WAIVING the TARGET ANIMAL BATCH SAFETY TEST at MSD ANIMAL HEALTH

HSI Symposium 2019 - Rome

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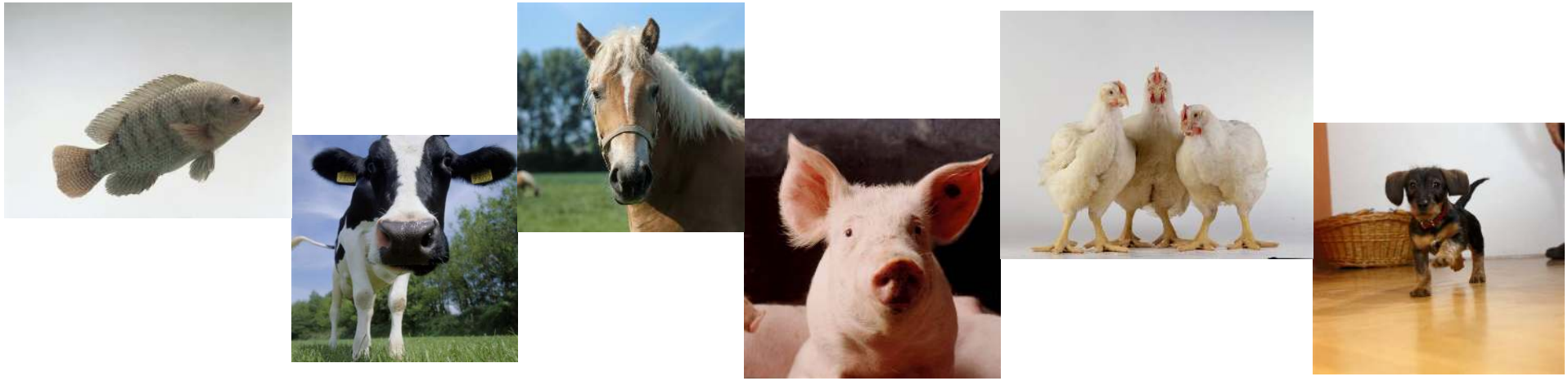
- One of the larger animal health companies in the world
- >130 different vaccines (for food production and companion animals)
- Registrations in 100+ countries



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TABST: Target Animal Batch Safety Test

- **Why:** Routine test to demonstrate that each batch is safe in the target animal. Required by EU guidelines until March 2013.

- **How:** Administration of repeated dose/overdose of final product to target animal (2 mammals, 10 birds, 10 fish) for each batch.
  Examination of animals for local or systemic clinical signs/reactions

- **Products:** All biological products

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Reasons to waive the TABST for veterinary vaccines

- The relevance of batch safety tests is questionable (relevance of n=2?)
- Consistency of production increased (GMP, GLP)
  - Quality incoming goods
  - Seed-lot-system
  - Manufacture according controlled processes
  - Standardised testing during production
- Pharmacovigilance (post-marketing surveillance of medicines)
  - No signaling for batch related issues
- 3Rs principle (Replacement, Refinement, Reduction)

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Waiving TABST: How it started

Date	Activity
May 2012	Ph. Eur. Commission adopted waiving of TABST for practically all veterinary vaccines
01-10-2012	Date of publication in Ph. Eur. • The general monograph on *Vaccines for veterinary use (0062)* • Deletion of the TABST from the European Pharmacopoeia for all veterinary vaccines
01-04-2013	**Required** implementation date (6 months after publication!)

Exceptions:

- *Porcine actinobacillosis vaccine (inactivated) (Ph. Eur. monograph 1360)*,
- *Porcine progressive atrophic rhinitis vaccine (inactivated) (Ph. Eur. monograph 1361)*
- *Tetanus vaccine for veterinary use (Ph. Eur. monograph 0697)*

These tests are now called: Residual toxicity test

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Expectations at start of project

- Reduction of animal use
- Financial benefits through reduction of animal testing costs (facilities, personnel)
- Project with medium complexity, enabling smooth implementation process

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Challenges

- 130 vaccines and 5 production sites in scope
- Impacted vaccines are not sold in the EU only but all over the world (≥107 non-EU countries)
- Many countries have their own regulatory requirements (not possible to simply remove the TABST)

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Approach

- Formation of cross-functional team:
  - Supply Chain, Regulatory Affairs, Planning, Quality, Global Tech Support
  - Core team 8 colleagues; in total 40 colleagues involved

- RA strategy:
  - EU countries:
    - No variations
    - One notification encompassing all products
  - Non-EU Ph. Eur. member countries (e.g. Switserland, Norway, Iceland)
    - One variation for all products involved
  - Extension of project to non-EU countries:
    - Pilot with variation to delete TABST for one product
    - Variation to delete TABST for all (other) products

- Grouping of products in 4 scenarios

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Defined scenarios

	Scenario		Action
1	**Product on TABST-free markets only**	→	Remove TABST
2	**Product on TABST-free and TABST-requiring markets:**	→	2 different product streams: batches with and without TABST (huge logistic impact !)
3	**Product on TABST-requiring markets only/mainly**	→	Keep TABST
4	**TABST is coupled to in-vivo extraneous agents test**	→	Keep TABST -for inac poultry vaccines [deleted in 2017] -for a number of vaccines for mammals

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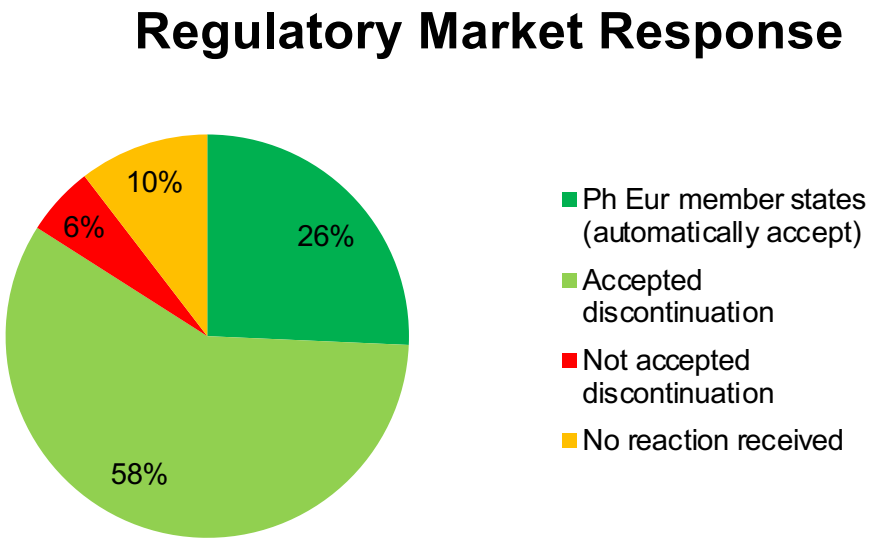
Initial acceptance (2015)



Response	Number of non-EU countries	TABST
Accepted waiving TABST	84	No
Did initially not accept waiving TABST	8	YES
No reaction	15	YES

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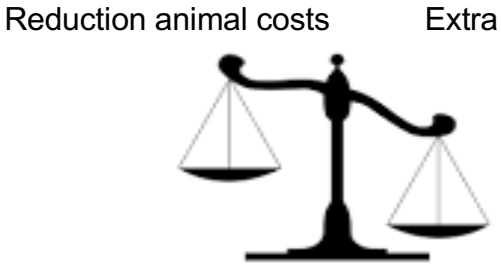
Initial effects of waiving TABST at MSD AH (2015)

- **Financial/logistic efforts and effects**
  - Minimal reduction in total animal costs (animal facilities + resources)
  - Extra costs due to stock building of batches with and without TABST
  - Project duration: 2 years
  - Implementation costs



- **Reduction of animal use**
  - 75% of the batches of the products in scope can be released without safety test
  - Reduction of > 600 animal tests/year
  - Saving of > 3000 experimental animals/year

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TABST deletion

Paraphrasing astronaut Neil Armstrong:

**“One simple (but welcome) regulatory step in Europe,
a giant operation for a global AH company !”**

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Current status (2019)

Further decline in number of countries asking for TABST:

- Some countries accepted deletion of TABST by manufacturer, but will test locally.
- Some countries accept deletion of TABST after presenting data on a large number of batches with a variation application.
- Some countries accept deletion of TABST for new products, but not for already registered products.
- Three countries still require TABST for most products.
- For each product double product streams still needed.
- Animal tests and facilities to be maintained.

- **To note: special permit to perform TABST expires April 2021.**

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Conclusion

Testing for TABST has no added value with respect to the safety of the products, but is a burden for the manufacturer and the animals.

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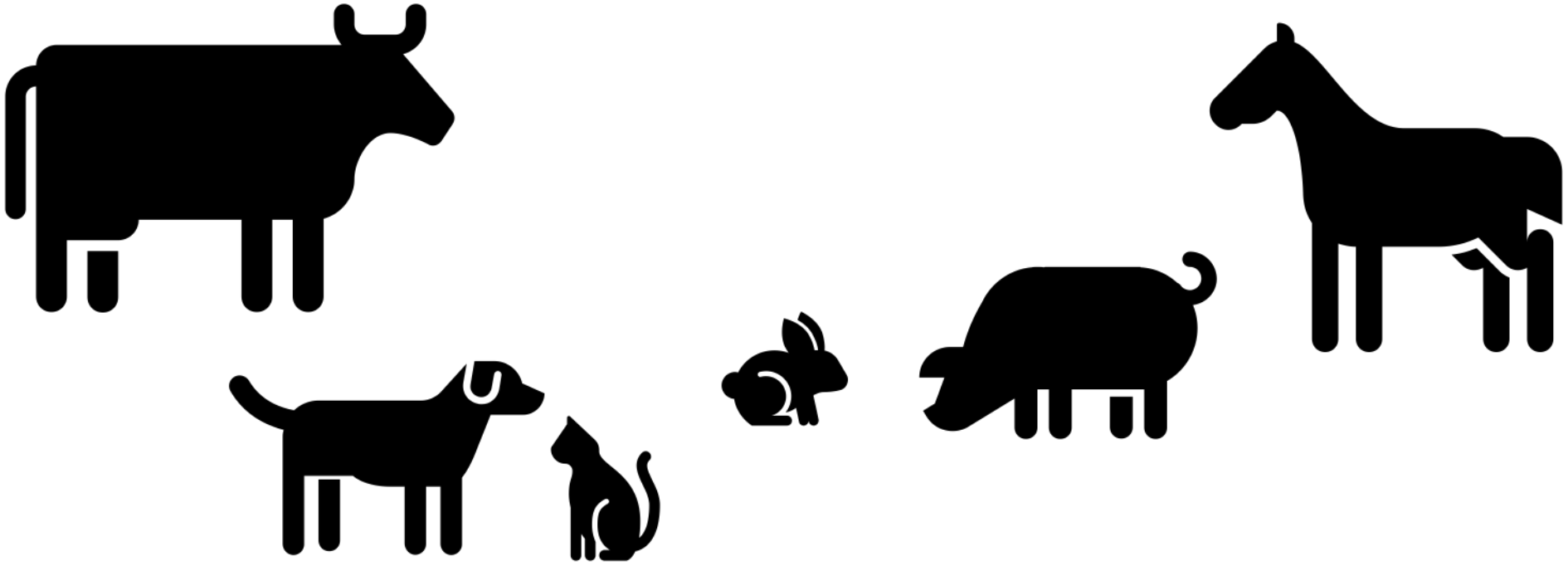
Thank you from all of us!



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