

# VACCINES CONSISTENCY APPROACH

## Workshop#3: Veterinary Rabies Vaccines

flash



The European Partnership  
for Alternative Approaches to Animal Testing

Brussels, Belgium, November 5-6 2012

### APPLICATION OF THE 3RS AND THE CONSISTENCY APPROACH FOR IMPROVED VACCINE QUALITY CONTROL

>>> EPAA workshop on implementation strategies of the consistency approach for veterinary inactivated rabies vaccines

As described in previous reports<sup>1</sup> from the EPAA vaccines project, the workshop on veterinary inactivated rabies vaccine addressed the third of the project's priority areas as defined by the Technical Committee at its meetings in 2011 and 2012. Application of the consistency approach for lot release of established vaccines provides a means of avoiding the use of animals for evaluating manufacturing quality, in particular the potency of final lots for which the use of challenge tests presents serious animal welfare issues.

The first of the focused workshops was on DTaP (diphtheria, tetanus and acellular pertussis) vaccine and was held in the Netherlands at the end of August 2012 while the second, on human rabies vaccine, and which was co-sponsored by EURL ECVAM and EPAA, took place in France in October 2012 (see flash reports). The third, on veterinary rabies vaccine, was held in Brussels on 5-6<sup>th</sup> November, and was attended by 19 participants from manufacturers, the academic sector and regulatory and standards bodies. In addition, US and Canadian participants joined the meeting by teleconference.

Following soon after the workshop on human rabies vaccine, it was extremely instructive to have some participants who had attended both meetings. While the scientific issues related to replacement of animal testing are essentially identical for both human and veterinary rabies vaccines, the differences in the starting points as well as the contrasting business models of the two sectors mean that the routes to the ultimate

goal are also different. Furthermore, the fact that veterinary rabies vaccines are the most part adjuvanted adds a further layer of complication that is not present for human rabies vaccines.

Although in vitro assays are used routinely to monitor the consistency of rabies production during the manufacture of vaccines, current regulatory requirements require the use of virus challenge testing in animals by both manufacturers and national authorities in order to validate the final lot before release. The focus of the workshop was therefore on the waiving of the in vivo veterinary rabies vaccine potency test with the ultimate goal of a clear vision and definition of the requirements for replacing it with consistency testing in lot release using in vitro antigenic quantification.

The aims of the workshop were:

- To make available and to present data from in-house testing that could support the waiving of the current test by in vitro methods
- To exchange information on reagents and methods that can be used for the in vitro quantification of rabies glycoprotein G for in-process control of key intermediates and for control of the final product
- To discuss standardization, pass-fail correlation approach, implementation strategies and potential gaps in consistency testing of veterinary rabies vaccines and to agree about possible solutions

**“Application of the consistency approach provides a means of avoiding the use of animals [...]”**

1 See page 3 for the links to these flash reports



- To discuss the way forward to implement globally a consistency approach incorporating the in vitro glycoprotein quantification method as an alternative to rabies challenge testing to measure potency of the final product.

There was no disagreement among the participants that the consistency approach can assure the quality of veterinary rabies vaccines through a package that should include monitoring parameters in raw materials, production, formulation and the finished product. Rabies glycoprotein G is the target of choice to monitor antigen quality both in-process and in the final product.

Presentations given by different manufacturers at the workshop showed that during the production stage, ELISA assays can reliably measure the glycoprotein G content of in-process product and demonstrate the consistency of production in manufactures. These in-process data represent a typical example of information that can be compiled and presented to the authorities as part of a consistency approach package.

In addition, results of in vitro tests for the final product were also presented by several participants. A number of manufacturers and academic organisations have their own tests either ready or currently in development. These tests are able to quantify the rabies antigenic content in

vaccines. However although one test format is desirable for the sake of harmonization, this is a complicated issue because of the different production and formulation processes used by veterinary vaccine manufacturers.

A decision was taken therefore that manufacturers would take advantage of the work going on in the parallel human rabies vaccine project to evaluate the suitability for their own products of in vitro tests(s) developed for human rabies vaccines. An important aspect of an in vitro potency test is its ability to discriminate between potent and sub-potent lots and this will be investigated in this pre-validation phase in collaboration with the human rabies vaccines group.

In contrast to human rabies vaccines, veterinary products are adjuvanted. The presence of adjuvant adds a further layer of complexity in the characterization of a vaccine especially as different adjuvants may be used for different products. The presentations and discussions at the workshop showed that current testing demonstrates consistency in formulation but that the in vitro characterization of adjuvants remains a technical challenge.

Finally the workshop participants indicated that novel technologies are also being investigated for quality control of rabies vaccines. The development of promising new techniques will benefit from the unique collaboration between the EPAA workshop participants.

**“Current testing demonstrates consistency in formulation but in vitro characterization of adjuvants remains a technical challenge”**

## Participating Organisations

- ANSES-ANMV (Agence Nationale du Medicament Veterinaire), France
- Bioveta, Czech Republic
- Boehringer-Ingelheim Animal Health, Germany
- Canadian Centre for Veterinary Biologics, Canada
- DG JRC, European Commission - EURL ECVAM (European Union Reference Laboratory for Alternatives to Animal Testing), Italy
- EPAA
- EDQM (European Directorate for the Quality of Medicines and Healthcare), France
- IVI (Institute of Virology and Immunoprophylaxis), Switzerland
- Justus Liebig University, Germany
- Merial, France
- MSD Animal Health, the Netherlands
- NEBIH (Nemzeti Élelmiszerlánc-biztonsági Hivatal), Hungary
- NICEATM ICCVAM (National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods and the Interagency Coordinating Committee on the Validation of Alternative Methods), USA
- USKVBL (Ústav pro státní kontrolu veterinárních biopreparátů a léčiv), Czech Republic
- Pfizer, UK
- Sanofi-Pasteur, France
- Virbac, France
- VLA (Veterinary Laboratories Agency), UK
- USDA APHIS (US Department of Agriculture, Animal and Plant Health Inspection Service), USA

# Previous Workshops reports

Reports from the previous Consistency Approach Workshops (DTaP and Human rabies vaccines) workshops are available for download on the EPAA website:



Download the flash report of the recent EPAA Human rabies vaccines Workshop

Download the flash report of the recent EPAA DTaP vaccines Workshop



# Next Steps

Consistency Approach Project Workshop #4 Clostridial Vaccines : Early 2013, TBD

## About...

The Vaccines Consistency Approach project is one of the flagships 3Rs projects of the EPAA.

Further information is available in the dedicated factsheet.

>>> Download it from the EPAA website



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