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## Session I-16: Alternatives for potency testing of rabies vaccines

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### Session I-16: Oral presentations

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I-16-381

## Drivers and barriers to acceptance and use of 3R models for the quality control of veterinary rabies vaccines

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Vaccines are subject to requirements that regulate their quality and safety. Due to their biological origin, vaccines are complex products which can be influenced by various factors. As a result, each batch of the finished product is tested on potency and safety. The use of animals in batch release testing is a regulatory obligation and represents around 80% of the total number of animals used in the vaccine industry. Over the last decades this heavy reliance on animal experimentation has met serious ethical, scientific and economic objections. However, despite the increase of 3R models to ensure vaccine quality and European legislation requiring the adoption of 3Rs alternatives where possible, the acceptance and use of 3Rs methods falls behind. This raises the question which factors influence the acceptance and use of 3R models for regulatory purposes and how should this process be optimised. The author aims at clarifying the mecha-

nism of regulatory acceptance and implementation by defining the main obstacles and drivers influencing this process. For this purpose a case study on the rabies vaccine has been conducted that examines the acceptance of 3R models, such as a serology test developed by the PEI in Germany, to replace the regulatory required NIH potency test for veterinary rabies vaccines. The case study consists of literature research and interviews with regulatory authorities and vaccine manufacturers. In order to fully understand the mechanism of regulatory acceptance, the findings are put in the context of technology acceptance in the area of risk regulation. This study serves as input to the discussion between regulatory authorities and industry on how to optimise the process of acceptance of 3R models for quality control of vaccines in general and veterinary-rabies vaccines in particular.



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## Potency testing of rabies vaccine: on the way to a new era

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According to current requirements the potency of rabies vaccine batches is determined in a vaccination/challenge experiment in mice. The test uses a large number of mice, causes severe animal distress and is poorly reproducible. Several attempts have been undertaken to replace the test taking into account the 3Rs without success to date. In 2009 a promising method testing antibodies induced after vaccination of mice was established and validated by Kraemer et al. for veterinary vaccines. The serological test distinguishes between potent batches and vaccine batches which do not fulfill the minimum potency requirement. It uses a single dose and thus saves many mice. It provides a qualitative result in contrast to the quantitative potency value of the classical mouse challenge potency test. Based on this and successful experience with the assay in German batch release, a collaborative study was organized in the framework of the EDQM Biological Standardisation Programme. The standard operating procedure to be followed, crucial reagents (e.g. reference sera, fluorescent anti-rabies-nucleoprotein conjugate), the reference vaccine and four rabies vaccine batches were supplied to the participants. Three independent repetitions of the assay were performed by 13 laboratories from Europe and North

America, including manufacturers and official control laboratories. The study clearly demonstrated the suitability of the alternative test method to identify potent and insufficient rabies vaccine batches. In addition, in depth statistical analysis provided data to recommend the most suitable number of animals to be used for routine batch testing. The study results are published in Kraemer et al. (2010).

Based on the results of the collaborative study, the monograph Rabies Vaccine (inactivated) for Veterinary Use of the European Pharmacopoeia has been adapted by the respective expert group. The revised monograph is currently published in PHARMEUROPA 23.13 for public consultation. Finally, potency testing of inactivated rabies vaccines may begin a new era involving lower animal usage and considerably less animal distress.

### References

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## Rabies vaccines for human use: Potency testing without mouse challenge?

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The conventional batch potency test for cell culture-based inactivated rabies vaccines involves vaccination and viral challenge of mice. The test is highly variable, very time-consuming, needs huge numbers of mice and causes significant suffering to the animals. It was established in the 1950s in the absence of GMP at the National Institutes of Health (NIH). It has been broadly used until now despite its multiple drawbacks. In line with the modern concept of the consistency approach for vaccine quality, future batch potency control will combine data of a panel of tests throughout manufacturing to have improved knowledge on product characteristics. Immunogenicity testing is a key element, providing valuable information that complements protein quantification.

Consequently, we propose the development of an immunogenicity assay based on vaccination of mice and determination

of neutralising antibodies. The assessment of the serum response is done by quantification with the WHO standard anti-rabies immunoglobulin based on the Ph. Eur. monograph on potency testing of human rabies immunoglobulin. Points for consideration of a potential impact on the antibody response are the vaccination scheme and the age of mice. The design for the development of a serological alternative assay should be harmonized worldwide to the greatest possible extent. Global acceptance is a pre-requisite for any alternative assay. The World Congress on Alternatives and Animal Use in the Life Sciences provides an opportunity to present this serological alternative assay for human rabies vaccine potency and to discuss its potential use in the global context.