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

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

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The European Partnership for Alternative Approaches to Animal Testing

European Commission

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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

Session 1: Activities of study stakeholders in the field of 3Rs: the EDQM

Catherine LANG, EDQM, Council of Europe, Group 15V Secretary

Outline

- Why are the 3Rs a priority for the EDQM?
- EDQM Main activities concerned by 3Rs
  - European Pharmacopoeia (Ph. Eur.)
  - OMCL Network - Official Control Authority Batch Release (OCABR) of human and veterinary biologicals
  - Biological Standardisation programme (BSP)

EDQM - The Council of Europe (COE) and the 3Rs commitment

1949	Foundation of the **Council of Europe**
1964	The **Ph. Eur. Convention**, a Council of Europe partial agreement *In 2021: 40 members - including the EU and 30 observers - including WHO* → Ph. Eur. texts are mandatory in all member states - harmonisation of technical requirements for the autorisation and manufacture of medicinal products
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 becomes full member of the Ph. Eur. Convention **Creation of the OMCL Network** *(66 OMCLs in 35 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*

Ph. Eur. 3Rs commitment: reference to CoE ETS 123 (1986)

Ph. Eur. Introduction

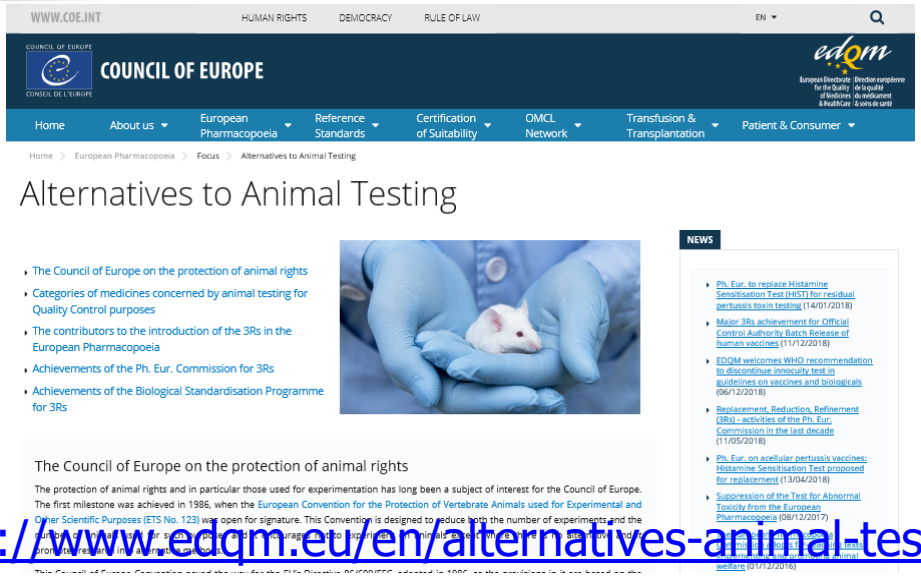
Use of animals. In accordance with the **European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (CETS No. 123)**, **elaborated under the auspices of the Council of Europe, the Commission is committed to reducing the use of animals wherever possible in pharmacopoeial testing**, and encourages its stakeholders to seek alternative procedures. …

General Notices, General chapters (ex: *5.2.14*), General monographs, individual monographs (ex: Rabies vaccine (inactivated) for veterinary use (0451))

How is this translated in Ph. Eur. texts?

1. Minimum number of animals for testing/least pain (humane endpoints)
2. Alternative methods, in particular for routine testing (serologic assay)
3. Door-openers to encourage stakeholders to develop 3R methods
4. Chapter *5.2.14.* Substitution of *in vivo* method(s) by *in vitro* method(s) for the quality control of vaccines
5. Consistency of production, risk assessment
6. Regular review of the requirements

EDQM website: a mine of information



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

Milestones

- **2012**: Suppression of the **TABST** (vet vaccines)
- **2016**: New chapter in Ph. Eur: *Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccines (5.2.14)*
- **2017**: Suppression of the Test for **Abnormal Toxicity** from the European Pharmacopoeia
- **2018**: Replacement of the **Histamine sensitisation test (HIST)** for residual pertussis toxin testing + removal of the test for irreversibility of pertussis toxoid and the requirement to test the final lot for residual pertussis toxin for acellular pertussis vaccines
- **2019**: Review of **toxicity testing requirements for tetanus vaccines**: 3 animal tests have been suppressed: the **Test for specific toxicity** and the **Test for residual toxicity** – performed on the final lot for human and veterinary vaccines, respectively – and the **Test for irreversibility of tetanus toxoid** carried out on the bulk purified toxoid (all tests in guinea pigs).

… More to come … stay connected via **Pharmeuropa** (free)

https://www.edqm.eu/en/replacement-reduction-and-refinement-animal-testing-3rs-latest-achievements

What is the **O**fficial **M**edicines **C**ontrol **L**aboratory Network?

- **OMCL** Programme co-financed by the Council of Europe (Strasbourg) and the EU Commission (Brussels)

Funded by the European Union and the Council of Europe — Implemented by the Council of Europe

- **Network of National control laboratories for batch release** performing tests on lots before release based on codified rules, mutual recognition of tests, harmonised working methods, Quality Management system referring to a commonly agreed standard, OCABR certificates issued and recognised in all MS – **One test for all**
- Participate in/lead **BSP** collaborative studies for alternative method validation
- Post market surveillance studies using a risk based approach
- **Development of alternative methods** for ex. for extraneous agents testing
- Regular technical **trainings** to facilitate knowledge and work sharing

https://www.edqm.eu/en/general-european-omcl-network-geon

What is the **B**iological **S**tandardisation **P**rogramme (BSP)?

- **BSP** Programme co-financed by the Council of Europe (Strasbourg) and the EU Commission (Brussels)

Funded by the European Union and the Council of Europe — Implemented by the Council of Europe

- coordinates large **collaborative studies** to:
  - establish of Ph. Eur. reference standards & reagents
  - standardise / **validate pharmacopoeial methods including alternative 3R** (refine, reduce, replace) methods to animal use for the quality control of biologicals

- is independent: no financial interest, neutral focal point for open discussions
- aims at **improving application of 3Rs concept** with focus on fostering implementation and regulatory acceptance

BSP Steering Committee open to proposals (but no method development).

BSP reports available (free) in **Pharmeuropa Bio & Scientific Notes**
https://www.edqm.eu/en/work-programme-bsp

Thank you for your attention

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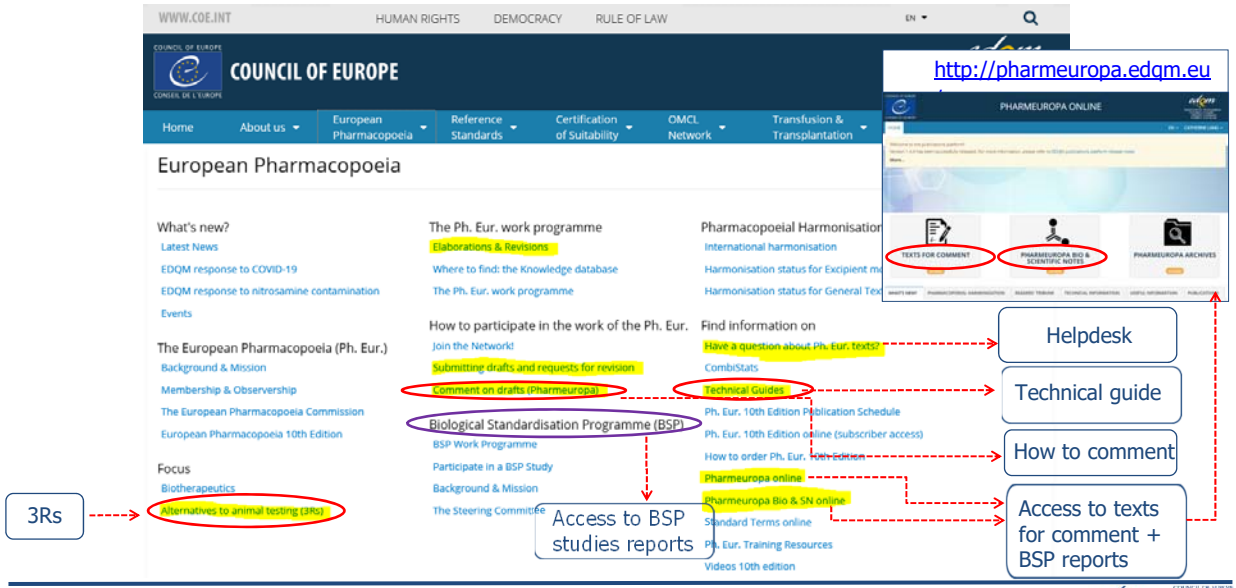
Back up slides

How to contact the EDQM? EDQM website: a mine of information



General & individual monographs

Ultimate goal → to completely eliminate animal testing

When this is not possible → Universal agreement

- most humane manner possible
- only the minimum number of animals
- while ensuring safety and potency

Use of humane endpoints

Yellow fever vaccine (live) (0537)	Tests in monkeys for neurotropism – performed on the seed lot
Rabies vaccine (inactivated) for veterinary use (0451)	Potency in mice "**Application of alternative end-points.** *Once a laboratory has established the above assay for routine use, the lethal end-point is replaced by an observation of clinical signs and application of an end-point earlier than death to reduce animal suffering.*"
Tick-borne encephalitis vaccine (inactivated) (1375)	Assay in mice "*Humane endpoints may be used to avoid unnecessary suffering of animals after the virulent challenge*"

Individual Ph. Eur. monographs: Reference to humane endpoints*

Individual monographs encourage humane endpoints (to find them, search "suffering" in the European Pharmacopoeia Online http://online.edqm.eu). **Examples** (non exhaustive list):

- *Rabies vaccine (inactivated) for veterinary use* (0451) – introduction of the possibility of replacing the lethal end-point by a more humane end-point. (**Supplement 6.1**)
- *Tick-borne encephalitis vaccine (inactivated)* (1375) - *« ASSAY:* Humane endpoints may be used to avoid unnecessary suffering of animals after the virulent challenge (**Supplement 5.3**)
- *Residual pertussis toxin and irreversibility of pertussis toxoid* (2.6.33) – "Alternatively, after validation, a histamine-sensitisation test based on body temperature measurements as end-points may be used instead of the lethal end-point test in mice."
- *Assay of tetanus vaccine (adsorbed)* (2.7.8) : guidelines – "In order to minimise suffering in the test animals, it is recommended to note the degree of paralysis on a scale such as that shown below …"
- *Cell substrates for the production of vaccines for human use* (5.2.3 - **Tests for tumorigenicity *in vivo*: "**Severely affected animals showing evident, progressively growing tumours are euthanised before the end of the test to avoid unnecessary suffering" (**3th Edition Addendum 2001**)
- **Immunogenicity tests** for *Canine adenovirus vaccine (inactivated)* (1298), *Canine adenovirus vaccine (live)* (1951), *Canine distemper vaccine (live)* (0448), *Distemper vaccine (live) for mustelids* (0449), *Mannheimia vaccine (inactivated) for cattle* (1944), *Mannheimia vaccine (inactivated) for sheep* (1946), *Pasteurella vaccine (inactivated) for sheep* (2072), *Porcine actinobacillosis vaccine (inactivated)* (1360)
- **Assay** for *Botulinum toxin type A for injection* (2113) and *Botulinum toxin type B for injection* (2581)
- **Potency** for *Clostridium chauvoei vaccine for veterinary use* (0361). "To avoid unnecessary suffering following virulent challenge, moribund animals are euthanised and are then considered to have died from C. chauvoei infection." (**6th Edition**)

* The European Pharmacopoeia and human endpoints. P. Castle

3R in the European Pharmacopoeia

A few examples of specific 3R improvements to vaccine monographs and chapters

Human

General monograph *(0153):*
- Addition of a section *Animal tests* which recommends use of humane end-points wherever possible (see list)
- **Deletion of abnormal toxicity** *(2.6.9)* test based on historical review (still performed during development for half of the specific monographs i.e. *36/61*) – complete deletion in **Suppl. 9.8**

Hepatitis A vaccine (inactivated, adsorbed) **Suppl. 8.5**
- Introduction of an *in vitro* assay (now "method A") + new vaccines can be developed without animal testing

Measles, Mumps, Rubella and Varicella Vaccines (live) (0213, 0538, 0162, 0648):
- Deletion of the neurovirulence test on seed lots **Suppl. 6.1**

Poliomyelitis vaccine (oral) *(0215):*
- Introduction of genome analysis for screening prior to neurovirulence testing in animals (MAPREC) **Suppl. 9.1**
- Allow use of mouse alternative neurovirulence assay **Suppl. 5.3**

Diphtheria, Tetanus, acellular Pertussis :
- Introduction of guinea-pig serology assay as an alternative to challenge with possibility to use the same animals for all components of a combined vaccine AND to introduce single dilution assays *(2.7.6, 2.7.7, 2.7.8,)* **Suppl. 5.7**
- Replacement of guinea-pig test for residual diphtheria toxin in bulk toxoid by an *in vitro* test using VERO cells
- replacement of specific toxicity test for D and T in guinea-pigs by an upstream validation requirement
- Replacement of HIST by CHO clustering assay for monitoring of pertussis toxin activity in acellular pertussis vaccines **(in progress)**

Rabies vaccine for human use prepared in cell cultures *(0216):*
- Introduction of an annex on humane end-points **Suppl. 6.1**
- use of an alternative validated serology method **Suppl. 8.2**

Replacement of the rabbit pyrogen test (after validation) with Bacterial endotoxin test (2.6.14) or Monocyte activation test (2.6.30) **Suppl. 9.2**

Veterinary

General monograph (0062):
- Addition of a section *Animal tests* which recommends to use humane end-points wherever possible (see list)
- **Deletion of the TABST** (April 2012) after possibility given to waive it

Avian vaccines:
- Replacement of test for extraneous agents in chicks by cell culture test (2.6.24 and 2.6.25) – **5th Edition**

Clostridium vaccines (*Clostridium novyi (0362), Clostridium perfringens (0363), Clostridium septicum (0364))* :
- Introduce a serological evaluation for batch potency test **3rd Edition Suppl. 2001**

Swine erysipelas vaccine (inactivated) (0064):
- Introduce a serological evaluation for batch potency test **3rd Edition Suppl. 2001**

Newcastle disease vaccine (inactivated) *(0870)*:**Suppl. 5.3**
- Introduce an *in vitro* alternative for batch potency test

Canine leptospirosis vaccine (0447):
- Introduce serological batch potency test possibility – **5th Edition**
- Introduce *in vitro* batch potency possibility for non-adjuvanted vaccines – **9th Edition**

Rabies vaccine (inactivated) *(0451)*:
- Introduction of an annex on humane end-points **Suppl. 6.1**
- Describe a serology assay for batch potency **Suppl. 7.7**

EDQM Biological Standardisation Programme (BSP)