



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Biological raw materials and viral/TSE safety



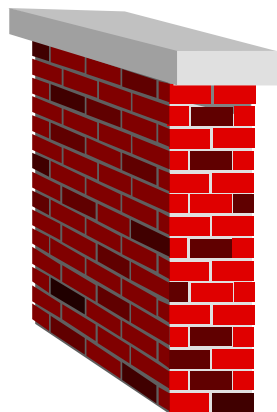
Presented by Johannes Bluemel on 16 April 2015
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An agency of the European Union

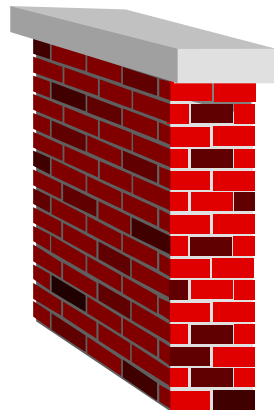




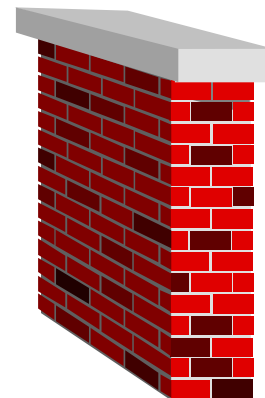
Three principles protecting from transmission of pathogens



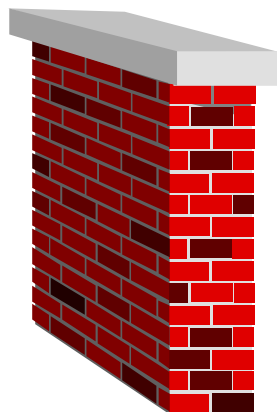
**Selection of starting materials/
raw materials**



testing

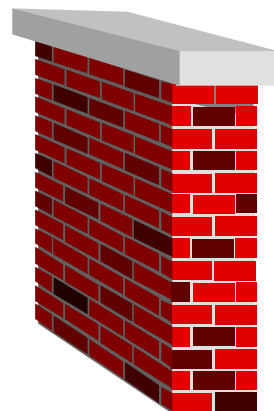


inactivation, removal

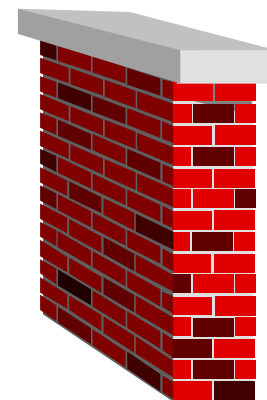


**Selection of starting/materials
raw materials**

**Availability of
Tissue/organ donors/
reagents**



testing



inactivation, removal

**Limitations
for ATMPs!**



Raw materials and contamination of cell cultures

Bovine Viral Diarrhoe Virus (BVDV)
Cache Valley Virus
Enterovirus/Reovirus
Vesivirus
Porcine Circovirus
Human Adenovirus
Minute virus of mice (MVM)
Minute virus of mice (MVM)

Bovine serum
Bovine serum
Bovine serum
Bovine serum?
Porcine trypsin
human?
raw material?
raw material?



Monograph on Bovine Serum (1)

(8th ed. Ph.Eur. 01/2008/2262)

Frequent source of virus contamination
(Bovine viral diarrhoea virus,
cache valley virus, reovirus,
bovine enterovirus,
polyoma virus, etc.)

An absolutely virus-safe serum (with biological activity)
does not exist.





Monograph on Bovine Serum (2)

- Specifies a minimum set of virus tests to be performed (before inactivation) congruent to US-regulation 9 CFR113.47 (this list is not exhaustive....).
- The manufacturer of the medicinal product makes the risk assessment. He decides and is responsible whether additional safety measures are necessary.
- requires use of gamma irradiated sera (30kGy) for immunological veterinary medicinal products.
- **requires justification for human medicinal products when no virus-inactivated serum is used.**
- Adequate validation of virus inactivation required.
- If BVDV was found before inactivation, a negative test after inactivation is required.

Regulations on Bovine Serum

Europe

USA

Bovine sera

CPMP/BWP/1793/02

(for human use)

CVMP/BWP/3354/99

(for vet. Use)

Ph. Eur. Monograph on
bovine sera

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

Bovine serum

versus

Human Serum or platelet lysate

- Xenogenic Proteins
 - Quality of virus testing?
 - Zoonotic viruses
 - TSE (BSE) Certification
 - Some virus inactivation (30kGy)
 - Compliance/control of suppliers
- Human proteins
 - established virus tests
 - Risk from non-tested human viruses
 - (v)CJD risk?
 - No inactivation
 - Compliance/control of suppliers

What is better / more safe?



**Do not use human serum (or other human materials)
from large pools without virus inactivation.**



„Animal-free“ cell culture medium does not mean „human free“

Human blood-derived media supplements

- 1.Human transferrin (virus inactivated)
- 2.Human albumin (virus inactivated)

Porcine Trypsin

EMA Guideline: EMA/CHMP/BWP/814397/2011

Sourcing: Documentation of origin

Virus testing: Risk analysis for virus testing: 55 porcine viruses? PCV, PPV, HEV?

Virus inactivation 2 steps recommended

Low pH (pH1.7, at room temperature or pH 1.0 at 4°C)

Gamma or UV-irradiation

Nanofiltration?

Virus inactivation can justify absence of testing



Alternative reagents for porcine Trypsin



- Bovine trypsin
- Invertebrae (Accutase from shrimp)
- Plant-derived recombinant
- **Recombinant bacterial**





Animal-derived reagents in cell culture

Bovine Serum

Porcine Trypsin

Bovine serum derivatives (lipids, albumin, cholesterol etc)

Antibodies (sheep, goat, monoclonals)

Cell culture derived reagents
(growth factors, etc)



Virus Control Strategy for raw materials

Multi-step approach including complementary steps applicable

Focus on:

- Qualification of the material and its supplier
- Sourcing, testing and manufacture of raw materials
- Testing prior and at production of biotech product
- Validation of virus inactivation and removal (at manufacture of raw material or at purification of active ingredient)



Example: Sheep antibody used at generation of MCB for Biotech product

1. Make a risk assessemnt

Origin of sheep antibody (documentation, veterinarian certificate)

TSE documentation (EDQM TSE certificate? other info?)

Testing of sheep antibody for viruses?

Manufacture/virus inactivation (low pH, virus filtration)

2. Are additional tests on sheep viruses necessary for MCB?



Main virus safety Issues at *ex-vivo* cell culture

(from authorization of clinical trials)

- **FBS:** Virus Inactivation, bovine virus testing
- **Human AB Serum:** Pool size, virus inactivation?
- **Porcine trypsin:** virus inactivation, virus testing
- “animal free“ cell culture medium contains:
 - information for **human transferrin?**
 - information for **human serum albumin?**
- **Human serum albumin** excipient
- Information for **cell-sorting antibodies**



Thank you for your attention

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