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A One Health View: Global Outlook and Future Strategy**
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Replacing the in vivo potency test for human rabies vaccines: a global collaborative initiative.

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For over 70 years, the release of human rabies vaccines has relied on a potency test consisting of an intracranial challenge test in mice (NIH test). While it has proved useful, this test has major scientific and ethical issues. The global replacement of the NIH test is a high priority for the worldwide implementation of the 3R concept but is conditioned by the validation of a global standardised method.

Given that the protection against rabies virus is induced by the native trimeric form of the virus glycoprotein G, the scientific community agreed that an ELISA based on highly characterised monoclonal antibodies would be the most appropriate replacement method.

In a first step towards this aim, a small international study involving 5 laboratories was organised by the European Partnership for Alternative Approaches to Animal testing (EPAA) to identify and evaluate available rabies ELISAs for the potency control of human rabies vaccines. The study concluded that the GP rabies ELISA was the most promising replacement method.

In a second step, a large collaborative study (BSP148) was organised by the Biological Standardisation Programme to standardise the method and evaluate its transferability to laboratories worldwide. During the first phase of BSP148, the 2 critical monoclonal antibodies were made available by 2 commercial suppliers, and a standardised protocol was elaborated. Thirty laboratories took part in the collaborative phase (Phase 2) of the study, using the standardised protocol with qualified batches of critical reagents and the WHO 7th International Standard for Rabies vaccine, to evaluate a common set of 11 vaccine samples covering 5 virus strains and various potencies.

The data centrally analysed at EDQM indicated that the method is transferrable to laboratories worldwide, that the potency of all tested vaccines can be quantified (in IU/mL) and that the GP ELISA has a very satisfactory precision, repeatability and reproducibility. The Phase 3 of the study aims at evaluating the applicability of the GP ELISA to routine QC testing of commercial batches. The Phase 3 study report is in preparation. The results of these studies will support the proposal for the global replacement of the in vivo potency test by a standardised ELISA (i.e. future revision of pharmacopoeial texts and WHO guidelines).

