



**HUMANE SOCIETY  
INTERNATIONAL**

## **Symposium on Global Harmonization of Vaccine Testing Requirements**

Making elimination of the  
ATT & TABST a concrete  
global achievement

**Rome, 19 March 2019**



Key experts and stakeholders in the field of human and veterinary vaccines met in Rome to discuss the need of global harmonization of batch release testing requirements, focusing on the elimination of the Abnormal Toxicity/General Safety (ATT / GST) Test for human vaccines, and the Target Animal Batch Safety Test (TABST) for veterinary vaccines.

Representatives from Argentina, Brazil, China, Europe, India, Russia, South Africa and the United States participated in a March 2019 symposium ‘*Global Harmonization of Vaccine Testing Requirements; Making the elimination of ATT and TABST a concrete global achievement*’, organized by Humane Society International as part of the Biomedical Research for the 21<sup>st</sup> Century (BioMed21) Collaboration<sup>1</sup>, to examine barriers to the removal of the ATT and TABST and agree to a possible strategy and roadmap to overcome them.

The symposium was kickstarted by Drs. Klaus Cussler (PEI, Germany) and Lukas Bruckner (Consultant, Switzerland), both nominated experts from the European Directorate for the Quality of Medicines (EDQM). Dr Cufßler traced the history of ATT, from its 19<sup>th</sup> century roots as an instrument to identify phenols-derived preservatives in diphtheria sera to its adoption into a host of regulations worldwide, and how in so doing, the test’s original purpose came to be forgotten.

He then expounded on the long time it took to delete ATT from the European regulations (from the 1980s until the test’s complete elimination from the European Pharmacopoeia in January 2019), and reported on the World Health Organisation’s November 2018 decision to discontinue the inclusion of the test from all guidelines for biologicals products.

Dr Bruckner focused his presentation on the TABST, highlighting the factors that render it unsuitable as a tool to demonstrate the safety of veterinary vaccines. He discussed the test’s inherent risk of false -positive and -negative results, as it is used to sample products created through already well-controlled processes (seed-lot system, extensive testing of starting materials, and GMP and/or quality assurance) which, as a consequence, may suffer usually only of very low concentration of potential contaminants. He also remarked on the impact on the test results’ reliability caused by the immune status of the tested animals and

<sup>1</sup> <http://www.biomed21.org>

their general health. Contrary to the case with ATT, he noted the relatively swift pace of its elimination from the European Pharmacopoeia, as well as the recent publication of VICH<sup>2</sup> GL50 and GL55 guidelines and the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals 2018<sup>3</sup> as examples of positive movement toward worldwide removal of the TABST. With these two presentations having laid a common background, each participant offered in turn specific details and reasons for the use, waiver or deletion of ATT and TABST in each represented country, offering all the participants a glance into the different world areas and regulations.

Time was also dedicated to the discussion of the Laboratory Animal Batch Safety Test (LABST), the equivalent of ATT for the veterinary products, and its elimination. Europe removed it from its Pharmacopoeia monographs for veterinary vaccines already in 1997, but it is still a required test for batch release in other countries. VICH has begun work on a specific guideline for its waiver in 2016.

## Discussion & Recommendations

The exchange of information culminated in a roundtable discussion regarding evidence supporting the deletion, or waiver, of the ATT and TABST, as well as barriers that continue to prevent some stakeholders from taking these steps. The majority of the countries represented have already taken significant steps toward deletion or waiving of both tests, while others continue to express concern that the elimination of those tests might adversely affect safety of vaccines or of other products.

Key points that emerged in this phase of the symposium included the following:

- **Lack of a full agreement on the reasons to stop the use of ATT and TABST**

A general consensus on the main scientific and regulatory reasons to remove ATT and TABST from vaccine batch release requirements can be reported. However, to facilitate the discussion among a few regional stakeholders that do not as yet have the removal of these tests in their agendas, case studies and more effective messaging and communication are needed to address specific concerns.

- **Need for streamlined implementation of waivers to the use of ATT and TABST**

In regions where these tests have been completely removed from relevant regulations, industry has ceased to employ them for vaccines marketed in those regions

alone. However, different countries that still maintain the tests as parts of their regulations/pharmacopoeias require manufacturers to submit to differing procedures to request a waiver. In Europe, to eliminate ATT a manufacturer is required only to communicate its decision to the regulatory authority; TABST and LABST aren't part of the pharmacopoeia since 2013 and 1997 respectively. In the United States the General Safety test (GST) has been revoked from regulations in 2015. In the case of those vaccines that have the GST already as part of the biologic license, manufacturers can request to discontinue its use from product release testing through an official request, and these requests are granted by the FDA when appropriate quality assurance safeguards existed for the vaccine. TABST is still a requirement in the USA, but the USDA-CVB has readied a memo with a defined pathway to request exemption for most products based on supportive data. In India, removal of the ATT requires establishing proof of consistency to the satisfaction of National Regulatory Authority. Brazil is contemplating the full removal of ATT, through the work of the Brazilian Pharmacopoeia Commission. A decision has been taken to remove it from 5 monographs – including those for tetanus, diphtheria and pertussis vaccines - for the next edition (April 2019). Removal of TABST will be a longer process, as no specific activity has been initiated yet. South Africa has decided to align with the WHO and Eu. Ph. guidelines. The South African regulatory authority has been informed of a complete halt of in vivo testing by the National Control Laboratory, which means that the ATT test is no longer performed for lot release. After formal acceptance by the regulatory authority of the deletion of the ATT, an amendment/variation will be made to the registration documents. In Argentina, ATT has been removed with the only exception of acellular pertussis, but it should be revoked in the next edition of the Pharmacopoeia.



This is just a brief overview of the different realities of

<sup>2</sup> <http://www.vichsec.org/guidelines/biologicals/bio-safety/target-animal-batch-safety.html>

<sup>3</sup> <http://www.oie.int/standard-setting/terrestrial-manual/access-online/>

vaccines production and testing, and yet the complexity and fragmentation of the regulatory landscape is already well evident, as is the lack of a sufficient level of harmonization. The consequence of this dishomogeneity is that a very relevant burden is imposed on manufacturers in terms of costs and complexities, which acts as a significant extra dimension to the challenge of achieving elimination of ATT, TABST and LABST.

- **Real and perceived issues for quality and safety assurance after the removal of ATT and TABST**

Stakeholders who have decided to accept waivers or exemptions rely on the demonstration of the consistency of the production and the quality assurance and pharmacovigilance tools that have proved to be a more effective approach than the use of ATT or TABST in the identification of non-conform or unsafe batches. However, doubts remain among some stakeholders on the efficacy of non-animal testing for their specific realities and purposes, which include not only contamination and degradation, but also counterfeit products. Further efforts are necessary to demonstrate the suitability of alternative approaches to demonstrate safety in those contexts.

- **Definition of a roadmap with a common and proactive strategy**

The participants agreed on the need to define a roadmap based on the reinforcement of key messages supported by data and case studies, and to the global promotion of such roadmap, targeting both new and existing stakeholders, which will be reached by the participants through their own networks (e.g. AVAREF, AU-PANVAC, DCVMN, and country specific pharmacopoeias' committees and/or regulatory authorities). To this end, Humane Society International offered assistance proposing to take an active role to facilitate this process and the creation and implementation of the roadmap, collaborating with each participant to define targeted actions for each stakeholder or agency, so to increase chance for discussion and to catalyze concrete decisions. Lastly, all the participants came to a shared vision on the cornerstones that the strategy should be built upon, which were identified in dialogue, mutual comprehension and information exchange as key instruments to be globally strengthened and fostered to proceed towards, and succeed in, in the elimination of ATT, TABST and LABST.



## Participants

*Dr. Patricia Aprea, National Administration of Drugs, Foods and Medical Devices (ANMAT), Argentina*

*Dr. Lukas Bruckner, Consultant / EDQM-nominated expert, Switzerland*

*Dr. Klaus Cussler, Paul-Ehrlich-Institut / EDQM-nominated expert, Germany*

*Dr. Sunil Goel, The Serum Institute of India, India*

*Dr. Marion Gruber, FDA Center for Biologics Evaluation and Research, USA*

*Dr. Marlies Halder, European Commission Joint Research Centre, Italy*

*Dr. Hongtao Jin, New Drug Safety Evaluation Center of Chinese Academy of Medical Sciences, China*

*Dr. Marianne Kaashoek, MSD Animal Health / VAC2VAC-nominated expert, The Netherlands*

*Dr. Derek Litthauer, University of Freestate / National Control Laboratory, South Africa*  
*Dr. Arthur Leonardo Lopes da Silva, ANVISA / Brazilian Pharmacopoeia Coordination (COFAR), Brazil*  
*Dr. Elena Sakanyan, Russian Pharmacopoeia Committee, FSBI "SCEEMP" of Ministry of Health, Russia*  
*Dr. Gautam Sanyal, Vaccines Analytics, USA*  
*Dr. Geetha Srinivas, USDA Center for Veterinary Biologics, USA*  
*Dr. Joris Vandeputte, International Alliance for Biological Standardization, Belgium*  
*Dr. Dimitriy Yakunin, Moscow Laboratory of control of medicines, FSBI "IMCESACMP" Roszdravnadzor, Russia*  
*Troy Seidle, Humane Society International, Canada*  
*Laura Viviani, Humane Society International, Switzerland*