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

Samantha Dozier, PhD, Policy Advisor, Nanotechnology and Medical Testing Issues; ¹Jeffrey Brown, Research Associate; ²Alastair Currie, Policy Advisor
³People for the Ethical Treatment of Animals Regulatory Testing Division; ²PETA UK

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-use 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 test methods 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 shared with and promoted by stakeholders, followed by efforts to confirm acceptance and implementation by manufacturers.

Case studies
Ensuring that implementation becomes a reality following validation of non-animal methods remains a consistent engagement with stakeholders. In the context of each vaccine scenario, the bridging paradigm can be utilized to ensure compliance. Depending on the vaccine in question, modifications to the general method depend on information obtained from researchers, regulators and manufacturers.

1. Erysipelas vaccine batch potency testing
2. Erysipelas vaccine batch potency testing, non-standardized batch potency testing technique, integrated into European Pharmacopoeia 6.2.6.¹
3. 2009: USDA asks USDA-ESAC-endorsed ELISA was accepted as a replacement for an in vivo test outlined in OCP 11.6.7.¹
4. 2009: September: USDA withdrew in vivo SAMs 601, 605 and 606, stating that, while USDA Endorsed ELISA has yet to be reviewed for acceptability, ELISA can be used in vitro SAM 60.5.2 may be a superior method of determining erysipelas bacteria potency.²
8. 2010: FDA records and APHIS annual reports indicate lack of implementation at one manufacturer and possible AWIA violations (e.g., failure to demonstrate annual search for non-animal replacement tests).

Conclusions
The bridging paradigm was successfully applied to expanding and fostering implementation of validated non-animal methods for U.S. batch potency testing of erysipelas, leptospira and pertussis vaccines. In the UK, this process was successfully applied to eliminating barriers to exemptions from BSAW for veterinary vaccines. In the European Union, this model is being applied to advancing the implementation of non-animal potency tests for pertussis and lepto vaccines.

This procedure establishes the acceptability of data from novel methods by regulatory authorities and provides a basis for implementable standards for all non-animal approaches via stakeholder alerts, involves the press in publicizing accepted non-animal techniques, and serves to promote manufacturer implementation of these methods. By engaging with regulators and manufacturers, PETA has effectively promoted 38 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 prioritizing for regulatory acceptance of internationally validated methods can hasten the approval of non-standard testing methods. Conversely, the removal of obstacles in vivo methodology can significantly delay regulatory decisions. Until international regulations are able to demonstrate that their approval of non-viral test results in the active implementation of these methods, PETA will continue to apply this bridging matrix for these and other vaccines.

Contact information
Jeffrey Brown, corresponding author
Tel: (310) 437-8201
Fax: (310) 644-2783
E-mail: JeffreyB@peta.org

References
2. ESAC. 2002. “Statement on the validity of a serological method (ELISA) for the batch potency testing of leptospira vaccine products.”
4. USDA 2009: USDA complaint against manufacturer.
5. USDA: USDA complaint against manufacturer.
6. USDA: USDA complaint against manufacturer.
7. USDA: USDA complaint against manufacturer.
8. USDA: USDA complaint against manufacturer.

Works cited and acronyms
3. CFR 1. ¹A list of key regulatory acronyms is available at http://ecvam.jrc.it/publication/TargetAnimalSafetyT_statement.PDF
4. “Review of the Three Rs in the context of the validation and implementation of non-animal methods for the regulatory assessment of vaccines.” ²A list of key regulatory acronyms is available at http://ecvam.jrc.it/publication/TargetAnimalSafetyT_statement.PDF
6. USDA: USDA complaint against manufacturer.
7. ESAC.
8. EMEA.
9. USDA: USDA complaint against manufacturer.
10. USDA: USDA complaint against manufacturer.
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12. USDA: USDA complaint against manufacturer.
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