Schiffelers et al.:

# Regulatory Acceptance and Use of Serology for Inactivated Veterinary Rabies Vaccines

## Supplementary Data

### Appendix 1
### Methodology

Appendix 1 defines the research approach, the methodology, the selection criteria for the SNT case and the respondent selection. This section is adapted from Schiffelers et al. 2014a and 2015.

*Case study approach: Causal process tracing*

Regulatory acceptance and use is a process which is influenced by a broad variety of drivers and barriers (Schiffelers, 2007, 2012, 2014a,b, 2015). With this manuscript the authors aim at creating a clarification of the underlying mechanism of regulatory non-acceptance of the SNT (and other 3R models) through the examination of the variables influencing the acceptance process. This means creating an in-depth picture to unravel causal mechanisms by reconstructing events and situations that have unfolded over time. The case study approach of causal process-tracing is used for this purpose (George and Bennett, 2005; Blatter and Haverland, 2012). The goal of process-tracing is to obtain information about specific events and steps within a process through the analysis of available documents and interviewing the central actors within this process (Tansey, 2007). With this qualitative analysis technique the intervening causal process between a dependent variable (i.e., regulatory acceptance and use of 3R models) and various independent variables (e.g., scientific information, level of risk aversion, concern about animal welfare, regulatory frame, etc.) is studied.

*Research methods*

Case study research relies on multiple sources of evidence. Different research methods are combined in order to arrive at a comprehensive representation of the examined situation (Yin, 2003). The variables influencing the process of regulatory acceptance and use of the SNT were identified through a combination of literature review and expert interviews. The literature research provided an overview of the regulatory framework, stakeholders involved, existing testing practices and variables influencing the regulatory acceptance and use. The examined sources consisted of scientific publications, meeting reports, websites – e.g., EDQM, EMA, EPAA, PEI – and press releases. Between 2010 and 2012 six international meetings on 3R models for vaccine testing in general and rabies vaccines in particular, were attended[1] (see also Schiffelers et al., 2014a). The official reports of these meeting were examined for factors that potentially drive or withhold regulatory acceptance and use of 3R models for (rabies) vaccine potency testing purposes (De Mattia et al., 2011; Jungbäck, 2012; Stokes et al., 2011, 2012).

Furthermore, 15 interviews were conducted with representatives from European and US vaccine regulators, European standardisation bodies and manufacturers in 2010-2012 to collect the respondents' perspectives on the variables influencing the process of acceptance and use of the SNT (see Section on respondent selection). To update this information, six of these experts were interviewed once more in 2014 to collect the most recent developments in this field. The combination of literature

[1] ECVAM/EPAA workshop: The Consistency Approach for Quality Control of Vaccines e a 3Rs Opportunity (January, 2010; Brussels, Belgium);

Workshop ICCVAM/NICEATM: 3Rs in Vaccine Potency Testing (September, 2010; Bethesda, USA);

Conference EDQM: Quality of Medicines in a Globalized World: Dream or Reality? (October, 2010; Prague, Czech Republic);

Workshop Paul-Ehrlich-Institut (PEI): Potency testing of veterinary vaccines: the way from *in vivo* to *in vitro* (December 2010; Langen, Germany);

International Workshop ICCVAM/NICEATM on Alternative Methods for Human and Veterinary Rabies Vaccine Testing: State of the Science and Planning the Way Forward (October 11-13, 2011; U.S. Department of Agriculture Center for Veterinary Biologics, Ames, Iowa, USA);

EPAA Workshop on Waiving of Human Rabies Vaccine Potency Testing: Validation Status and Implementation Strategies of *in vitro* Glycoprotein Quantification Methods (8-9 October 2012; Arcachon, France).



http://dx.doi.org/10.14573/altex.1501261s

research, attendance of meetings and interviews resulted in an overview of factors that have influenced the acceptance and use of the SNT for the potency testing of inactivated veterinary rabies vaccines and of suggestions to optimize this process. The interviews were semi-structured, asking open-ended questions designed to reconstruct the process and identify the drivers and barriers per subsequent substage (see Section 1). The interviews began with the question of the involvement of the respondent in the process, a short chronology of this involvement and the position of his/her organization regarding the SNT. Next, a series of questions were asked concerning the barriers and drivers per sub stage of the process. Lastly, interviewees were asked to give their views on optimizing the current process of regulatory acceptance and use of the SNT within – and where possible outside – Europe. The main questions were the same for every respondent, but the focus differed depending on the respondent's involvement in the process.

*Case selection*

To be able to illustrate the process of regulatory acceptance and use, the case study had to meet the following criteria:

– The existing regulatory test is an animal model which is under discussion;
– there is a model available to reduce, replace or refine the existing animal model (3R model);
– this 3R model is in the process of becoming accepted/used for regulatory purposes.

The SNT case formally meets all three criteria. Furthermore, the fact that the SNT is formally accepted for regulatory purposes within the European context, offers the chance to give an in-depth description of the process and of the influence of the different causes (independent variables) on the outcome of regulatory acceptance (dependent variable).

*Respondent selection*

The respondent selection was done through a combination of criterion and snowball sampling (Patton, 2001). Through criterion sampling[2] a small group of relevant respondents was selected beforehand using the selection criteria of being a (scientific, legal and/or political) expert with experience in/or knowledge of the SNT case study and with former or current involvement in this case study. Involvement means having been able to closely follow or take part in (parts of) the process of acceptance and use of the SNT. The first sample consisted of a group of 5 experts involved in the process of regulatory acceptance and use. Next, the population was broadened though snowball sampling by asking each respondent for other suitable candidates. Suitability was defined as being directly or indirectly involved in one or more of the substages of FI, ARA or UI. This might have led to a certain level of bias in the sample, since people directly or indirectly involved might be more positive about the 3R model under discussion and the strategy that was followed. However, it should be mentioned that we explicitly observed the diverging opinions during the meetings to be able to select respondents with potentially different perspectives concerning this case study. The respondents in the first round of interviews originated from the following stakeholder groups: European standardisation body (4), national regulatory authority (4) and industry (7). In the second round this division was as follows: European standardisation body (2), national regulatory authority (2) and industry (2).

[2] Criterion sampling involves selecting respondents through some predetermined criteria of importance (Patton, 2001).