



**HUMANE SOCIETY
INTERNATIONAL**

HSI/HSUS Symposium on Global Harmonization of Vaccine Testing Requirements. Making the elimination of ATT and TABST a concrete global achievement.

19th March, 2019 – Rome (Italy)

Motivations

For the last 60 years, abnormal toxicity tests (ATT), or general safety tests (GST), and target animal batch safety tests (TABST) have been worldwide requisite tests for the release of biologicals and immunologicals for human and veterinary use. At long last, progress in the field is finally bringing about much needed change: since 1996, a series of papers have highlighted the inherent limits of those tests – in particular, their lack of specificity and the difficulties related to reproducibility¹, calling into question their rationale and the scientific bases they rely upon. The relevance of the ATT and TABST was questioned due to the introduction of more specific safety tests, strict control of starting material and the introduction of Good Manufacturing Practice.

As a result, a number of national agencies, regulatory bodies, and international standards organizations are already in the process of eliminating (or have already eliminated) ATT and TABST from their requirements; however, a series of factors are still hindering a full transition away from them, namely a lack of global coordination, inadequate communication between manufacturers and regulators, “regionalism” (the desire for retesting in different regions, usually with slightly different locally preferred methods), and regional unfamiliarity with new approaches or technologies.

Overcoming some of these difficulties would be the key step to finally eliminate globally ATT and TABST, a success that would entail both sparing the lives of countless animals, *and* an increase in safety and availability of vaccines worldwide.

The symposium we are organizing to this end will have two key characteristics: *pragmatism* and *inclusion*. Pragmatism because at this junction the need is not much that of conceptually re-framing the problem, rather reaching conclusions and deciding/taking charge of further actions to secure elimination of those tests.

Inclusion because besides those stakeholders already actively engaged in the field, a host of new stakeholders will participate: representatives of regulatory, manufacturers, associations of the developing countries and BRICS (where the transition is still undecided or being evaluated), and other non-technical stakeholders with a keen interest in improved availability of safe and effective vaccines, such as international health organizations and global foundations for humanitarian help, that could contribute other perspectives – and unavailable before instruments – to address the problem.

In this context, what we aim for is a bi-directional flow of information: from one side, stakeholders that already secured the successful elimination of ATT and TABST in some countries/regions sharing their experiences as case studies (including the differing perspectives of manufacturers and regulatory authorities), and sharing ongoing projects (such as the ones promoted by the EPAA Harmonization of 3Rs in Biologicals and the IMI Vac2Vac project). From the other, representatives from developing countries/BRICS to

¹ Duchow et al, 1996; Kramer, et al. 1996; Schwanig et al., 1997; AGAATI, 2002; Garbe et al., 2014

share the local contexts and difficulties they face in considering/embracing the elimination of ATT and TABST, and to foster discussion on practical possibilities to tackle those issues to lead to ATT and TABST elimination in as many countries as possible. A circular flow of information and exchanges to surface a truthful overview on the drivers and barriers affecting ATT and TABST globally, and to discuss possible/needed actions.

Objectives

In brief summary, the key objectives for the symposium are:

1. Bringing together a wider range of global stakeholders – including new ones with a keen interest in vaccines' innovation and increased accessibility through diminished reliance on in vivo testing – to strategically plan for the harmonized deletion of ATT and TABST.
2. Identifying positive case studies from the regulatory agencies and manufacturers that have already implemented the deletion of ATT and TABST, laying out a strategy to publicize those case studies.
3. Identifying the barriers and difficulties hindering the deletion of ATT and TABST in the regions that are still undecided on evaluating/implementing this opportunity.
4. Defining a roadmap populated with concrete actions to overcome those difficulties.

Current status of the Abnormal Toxicity Test

A full removal of the ATT has been approved by the European Pharmacopoeia (EDQM, Dec 2017), and, beginning in 2019, no further reference will be made to this test in this publication. The test for batch release testing of human and veterinary vaccines was first removed in 1997; however, it remained in some monographs in the "production section" and it had been deleted from this section recently.

In the US, removal of GST (the equivalent to ATT) had been proposed by FDA already in 2014; in 2015 the FDA formally stipulated that the "GST requirements are no longer necessary or appropriate to help ensure the safety, purity, and potency of licensed biological products"², however for each product is requested to submit a post approval major change to be approved by FDA prior the deletion of the test.

In November 2018, the WHO Expert Committee on Biologicals Standardization (ECBS) took the historical decision to discontinue "*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*"³.

Despite these successes, ATT and GST are still stipulated in the requirements of many countries, like China, Japan, Argentina, Mexico, Russia; only in limited cases (i.e. India) the possibility of waivers upon approval by the given national regulatory authority (based on previous WHO recommendations)⁴ is being assessed.

² <https://www.federalregister.gov/documents/2015/07/02/2015-16366/revocation-of-general-safety-test-regulations-that-are-duplicative-of-requirements-in-biologics>

³ Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 29 October to 2 November 2018:

http://www.who.int/biologicals/expert_committee/ECBS_Executive_Summary_final_20_NOV_2018.IK.pdf

⁴ Modern science for better quality control of medicinal products "Towards global harmonization of 3Rs in biologicals": The report of an EPAA workshop. K. Schutte, et al. - Biologicals, 2017.
<https://www.sciencedirect.com/science/article/pii/S1045105617300647>

Current status of the Target Animal Batch Safety Test

Two VICH guidelines, the revised GL50 *Harmonisation of criteria to waive target animal batch safety testing for inactivated vaccines for veterinary use*⁵ and the new GL55 *Harmonisation of criteria to waive target animal batch safety testing for live vaccines for veterinary use*⁶ have been recently finalized. These guidelines were published in 2017, becoming operative in May 2018 (the guidelines also ease requirements on manufacturers by changing the way they are required to show consistency).

In 2012, the test was deleted from the Eu. Ph. monographs for all but 3 veterinary vaccines: Porcine actinobacillosis vaccine, Porcine progressive atrophic rhinitis vaccine and Tetanus vaccine for veterinary use. In the 3 remaining instances, it has been renamed "Residual toxicity test".

The USDA has updated in 2017 the Veterinary Science Memorandum No. 800.116 to implement the VICH GL50 & 55, stating that it "will consider granting an exemption to target animal safety testing for specific products with a documented history of acceptable safety results and controlled manufacturing processes that have ensured batch-to-batch consistency and sterility".

Also, Japan is a VICH region and has implemented the VICH GL50 & 55, and the authorities are receptive to granting waivers following VICH guidelines.

The World Organization for Animal Health (OIE) accepted a comment (from EPAA, submitted via the European DG SANTE in December 2017) on the possibility to mention VICH Guidelines 50 and 55 on the removal of the test in two chapters of its *Terrestrial Manual*. Amendments were adopted by the OIE World Assembly of Delegates at the end of May 2018: "Safety tests are not required by many regulatory authorities for the release of each batch or serial where the seed-lot system is used. Other regulatory authorities may allow waiving of target animal batch safety tests in line with VICH GL50 and 55"⁷.

In addition to TABST, there is also the ATT/GST or laboratory animal batch safety test (LABST) for veterinary vaccines still required in many countries. At VICH level, work is ongoing to draft a GL comparable to those for the TABST, which would allow waivers. As it happened for TABST, retrospective analysis of LABST⁸ data revealed that the test is no longer relevant and not able to detect problematic batches. In Europe, the LABST has been removed from European Pharmacopoeia monographs for veterinary vaccines in 1997⁹.

⁵ Harmonisation of criteria to waive target animal batch safety testing for inactivated vaccines for veterinary use: <http://www.vichsec.org/component/attachments/attachments/1325.html?task=download>

⁶ Harmonisation of criteria to waive target animal batch safety testing for live vaccines for veterinary use: <http://www.vichsec.org/component/attachments/attachments/1326.html?task=download>

⁷ OIE Manual of Diagnostics Tests and Vaccines for Terrestrial Animals 2018 – Chapter 3.7.2. Minimum requirements for the production and quality control of vaccines: http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/3.7.02_MANU_SITES_VACCINE_PROD_CONT_ROL.pdf

⁸ Duchow et al (1996). Abnormal Toxicity: a Study in the Relevance of the Requirement V.2.1.5 of the German Pharmacopoeia for Vaccines, Immunosera and Immunoglobulins. German Ministry of Research and Technology. Project No. 0310624, Final Report. Langen, Germany: Paul-Ehrlich-Institut

⁹ Schwanig M, Nagel M, Duchow K and Krämer B (1997). Elimination of abnormal toxicity test for sera and certain vaccines in the European Pharmacopoeia. Vaccine 15(10): 1047-1048.