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

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Removal of the ATT from the European Pharmacopoeia

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AFSA/HSI, EFPIA IABS workshop on Accelerating Global Deletion of the Abnormal Toxicity Test

October 14, 2021

Overview

- History of COE EDQM commitment to 3Rs
- 3Rs in European Pharmacopoeia testing
- Abnormal Toxicity Test (ATT)
- Background of ATT
- Move towards removal
- Converging Regulatory Agreement on ATT
- Suppression of ATT from the Ph. Eur.
- and beyond !
- Progress for veterinary medicines too!
- Other recent progress
- Key players and contributors

HISTORY: EDQM - The Council of Europe and the 3Rs commitment

1949	Foundation of the **Council of Europe** *To date 47 member countries & 6 observer states* *Human Rights, Democracy, Rule of Law*
1964	The **Ph. Eur. Convention**, an international treaty *To date 39 members states and the EU & 30 observers - including WHO* → Ph. Eur. texts are mandatory in all member states - harmonisation of technical requirements for the authorisation 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 signs the Ph. Eur. Convention **Creation of the OMCL Network** *(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 European pharmacopoeial testing

- 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 human use* on reducing animal numbers and suffering
  - "*In accordance with the [...] European Convention [...], tests must be carried out in such a way as to use the minimum number of animals and to cause the least pain, suffering, distress or lasting harm*".
- Individual vaccine monographs encourage the use of alternative 3Rs methods, humane endpoints
  - The detailed protocol of a validated 3Rs method may be provided as an example, where available (e.g. Residual pertussis toxin (2.6.33)), use of 'door openers' (e.g. rabies vaccines human use (0216) and veterinary use (0451))
- Guidance in chapter 5.2.14 on concept of "substitution" of animal tests for QC of vaccines
- Ongoing review of Ph. Eur. texts in line with scientific understanding to employ 3R or the 4th R 'REMOVAL'

Abnormal Toxicity Test (ATT)

= General Safety Test (US), Innocuity Test (WHO) – formats vary in different pharmacopoeias

- Principle: inject batches of product into guinea pigs/mice. A batch passes the test if no animal shows any sign of illness, or dies within a defined timeframe

  → Animal suffering

- Considerable usage of animals: e.g. for vaccines, 5 mice and 2 guinea pigs for each batch
- Questionable scientific usefulness

- One of the most controversial animal tests in the Ph. Eur.

  → *Priority target for reevaluation!*

Background of ATT

- Safety tests in mice and guinea pigs date back to the early 1900s
  - Detection of toxic levels of phenol in sera (mice) – since the 1890s!!!!
    - Phenol used as preservative in early sera products (diphtheria, tetanus) and later bacterial vaccines
    - Mouse sensitivity to phenol used in a test to check preservative content
  - Detection of contamination with tetanus toxin & spores in sera (guinea pigs)
    - Incidences of contamination of diphtheria antisera with toxin spores in the early 1900s lead to introduction of a guinea pig test as a biological indicator for extraneous clostridia toxins (tetanus) initially for diphtheria sera but later in other sera and vaccines
- In 1940s both tests were combined to become a general safety test.
  - ATT was mentioned as such for the first time when WHO began developing international guidelines after WW2 and was introduced into almost all general testing requirements for immunological and biological medicines, human and vet, around the world
- ATT largely unchanged since then, despite evolution of analytical techniques, manufacturing processes

Move Towards Removal

With increasing sensitivity to 3Rs in the 90s, ATT was a clear target

Conundrum

ATT used historically as a ‘catchall’ but purpose/validation parameters not clearly defined

Refine, Reduce, Replace difficult to apply

REMOVE????? – A BIG STEP

Regulators and QC experts stress successful past use and ‘low’ severity and number of animals – reluctant to take the leap

Extensive review by the Paul Ehrlich Institute (PEI) supported by the German Ministry for Education and Research 1994-1995

- **Retrospective analysis concluded**: the ATT is neither specific, reproducible, reliable, nor suitable for the intended purpose (*Duchow et al, 1994, Krämer et al, 1996)*
  - More relevant tests available for testing phenols, toxins
- Use of GMP and stringent QC measures to prevent contamination also puts in question the relevance of the ATT

Move Towards Removal

- Request for Deletion of the ATT from the Ph. Eur. (1995)
- Deletion as a routine batch release test from >80 monographs in 1998
  - Complete deletion accepted for veterinary products
  - Different approaches for human products:
    - Complete deletion for sera and immunoglobulins
    - Complete deletion for DTP
    - For all other products
      - Deletion as a routine batch release test
      - Moved to Production section (development test)

Significant reduction in the unnecessary, unscientific use of animals

Situation improved but ATT still in the Ph. Eur.

Since that time hundreds of thousands of lots of sera, immunoglobulins, vaccine for human and veterinary use released in the EU without any noticeable problems

Converging regulatory agreement on ATT

European Partnership for Alternative Approaches to Animal Testing (EPAA)

- Discussed the ATT issue in depth in a Workshop in 2015* with global stakeholders
- Workshop included review of case studies and data
- Conclusion: the ATT lacks scientific relevance and its omission does not compromise the safety of biologics. *Consensus to strive for deletion of the ATT from regulatory requirements*
- Deletion of ATT should be addressed at a global level
  - A harmonised approach by all regulators across the globe is important for a real and effective deletion

* Modern Science for better quality control of medicinal products “Towards global harmonisation of 3Rs in biologicals”: The report of an EPAA workshop; K. Schutte et.al. Biologicals 2017 Vol 48

Suppression of ATT from the Ph. Eur.

Ph. Eur.

- Based on this review, the Ph. Eur. Commission decided to embark on the deletion of ATT from 49 monographs
- A detailed evaluation was conducted for each monograph in the relevant groups
- Concerned human vaccines, antibiotics/anti-fungals, allergen products, sterile plastic containers for human blood components, general chapter 2.6.9
- Decision to suppress the ATT (Nov 2017)
  - Revised monographs omitting the ATT published in Supplement 9.6 (July 2018)
  - Simultaneous suppression of chapter *2.6.9 Abnormal toxicity*, no longer referenced in any monograph

No More ATT in the Ph. Eur.!
A MAJOR STEP FORWARD FOR 3Rs

… and beyond!

World Health Organisation (WHO)

From 2015 EDQM presented regularly at the WHO Expert Committee for Biological Standardisation (ECBS) plenary sessions a request to consider the removal of the ATT from WHO guidelines – with presentations and updates from K.H. Buchheit

November 2018 ECBS: WHO and stakeholders make a proposal to discontinue the test in all guidelines

- WHO's ECBS recommendation to discontinue ATT in guidelines on vaccines and biologicals is adopted → A further step towards global acceptance

Text remains in the guidelines (to be updated when next reviewed) but is over-ridden by ECBS statement

Next step – update the texts!!

... and beyond!

World Health Orga

From 2015 EDQM prese … e for Biological Standardisation (ECBS) … emoval of the ATT from WHO guidelines – … uchheit

November 2018 ECBS: … discontinue the test in all guidelines

- WHO's ECBS reco … n vaccines and biologicals is a … tance

Text remains in the gu …) but is over-ridden by ECBS statement

Next step – update the …

Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 29 October to 2 November 2018

In addition to adoption of the written standards and establishment of reference preparations, the ECBS also recommended:

1. The immediate discontinuation of the inclusion of the innocuity test in all future WHO documents on vaccines and other biologicals published in the Technical Report Series (including WHO Recommendations, Guidelines and manuals). As a result of this recommendation, this test does not appear in the WHO Recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines listed above. In addition, it was agreed that a statement should be made in the full report of the ECBS indicating that the inclusion of this test in previously published WHO Technical Report Series documents should now be disregarded. In the words of the ECBS:

The scientific rationale and evidence for performing the innocuity test (also called the abnormal toxicity test or general safety test) as a measure of the safety of vaccines and other biological products for the purpose of marketing authorization and lot release were discussed by the Committee. Current manufacturing processes, which include the implementation of Good Manufacturing Practices (GMP) and comprehensive quality control measures (including in-process controls), were considered to be more appropriate than the innocuity test in assuring the quality and safety of vaccines and other biological products. The Committee reviewed the historical inclusion of the innocuity test in the documents published in the WHO Technical Report Series and concluded that its complete omission would not compromise the quality and safety of vaccines and other biological products. Therefore, the Committee recommends the discontinuation of the inclusion of the innocuity test in all future WHO Recommendations, Guidelines and manuals for biological products published in the Technical Report Series, and that a clear indication be made in its report that the inclusion of this test in previously published WHO Technical Report Series documents be disregarded.

https://www.who.int/biologicals/expert_committee/ECBS_Executive_Summary_final_20_NOV_2018.IK.pdf?ua=1

Progress for veterinary medicines too

- Target animal batch safety test (TABST)
  - Requirement to test the inocuity of inactivated or live veterinary vaccines by administering an overdose
    - of each batch
    - to the intended target animal species

- 2004: waiving option included in the Ph. Eur. for established vaccines
- 2012: Ph. Eur. experts performed an extensive review of all veterinary vaccine texts
- 2013: TABST removed from the Ph. Eur. (80 monographs, general monograph and 2 chapters)

VICH Guidelines 50 and 55; harmonised criteria to waive TABST in inactivated and live vaccines implemented from 05/2018 to promote removal in other regions

Other recent progress

Re-evaluating the need for historic tests in a scientific context; in all cases careful review by the group with respect to rational and historic evidence from vaccine lots was undertaken

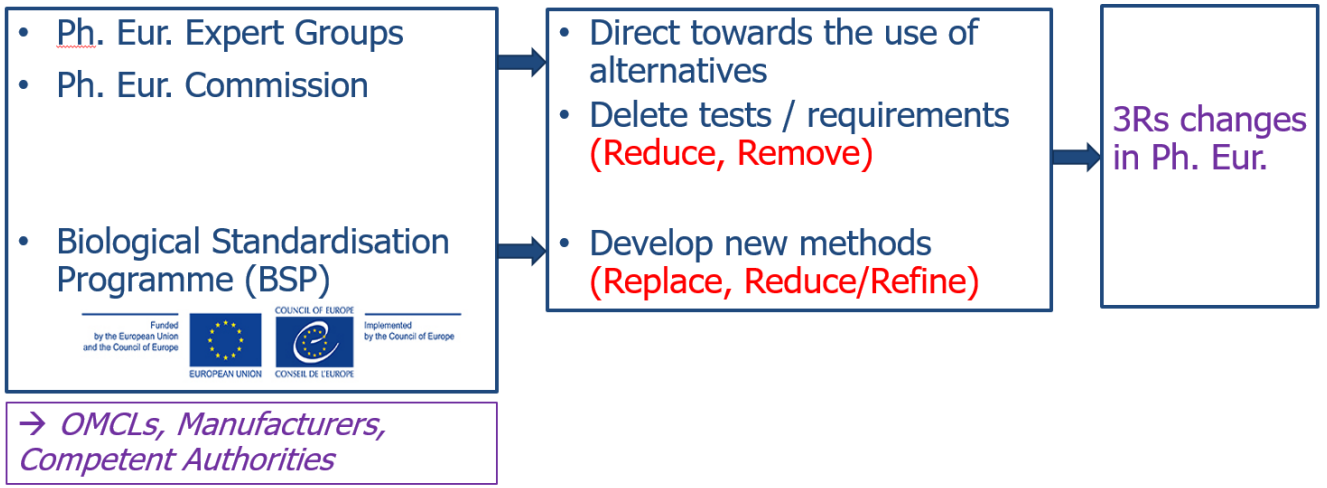
- Histamine sensitisation test in mice (acellular Pertussis vaccines)
  - Residual toxin by standardised* cell-based (CHO) test performed on non-adsorbed purified pertussis components (validated detoxification procedure), irreversibility of toxoid test deleted, no toxicity test on final lot – effective 01/01/2020
- Toxicity for tetanus vaccines
  - Removal of test for specific toxicity (process validation guinea-pig test), removal of test for irreversibility of toxoid (guinea-pig test), (test for residual toxin (in guinea-pig@) retained on bulk purified toxoid) – effective 01/01/21
- Toxicity for Diphtheria vaccines
  - Removal of test for specific toxicity (process validation guinea-pig test) (test for residual toxin retained on bulk purified toxoid (vero cell assay)) – effective 01/01/22 (publication date 01/07/2022)

* EDQM Biological Standardisation Program (BSP) study BSP114

@ EDQM Biological Standardisation Program study BSP136 BINACLE assay for *in vitro* replacement ongoing

Key players and contributors

EDQM, the Ph. Eur. Commission and experts and stakeholders are committed to the principles of good science and to supporting the concepts in Directive 2010/63 – work continues to review Ph. Eur. texts with this in mind



Special mention for Klaus Cussler (formerly PEI) and his colleagues for their dedication and effort to use science and evidence to support relevant change for ATT in the Ph. Eur. and beyond and to Lukas Bruckner for his efforts for TABST

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Thank you for your attention

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