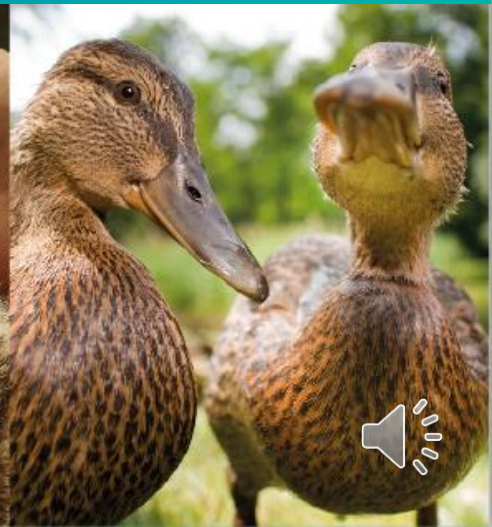


AFSA/IABS/HfA 3Rs Webinars (6th and 20th Oct 2022)

Rabies potency test status

Dr Catrina Stirling

Director, Regulatory Affairs - Zoetis



Drivers for non-animal based Rabies potency test

- **3Rs benefit – reduction in the number of mice used by both industry and OMCLs in testing Rabies vaccines.**
- **More consistent and better discriminatory power for release testing using the immunoassay tests***
 - Antigen (Glycoprotein (GP)) content as measured by immunoassay can also be used for formulation – more consistent products
 - GP immunoassay tests have better discriminatory power – detect differences in antigen content before the animal test could
 - Tests and reagents used are validated and shown to link directly to the key antigen (GP) for efficacy of vaccines for Rabies
- **Faster and cheaper testing which reduces costs and improves availability**

* ELISA or AlphaLISA approaches currently being used



European Pharmacopeia

Both Human and Vet Rabies monograph still indicate challenge or serology based mouse test but have indicate an immunoassay is possible - legally possible to use the immunoassays

- Human Health monograph (0216)
 - Includes the use of an immunochemical test to determine glycoprotein content but still includes the challenge test in mice
- Revised Vet monograph (0451)
 - **2-4-4. Batch potency test.** It is not necessary to carry out the potency test (section 3-4) for each batch of vaccine if it has been carried out using a batch of vaccine with a minimum potency. **An alternative validated method such as an immunosorbent assay is used, the criteria for acceptance being set with reference to a batch of vaccine that has given satisfactory results in the test described under Potency.** In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, such an alternative validated method must be used for routine testing
- **5.2.14. Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccines**
<https://pheur.edqm.eu/app/11-1/content/11-1/50214E.htm>



Human Rabies Vaccines (Potency test replacement) Supported by EPAA



Project BSP 148: S MORGEAUX (ANSM), JM CHAPSAL (EPAA), E TERAQ (Coordinator EDQM)

Objective: Replacement of in Vivo Rabies potency test by in vitro method

Status: BSP 148 Participants: 31 labs (8 manufacturers) in phase 2, 18 labs (6 manufacturers +2 state public manufacturers) in phase 3, 9 labs with in house ELISA (from Europe and other regions (North & Latin America, India, Indonesia, Philippines, Japan, China, Vietnam, North Africa...)). BSP148 Phase 1 completed & report ongoing

BSP148 Phase 2 : Statistical analysis report available (25 labs, others will be included later). Final report ongoing (acceptability criteria for the test still in debate)

BSP148 Phase 3: Qualification of capture mAbs done, questionnaire to participants to update the schedule of tests

Next Milestones: BSP Phase 2 final report Q3 2022, BSP 148 project team meeting schedule in September 2022, Phase 3 start Q3 2022, Workshop on Phase 2 results beginning 2023



Veterinary Rabies vaccines within VAC2VAC project (IMI 2)

Within VAC2VAC Veterinary industry partners tested the Boehringer Ingelheim (BI) ELISA to determine if a common ELISA approach was viable for Vet Med

It was concluded that this was not an option for Vet products

- Variable Rabies strains and adjuvant systems complicate this option
- This is also the reason Vet vaccines are not part of BSP 148
- Rabies GP mAbs used in BSP 148 are now commercially available for any company to use

Each company progressed an Immunoassay system that works for their product

Acceptance from EU regulatory authorities and Batch release authorities that a common format GP Immunoassay is not viable

[Home | Vac2Vac \(europevaccine.wixsite.com\)](http://europevaccine.wixsite.com)

[VAC2VAC | IMI Innovative Medicines Initiative \(europa.eu\)](http://europa.eu)



Industry Progress towards Rabies antigen test registration - EU

- Multinational Companies in the EU have now either fully implemented with relevant regulatory changes the GP Assay or are in the process of doing so
- At least 3 different GP immunoassay methods are being used, all with different antibodies suitable for the Rabies strains and adjuvant combinations
- For OMCL re-testing these are transferred to an agreed EU authority laboratory such that all release testing for a given vaccine uses the same test
- EDQM/WHO standard or a qualified company reference standard vaccine are used to determine GP content.
- The consistency approach has been used to determine specifications



Industry Progress towards Rabies antigen test registration - ROW

- **In the US***

USDA preference for a common format immunoassay method if possible

Companies have been working with a USDA as part of an AHI/USDA working group

- **In Japan**

Glycoprotein ELISA test method has been accepted and used for many years

- **ROW**

For EU made product that has been moved to immunochemical antigen test – working towards regulatory acceptance for other markets taking the same vaccines

*USDA may be able to comment further directly

Challenges for Global acceptance

Progress in the EU is good and on going discussions in the US are positive but will take time

Biggest challenge for industry and animal welfare to fully realise the benefits of transitioning from the challenge/serology tests for Rabies vaccine release to GP immunoassays will be global acceptance

It can take 4-5 years from approval of a NAM test for vaccine potency batch release in a major market like the EU or US to fully implement

- Approval of the change is required in all global markets to phase out the animal test, the process can be very slow

This is a major point for discussion in the F2F meeting in Brussels in Nov.

