HUMANE SOCIETY INTERNATIONAL

AFSA

The Process for the Deletion of ATT, TABST and LABST in India

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History of ATT, TABST, & LABST

- Developed - 1900s
- Phenol derived preservatives in diphtheria sera 
- Tetanus toxin in antiserum preparations. 

- Regulatory mandated general safety test
- To avoid batch-to-batch differences in quality
- Use extended well beyond its original scope.

- No reliable conclusions
- Variable and non-reproducible
- Non-specific – body weight, species, strain

- Do Not conform to ICH validation criteria for a QC test
  - specificity
  - reproducibility
  - detection limit
- False positive results
- Lack evidence for usefulness to predict/control harmful batches/adverse events

Rationale for deletion

- Seed lot system
- In-process testing requirements
- Controls of starting materials
- GMP, GLP
- Pharmacovigilance
- 3Rs as scientific and business relevant approach

Deleted by European regulatory authorities
- 1997 – ATT and LABST
- 2013 - TABST

Exception: LABST – vaccines of inherent safety risk
- residual toxicity of bacterial toxin in bacterial and/or toxoid vaccines
- residual live virus in vaccines containing an agent of public health concern

Global Regulatory Harmonization
- Reduce burden on production's logistics
- Reduce overall costs
- Facilitate products' availability across various markets.

ATT Deletion from the Indian Pharmacopoeia Monographs

INDIAN PHARMACOPOEIA COMMISSION
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F. No. T.11013/02/2018-AR&D

Date: 15th / 22nd July, 2020

To,

1. The Drugs Controller General (India)
2. CDSCO Zonal Offices
3. All State Drug Controllers
4. Members of the Scientific Body of IPC
5. Members of Sub-Committees of the Scientific Body of IPC
6. Directors of Drugs Testing Laboratories
7. Government Analysts
8. IDMA/OPPI/BDMA/FSSAI/Small Scale Industry Associations

Subject: Amendment List-06 to IP 2018

The 8th Edition of Indian Pharmacopoeia (IP) 2018 has become effective from 1st January, 2018. Based on scientific inputs, some IP monographs needed up-gradation and accordingly Amendment List-06 to IP 2018 is issued containing such amendments.

This is for notice and compliance with the IP 2018.

(Dr. Jai Prakash) 22/07/2020
Secretary-cum-Scientific Director (I/c)

Encl. Amendment List-06 to IP 2018

Process of TABST and LABST deletion in India

HUMANE SOCIETY INTERNATIONAL INDIA

Future of TABST and LABST in the Indian Pharmacopoeia Monographs

Key international and Indian experts and stakeholders in the field of veterinary vaccines met to discuss the future of the Target and the Laboratory Animal Batch Safety Test (TABST &LABST) in the Indian Pharmacopoeia monographs.

Representatives from the Indian Pharmacopoeia Commission (IPC), the Central Drugs Standard Control Organisation (CDSCO), industry representatives from both – the Indian Federation for Animal Health Companies (INFAH) and the Asian Animal Health Association (AAHA), together with experts from Europe and Humane Society International (HSI) joined an online workshop on February11th, 2021, 'Future of TABST and LABST in the Indian Pharmacopoeia Monographs' organized by Humane Society International/India (HSI/India) to agree on a concrete way forward for the deletion or waiver of both the Target Animal Batch Safety Test (TABST) and the Laboratory Animal Batch Safety Test (LABST[1]).

The online workshop was kickstarted with a welcome note by the Managing Director of HSI/India, Ms. Alokparna Sengupta, who explained the rationale behind their initiative to conduct a workshop to discuss the deletion of these two obsolete animal tests, based on the suggestion from the latest IPC Expert Committee on Veterinary Vaccines meetings on 24th June 2020 and on 28th October 2020. Dr Brinda Poojary, the Science Advisor at HSI/India, continued by summarizing the history of these tests, originally used to control the phenol levels in diphtheria vaccines, and to detect contamination of tetanus toxin in diphtheria and other sera. Over time, these tests were applied to test the general safety of the vaccine, where the endpoint checked was 'unfavourable changes' attributable to the biological product, or 'ill-health', or 'death' of the animals. However, these results do not specifically point out the issue with the vaccine nor the erroneous steps during production. Today, with the establishment of good manufacturing practices, QA and QC in-process control production's processes in place, TABST and LABST have become redundant, unnecessary, time and cost intensive. The deletion of TABST and LABST will not compromise the quality of the product in any way. Unlike what is commonly believed, there is no requirement for any alternative model. The pre-requisite for the deletion of these tests is the establishment of good manufacturing practices and quality assurance, quality control and seed lot system, to avoid contamination or production related issues.

Presentations

Dr Lukas Bruckner, consultant representing the European Directorate for the Quality of Medicines & Healthcare (EDQM), 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. The test 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), as a result, it may suffer only a very low concentration of potential contaminants. He also

[1] LABST is the veterinary vaccineequivalent of the Abnormal Toxicity Test, recently deleted for human vaccines in the IP2018 (date and link)

2019 HSI India engagement with IPC

2020 HSI India involvement in IPC Expert Committee meetings for Veterinary Vaccines

Suggestion for dedicated workshop for discussion of future of TABST and LABST during Expert Meetings

2021 HSI India organized the workshop on 11th Feb 2021

- IPC
- National industry stakeholders
- Industry association – INFAH and AAHA
- International stakeholders - European Pharmacopoeia, VICH, and MSD

Future steps discussed and mutually agreed upon by industry and regulatory stakeholders

4 Possible Scenarios Discussed for the Future of TABST and LABST in the IP Monographs

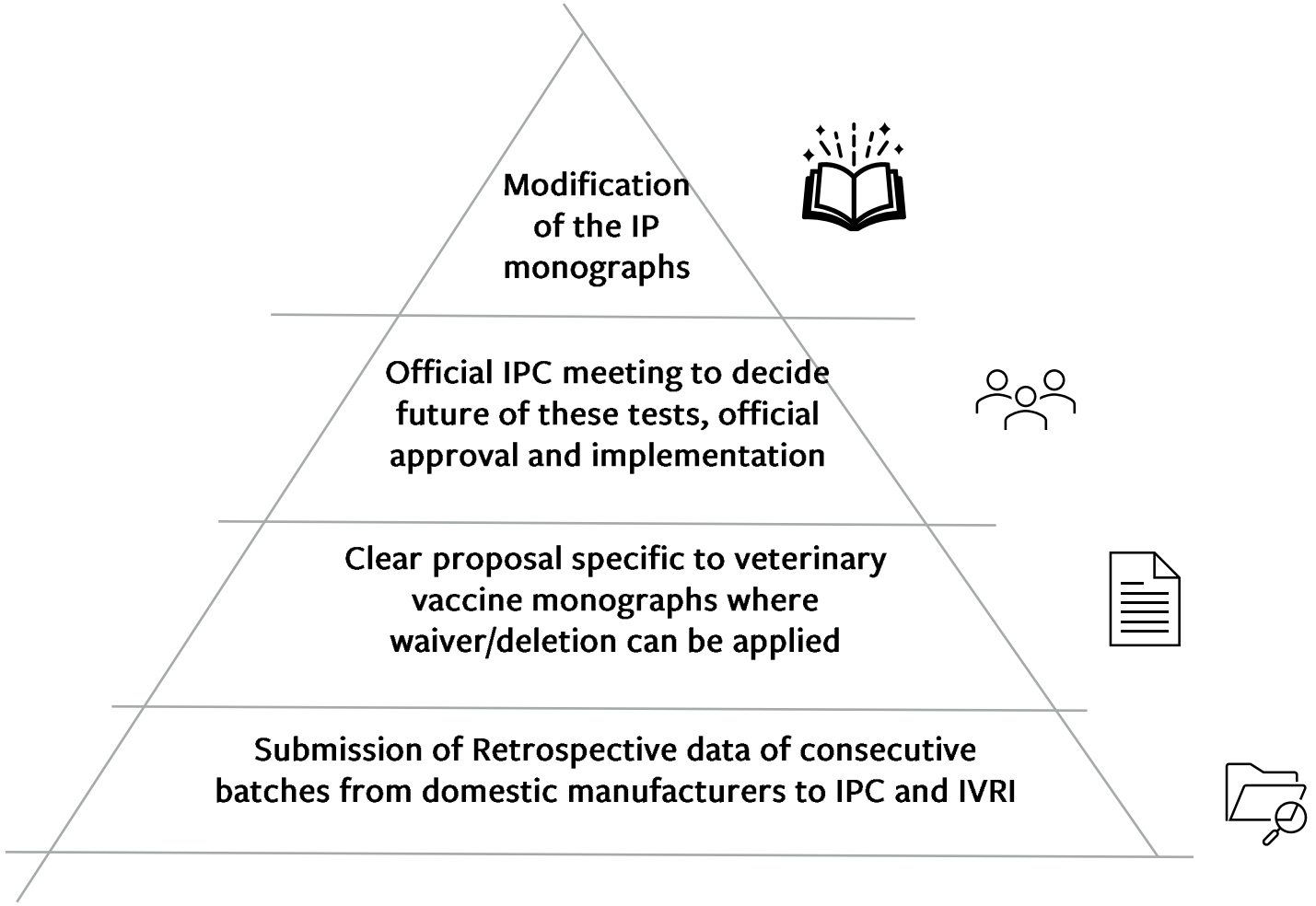
Deletion of general batch safety testing from Pharmacopeia(s) and Regulatory Requirements by Committee(s) or Authority(ies)

Product specific **variation** with data package to support **deletion** of TABST from dossier

Stepwise approach:
1st step - temporary waiver
2nd step - deletion

Product specific **variation** with data package to support **waiver** of TABST from dossier

Future of TABST and LABST in the Indian Pharmacopoeia Monographs – Next Steps



HSI India Activities to Promote Non-Animal Methodologies

Collaboration

- Atal Incubation Centre – Centre for Cellular and Molecular Biology - 2019
- Establishment of the Centre for Predictive Human Model Systems - 2019

Funding

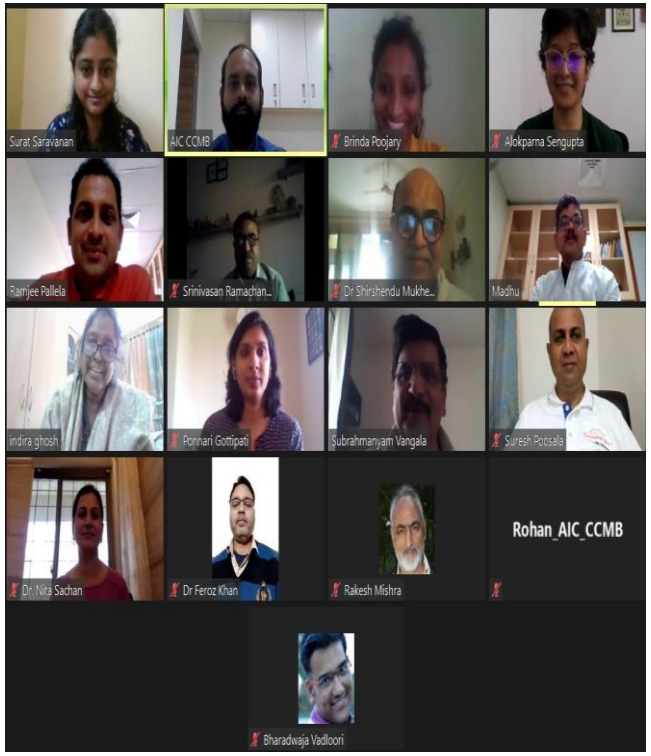
- Scientific and Regulatory Roundtables
- Proposals and representations for increasing funding into non-animal science

Capacity Building

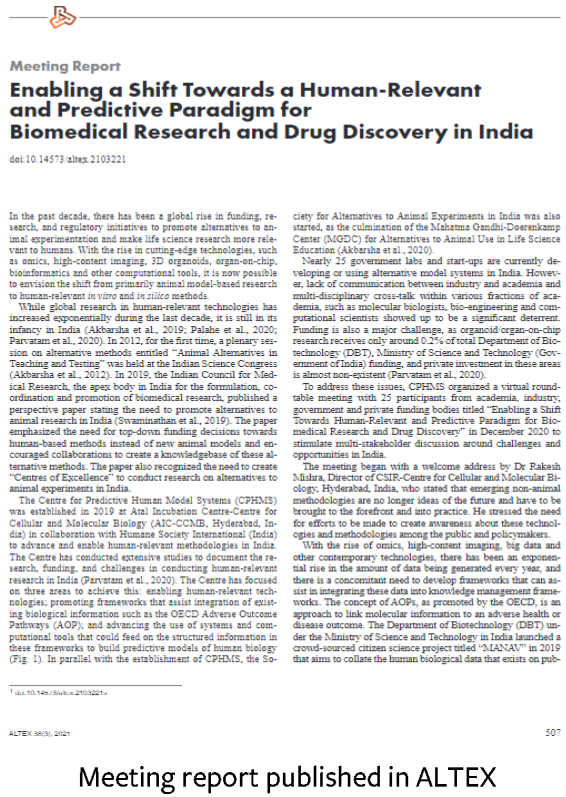
- Grant for review papers on failing animal models for disease research
- Grant for development of Adverse Outcome Pathways and submission into OECD AOP Wiki
- Workshops on Adverse Outcome Pathways
- Free webinar series on Non-Animal Methodologies
- Whitepapers and scientific publications on non-animal methods

Regulatory Engagement

- Harmonization in regulatory requirements to increase uptake of non-animal methodologies and reduce/replace the use of animals across toxicity testing of substances



Scientific Roundtable to Promote Funding into Non-Animal Science in 2020



Meeting Report

Enabling a Shift Towards a Human-Relevant and Predictive Paradigm for Biomedical Research and Drug Discovery in India

doi:10.14573/altex.2103221

In the past decade, there has been a global rise in funding, research, and regulatory initiatives to promote alternatives to animal experimentation and make life science research more relevant to humans. With the rise in cutting-edge technologies, such as omics, high-content imaging, 3D organoids, organ-on-chip, bioinformatics and other computational tools, it is now possible to envision the shift from primarily animal model-based research to human-relevant *in vitro* and *in silico* methods.

While global research in human-relevant technologies has increased exponentially during the last decade, it is still in its infancy in India (Akbarsha et al., 2019; Palahe et al., 2020; Parvatam et al., 2020). In 2012, for the first time, a plenary session on alternative methods entitled "Animal Alternatives in Teaching and Testing" was held at the Indian Science Congress (Akbarsha et al., 2012). In 2019, the Indian Council for Medical Research, the apex body in India for the formulation, coordination and promotion of biomedical research, published a perspective paper stating the need to promote alternatives to animal research in India (Swaminathan et al., 2019). The paper emphasized the need for top-down funding decisions towards human-based methods instead of new animal models and encouraged collaborations to create a knowledgebase of these alternative methods. The paper also recognized the need to create "Centres of Excellence" to conduct research on alternatives to animal experiments in India.

The Centre for Predictive Human Model Systems (CPHMS) was established in 2019 at Atal Incubation Centre-Centre for Cellular and Molecular Biology (AIC-CCMB, Hyderabad, India) in collaboration with Humane Society International (India) to advance and enable human-relevant methodologies in India. The Centre has conducted extensive studies to document the research, funding, and challenges in conducting human-relevant research in India (Parvatam et al., 2020). The Centre has focused on three areas to achieve this: enabling human-relevant technologies; promoting frameworks that assist integration of existing biological information such as the OECD Adverse Outcome Pathways (AOP); and advancing the use of systems and computational tools that could feed on the structured information in these frameworks to build predictive models of human biology (Fig. 1). In parallel with the establishment of CPHMS, the Society for Alternatives to Animal Experiments in India was also started, as the culmination of the Mahatma Gandhi-Doerenkamp Center (MGDC) for Alternatives to Animal Use in Life Science Education (Akbarsha et al., 2020).

Nearly 25 government labs and start-ups are currently developing or using alternative model systems in India. However, lack of communication between industry and academia and multi-disciplinary cross-talk within various fractions of academia, such as molecular biologists, bio-engineering and computational scientists showed up to be a significant deterrent. Funding is also a major challenge, as organoid/organ-on-chip research receives only around 0.2% of total Department of Biotechnology (DBT), Ministry of Science and Technology (Government of India) funding, and private investment in these areas is almost non-existent (Parvatam et al., 2020).

To address these issues, CPHMS organized a virtual roundtable meeting with 25 participants from academia, industry, government and private funding bodies titled "Enabling a Shift Towards Human-Relevant and Predictive Paradigm for Biomedical Research and Drug Discovery" in December 2020 to stimulate multi-stakeholder discussion around challenges and opportunities in India.

The meeting began with a welcome address by Dr Rakesh Mishra, Director of CSIR-Centre for Cellular and Molecular Biology, Hyderabad, India, who stated that emerging non-animal methodologies are no longer ideas of the future and have to be brought to the forefront and into practice. He stressed the need for efforts to be made to create awareness about these technologies and methodologies among the public and policymakers.

With the rise of omics, high-content imaging, big data and other contemporary technologies, there has been an exponential rise in the amount of data being generated every year, and there is a concomitant need to develop frameworks that can assist in integrating these data into knowledge management frameworks. The concept of AOPs, as promoted by the OECD, is an approach to link molecular information to an adverse health or disease outcome. The Department of Biotechnology (DBT) under the Ministry of Science and Technology in India launched a crowd-sourced citizen science project titled "MANAV" in 2019 that aims to collate the human biological data that exists on pub-

ALTEX 38(3), 2021

Meeting report published in ALTEX

Thank you!