S21: Remove ATT, TABST & LABST. How far away are we to global harmonization for those safety tests?

HUMANE SOCIETY INTERNATIONAL

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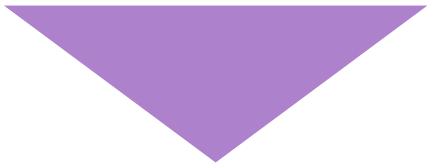
This Session

- Laura Viviani (Humane Society International): Remove ATT, TABST & LABST. How far away are we to global harmonization for those safety tests?
- Katrin Schutte (EPAA - European Partnership for Alternative Approaches to Animal Testing): REMOVE ATT, TABST & LABST. The journey of how they became obsolete.
- Corinne Philippe (Boehringer Ingelheim): Waiving the Target Animal Batch Safety Tests of veterinary vaccines. An industry perspective.
- Marcos Vinicius de Santana Leandro (Ministry of Agriculture Brazil): The interest to adopt a change on TABST & LABST in Brazil.
- Brinda Poojary (Humane Society International, India): The process for the deletion of ATT, TABST and LABST in India.
- Sunil Kumar Goel (Serum Institute of India): Removal of Abnormal Toxicity Test from human vaccines in India: a successful approach.

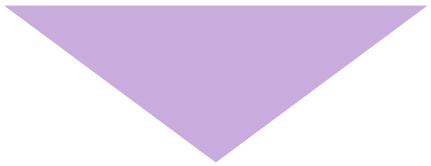
Objectives

Many institutions and organization have been working independently or jointly to remove those obsolete safety testing from the batch release testing for human (ATT) and veterinary vaccines (TABST, LABST). Many regulatory agencies and international organizations have successfully removed or recommended the deletion or the waiver of those tests. How far away are we from the global elimination of those tests?

Map the status of ATT, TABST & LABST deletion



Present the process and the stakeholders involved



Share some concrete and successful examples

Remove ATT, TABST & LABST. How far away are we to global harmonization for those safety tests?

Laura Viviani
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Research &Toxicology
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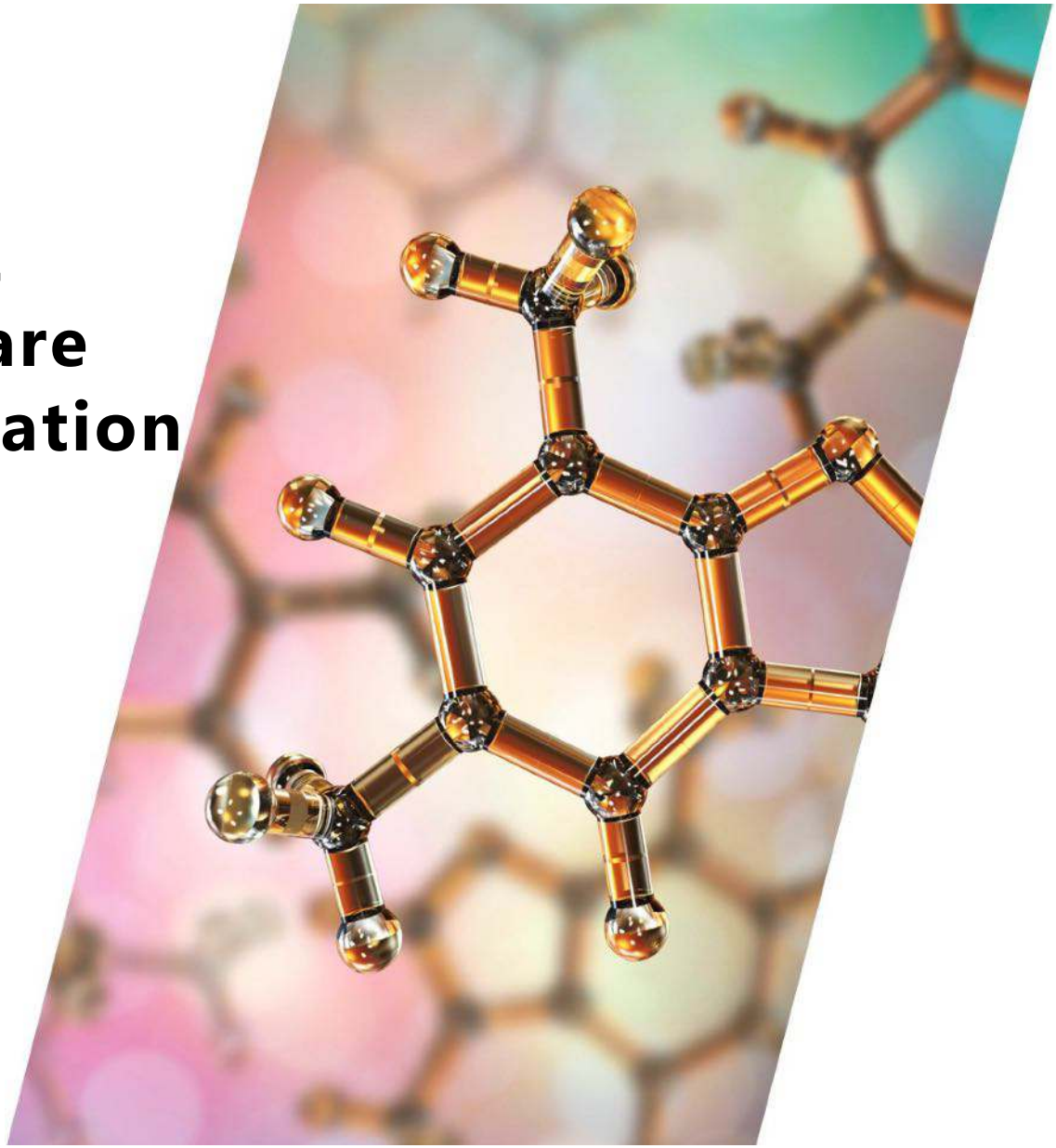


ADVANCING

PREDICTIVE, NON-ANIMAL

APPROACHES IN TOXICOLOGY

& BIOMEDICAL RESEARCH

WORLDWIDE

About the Humane Society family of organizations

- HSI & its affiliates together represent the largest force for animal protection globally, active on the ground in >50 countries across the Americas, Europe, Asia & Africa
- Our team brings together experts in human & environmental toxicology, regulatory science, public policy, law, biomedicine, etc.
- Working with lawmakers, regulators, industry, test developers & other stakeholders
- Stakeholder status with the OECD, governmental & corporate advisory bodies on alternative methods & product safety, etc.

HUMANE SOCIETY INTERNATIONAL | THE HUMANE SOCIETY OF THE UNITED STATES | HUMANE SOCIETY LEGISLATIVE FUND

AFSA COLLABORATION

The AFSA Collaboration works to accelerate global adoption of a modern, species-relevant approach to safety assessment that will better protect people and our planet, and hasten the replacement of animal testing.

COSMETICS

CHEMICALS

BIOLOGICALS

TOX21

P&G

Unilever

L'ORÉAL

Firmenich

ExxonMobil

ATAL INCUBATION CENTRE CENTRE FOR CELLULAR & MOLECULAR BIOLOGY

IABS

LUSH
FRESH HANDMADE COSMETICS

H&M

AVON

iff

symrise

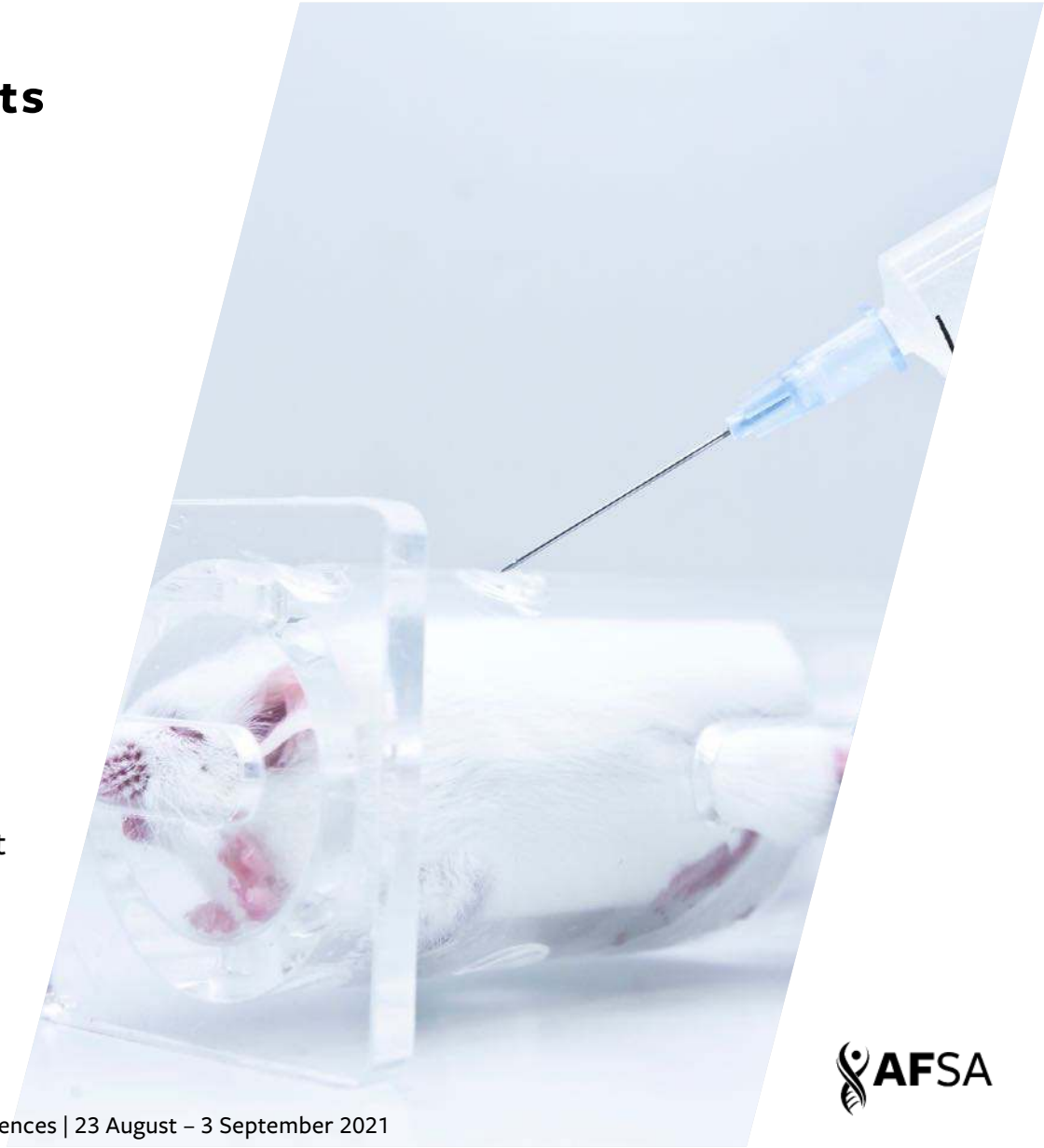
Lhasa Limited

IIVS
Institute for In Vitro Sciences

Listed organizations are members of at least 1 AFSA workstream; listing does not imply participation in or endorsement of other work areas

Biologicals Regulatory Requirements
Issue overview

- 10-15 million animals used for batch release testing*
- Final animal-based batch release testing is still viewed as the 'gold standard' in many countries
- Legacy vaccines: fundamental vaccines for worldwide health safety & highest consumption of animals; also where we can have the most significant economic, safety & availability impacts
- 3Rs + consistency approach being introduced & sometimes implemented in WHO, OIE, EU, US, Canadian & Indian regulations; others are considering it
- 3Rs + consistency approach can significantly reduce the cost of vaccines eliminating, reducing/replacing *in vivo* testing & can reduce lead-time of batch release**



* It is an estimation: few countries/regions collect precise numbers of animals used for research purposed

** ~$1K USD for a 28 days batch release test in India vs 5 USD for 1 day in vitro potency test. Source Vaccine Manufacturer, India

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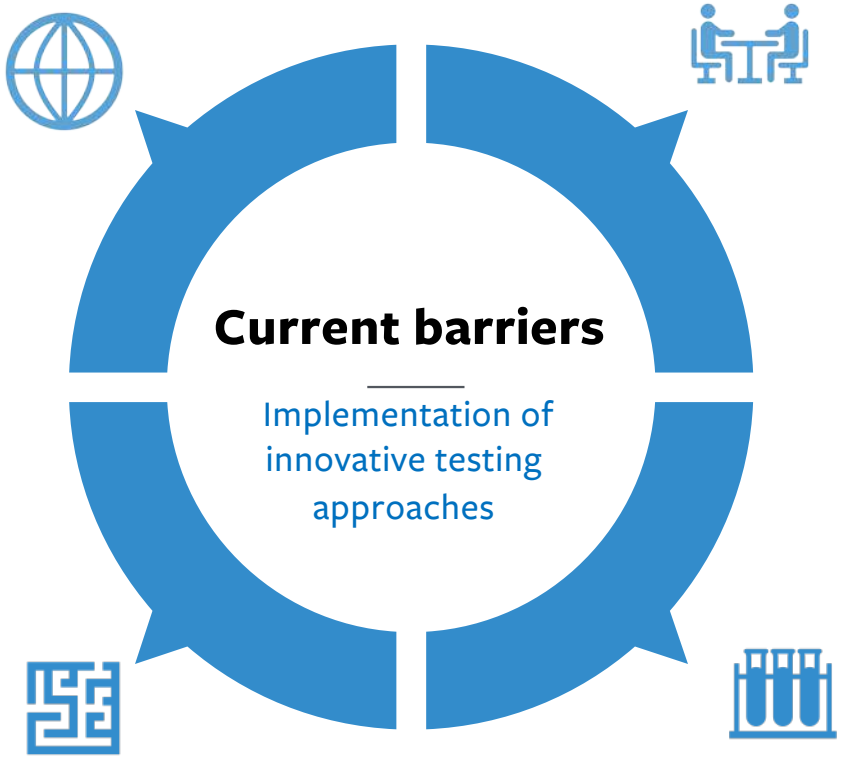
Lack of regulatory alignment

Varying national requirements challenge manufacturers, drive up costs & hinder transition to NAMs.



Industry/regulator relationships

The relationship between industry & regulators is complex, often hindered by uncertainty regarding data, priorities, perspectives & responsibilities; need greater openness regarding expectations, data requirements & information availability

Regional infrastructures

Economic, technical & human resources challenges/possibilities differ among countries. No silver bullet; tailored approach is needed, based on a thorough understanding of local issues & complexities

New methods for old products

Transitioning old products to non-animal-based methods can be a challenge due to poor product characterization &/or complexities in new methods development & validation

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Based on HSI's experience and on the exercise reported in Bruyster et al. Biologicals 2017 and in Akkermans et al, 2020.

Biologicals Workstream Strategy

IDENTIFY 'RIPE' 3R OPPORTUNITIES

- Deletion/waiving of Abnormal Toxicity & Target Animal Batch Safety tests
- Replacement of Rabbit Pyrogen & LAL tests with Monocyte Activation Test or recombinant Factor C.

ENGAGE & INFORM KEY STAKEHOLDERS

- Recruit interested regulators, companies & other stakeholders
- Host workshops to share best practices, success stories, identify barriers & possible solutions
- Peer reviewed publications

GLOBAL REGULATORY ALIGNMENT

- Advance changes to national regulations, pharmacopeia monographs/test guidelines, etc.
- Communicate best practices

"We are working to accelerate the removal of obsolete *in vivo* testing requirements from human & veterinary vaccine regulatory frameworks globally"

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Biologicals Workstream Projects

Scheduled Activities in 2021-22

ABNORMAL TOXICITY TEST DELETION

Human Immonobiologicals (incl. Vaccines)

Global
Prioritized Countries:
India (*done for vaccines*)
South Korea
Indonesia
China
Russia
Japan
South America

ANIMAL BATCH SAFETY TEST DELETION

Veterinary Vaccines

Global
Prioritized Countries:
North America
India
Brazil
South Korea
Indonesia
China
Russia

PYROGENICITY

Biologicals

Global
Brazil
India

International workshop on deletion of ATT & TABST

March 2019, Rome

- Brought together experts, regulators & industry from Argentina, Brazil, China, Europe, India, Russia, South Africa, Switzerland & USA
- Report accepted for publication in *Biologicals*
- Secured funding with the Bill & Melinda Gates Foundation to advance tests deletion in Russia, India, South Korea, Indonesia, China and Brazil till 2022.

https://www.gatesfoundation.org/How-We-Work/Quick-Links/Grants-Database/Grants/2019/10/INV-003740

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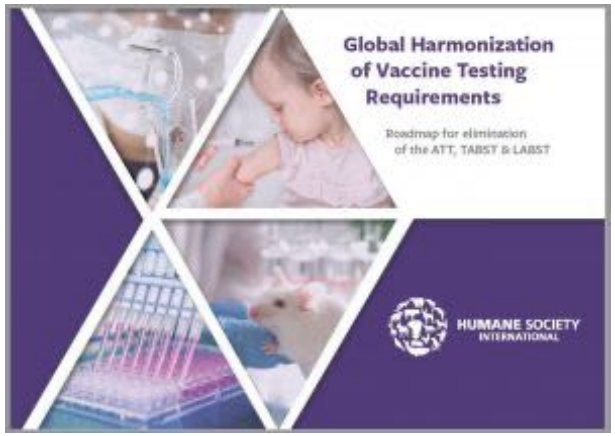
AFSA Roadmap for the Elimination of ATT, TABST & LABST

- ✓ Establish a climate that is conducive, and fertile, to the use of innovative non-animal methods and delete obsolete testing.
- ✓ Build multi-stakeholders collaborations: involving all stakeholders in an exercise of mutual transparent **cooperation and trust-building**.
- ✓ Facilitate science-driven dialogue, mindful of various cultural and policy difference.
- ✓ Share virtuous examples to promote what is possible
- ✓ Leverage benefits in terms of costs, time and safety to stimulate regulatory and industry to take onboard innovation.



Download the AFSA Roadmap for the Elimination of ATT, TABST & LABST:
English, Chinese, Korean, Portuguese, Russian
www.afsacollaboration.org/biologicals/vaccines-regulatory-alignment

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ATT Global Status

CONFIRMED DELETION

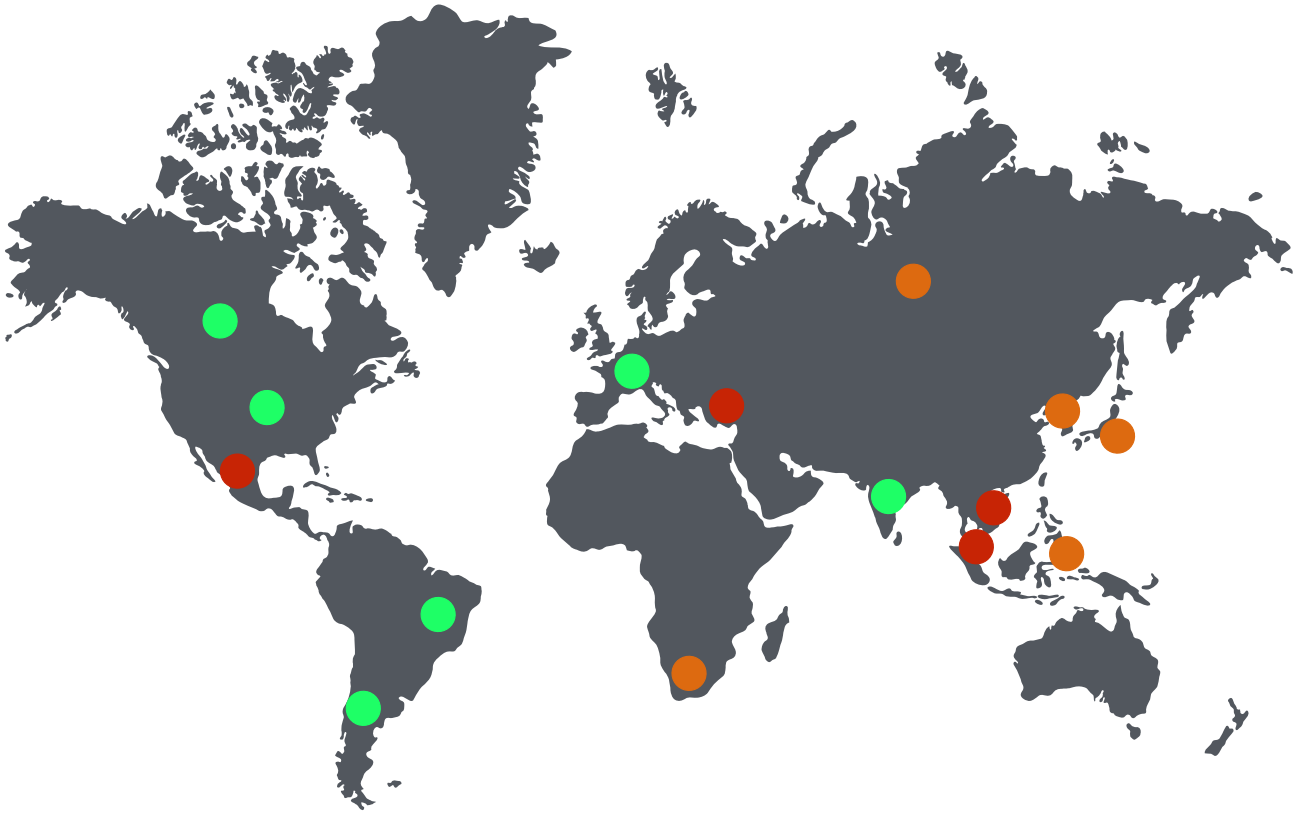
(Test removed from regulatory requirements)

- → Europe
- → Canada
- → United States
- → India (almost all vaccines)
- → Brazil (one expection)
- → Argentina (one exception)

STILL REQUIRED

(Recently reported interest in advancing discussions)

- → Mexico
- → Turkey
- → Vietnam



DISCUSSION on DELETION or WAIVER ONGOING

(different level of engagement and planning, test still required)

- → South Korea
- → Indonesia
- → China
- → Japan (waivers)
- → South Africa
- → Russia
- → Thailand

WHO RTS 1016, 2018 recommended the deletion of the test

* Eurasian Pharmacopoea will replace the Russian Pharmacopoeia and will be the regulation for Russia, Armenia, Belarus, Kazakistan, Kirgizistan. The regulatory requirements will be the same as per the current Russian Pharmacopoeia.

** Africa has not yet an harmonized regulatory system. Laboratories follows mainly the WHO International Pharmacopoeia.

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ATT Deletion Status

WHAT IS HAPPENING AND WHERE

→ **Brazil**, deleted for all but one injectable product, 6th Edition of the Brazilian Pharmacopoeia (2019).

→ **Argentina**, 7th Edition, 2013 - not required in the vaccines' marketing authorization and in the batch release testing. (aP vaccine still has ATT but the monograph is under review).

→ **South Africa**, the NCL stopped to perform ATT in December 2019.

→ **Japan**, May 2020, the notification No.221 introduced ATT exemption rule for the Influenza HA vaccine, Haemophilus b conjugate vaccines, pneumococcal polysaccharide vaccine and Japanese encephalitis vaccine lot release (Hepatitis B vaccine exemption was already in place).

→ **India**, deleted from IP2018 for almost all human vaccines in July 2020.

→ **South Korea** plans to delete ATT within 2021 (not performed by the NCL since 2020).

→ **China:** still required in the Chinese Pharmacopoeia 2020.

→ **Russia:** long-term plan to reduce the testing, products for which the production stability has been confirmed, the ATT can be performed only for 1 series every 5.

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TABST&LABST Global Status

International Guidelines for the waivers: VICH GL 50, GL55, GL59 – Reported into the OIE Guidance.

CONFIRMED DELETION

(Tests removed from regulatory requirements)

→ Europe

CONFIRMED WAIVER

(Waivers are approved based on data submission to regulatory authorities)

→ United States

→ Japan

→ Canada

DISCUSSION on DELETION or WAIVER ONGOING

(different level of engagement and planning, test still required)

→ India

→ Brazil

STILL REQUIRED

(Tests required, limited options for policy changes or difficulties in stakeholders engagement)

→ South Korea

→ China

→ Russia

AD-HOC WAIVER AUTHORIZED

Leading multinational veterinary vaccines manufacturers have been able to waive TABST for some products based on variations requests submitted to local regulatory authorities even where the waiver is not officially recognized within the regulatory framework. Company specific and product specific experience.

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TABST&LABST Global Status

- ✓ Harmonisation of criteria to waive TABST / LABST for veterinary vaccines
- ✓ GLs developed by VICH experts
- ✓ Outreach to VICH Forum members to extend waivers implementation
- ✓ Country/region differences in quality standards and pharmacovigilance systems
- ✓ Country specific strategy (Brazil, India)

Animal species	Inactivated vaccines	Live vaccines
Target animals	GL50R (2017) 1st release in 2013	GL55 (2017)
Laboratory animals (mice, guinea pigs)	GL59 (2020)	

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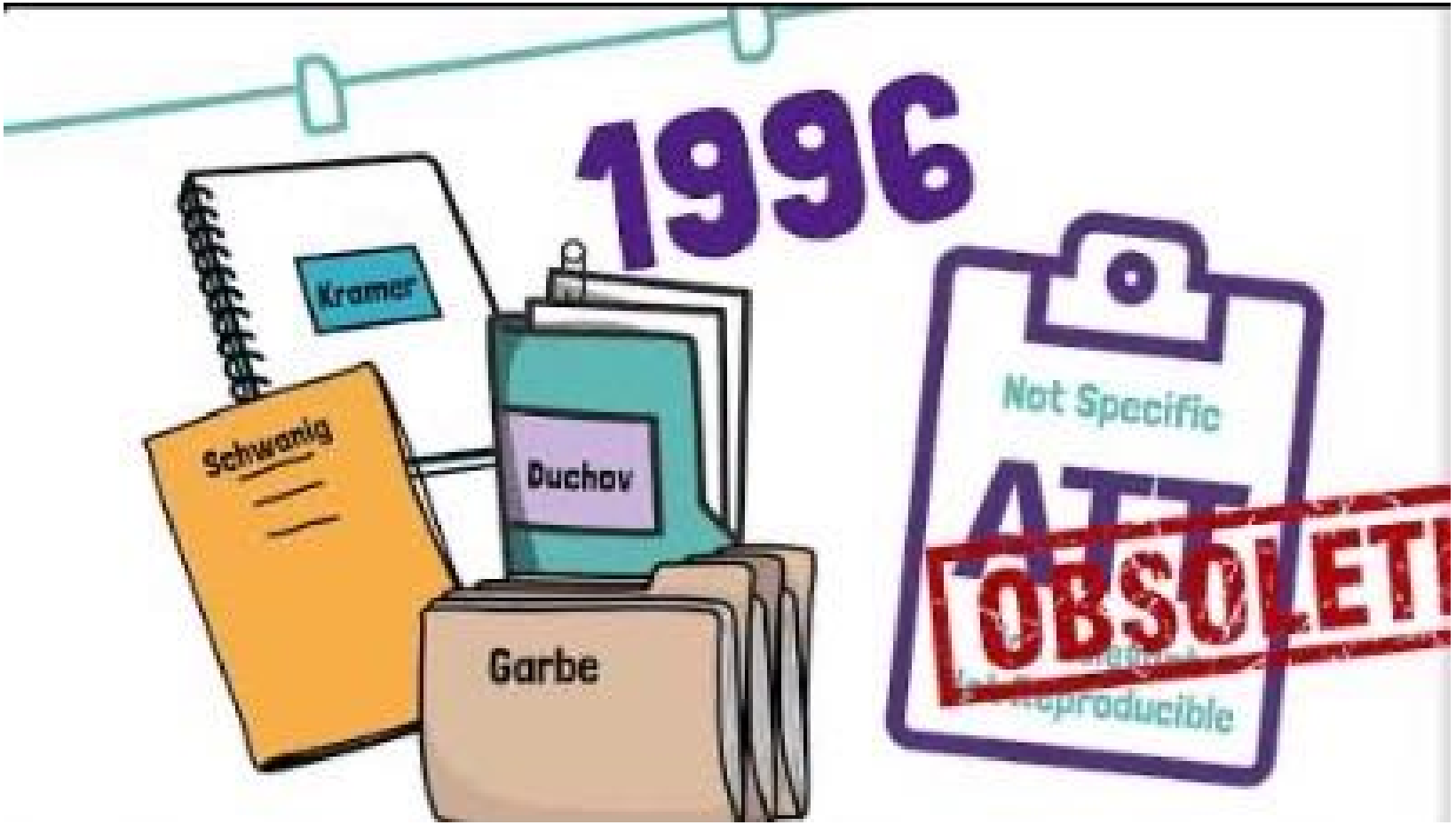
Next Steps

Accelerating Global Deletion of the Abnormal Toxicity Test.
Planning common next steps.

A workshop organized by AFSA/HSI and EFPIA in collaboration with IABS
October 14th, 2021 // 12:30 – 16:30 CET
To register go to
www.afsacollaboration.org
www.efpia.eu


1996
Kramer
Schwanig
Duchov
Garbe
Not Specific
OBSOLETE

Thank you!

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