WAIVING the TARGET ANIMAL BATCH SAFETY TEST at MSD ANIMAL HEALTH

HSI Symposium 2019 - Rome
MSD Animal Health

- One of the larger animal health companies in the world
- >130 different vaccines (for food production and companion animals)
- Registrations in 100+ countries
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
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)
**Waiving TABST: How it started**

<table>
<thead>
<tr>
<th>Date</th>
<th>Activity</th>
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<tbody>
<tr>
<td>May 2012</td>
<td>Ph. Eur. Commission adopted waiving of TABST for practically all veterinary vaccines</td>
</tr>
<tr>
<td>01-10-2012</td>
<td>Date of publication in Ph. Eur.</td>
</tr>
<tr>
<td>01-04-2013</td>
<td><strong>Required</strong> implementation date (6 months after publication!)</td>
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**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
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
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)
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. Switzerland, 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
<table>
<thead>
<tr>
<th>Scenario</th>
<th>Action</th>
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<tbody>
<tr>
<td>1 Product on TABST-free markets only</td>
<td>Remove TABST</td>
</tr>
<tr>
<td>2 Product on TABST-free and TABST-requiring markets:</td>
<td>2 different product streams: batches with and without TABST (huge logistic impact !)</td>
</tr>
<tr>
<td>3 Product on TABST-requiring markets only/mainly</td>
<td>Keep TABST</td>
</tr>
<tr>
<td>4 TABST is coupled to in-vivo extraneous agents test</td>
<td>Keep TABST -for inac poultry vaccines [deleted in 2017] -for a number of vaccines for mammals</td>
</tr>
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Initial acceptance (2015)

Regulatory Market Response

<table>
<thead>
<tr>
<th>Response</th>
<th>Number of non-EU countries</th>
<th>TABST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accepted waiving TABST</td>
<td>84</td>
<td>No</td>
</tr>
<tr>
<td>Did initially not accept waiving TABST</td>
<td>8</td>
<td>YES</td>
</tr>
<tr>
<td>No reaction</td>
<td>15</td>
<td>YES</td>
</tr>
</tbody>
</table>
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 animal costs vs Extra costs](balance_icon)

• **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
Paraphrasing astronaut Neil Armstrong:

“One simple (but welcome) regulatory step in Europe, a giant operation for a global AH company!”
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.
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.
Thank you from all of us!