

**International Workshop on Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning the Way Forward**

**October 11-13, 2011**

**U.S. Department of Agriculture  
National Centers for Animal Health  
Ames, IA, USA**

**Organized by:**

NICEATM- National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods  
ICCVAM- Interagency Coordinating Committee on the Validation of Alternative Methods  
ECVAM- European Centre for the Validation of Alternative Methods  
JaCVAM- Japanese Center for the Validation of Alternative Methods  
Health Canada

**Co-Sponsored by:**

Center for Veterinary Biologics, U.S. Department of Agriculture  
International Alliance for Biological Standardization

**Overview**

Rabies in humans is a uniformly fatal disease, with infections killing over 70,000 people worldwide each year. Rabies vaccines serve a vital role in preventing further deaths and controlling the disease in certain animal populations. According to the World Health Organization, an estimated 15 million people receive post-exposure vaccine prophylaxis annually due to actual or suspected exposures to the rabies virus. In the U.S. and other developed countries, rabies vaccines have effectively eliminated domestic canine rabies virus strains. However, determining the safety and effectiveness of rabies vaccines requires large numbers of laboratory animals and involves significant pain and distress. New methods and approaches are sought that: 1) are more humane and use fewer or no animals, 2) are faster, cheaper, and more accurate, and 3) are safer for laboratory workers.

A recent international workshop<sup>1</sup> organized by NICEATM, ICCVAM, and its international partners identified rabies vaccines as one of the three highest priorities for future research, development, and validation of alternative test methods that could further refine, reduce, and ultimately replace animal use for potency and safety testing. One of the highest priority implementation activities was organization of an international workshop on alternative methods for rabies vaccine potency testing. Based on recent scientific and technological advances, several alternative approaches have been proposed or are currently available. For example, scientists at the Paul-Ehrlich-Institut recently conducted an international collaborative study for the validation of a serological potency assay for rabies vaccine (inactivated) for veterinary use. Protective antigen quantification methods that do not require

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<sup>1</sup>International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions, September 14-16, 2010, Bethesda, MD, USA. Workshop materials available at: <http://iccvam.niehs.nih.gov/meetings/BiologicsWksp-2010/BiologicsWksp.htm>

animals or the use of live rabies virus are now available and may be applicable to batch release testing for rabies vaccines.

This workshop will bring together international scientific experts from government, industry, and academia to review these methods and to define efforts necessary to achieve global acceptance and implementation. The workshop will identify critical components of manufacturing processes necessary to demonstrate batch-to-batch consistency and how monitoring these components can be used with *in vivo* and *in vitro* potency tests in an integrated approach to reduce and replace animal use for rabies batch release. Finally, workshop participants will identify the most appropriate source(s) for reference reagents to ensure standardization of *in vitro* rabies potency testing methods.

### **Workshop Objectives**

1. Review the state of the science of currently available alternative methods that reduce, refine (less pain and distress), and replace (3Rs) the use of animals in the potency testing of rabies vaccines, and identify any unresolved data gaps that must be addressed to allow immediate implementation of the methods in regulatory testing.
2. Develop an implementation strategy and plan to address these knowledge and data gaps in order to achieve regulatory acceptance, implementation, and use of alternative methods for routine potency testing of rabies vaccines while ensuring continued protection of human and animal health.
3. Assess and identify ways to improve (i.e., implementation of reduction and refinement procedures) the current rabies potency challenge test
4. Define the current availability and validity of process control parameters and assays for demonstrating batch-to-batch consistency in conjunction with *in vitro* assays for the potency testing of rabies vaccines.
5. Identify best practices for current and future integrated approaches to rabies vaccine potency testing to minimize the use of animals.

**Draft Agenda  
Day 1  
Tuesday, October 11, 2011**

- 7:30-8:30 Registration and Poster Setup**
- 8:30 Opening Session: Welcoming Remarks and Overview of Workshop Objectives**
- 8:30-8:40** *William Stokes, D.V.M., RADM, USPHS, National Institute of Environmental Health Sciences, NIH.*
- Jodie Kulpa-Eddy, D.V.M., Animal & Plant Health Inspection Service, USDA.*
- 8:40-8:50** *Richard E. Hill Jr., D.V.M., Center for Veterinary Biologics, USDA.*
- 8:50-9:00** *Richard McFarland, M.D., Ph.D., Center for Biologics Evaluation and Research, U.S. FDA.*
- 9:00 Session 1**
- Overview of Public Health Needs and Regulatory Requirements for Rabies Vaccine Potency Testing**
- Co-chairs:
- Richard McFarland, M.D., Ph.D., Center for Biologics Evaluation and Research, U.S. FDA.*
- Jodie Kulpa-Eddy, D.V.M., Animal & Plant Health Inspection Service, USDA.*
- 9:00 Rabies Vaccines for Humans and Animals: Public Health Perspectives**
- Charles Rupprecht, V.M.D., M.S., Ph.D., National Center for Infectious Diseases, CDC.*
- 9:25 Current Requirements and Guidance on Product Specific Validation of 3Rs Alternatives for Human Rabies Vaccine Potency Testing**
- Robin Levis, Ph.D., Center for Biologics Evaluation and Research, U.S. FDA.*
- 9:45 Current Requirements and Guidance on Product Specific Validation of 3Rs Alternatives for Veterinary Rabies Vaccine Potency Testing**
- Donna Gatewood, D.V.M., M.S., Center for Veterinary Biologics, USDA.*
- 10:05-10:25 Break**
- 10:25 International Guidelines for Rabies Vaccine Potency Testing: WHO Perspective**
- Jinho Shin, D.V.M., Ph.D., WHO, Switzerland.*
- 10:45 International Guidelines for Rabies Vaccine Potency Testing: World Organisation for Animal Health (OIE) Perspective**
- Vincenzo Caporale, D.V.M., Ph.D., OIE Biological Standards Commission, France.*

- 11:05**      **Incorporating the 3Rs into Human Rabies Vaccine Potency Testing: An Industry Perspective**  
*1. Jean-Michel Chapsal, Ph.D., Sanofi-Pasteur, France.*  
*2. Holger Kost, Ph.D., Novartis, Germany.*
- 11:35**      **Incorporating the 3Rs into Veterinary Rabies Vaccine Potency Testing: An Industry Perspective**  
*Alexander Gaydamaka, D.V.M., Ph.D., Animal Health Institute.*
- 12:00-1:00**      **Lunch**  
*Posters available for discussion*
- 1:00**      **Session 2**  
**Currently Available *In Vivo* Assays for Rabies Vaccine Potency Testing: Opportunities for the Reduction and Refinement of Animal Use**  
Co-chairs:  
*Timothy Miller, Ph.D., Benchmark Biolabs Inc.*  
*Marlies Halder, V.M.D., European Commission, Joint Research Centre, ECVAM.*
- 1:00**      **Critical Analysis of The *In Vivo* Potency Challenge Test for Inactivated Rabies Vaccines: Current Challenge Tests and Potential for Reduction, Refinement and Replacement**  
*Peter Wunderli, Ph.D., ALPCO Immunoassays.*
- 1:30**      **Development and International Validation of a Serological Method for Veterinary Rabies Vaccine Potency Testing**  
*Lukas Bruckner, D.V.M., Institut für Viruskrankheiten und Immunprophylaxe, Switzerland.*
- 2:00**      **Batch Potency Testing of Human and Veterinary Rabies Vaccines By Serology**  
*Elisabeth Kamphuis, Ph.D., Paul-Ehrlich-Institut, Germany.*
- 2:30-2:45**      **Break**

- 2:45      Session 3**  
**Non-Animal Methods and Strategies for Rabies Vaccine Potency Testing**  
Co-chairs:  
*Gayle Pulle, Ph.D., Health Canada, Canada.*  
*Hajime Kojima, Ph.D., JaCVAM, National Institute of Health Sciences, Japan.*
- 2:45      Antigen Quantification Assays for Assessing Rabies Vaccine Potency:**  
**Application and New Technologies**  
*Claudia Carolina Lopez-Yomayuzza, D.V.M., Justus Liebig University, Germany.*
- 3:15      Current Status of Antigen Quantification Assays for Human Rabies Vaccine**  
**Potency Testing**  
*Lorraine McElhinney, Ph.D., Animal Health and Veterinary Laboratories Agency, UK.*
- 3:45      Development of an *In Vitro* ELISA Antigen Quantification Assay for**  
**Veterinary Rabies Vaccine Potency Testing**  
*Fabrizio De Mattia, Ph.D., MSD Animal Health, The Netherlands.*
- 4:15-4:30      Break**
- 4:30      An *In Vitro* Veterinary Rabies Vaccine Potency Assay Currently Approved**  
**for Use in Japan**  
*Koichiro Gamoh, D.V.M., Ph.D., National Veterinary Assay Laboratory, Japan.*
- 5:00      Application of Consistency Parameters and Integrated Approaches to**  
**Replace Animal Use for Rabies Vaccine Potency Testing**  
*Sunil Gairola, Ph.D., Serum Institute of India Inc., India.*
- 5:30      Current NIH Research on Improved Rabies Vaccines**  
*Cristina Cassetti, Ph.D., Virology Branch, NIAID.*
- 5:45      Adjournment**

**Day 2**  
**Wednesday, October 12, 2011**

**7:30-8:00 Registration**

**8:00-8:15 Opening Remarks and Instructions for Breakout Sessions**

*William Stokes, D.V.M., RADM, USPHS, National Institute of Environmental Health Sciences, NIH.*

**8:15 Breakout Session #1: Antibody Quantification (Serologic) Methods for Rabies Vaccine Potency Testing: Validation Status, Data Gaps, and Implementation Strategies**

- Breakout Group 1A  
Room 1055

Co-moderators:

*Warren Casey, Ph.D., National Institute of Environmental Health Sciences, NIH.*

*Karen Brown, Ph.D., Pair O' Docs Consultants.*

- Breakout Group 1B  
Room 1057

Co-moderators:

*Richard McFarland, M.D., Ph.D., Center for Biologics Evaluation and Research, U.S. FDA.*

*Timothy Miller, Ph.D., Benchmark Biolabs Inc.*

**10:30-11:00 Break**

**11:00 Report from Breakout Session #1: Antibody Quantification (Serologic) Methods for Rabies Vaccine Potency Testing: Validation Status, Data Gaps, and Implementation Strategies**

- Breakout Group 1A Report
- Breakout Group 1B Report

**12:00-1:00 Lunch**

*Posters available for discussion*

**1:00 Breakout Session #2: In Vitro Antigen Quantification Methods for Rabies Vaccine Potency Testing: Validation Status, Data Gaps, and Implementation Strategies**

- Breakout Group 2A  
Room 1055

Co-moderators:

*Gayle Pulle, Ph.D., Health Canada, Canada.*

*Jean-Michel Chapsal, Ph.D., Sanofi Pasteur, France.*

- Breakout Group 2B  
Room 1057  
Co-moderators:  
*Robin Levis, Ph.D., Center for Biologics Evaluation and Research, U.S. FDA.*  
*Lukas Bruckner, D.V.M., Institut für Viruskrankheiten und Immunprophylaxe, Switzerland.*

**4:00-5:00**     **Poster Session**

**Day 3**  
**Thursday, October 13, 2011**

- 7:30-8:00 Registration**
- 8:00 Report for Breakout Session #2: *In Vitro* Antigen Quantification Methods for Rabies Vaccine Potency Testing: Validation Status, Data Gaps, and Implementation Strategies**
- Breakout Group 2A Report
  - Breakout Group 2B Report
- 9:00 Breakout Session #3: The *In Vivo* Potency Challenge Test for Inactivated Rabies Vaccines: Refinement and Reduction Opportunities**
- Breakout Group 3A  
Room 1055  
Co-moderators:  
*Marlies Halder, V.M.D., European Commission, Joint Research Centre, ECVAM*  
*Alexander Gaydamaka, D.V.M., Ph.D., Animal Health Institute.*
  - Breakout Group 3B  
Room 1057  
Co-moderators:  
*Donna Gatewood, D.V.M., M.S., Center for Veterinary Biologics, USDA.*  
*Sunil Gairola, Ph.D., Serum Institute of India Inc., India.*
- 10:30-10:45 Break**
- 10:45 Report for Breakout Session #3: The *In Vivo* Potency Challenge Test for Inactivated Rabies Vaccines: Refinement and Reduction Opportunities**
- Breakout Group 3A Report
  - Breakout Group 3B Report
- 11:15 Closing Session**  
**Review of Conclusions and Recommendations**
- 11:15-11:35 Session 1 Report: Antibody Quantification (Serologic) Methods**
- 11:35-11:55 Session 2 Report: *In Vitro* Antigen Quantification Methods**
- 11:55- 12:15 Session 3 Report: The *In Vivo* Potency Challenge Test**
- 12:15 Closing Remarks and Adjournment**
- 12:30 End of Meeting**