TOWARDS GLOBAL HARMONIZATION OF 3RS IN BIOLOGICALS – EFFORTS OF THE EPAA BIOLOGICALS TEAM

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1. WHAT IS EPAA?

STATUS
**Partnership** between European Commission & Industry stakeholders.

PURPOSE
To facilitate development, acceptance and validation of alternative approaches.

MILESTONES
Created in 2005. Renewed for the 2**nd** time in 2015.

SCOPE
Operates **across 7 industry sectors**. Covers Regulatory testing.
1. EPAA VISION & MISSION

Vision

The vision of EPAA is the replacement, reduction and refinement (3Rs) of animal use for meeting regulatory requirements through better and more predictive science.

Mission

- Promote development and acceptance of alternative methods
- Enhance international collaboration & mutual recognition of alternatives
- Foster knowledge sharing on 3Rs among the partners
- Facilitate dialogue between stakeholders contributing to animal welfare
1. EPAA Membership

- 5 Commission Directorate Generals (DG)
- 7 European trade federations for 7 industry sectors
- 35 Companies
1. EPAA Remit

7 industry sectors committed to support alternative methods for regulatory safety testing and/or quality & potency testing:

- Animal Health
- Chemicals
- Cosmetics
- Crop Protection
- Fragrances
- Pharmaceuticals (incl. vaccines)
- Soaps & Detergents
1. EPAA Ongoing Projects list

- **Harmonization of 3Rs in Biologicals**
- Exposure predictions (ADME)
- Human rabies vaccines (potency test replacement)
- Clostridial vaccines (validation of alternative to in-process control tests)
- Advancing 3Rs in Regulatory Toxicology: Carcinogenicity
- Acute toxicity testing
- Skin sensitisation – optimised strategies
- Skin sensitisation – difficult substances
2. EPAA BIOLOGICALS PROJECT
TEAM MEMBERS

EFPIA  (EU Pharmaceutical Industry Association, Anna Szczepanska, co-chair)
EU-Commission (DG Environment, DG SANTE, JRC-ECVAM)
EDQM
IFAH-Europe
VACCINES EUROPE
ZOETIS
SANOFI-PASTEUR
GSK Vaccines
Paul Ehrlich Institute
2. BIOLOGICALS PROJECT BACKGROUND

- Biologicals (vaccines, hormones, immunoglobulins, blood products) are manufactured by biological processes of inherent variability, and require a strict quality control strategy to secure consistent quality from batch to batch.

- Required safety and potency control tests (in vivo or in vitro) are incorporated in monographs of relevant pharmacopoeias.

- Differences in test requirements and protocols between countries still give rise to unnecessary repetition of testing.

- Art. 13 of **DIR 2010/63** asks that a procedure using animals is not carried out if another method for obtaining the same result is recognized under EU legislation.
2. BIOLOGICALS PROJECT APPROACH

Differences in testing requirements seemed to have more of a historical than scientific basis and merited evaluation to see where scientific evidence allows moving towards acceptance of a 3Rs-approach.

After an initial mapping of international requirements and key players, EPAA hosted an international workshop mid September 2015 to discuss four case studies (human and veterinary vaccines) and to define the most effective pathways for international convergence.
3. INTERNATIONAL WORKSHOP ON BIOLOGICALS
15-16 Sept 2015, Netherlands

45 Participants from:

Brazil
Canada
China
India
Japan
Mexico
US
Several EU countries & Switzerland

OIE (World Organisation for Animal Health)
WHO (World Health Organisation)
EMA (EU Medicines Agency)
EDQM (EU Directorate for Quality of Medicines and Health Care)
3. Expected deliverables – how to move towards better regulatory science?

• Understand **reasons for differences** in regulatory acceptance of 3Rs methods across regions

• Understand **barriers to harmonized implementation of 3Rs** in regulatory practice and on data requirements that would facilitate implementation

• **How could alternative methods improve the efficacy and scientific reliability** of safety or potency testing?

• Define **steps towards harmonized translation/uptake of 3Rs** into regulatory practice

- which concrete area(s) / case study(ies) could become a subject of a specific coordinated action at a global level?
3. Case studies discussed at the workshop

1. Deletion/waiving of *general safety tests* (ATT, GST) at WHO level and from national regulatory requirements

2. Deletion/waiving of *general safety tests* (ATT/GST; TABST) at VICH level and from national regulatory requirements

3. Towards replacement of in *vivo potency assays* for Diphtheria and Tetanus vaccines

4. Swine Erysipelas vaccine: *in vitro* ELISA assay to replace *in vivo* immunization-challenge test
The German government introduced specific regulations for diphtheria sera in 1894.

A serum sample was considered as “safe” if it

- is entirely clear and free from major precipitation,
- does not contain any bacterial impurities,
- does not contain more than 0.5% phenol*,
- is free from toxins, in particular tetanus toxin.

* Phenol and cresol were considered as most effective preservatives at the time:
  - The content had to be restricted due to the toxicity
  - but needed to be effective
  → A limit of 0.5% phenol (0.4% tricresol) was requested.
History of the ATT in mice

Paul Ehrlich inspecting laboratory mice, around 1910
History of the ATT in mice

Mice are very sensitive to phenol:
• with 0.5% phenol in 0.5 ml of serum s.c. they start trembling and shaking
• more than 0.5% result in convulsions and death

→ The laboratory mouse was used as a biological test tube (already in 1895; Throm, 1995)
→ This safety test for diphtheria & tetanus serum was maintained for the first bacterial vaccines (typhoid & cholera), also preserved with phenols.
→ The mouse test became a standard test (to check the preservative content)
History of the ATT in mice

- In **1943** a “colour test for phenolic compounds” was established which was then adapted to measure phenol derivatives in medicines.

→ From today's point of view this would have been the time to remove the mouse safety test.
3. Workshop recommendations

SAFETY TESTS

- Encourage deletion of ATT / GSTs / TABST from all national / jurisdictional requirements & international guidance
  - Ph. Eur. Monographs
  - WHO recommendations
  - OIE guidelines

- Explore means to contact key countries at legislator level
3. Workshop recommendations

POTENCY TESTS

- Achieve convergence on the scientific principles of the use of appropriately validated *in vitro* replacement methods
- Include key regulators and manufacturers from the start in discussions
- Collaborative studies could result
- New assays as means to unify different regulatory approaches in different jurisdictions
- Harmonised assays desirable, but product-specific assays may also be acceptable
3. Achievements: Eur Pharmacopeia

Currently the ATT is still mentioned in the production section of 51 monographs for a diverse range of products in the Ph. Eur. including vaccines for human use, antibiotics and other pharmaceuticals.

<table>
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<th>Abnormal Toxicity in Ph.-Eur.</th>
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| The test still applies to 51 monographs:
  - 4 monogr. on antibiotics
  - 2 monogr. on antifungal drugs
  - 4 monogr. on (anti-)coagulants
  ✓ 2 monogr. on botulinum toxins
  ✓ 1 monogr. on containers for blood products
  ✓ 1 monogr. allergens
  - 29 monogr. vaccines (ref. to 2.6.9)
  - 2 monogr. vaccines (ref. to 2.6.9 but modified)
  - 4 monogr. vaccines (Request for deletion, outdated)
  ✓ 1 monogr. anthrax vaccine (no ref. to 2.6.9)
  ✓ 1 Immunosera for human use (animal)

Requests for revision to delete the ATT are submitted for all monographs and passed on to relevant Expert Groups 15, 7 and 6. Decisions on the deletion are expected for the Commission Meetings in November 2016 and March 2017.
3. Achievements: WHO & OIE

Revision of WHO guidelines
Formal letter from EPAA to encourage deletion of GST/ATT/test for innocuity from WHO recommendations was discussed by ECBS in **October 2016**.

Revision of OIE guidelines
Formal letter from EPAA requesting the deletion of TABST from OIE recommendations was discussed at meeting of the OIE Biological Standards Commission in **September 2016** - OIE Collaborating Centres involved in veterinary vaccine production will evaluate further.
3. Next steps: Dialogue with non-EU countries if ATT/GST and TABST could be deleted

- **Asia**
  Aim to discuss the way forward towards implementation of the workshop recommendations at 2016 Asian Congress on Alternatives and Animal Use in Life Sciences (15-18 November 2016)

- **Brazil**
  EPAA to interact with BRACVAM which is already collecting data to propose to Brazilian Pharmacopoeia the deletion of ATT from the monographs.
Thanks for your attention!

- **EPAA website:**  
  http://ec.europa.eu/growth/sectors/chemicals/epaa_en

- **Biologicals Workshop report:**  