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# Bridging the gap between validation and implementation of non-animal potency testing methods

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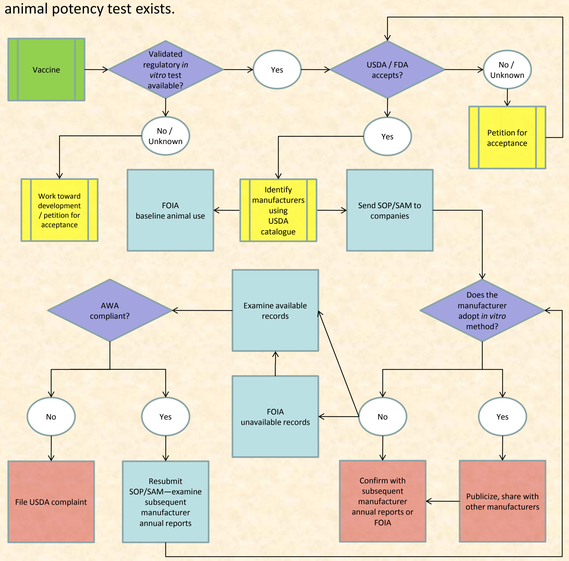
## Objective

As technologically advanced high-throughput techniques are developed that replace, reduce or refine animal use, harmonization of validated protocols between international regulatory authorities is necessary to foster wide-reaching implementation.[1] Because regulatory acceptance itself does not guarantee that an approved non-animal method will be adopted by manufacturers, interfacing with industry to disseminate information regarding exemptions from *in vivo* regulatory standards is necessary to confirm the preferential use of validated non-animal methods at the point of production. Here, we outline the process of bridging the gap between approval of non-animal vaccine batch potency tests by a regulatory body and the demonstrable implementation of those tests. We present our bridging paradigm, along with applications tailored to specific vaccine scenarios, in order to demonstrate a successful strategy that increases the use of available non-animal potency testing methods.

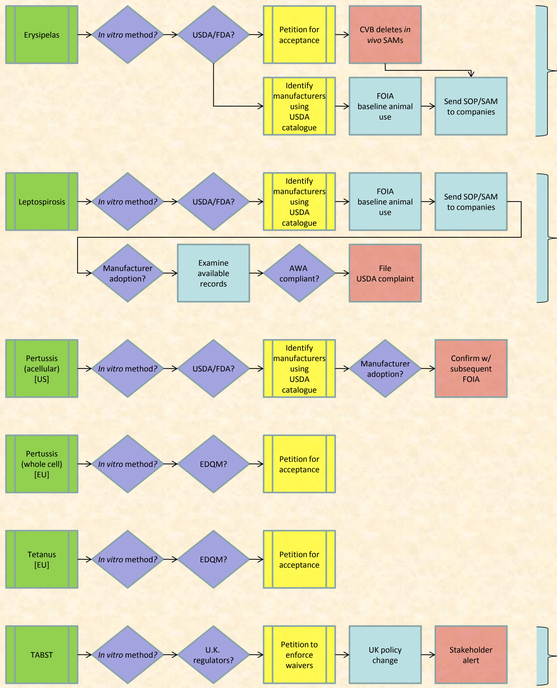
## Methods

This bridging paradigm can be visualized as an information collection and dissemination matrix that is customized to the needs of each vaccine for which a non-animal potency test exists.




## Methods in application

PETA's bridging paradigm can be applied and customized according to the information available for a given non-animal potency testing method. PETA has initiated this process for each of the vaccines in discussion at this workshop, as summarized below. For each vaccine, information collection and confirmation of regulatory use are necessary prerequisites for identifying essential next steps in the process. In some cases, the process of promoting implementation of a non-animal method identifies instances of possible non-compliance with the Animal Welfare Act or other regulations. In all cases, validation data and SOPs or SAMs for non-animal methods are supplied to regulators and manufacturers, followed by efforts to confirm acceptance and implementation by manufacturers.




## Case studies

Ensuring that implementation becomes a reality following validation of non-animal methods requires a non-standardized but consistent engagement with stakeholders. In the context of each vaccine scenario, the bridging paradigm can be distilled to a series of cumulative steps that advance a validated method closer to implementation. In each case, modifications to the general method depend on information obtained from researchers, regulators and manufacturers.

**Erysipelas vaccine batch potency testing**

*2002*: ESAC endorses ELISA as batch potency testing technique, integrated into European Pharmacopoeia 6.0.[2,3]

*2009, August*: PETA asks USDA if ESAC-endorsed ELISA is accepted as a replacement for *in vivo* potency test outlined in 9 CFR 113.67.

*2009, September*: USDA withdraws *in vivo* SAMs 601, 605 and 606, states that, while ESAC-endorsed ELISA has yet to be reviewed for acceptability, ELISA-based *in vitro* SAM 613 may be a superior method of determining erysipelas bacterin potency.[4]

*2010*: Manufacturers of U.S.-licensed erysipelas vaccines identified using USDA Product Catalogue; FOIA requests issued for lot release protocols of erysipelas vaccine products.

**Leptospirosis vaccine batch potency testing**

*2006*: USDA publishes *in vitro* SAMs 624—627 for leptospirosis vaccine batch potency testing for four serovars.[5]

*2009:* Manufacturers of U.S.-licensed leptospirosis vaccines identified using USDA Product Catalogue; FOIA requests issued for lot release protocols of leptospirosis vaccine products; SAMs 624—627 mailed to manufacturers.

*2010*: FOIA records and APHIS annual reports indicate lack of implementation at one manufacturer and possible AWA violations (e.g., failure to demonstrate annual search for non-animal replacement tests).

*2010, August*: USDA complaint against manufacturer.

**Target Animal Batch Safety Testing**

*2005*: European Pharmacopoeia and EMEA acknowledge 2002 ESAC statement in support of waivers for TABST; no oversight mechanism for issuance of waivers is described.[6]

*2008*: PETA UK contacts VMD and HO seeking measures to ensure compliance.

*2010*: VMD ceases charging fees for waivers and HO changes policies to ensure greater regulatory oversight; PETA alerts UK stakeholders.

## Conclusions

The bridging paradigm was successfully applied to expanding and fostering implementation of available non-animal methods for U.S. batch potency testing of erysipelas, leptospirosis and pertussis vaccines. In the U.K., this process was successfully applied to eliminating barriers to exemptions from avoidable TABST for all veterinary vaccines. In the European Union, this matrix is being applied to advancing the implementation of non-animal potency tests for pertussis and tetanus vaccines.

This procedure establishes the acceptability of data from novel methods by regulatory authorities, distributes information on available and accepted non-animal approaches via stakeholder alerts, involves the press in publicizing accepted non-animal techniques, and confirms manufacturer implementation of these methods.

By engaging with regulators and manufacturers, PETA has effectively promoted 3Rs approaches to vaccine batch potency testing. Despite a lack of transparency in the process of non-animal test method approval in the U.S., we have shown that petitioning for regulatory acceptance of internationally validated methods can hasten the approval of existing non-animal methods or, conversely, the removal an obsolete *in vivo* method from use. Until international regulators are able to demonstrate that their approval of non-animal tests results in the active implementation of those methods, PETA will continue to apply this bridging matrix for these and other vaccines.

## Works cited and acronyms

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3. EDQM. 2007. "Swine erysipelas vaccine (inactivated)." European Pharmacopoeia 6.0: monograph 0064; 955-956.
4. Hill, Jr. R. 2009. "Withdrawal of supplemental assay methods 601, 605 and 606." Center for Veterinary Biologics Notice No. 09-20.
5. Clifford J. 2006. "Supplemental assay methods." Center for Veterinary Biologics Memorandum 800.93.
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| **AWA** | Animal Welfare Act of 1966 | **FOIA** | Freedom of Information Act |
| **CFR** | Code of Federal Regulations | **HO** | U.K. Home Office |
| **CVB** | Center for Veterinary Biologics | **PETA** | People for the Ethical Treatment of Animals |
| **EDQM** | European Directorate for the Quality of Medicines and HealthCare | **SAM** | Supplemental assay method |
| | | **SOP** | Standard operating procedures |
| **ELISA** | Enzyme-linked immunosorbent assay | **TABST** | Target animal batch safety testing |
| **EMEA** | European Medicines Agency | **USDA** | United States Department of Agriculture |
| **ESAC** | European Center for the Validation of Alternative Methods Scientific Advisory Committee | **VMD** | Veterinary Medicines Directorate |

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