European Commission

Progress in Establishing VICH guidelines on Waiving Criteria for Target Animal Batch Safety Tests

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EURL ECVAM
European Union Reference Laboratory for Alternatives to Animal Testing

VICH 5
International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
-Reaching Out to the World-

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Joint Research Centre

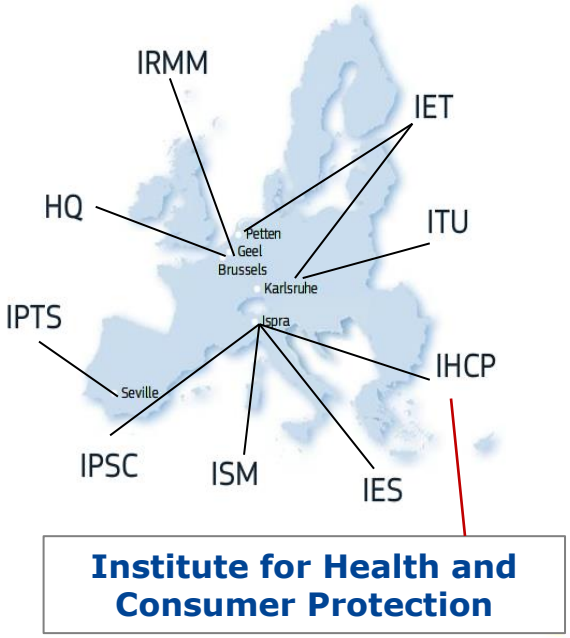
Outline

- **Introduction to EURL ECVAM**
- **Batch safety testing**
- **Background to deletion of LABST & TABST in EU**
- **Development of VICH GL50 – inactivated vaccines**
- **Ongoing work & discussion**

Joint Research Centre (JRC) -

The European Commission's in-house science service

- **Seven Scientific Institutes**
- **Sites in five EU Member States**



Institute for Health and Consumer Protection

Directive 2010/63 on protection of animals used for scientific purposes

- **Improve the welfare of those animals still needed to be used, as well as to firmly anchor the principle of the 3Rs, to Replace, Reduce and Refine the use of animals.**
- **Develop and validate 3Rs methods**
- **Formal establishment of EURL ECVAM through Article 48**

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https://ec.europa.eu/jrc/

The European Union Reference Laboratory for Alternatives to Animal Testing

Key responsibilities (Annex VII to Directive 2010/63)

1. **Coordinate and promote development and use of alternative methods**
2. **Coordinate their validation at Union level**
3. **Focal point for the exchange of information on development of alternative methods**
4. **Managing databases and information systems**
5. **Promote dialogue between legislators, regulators, and stakeholders**

… EURL ECVAM* shall participate in the validation of alternative methods.

* European Centre for Validation of Alternative Methods established in 1991 by the European Commission

EURL ECVAM & reduction of target animal batch safety testing

- **Funding of study "Evaluation of the relevance of the target animal safety test for the quality control of veterinary immunological medicinal products" (contract 134 10-97-11F 1 EI ISP NL; AGAATI, 2002);**
- **ECVAM statement on the Relevance of the TABST recommends its omission for routine quality control (2002);**
- **In 2009, EMA appointed EURL ECVAM as topic leader at VICH level.**

General Batch Safety Tests

Target Animal Batch Safety Test (TABST)

- **Target species**
- **Pass/fail criteria:**
  - **"abnormal local or systemic reactions"**
  - **"unfavorable reactions attributable to the biological product …"**
  - **"abnormal changes"**
- **Test design (number of animals, route, observation period, volume) varies across regions**

Laboratory Animal Batch Safety Test (LABST)

- **Mice and/or guinea pigs**
- **Pass/fail criteria:**
  - **"ill health",**
  - **"death"**
  - **"unfavorable reactions attributable to the biological product …"**
  - **"no abnormal changes"**
- **Test design (number of animals, route, observation period, volume) varies across regions**

Background to deletion of LABST & TABST in EU

1. LABST or Abnormal Toxicity Test (ATT)

- **1993-1994: German Paul-Ehrlich-Institute carries out survey on relevance of ATT – human and veterinary immunobiologicals**

❖**Would we have missed unsafe batches without ATT ?**

❖**No, the ATT does not provide additional safety !**

- **1996: deletion of ATT from European Pharmacopoeia monographs**
  - ✓ **Complete deletion for veterinary immunobiologicals**
  - ✓ **Deletion as final product test for all human immunobiologicals**
- **In force since 1997**
- **Discussion on complete deletion for human immunobiologicals**

Duchow et al, 1994; PEI study report
Kraemer et al, 1996; ALTEX 13, 7-16
Schwanig et al, 1997; Vaccine 15, 1047-8

2. TABST

- **Relevance questioned by manufacturers and regulators since early 1990s**
- **1997 – 2001: retrospective analysis of TABST covering data from manufacturers and OMCLs**
  - ~ **12 000 batches; TABST failure < 0.1%**
  - **evidence that problematic batches passed the TABST**
  - **Deletion of TABST is recommended**
- **2004: European Pharmacopoeia introduces waiving of TABST**
  - **subject to 10 consecutive batches with no findings showing consistency of production in light of experience gained**
- **2012: Revision of European Pharmacopoeia monographs**
  - **Harmonisation with VICH GL41 (Reversion to virulence) and GL44 (Developmental safety tests)**
  - **Deletion of TABST (in force since 2013) - only in specific cases, on ad-hoc basis, further testing**
  - **Residual toxicity testing for three vaccines**

AGAATI, 2002; Biologicals 30, 277–287
EC Study contract: 134 10-97-11F 1 EI ISP NL

3. Reasons that allowed deletion of TABST in EU

- **Experience with testing/analysis made:**
  - **poor sensitivity despite using numerous animals in testing each year**
  - **very limited number of batches failing test**
  - **observation of field safety issues with batches compliant with TABST**

- **New guarantees: General improvements in the manufacturing process of veterinary vaccines, introduction of new requirements of in-process testing, controls of starting materials, etc.**

- **GMP, pharmacovigilance**

- **In the spirit of the 3Rs unnecessary use of animals must be avoided**

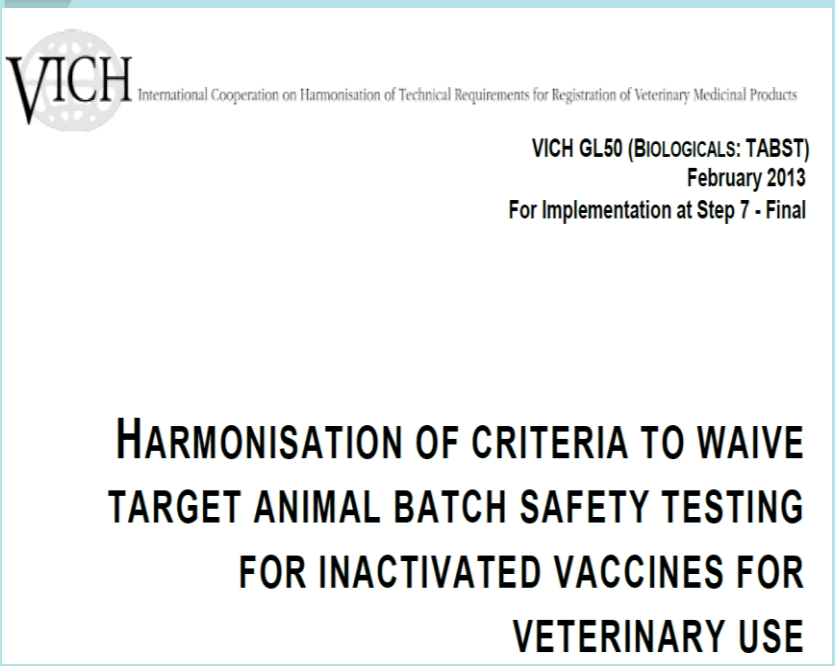
Press release EDQM:
http://www.edqm.eu/medias/fichiers/vaccines_for_veterinary_use_adopted.pdf
Pharmeuropa 2012 – September issue

International harmonisation and waiving of batch safety testing - VICH guidelines

- **Different requirements in different regions lead to duplication of tests (costs, unnecessary animal testing).**
- **Regional approach for waiving batch safety testing only of limited effect if not embraced at international level.**
- **In US and Japan: BST mainly abnormal toxicity testing, also some TABST.**
- **VICH supports 3Rs principles.**

Development of VICH GL50 - Harmonisation of criteria to waive Target Animal Batch Safety Testing (TABST) for inactivated vaccines for veterinary use

2008	• **Europe proposed to VICH to aim at harmonisation of general batch safety tests across the VICH regions** • **Due to the great divergence in requirements between the regions it was concluded to adopt a phased approach and start with the TABST for inactivated vaccines**
2009 - 2012	• **VICH Biologicals Quality Monitoring Expert Working Group – subgroup TABST elaborated the draft guideline**
2012	• **VICH Steering Committee approved draft.** • **Draft VICH GL50 underwent public consultation in the VICH regions, observer countries (Australia/New Zealand, Canada, South Africa) and associated members (OIE).**
2013	• **Revised draft is approved by VICH and published, giving 1 year for implementation.**
2014	• **VICH GL50 came into force**


VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL50 (BIOLOGICALS: TABST)
February 2013
For Implementation at Step 7 - Final

HARMONISATION OF CRITERIA TO WAIVE TARGET ANIMAL BATCH SAFETY TESTING FOR INACTIVATED VACCINES FOR VETERINARY USE

Without prejudice to the decision of the competent authority in light of the information available for a given vaccine, TABST data of 10 consecutive batches is likely to be sufficient for most products.

Ongoing work & discussion

- **Drafting of similar GL on waiving TABST for live vaccines, at step 2**
- **Future: develop LABST guideline?**
- **At a recent EPAA* workshop on harmonisation there was agreement that both, LABST and TABST, nowadays lack scientific relevance and should be deleted on a global level.**
- **International harmonisation/collaboration is crucial to achieve reduction of animal testing.**

EPAA = The European Partnership for Alternative Approaches to Animal Testing; voluntary collaboration between the European Commission, European trade associations, and companies from seven industry sectors.
http://ec.europa.eu/growth/sectors/chemicals/epaa/index_en.htm

Thank you for your attention!

Questions?