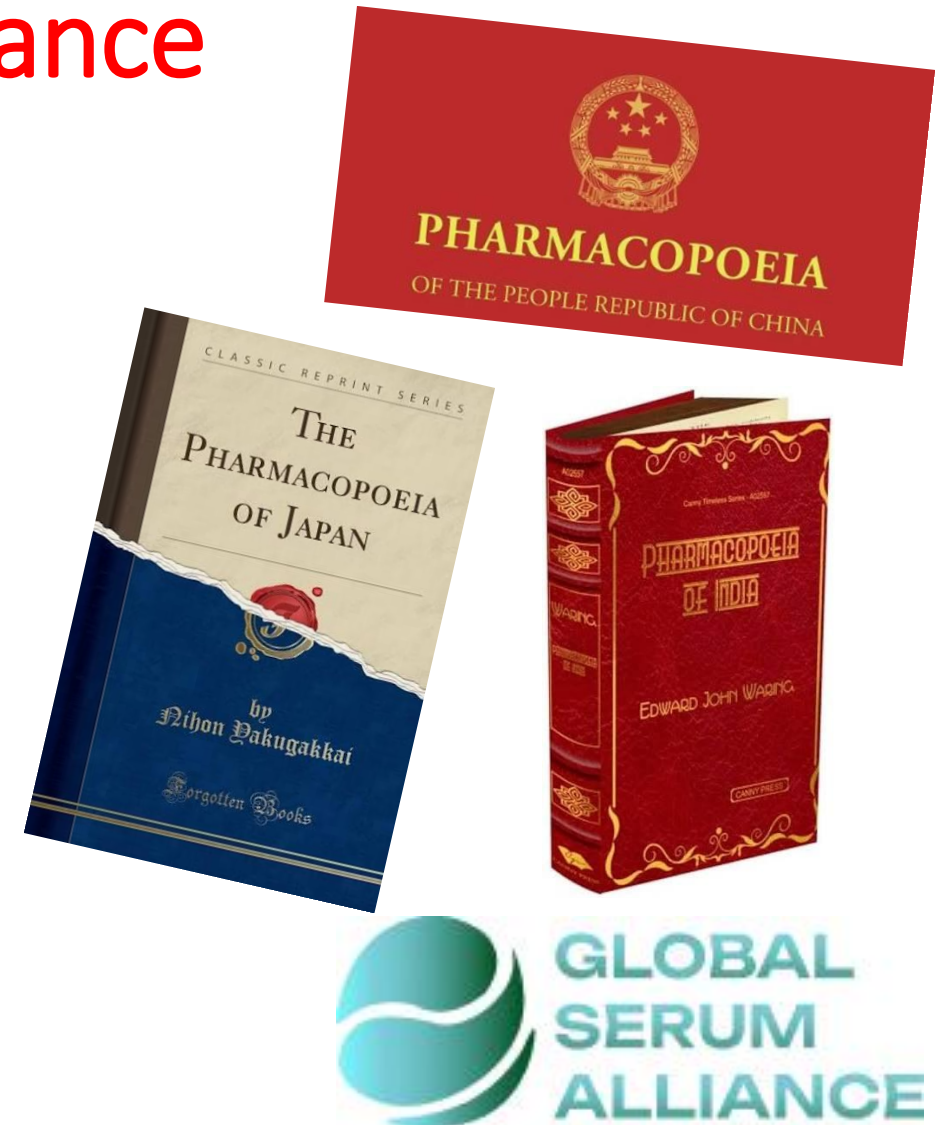
Testing for Regulatory Compliance

EUROPEAN PHARMACOPOEIA
Bovine serum

07/2025:2262



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Serum Proportionate Risk Assessment (4)

- Testing results are favourable => are we safe?
- For example, it's common knowledge that live BVDV is present in all untreated batches of bovine serum except if:
 - Blood was collected in countries where BVDV is eradicated/under control
 - Individual blood bags are screened prior to pooling => very labour intensive = very expensive.

Reduction number of viruses on the list (4) ?



Serum Proportionate Risk Assessment (5)



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Serum Proportionate Risk Assessment (5)

TABLE 2. Efficacy of gamma irradiation from dose/inactivation response studies with seven viruses spiked into FBS.*

Virus	Family	Genome	Envelope	Particle Size (nm)	Log ₁₀ Reduction in Titer per kGy	Log ₁₀ Reduction per 30 kGy
CAV	<i>Adenoviridae</i>	ds-DNA	No	70–100	0.203	6.1
BVDV	<i>Flaviviridae</i>	ss-RNA	Yes	40–60	0.198	5.9
IBRV	<i>Herpetoviridae</i>	ds-DNA	Yes	120–200	0.310	9.3
PIV-3	<i>Paramyxoviridae</i>	ss-RNA	Yes	150–300	0.209	6.3
MMV	<i>Parvoviridae</i>	ss-DNA	No	18–25	0.071	2.1
PPV	<i>Parvoviridae</i>	ss-DNA	No	18–25	0.055	1.7
REO-3	<i>Reoviridae</i>	ds-RNA, segmented	No	60–80	0.194	5.8

*Table modified from reference^[9]

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Serum Risk Assessment (5)

- We propose to mimic Virbac - IFAH reference document on “Viral inactivation related to steam sterilisation of biological products.”



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Serum Proportionate Risk Assessment

Step-by-step reduction of the list for FBS

What about our list after 5 steps and before going towards the ultimate step ?

6) Strategic testing on the remaining viruses.

Serum Proportionate Risk Assessment

Which ones to “strategically” test for?

11	Bovine papillomavirus	Fetal susceptibility: Very low to none		Papillomaviridae
12	Bovine papular stomatitis virus	Transmission to foetus: Unlikely		Poxviridae
13	Bovine parainfluenza virus 3	Fetal susceptibility: Low		Paramyxoviridae
14	Bovine parvovirus	Fetal susceptibility: Moderate to high - Can cause abortion, mummification, stillbirth, or weak calves, especially during early gestation. One of the few parvoviruses with documented in utero fetal effects in cattle.	?	Parvoviridae
15	Bovine polyomavirus	Transmission to foetus: Unclear/possible - Fetal susceptibility: Not well studied - Detected in aborted fetuses in some studies, but causal role not clearly established.	?	Polyomaviridae

Serum Proportionate Risk Assessment (5)

Strategic testing remaining viruses

- Strategic testing should be based on proportionate added value of the method:
 - Live BVDV is present in all untreated batches (except some very specific areas) of bovine serum =>
 - Classical growth test will result in many false negatives.
 - PCR (-) for BVDV is to be avoided as a selection criterion.
 - On the other hand, PCR is a good method to show evidence of absence of LSD, BT, Akabane ... in FBS.

Serum Proportionate Risk Assessment (5)

- New testing methods to distinguish live from death virus, such as NGS based technology.



Serum Proportionate Risk Assessment

Conclusions

- FBS can be equally safe, regardless of where it comes from, providing that we do the right things:
 - 30 kGy gamma-irradiation
 - Strategic testing, where needed, for your specific application/need.
- Trusting classical testing only, as a safety parameter, is to be avoided.
- The compilation of a robust virus inactivation by gamma-irradiation reference document, will add a lot of value for serum using producers of medicinal products, when preparing the serum related risk assessment in the Market Approval Application.
- We may even be able, to make standard risk assessment files for most, if not all types of animal serum.



Please feel free to contact us for:

- Further information.
- Membership (serum producers & suppliers)
- Associate membership (companies in other serum related sectors and serum using organisations)



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