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3R Issues for method validation and maintenance of competence

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3R Issues for method validation and maintenance of competence

Position paper regarding the need to rationalize use of animals during method validation for 3R alternatives and maintenance of competence of methods involving animals

(VBRN and Human OCABR Networks)

Background and aim

Demonstration of appropriate method validation and maintenance of testing competence are important elements of current quality management systems which are internally and externally monitored. The testing of medicines for human or animal use, in particular biological medicines, may require the use of tests involving animals. Alternative methods can be used to replace the use of animals (replacement), reduce their numbers (reduction) or reduce their suffering (refinement). This “3Rs” approach is currently promoted through numerous EU policies. With the implementation of the new Directive 2010/63/EU, in force from 01/1/2013, and the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes, special attention is needed to be sure the use of animals in analytical procedures is in line with the new EU legal obligations concerning animal use for scientific or educational purposes, in particular in relation to Article 4 and Article 13 of Directive 2010/63/EU.

The current General European OMCL Network (GEON) Guideline on Validation of Analytical Procedures provides detailed recommendations on the extent of validation needed for analytical procedures specifically addressed to the needs of OMCLs. The goal is to maintain high quality standards also when validating testing methods that implement the 3Rs while taking into consideration the ethical use of animals and the provisions of the Directive.

The aim of this position paper is to raise the awareness of the need for prudent use of animals in the course of method validation and also for maintenance of competence, especially when the particular techniques are not performed on a regular basis in an OMCL. Animal use should be rationalised and restricted to a necessary minimum based on a thorough analysis of the particular situation and performance characteristics should be carefully selected.

Method validation

In practice, full method validation generally involves a comparative study using both the *in vivo* method that is to be replaced and the new method. As a result, unfortunately animals will be used. For development of new analytical procedures, any relevant advice provided by the European Pharmacopoeia, EURL-ECVAM and the EMA on the reduction of animals used in validation of new procedures/test methods should be applied. In order to promote acceptance by accreditation bodies and other regulatory frameworks it is important to demonstrate that the methods perform well under the operating conditions. However, it should be remembered that the objective is really to assess and verify performance characteristics of the "new" method.

Ideally, for the transfer of already validated 3R methods OMCLs should first evaluate the validation previously performed in other labs (e.g. at the manufacturer's or other OMCLs) and identify the key parameter(s) which should ensure the precision of the test procedure. These aspects should then be the focus of the transfer validation.

Maintaining Competence

When maintaining competence in a method involving animals, the steps involved should be assessed to see if it is possible to separate elements that may be ethically repeated for maintenance purposes only from those which ethically are not appropriate and may be demonstrated through other means. For example full performance of an *in vivo* test for maintenance of accreditation/attestation purposes only is generally not required. Proof is necessary, that the OMCL is competent to perform all steps of an *in vivo* test. The proof can be made by regular use of the different process steps for other purposes than the test in question. Steps that can be considered from other contexts could include:

- Husbandry conditions, if necessary under high safety conditions
- Handling of infectious material
- Anesthesia
- Routes of inoculation
- Blood sampling
- Euthanasing
- Post mortem investigations
- Etc.

Further examples for OMCLs of strategies to demonstrate competence can be found in the 2013 annual meeting presentation on PTS alternatives (available on omclnet).

Recommendations

It is important to validate alternative methods that implement the 3Rs to demonstrate that tests perform well under the operating conditions of the OMCL. For ethical reasons however animal testing for validation purposes should be minimized wherever possible and use of animals only to show maintenance of competence should be avoided completely. Strategies to limit animal use should be rationalised and documented by the OMCLs and auditors should take the ethical considerations and requirements of the Directive 2010/63/EU into account when evaluating these validation and maintenance strategies.