

THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)



EDQM's 3R Achievements for Veterinary Vaccines

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AFSA, HFA, IABS Workshop on 3Rs implementation in veterinary vaccine batch release testing
16 November 2022, Brussels

Presentation Overview

- Council of Europe (COE)
- EDQM of the COE
- COE, EDQM and the Commitment to 3Rs
- European Pharmacopoeia
 - 3Rs in the European Pharmacopoeia
 - Examples; TABST, Extraneous agents testing, Tetanus toxicity
- Biological Standardisation Programme
 - Mission, Scope, Major Steps
 - Examples; past, ongoing and future
 - Dissemination
- Official Medicines Control Laboratories
- EDQM 3R Webpage
- Challenges and Opportunities
- Summary

Council of Europe (COE)



- **Founded in 1949**
- **Headquarters in Strasbourg, France**
- **46 member states (27 EU) and 6 observer states**
- **>700 million citizens**
- **The oldest pan-European organisation dedicated to fostering co-operation in Europe**

- **Promotes democracy**
- **Protects human rights**
- **Protects the rule of law**

EDQM: COE Directorate



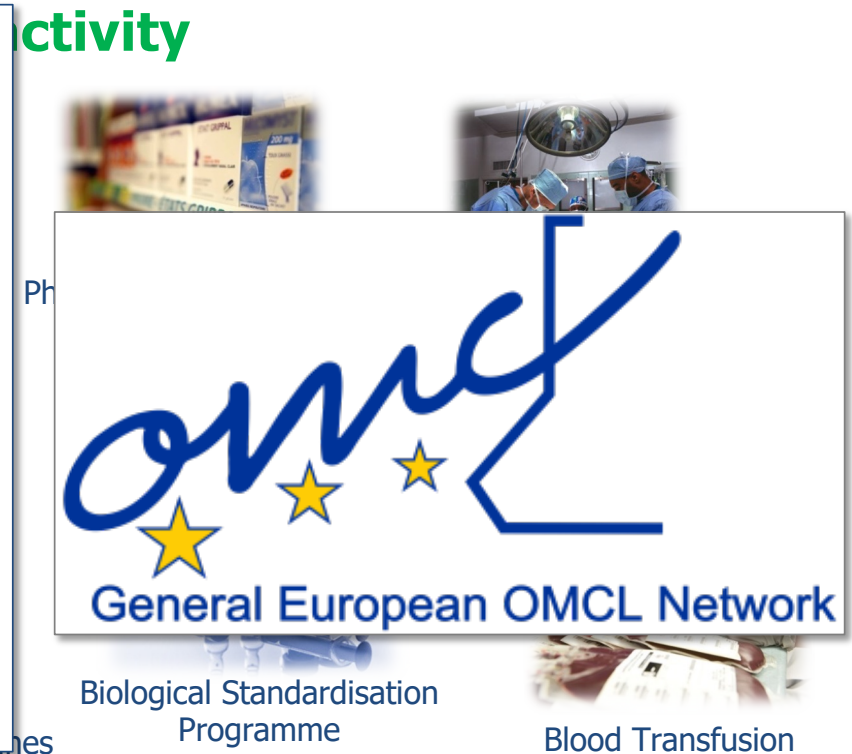
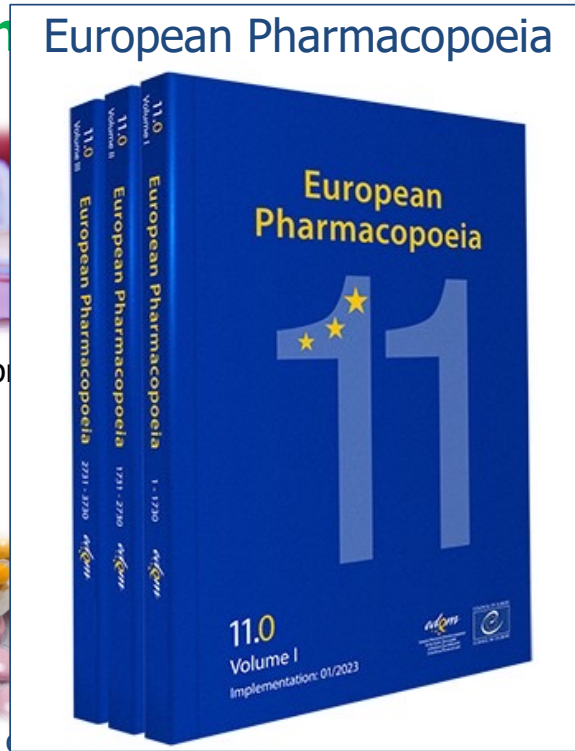
EDQM of the COE

Shared work and shared benefits for members and observers in European Pharmacopoeia activity



Food packaging

Classification
as regards their supply



COE, EDQM and the Commitment to 3Rs

1949	Foundation of the Council of Europe	<i>46 member countries & 6 observer states</i>
1964	The Ph. Eur. Convention , an international treaty → <u>Ph. Eur. texts are mandatory in all member states</u> - harmonisation of technical requirements for the authorisation and manufacture of medicinal products for human and veterinary use	<i>39 members states, the EU & 28 observers - including WHO</i>
1986	<u>European Convention (ETS 123) for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes</u>	
1991	Biological Standardisation Programme (BSP) <i>* agreement between the Council of Europe (Strasbourg) & the EU Commission (Brussels)</i>	
1994	EU signs the Ph. Eur. Convention Creation of the OMCL Network <i>* as above (71 OMCLs in 43 countries)</i>	
2010	Directive 2010/63/EU entry into force on 10 November 2010 <i>Transposition completed by 10 November 2012 and full effect on 1st January 2013</i>	

3Rs in the European Pharmacopoeia ⁽¹⁾



- The **General Notices** foster and enable the application of 3Rs
 - Encourage reduction of animal usage, allow use of **alternative methods** and **consistency approach**
- Requirements in **General monograph *Vaccines for veterinary use*** on reducing animal numbers and suffering and promotion of replacing routine *in vivo* tests for well characterised products when consistency is demonstrated
- **Individual vaccine monographs** encourage the use of alternative 3Rs methods, humane endpoints and general 3R principles
 - Example of a validated 3R method provided, where available (e.g. Swine Erysipelas Vaccine (inactivated) (0064)). 3R/*in vitro* approach promoted as the preferred option (canine and bovine leptospirosis vaccine (inactivated) (0447,1939) or use of 'door openers' to facilitate regulatory acceptance of validated *in vitro* options (e.g. rabies vaccines for veterinary use (0451))
- Ongoing review of Ph. Eur. texts in line with scientific understanding to employ 3Rs or the **4th R 'REMOVAL'**
 - e.g. **humane endpoints** included, **fewer control animals** included in the tests, introduction of **risk assessment strategy** and **new analytical methods** such as PCR/NGS for example for extraneous agents testing and **rationalise** the requirements



3Rs in the European Pharmacopoeia ⁽²⁾

- Guidance in **chapter 5.2.14** on concept of “substitution” of animal tests for QC of vaccines

When a direct head-to-head comparison with an existing *in vivo* method is not possible



Potential roadblock for new methods

- Due to the variability inherent in the *in vivo* methods
- Different scientific concept/readout of the alternate method



Chapter 5.2.14
Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccines

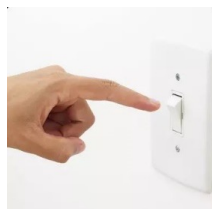
- encourages transition from *in vivo* to *in vitro* methods
- provides guidance on validation of substitute methods



3Rs was the initial impetus but scientific benefits and improved test-performance potential are key drivers to this approach

Deletion of the Target Animal Batch Safety Test (TABST)

From 2004 Ph. Eur.:
waiving TABST in established
vaccines with justification



**VICH GL 41
and 44**

Animals saved:
horses, cattle/calves,
pigs/piglets,
sheep/lamb, dogs,
ferrets, cats (often
8-12 weeks old),
rabbits, guinea-pigs
(tetanus vaccine),
chickens and turkeys
(often 14 to 28 days
old), domestic
ducks, fish
(salmonids).

Experts of the Ph. Eur.



- Discuss the scientific justification
- Retrospective analysis carried out

2018 *Terrestrial Manual*
chapters on vaccine production
and manufacturing sites



**VICH GL 50R
and 55**



**Deletion of
TABST from
the Ph. Eur.**

**Ph. Eur.
2013**

Testing for extraneous agents

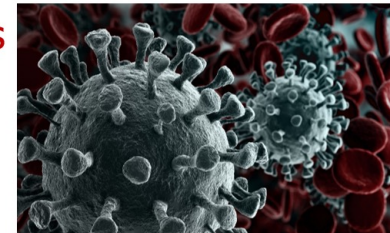
- ❑ Revision of testing strategy for extraneous agents: **risk-based approach**
- ❑ Moving quality requirements upstream (healthy flocks)
- ❑ Revision of chapters to delete animal tests as far as possible
- ❑ Reference to molecular methods

For more details, please refer to EDQM online training resources

<https://www.edqm.eu/en/-/conference-collaboration-innovation-and-scientific-excellence-the-european-pharmacopoeia-11th-edition>

Session 5: Supporting microbiological and viral safety

► EDQM/Ph. Eur. achievements in the control of extraneous agents for vaccines & perspectives on HTS



Featured Session on Microbiological and Viral Safety
20 September 2022

Catherine Lang and Gwenael Cirefice, EDQM

Tetanus Toxicity

Revised toxicity test requirements for Tetanus Vaccines (Vet and Human)

0697 and 0452 – applicable 01/01/21

- **Removal** of test for specific toxicity (process validation, GP test)
- **Removal** of test for irreversibility of toxoid (GP test)

0697

- **Align** remaining test conditions with 0452
- Test in GP for residual toxicity during process validation considered redundant with more sensitive test performed routinely on the bulk purified toxoid
- Test for irreversibility of the toxoid no longer relevant based on data on the toxoid stability and because the toxin was shown to lose neurotoxic activity under the conditions of the storage test at 37 °C

Tetanus Vaccine for vet. use [0697] Tetanus vaccine (adsorbed) [0452]

Absence of tetanus toxin

Non-adsorbed, bulk purified **toxoid** injected into guinea pigs (250-350 g):

1 ml, **concentrated** (≥ 500 Lf/ml) **[5 animals]**

⇒ **Toxoid passes if no animal shows tetanus symptoms within 21 days.**

in vivo assay still present but use is reduced

Biological Standardisation Programme (BSP)

Mission

- Establish and maintain European Pharmacopoeia Reference Standards and working standards for biologicals
- Standardisation of test methods for the quality control of biologicals in the Ph. Eur.
- Promote, through collaborative studies, alternative methods for the quality control of biologicals in order to apply the 3Rs concept (refine, reduce, replace)
- Contribute to the activities of international harmonisation e.g. with WHO, WOH, and the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) in the field of biologicals.

BSP Scope



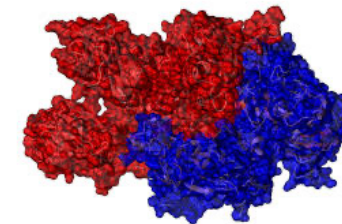
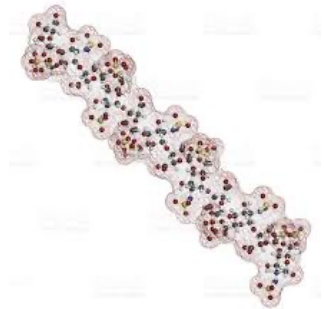
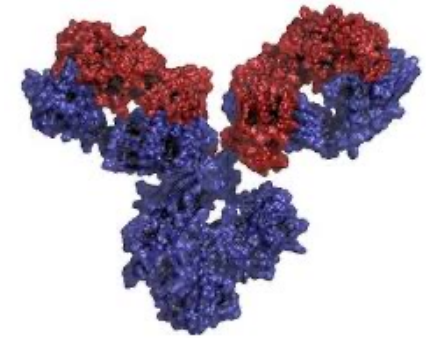
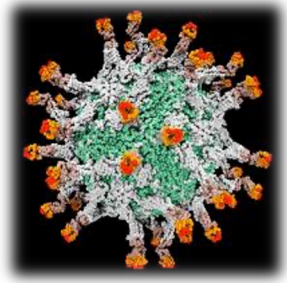
➤ **Biotech products** (Group 6, (MAB, P4BIO))
(hormones, cytokines, anticoagulants (heparins), mAbs...)

➤ **Blood derived medicinal products, contaminants** (Group 6B)
(immunoglobulins, coagulation factors...)

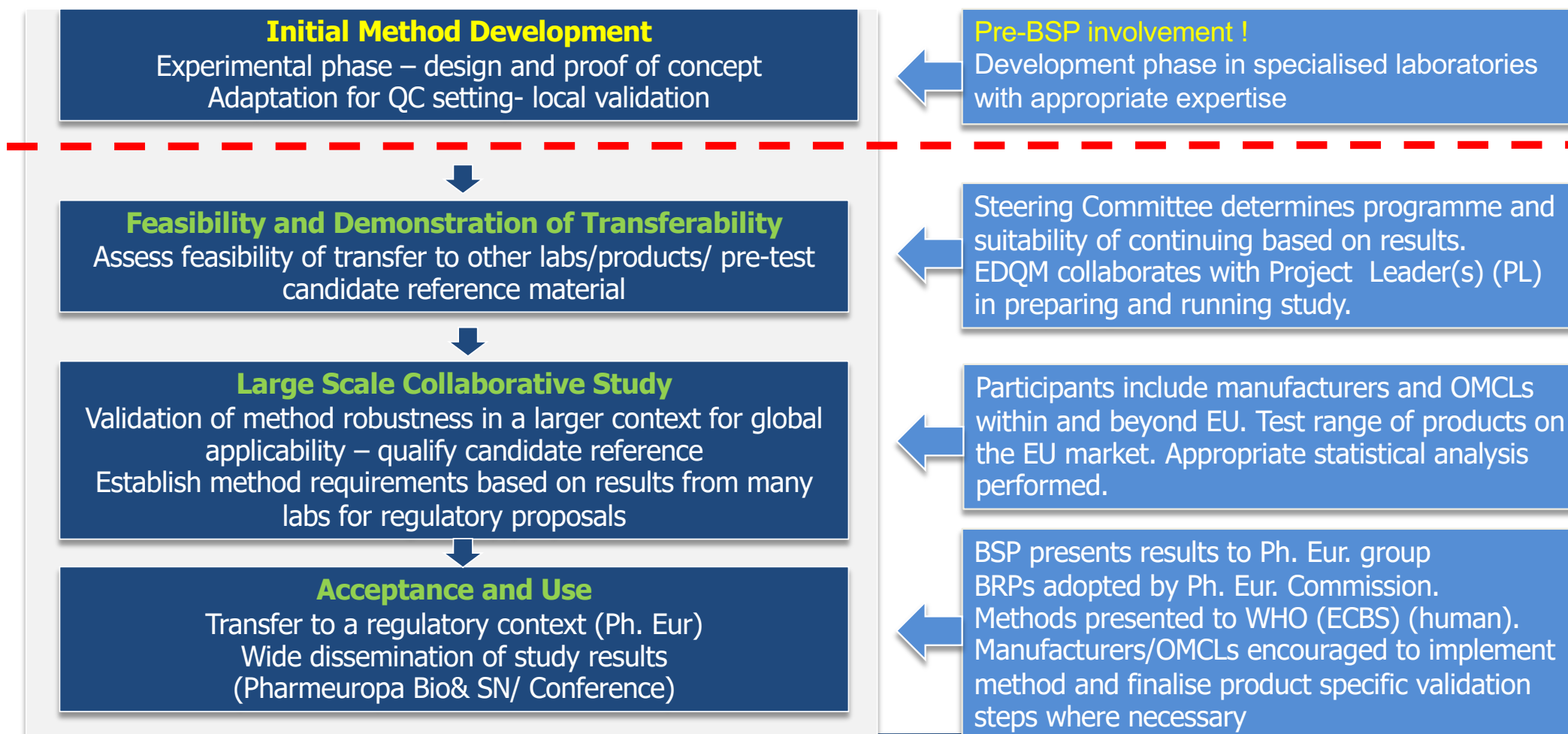
➤ **Vaccines, sera for human use** (Group 15)

➤ **Vaccines, sera for veterinary use** (Group 15V)

➤ **Miscellaneous** (specific working groups)
(allergens, endotoxins, mycoplasma...)



Overview of Major Steps in a BSP Study

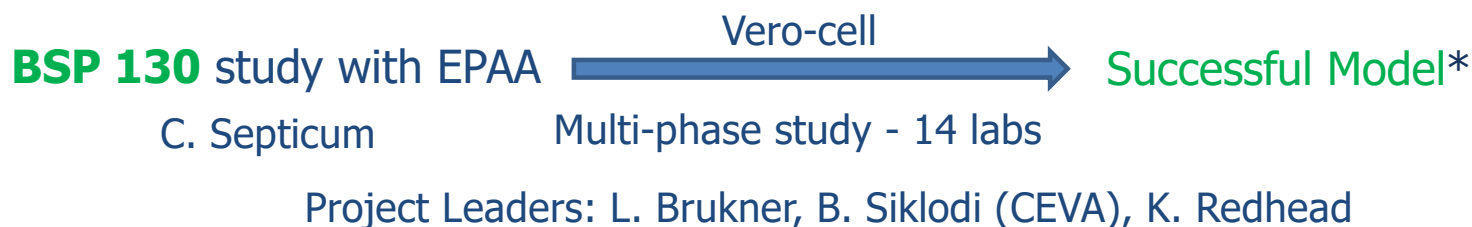


Recent Example: Cytotoxic Clostridium vaccines

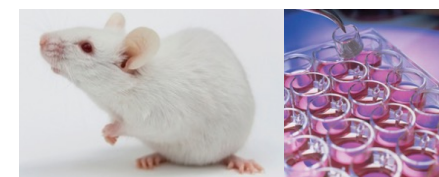
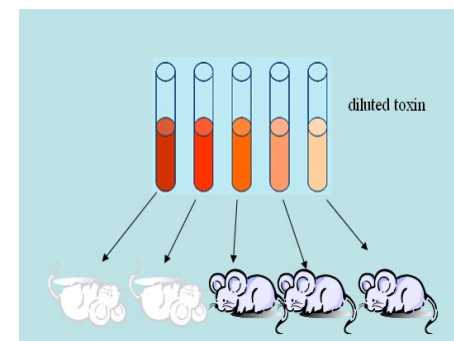
MLD and TCP tests (replacement of mice by specific cell lines as an indicator of toxicity) developed by K. Redhead (formerly MSD Animal Health) and colleagues

Advantages of alternative method

- No mice used (*in process tests*)
- According to a VMD report; in 2010 Clostridial vaccines represented only **1% of all UK authorised IVMPs** but testing these vaccines represented **42% of all animals used!**
- Can be completed in less time (~ 3 days versus > 4 weeks)



Revision introduced in monographs 0362, 0363, 0364 once the BSP study was completed



Revisions adopted at Ph. Eur. Commission June 2021, **applicable as of 01/07/22**

Selection of completed BSP method examples for IVMPs

BSP038: Swine-erysipelas vaccine, serological assay (Refinement / Reduction)

- Developed at Paul Ehrlich Institute (PEI), DE. PLs: K. Cussler, U. Roskopf (PEI)

BSP055: Newcastle disease vaccine, *in vitro* assay (Replacement)

- Developed at CIDC-Lelystad, NL. PL: I. Claassen (CIDC-Lelystad)

BSP105: Rabies vaccine (vet.), serological assay (Refinement / Reduction)

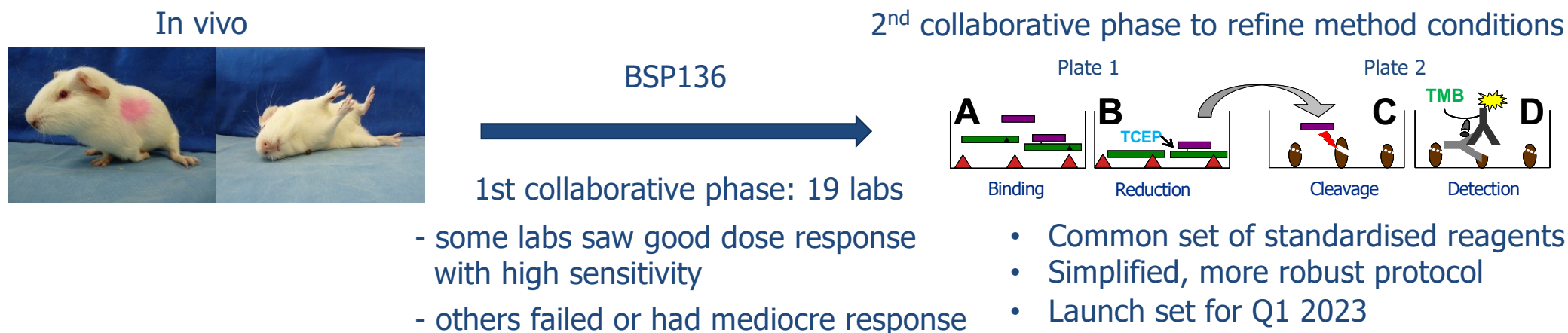
- Developed at PEI, DE. PL: B. Kraemer (PEI)

All were referenced in the relevant Ph. Eur. monographs by the Ph. Eur. group of experts following the successful study outcome

Ongoing and future projects ⁽¹⁾

BSP136: BINACLE assay Project Leaders: H. Behrendorf-Nicol, B. Kraemer, PEI

'BINding And CLEavage' assay – 2 step – fully *in vitro* assay based on toxin function



Goal to provide an option for complete replacement of GP test for eligible products (as determined by product-specific suitability experiments)

Ongoing and future projects ⁽²⁾

- **BRP168 - Clostridia (multi-component) rabbit antiserum BRP**

PLs: G. Leite (CEVA), E. Balks (PEI)

- Study to replace BRP1– BRP calibrated for use as a reference *serum in the potency and batch potency tests (Clostridium vaccines: novyi (0362), perfringens (0363), septicum (0364))* and immunogenicity/potency test in tetanus vaccine vet use (0697), horses excepted)

- **BSP TBD** – upon completion and publication of VAC2VAC study outcome, the potential for full *in vitro* consistency testing for potency of tetanus toxoid vaccines using mAbs identified during the project and available from NIBSC will be determined

New project proposals in scope are welcome

BSP works thanks to the combined efforts of EDQM and partners from industry, OMCLs/academia and organisations such as EPAA and EURL-ECVAM.

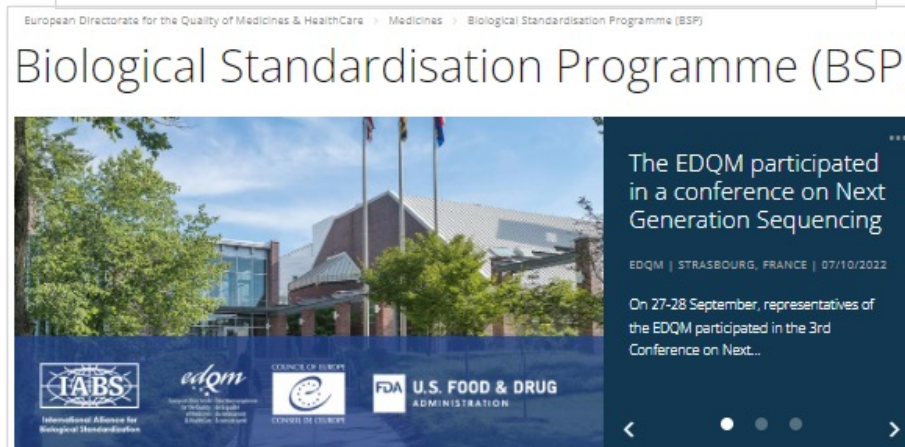
Dissemination

Free publication



<https://pbiosn.edqm.eu>

<https://www.edqm.eu/en/biological-standardisation-programme>



Website

Events



Official Medicines Control Laboratories (OMCLs)

- Independent national laboratories involved in testing IVMPs
 - Official Control Authority Batch Release (OCABR) and Official Batch Protocol Review (OBPR) (EU/EEA/CH)
 - Post-market surveillance testing
- Work together as part of a network **Veterinary Batch Release Network (VBRN)** which is a part of the General European OMCL Network (GEON)
- OMCLs have an overview of products from different manufacturers and contribute to:
 - Development and validation of 3R methods
 - Practical experience with methods to support assessors in evaluating new proposals for 3R alternatives coming directly via the marketing authorisation application

EDQM 3R Webpage



Alternatives to Animal Testing



- » The Council of Europe on the protection of animal rights
- » Categories of medicines concerned by animal testing for Quality Control purposes
- » The contributors to the introduction of the 3Rs in the European Pharmacopoeia
- » Achievements of the Ph. Eur. Commission for 3Rs
- » Achievements of the Biological Standardisation Programme for 3Rs

The Council of Europe on the protection of animal rights

The protection of animal rights and in particular those used for experimentation has long been a subject of interest for the Council of Europe. The first milestone was achieved in 1986, when the *European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes* (ETS No. 123) was open for signature. This Convention is designed to reduce both the number of experiments and the number of animals used for such purposes and it encourages not to experiment on animals except where there is no alternative and it promotes research into alternative methods.

NEWS

EDQM 29/06/2021 STRASBOURG, FRANCE
Clostridium septicum vaccine antigen assays: new article available online in *Pharmeuropa Bio & Scientific Notes*

EDQM 28/06/2021 STRASBOURG, FRANCE
European Pharmacopoeia to put an end to the rabbit pyrogen test

EDQM 24/03/2021 STRASBOURG, FRANCE
Phasing out animal testing for in-process control of veterinary vaccines: Clostridium septicum as a proof of concept

EDQM 14/01/2019 STRASBOURG, FRANCE
Ph. Eur. to replace Histamine Sensitisation Test (HIST) for residual pertussis toxin testing

EDQM 11/12/2018 STRASBOURG, FRANCE
Major 3Rs achievement for Official Control Authority Batch Release of human vaccines

EDQM's Alternatives to Animal Testing Updates at a Glance

<https://www.edqm.eu/en/alternatives-to-animal-testing>

Challenges and opportunities ⁽¹⁾

Challenges

- Product specificity and different/multiple strains
- Adjuvanted final products
- Traditional products less well characterised
- Resources for developmental work
- Working together (synergistically) across manufacturers
- Access to relevant reagents/reference material
- Global market and non-uniform regulatory environments

Challenges and opportunities ⁽²⁾

Opportunities

- Newer vaccines are better characterised and QC strategies can be developed from the start with the 3Rs already in mind
- Robust GMP and consistency of production is now the norm
- New vaccine platforms e.g. mRNA vaccines, provide potential to remove animal use for batch release
- Techniques available continue to evolve e.g. Next Generation Sequencing (NGS)
- New mind-set (regulators and manufacturers) regarding method substitution approach is gaining ground
- Science is a key driver – fewer animals but also better tests

Conclusions on 3Rs in the Ph. Eur.

- After 3 decades of the Convention significant achievements in animal welfare have been made
- The animal tests that remain in the Ph. Eur. are the most difficult to eliminate (e.g. potency assays for inactivated vaccines)
- Achievements have been possible thanks to collaboration between Ph. Eur./EDQM and its stakeholders from OMCLs, regulators, industry and other partners
- Efforts to implement 3Rs need to be sustained
 - Continue to review remaining animal tests in monographs to assess their current relevance and identify opportunities for application of 4Rs
 - Continue to welcome relevant project proposals for 3R methods in the BSP
- Engagement and exchange of information with partners outside Europe remains important to foster acceptance of 3Rs advances at a global level

We count on all our partners to help make progress happen!

Thank you for your attention

And thanks to all the EDQM colleagues involved in the work of the European Pharmacopoeia, Biological Standardisation and Official Batch Release



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