THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)
EDQM’s 3R Achievements for Veterinary Vaccines

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Presentation Overview

• Council of Europe (COE)
• EDQM of the COE
• COE, EDQM and the Commitment to 3Rs
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  • Examples; TABST, Extraneous agents testing, Tetanus toxicity
• Biological Standardisation Programme
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• 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 of the COE

Shared work and shared benefits for members and observers in numerous fields of activity

- Cosmetic products
- Classification of medicines as regards their supply
- Pharmaceutical Practices & Care
- Fight against falsified medicines
- Food packaging
- Organ Transplantation, Use of Tissues and Cells
- Blood Transfusion
- Quality Control of Medicines
- Biological Standardisation Programme

European Pharmacopoeia

General European OMCL Network
COE, EDQM and the Commitment to 3Rs

1949 | Foundation of the **Council of Europe**

1964 | The **Ph. Eur. Convention**, an international treaty

→ Ph. Eur. texts are mandatory in all member states - harmonisation of technical requirements for the authorisation and manufacture of medicinal products for human and veterinary use

| 1986 | **European Convention (ETS 123) for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes**

| 1991 | **Biological Standardisation Programme** (BSP)

* agreement between the Council of Europe (Strasbourg) & the EU Commission (Brussels)

1994 | EU signs the Ph. Eur. Convention

**Creation of the OMCL Network** *as above (71 OMCLs in 43 countries)*

2010 | **Directive 2010/63/EU** entry into force on 10 November 2010

*Transposition completed by 10 November 2012 and full effect on 1st January 2013*
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

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

**Potential roadblock for new methods**

**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

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

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).
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


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, WOAH, 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

**Initial Method Development**
Experimental phase – design and proof of concept
Adaptation for QC setting- local validation

**Feasibility and Demonstration of Transferability**
Assess feasibility of transfer to other labs/products/ pre-test candidate reference material

**Large Scale Collaborative Study**
Validation of method robustness in a larger context for global applicability – qualify candidate reference
Establish method requirements based on results from many labs for regulatory proposals

**Acceptance and Use**
Transfer to a regulatory context (Ph. Eur)
Wide dissemination of study results (Pharmeuropa Bio& SN/ Conference)

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**Pre-BSP involvement!**
Development phase in specialised laboratories with appropriate expertise

**Steering Committee** determines programme and suitability of continuing based on results.
EDQM collaborates with Project Leader(s) (PL) in preparing and running study.

**Participants** include manufacturers and OMCLs within and beyond EU. Test range of products on the EU market. Appropriate statistical analysis performed.

**BSP presents results to Ph. Eur. group**
Methods presented to WHO (ECBS) (human).
Manufacturers/OMCLs encouraged to implement method and finalise product specific validation steps where necessary.
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)

BSP 130 study with EPAA
C. Septicum Multi-phase study - 14 labs

Vero-cell
Successful Model*

Project Leaders: L. Brukner, B. Siklodi (CEVA), K. Redhead

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. Rosskopf (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. Behrensdorf-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)

1st collaborative phase: 19 labs
- some labs saw good dose response with high sensitivity
- others failed or had mediocre response

2nd collaborative phase to refine method conditions
- Common set of standardised reagents
- Simplified, more robust protocol
- Launch set for Q1 2023
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

Biological Standardisation Programme (BSP)

The EDQM participated in a conference on Next Generation Sequencing

On 27-28 September, representatives of the EDQM participated in the 3rd Conference on Next...

Novel in-vitro model as alternative to in-vivo toxoid vaccines testing: Clostridium septicum vaccine as proof of concept

Virtual Workshop
Webinar Sessions on 9 & 10 March 2021
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’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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