VACCINES CONSISTENCY APPROACH
Workshop#2: Human Rabies Vaccines

flash

The European Partnership for Alternative Approaches to Animal Testing

Arcachon, France, October 8-9 2012

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

>>> EPAA-EURL ECVAM Workshop on Replacement of In Vivo Human Rabies Vaccine Potency Testing by In Vitro Glycoprotein Quantification Methods: Validation Status and Implementation Strategies

This is the second of a series of workshops on implementing the consistency approach for lot release of established vaccines, with the ultimate goal of avoiding the use of animals. Following the launch of the vaccine project in April 2011 (see flash report), the project's Technical Committee identified four priority areas for future work: human rabies vaccine, veterinary rabies vaccines, DTaP (diphtheria, tetanus and acellular pertussis combination vaccine) and clostridial vaccines. The four projects, two on human and two on veterinary vaccines, present serious animal welfare issues through the current use of large numbers of animals in challenge tests for evaluating the potency of final lots.

"Cross-fertilization between veterinary and human vaccines sectors would be mutually beneficial"

The first of the focused workshops was on DTaP vaccine and was held in the Netherlands at the end of August 2012 (see flash report). The meeting on human rabies vaccine, co-sponsored by the EURL ECVAM and EPAA, took place on October 8th and 9th and was attended by 22 participants* from manufacturers, the academic sector and regulatory and standards bodies, including non-European representatives from Brazil, Canada, China and USA.

It is well understood that the native form of the surface protein of the rabies virus (glycoprotein G) included in rabies vaccines is responsible for the production of virus neutralizing, thus, protective antibodies. In rabies vaccines for human use, quantification of this protein is currently used in routine manufacture at different process stages and in particular at final bulk, allowing definition of the final antigen content per dose of vaccine. However, in order to conform to current regulatory requirements, virus challenge testing in animals (the so-called NIH test) must be used in addition by both manufacturers and national authorities to validate the final lot before release.

The purpose of the workshop was to focus on gaps in technical knowledge and validation of in vitro antigen quantification methods and to propose solutions for the replacement of the NIH test. The ultimate objective is an EDQM collaborative study to validate a replacement test and list it in the European Pharmacopoeia as a first step to global acceptance.

The experts were therefore invited to:

- Review the available in vitro antigen quantification methods (e.g. ELISA formats, reagents and reference standards);
- Agree a pre-validation strategy for selecting the best method;
- Develop an implementation strategy with a validation scheme and a future EDQM collaborative study aiming to achieve global acceptance by regulators and industry

An important aspect of the strategy is the understanding that the replacement test should not be required to correlate with the NIH test since the latter is inherently very variable. Rather, the new test should be in concordance with clinical potency of the vaccine and should be able to discriminate between potent and sub-potent batches. We refer to "concordance" in preference to "correlation".

There is already a consensus on the general format of a suitable assay and it remains to determine which of the ELISAs including a small number of antibody reagents currently in use by manufacturers and national authorities are the most suitable. This will be the topic of a pre-validation study for which a small international working group has already been formed. The results will then be presented to EDQM to validate the test and establish its transferability in an international collaborative study. After the pre-validation stage it will also be necessary to agree on what kind of validation package will be needed for regulatory acceptance of the test in order to waive animal testing of final lots. For this, the project will seek the advice of a broad range of regulators and manufacturers.

The limited range of options for a replacement in vitro assay and the comparatively small number of manufacturers of rabies vaccine for human use, encourage our belief that this project can make rapid progress. Clearly safeguarding human safety is paramount and any proposals will be thoroughly scrutinized by the regulatory authorities. However, the scientific and ethical case for abandoning the NIH test is compelling.

We hope that success for this vaccine will have wider impact on the use of challenge tests in other areas, in particular on its use for batch release of rabies vaccine for veterinary use. As will be become clear from the reports of the very recent workshop on the latter project, the issues over manufacture and release of veterinary vaccines are quite different from those for human use and a different strategy will be needed. However, the pre-validation work to be undertaken by the human rabies team will be of great value to the veterinary project, illustrating our original concept that cross-fertilization between the two sectors would be mutually beneficial.

Participating Organisations

ANSM (Agence Nationale de Sécurité du Médicament et des Produits de Santé), France
BGTD (Biologics and Genetic Therapies Directorate, Health Canada), Canada
CBER (Center for Biologics Evaluation and Research, Food and Drug Administration), USA
CDC (Center for Disease Control and Prevention), USA
DG Environment, European Commission, Belgium
Institut Pasteur, France
EDQM (European Directorate for the Quality of Medicines and Healthcare), France
EPAA
DG JRC, European Commission - EURL ECVAM (European Union Reference Laboratory for Alternatives to Animal Testing), Italy
NIFDC (National Institutes for Food and Drug Control), China
NVI (Nederlands Vaccin Instituut), The Netherlands
NVD (Novartis Vaccines and Diagnostics), Switzerland
PEI (Paul Ehrlich Institute), Germany
INCQS- Fiocruz (Instituto Nacional de Controle de Qualidade em Saúde), Brazil
Sanofi-Pasteur, France
Global Alliance for Rabies Control, USA
University of Utrecht, The Netherlands
WHO (World Health Organisation), Switzerland

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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