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Guidance for individual laboratories for transfer of quality control methods validated in collaborative trials with a view to implementing 3Rs

Draft

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Executive summary

In accordance with Directive 2010/63/EU, the principle of the 3Rs (Replacement, Reduction and Refinement) needs to be considered when selecting approaches for validating quality control tests in laboratories for regulatory testing of human and veterinary medicinal products.

Collaborative studies between laboratories may be carried out to introduce new 3Rs methods for regulatory purposes where animal tests have been traditionally used. This guidance aims to facilitate transfer of the new methods validated in such trials with a view to implementing 3Rs for testing in a product specific context in laboratories originally involved in the collaborative trial or in new laboratories.

1. Introduction (background)

To comply with Directives 2001/83/EC and 2001/82/EC and associated relevant guidelines as well as with the European Pharmacopoeia (Ph. Eur.), quality testing may require the use of animals. Ethical and animal welfare considerations require that animal use is limited as much as possible. In this respect, Directive 2010/63/EU on the protection of animals used for scientific purposes, which is fully applicable to regulatory testing of human and veterinary medicinal products, unambiguously fosters the application of the 3Rs) when considering the choice of methods to be used.

Regulatory testing covers all tests performed on starting materials, in process and final product control as required for licensing and final product testing (batch release), where applicable.

Various large scale international initiatives and organisations[1] are involved either directly or indirectly in the development, validation and dissemination of 3Rs approaches.

Several collaborative studies for quality control have already been carried out to replace, reduce or refine animal testing required for regulatory purposes. In Europe such studies have been organised in the Biologicals Standardisation Programme[2] of the European Directorate for the Quality of Medicines & HealthCare (EDQM, Council of Europe).

Collaborative studies provide the opportunity to determine how a test method behaves in different laboratories and with a variety of products. A well-designed study allows an assessment of transferability, repeatability, reproducibility and ultimately whether the method is fit for the intended purpose. It is, however, generally not the goal of a large-scale, collaborative study to carry out product specific validation for individual products. In some cases the data generated in the study may allow suggestions for the establishment of generalised specification against a common standard. However, it may also become apparent that product specific references and/or specifications are the only way forward. These factors and others, as outlined below, will influence the amount of data generation required later for the implementation of the alternative method in an individual laboratory and the extent of validation of the method for a specific product.

[1] (e.g. European Directorate for the Quality of Medicines & Healthcare (EDQM), European Partnership for Alternative Approaches to Animal Testing (EPAA), The European Union Reference Laboratory for alternatives to animal testing (EURL ECVAM), The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM/NICEATM), Japanese Center for the Validation of Alternative Methods (JACVAM), Organisation for Economic Co-operation and Development (OECD), Korean Centre for the Validation of Alternative Methods (KocVAM), World Health Organization (WHO)

[2] https://www.edqm.eu/en/Biological-Standardisation-Programme-mission-60.html

2. Scope

The guideline applies to regulatory testing used for quality control of medicinal products where animals have been traditionally used. It aims to facilitate transfer of quality control methods validated in collaborative trials with a view to implementing 3Rs, for testing in a product specific context.

The guideline should be helpful in supporting regulatory applications for variations to existing marketing authorisations as well as new applications.

3. Legal basis

This guideline has to be read in conjunction with:

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version: 05/10/2009);
- Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (consolidated version: 18/7/2009);
- Directive 2010/63/EU on the protection of animals used for scientific purposes on 3 June 2010.

4. General features of a collaborative study and its role in method validation

Collaborative studies usually follow a step-wise approach. The number and breakdown of the steps depends on the individual case, but generally they include pre-validation steps such as proof of concept and transferability.

Proof of concept takes place in one laboratory or a small group of laboratories. Usually it involves one or a small number of products. It includes development of the rationale, protocol development and optimisation to obtain sufficient specificity, sensitivity, repeatability, and reproducibility. Comparison with, but not necessarily correlation to, the existing method is demonstrated [1]. There is evaluation of the need for reagents, controls and reference materials. Also, initial proposals for statistical methods for the design of the collaborative study and to evaluate the results are evaluated.

Once proof of concept is established, the method is transferred to at least one additional laboratory. This step determines if the protocol is sufficiently robust to be reproducible and can lead to modifications of the protocol and/or the statistical approach for evaluation of the data. When additional data are needed to compare the new method with an existing animal method, a rationalised strategy at this small-scale stage can also provide a larger data set and help avoid unnecessary repetition of the animal test in a large number of laboratories at the final stage in the large-scale collaborative study.

The large-scale collaborative study stage involves many laboratories and includes a range of representative products. At this stage, the protocol should be well defined. Reagents, controls and reference materials should also be defined or at least clearly proposed. The data generated in the large-scale study should reveal the best way forward for setting specifications and possibly suggestions for the specifications themselves. Generally, the outcome of the study allows a decision on whether the proposed method is indeed fit for the intended purpose for a range of products. If the outcome is positive, the method may be considered for integration into a recognised regulatory context (e.g. European Pharmacopoeia (Ph. Eur.) monograph, EMA guidelines or WHO recommendations).

Laboratories participating in the study may add, for their own purpose, other related products and/or may include additional in-house validation studies alongside the collaborative study, if needed.

Reports (including data, anonymised as appropriate) on all of the different steps should be published and made available to the public, ideally in a peer reviewed scientific journal.

5. Validation of 3Rs methods for regulatory acceptance

Demonstration of scientific validity is a necessary condition for regulatory acceptance of any test method including methods developed to replace, reduce and refine *in vivo* tests. For regulatory acceptance at the individual product dossier level, the criteria and scientific principles for test method validation need to be fulfilled and sufficient relevant data submitted. Criteria are defined in different existing guidance documents (e.g. (V)ICH)) and should include:

1) Definition of test methodology/standard protocol

2) Relevance

3) Reliability

The level of experimental work required by an individual laboratory to demonstrate method validation is dependent on the approach taken, the starting point and the additional information available from other sources (e.g. collaborative studies).

The method validation may involve some level of testing in animals, for example as part of the test method itself (in the case of reduction and refinement) and/or when comparing to the existing method. In order to limit the use of animals and to avoid duplication of work, laboratories are encouraged, wherever possible, to maximise the use of data and information available from other sources in a rationalised strategy.

Supporting data can come from a number of sources, including accumulation of product data, published data from individual laboratories, and published study reports from collaborative trials. A laboratory's own data from participation in a given collaborative study can also be used to support final product specific validation for regulatory acceptance.

6. Transferring collaborative study validated methods to specific products/laboratories

The amount of additional validation required for transferring/implementing a new alternative method will vary case-by-case. Therefore, only high-level guidance on the type of validation and data that might be expected are provided in the following sections. For each of the possible cases below, the choice and suitability of proposed product specifications need to be supported by data generated by the applicant and/or in the collaborative study. This should include use of the method for batches found to be safe and efficacious through clinical studies or equivalent batches released on to the market for routine use. The method should be capable of detecting non-compliant batches.

When transferring a method from a collaborative study, if a relevant International Standard (IS) or Biological Reference Preparation (BRP) has been assessed / established in the study, these are used either directly as the assay reference or as part of the establishment and calibration of in-house product-specific reference materials [2]. In house working reference materials are qualified according to ICH guideline Q6B or VICH GL 40. Direct use of a recognised common reference such as an IS or BRP will reduce the amount of in-house validation required. It would normally suffice to confirm the

suitability of the reference to the product under study either through evidence from the collaborative study or through new studies by the applicant as appropriate

By implementing methods validated through collaborative studies, various scenarios can be possible. The main different types of possible cases are summarised in Table 1.

Table 1. Guidance on the extent of validation needed is reported for each circumstance in the column "Action".

Case	Scenario	Action
1	The laboratory participated in the collaborative study and intends to test a product that was included in that study.	No additional method validation is normally needed provided the method procedure is aligned with the method used in the collaborative study and the results from the laboratory were satisfactory. Supporting documentation demonstrating the transfer should be provided. The laboratory's data from the collaborative study may be used as part of the supporting documentation.
2	The laboratory participated in the collaborative study and intends to test a product included in that study but one or more changes have been introduced to the test protocol compared to the one used in the collaborative study.	Supporting documentation demonstrating the transfer should be provided. The laboratory's data from the collaborative study may be used as part of the supporting documentation. In addition data should be presented showing that the modification(s) to the validated method do not have an impact on performance of the method and that validity criteria are met. If an impact is observed this should be evaluated and any revision to validity and/or acceptance criteria should be supported by appropriate validation data.
3.1	The laboratory participated in the collaborative study and intends to test an active substance in a product related to one that was included in that study (for example a product using the same manufacturing process that may contain fewer or additional antigens, a different adjuvant or excipients).	Supporting documentation demonstrating the transfer should be provided. The laboratory's data from the collaborative study may be used as part of the supporting documentation. In addition data should be presented showing that the validated method is suitable for testing the product in question and that there is no impact on method performance or validity criteria. If an impact is observed this should be evaluated and any revision to validity and/or acceptance criteria should be supported by appropriate validation data.
3.2	The laboratory participated in the collaborative study and intends to test a related active substance in a product from a different manufacturer or manufacturing process, or newly developed product.	

4	The laboratory did not participate in the study and intends to test a product that was included in the study.	The method must be successfully transferred to the testing laboratory (for example by testing reference and or control materials, if available, used in the collaborative study to confirm adequate method performance within the laboratory). If modifications are introduced to the test protocol data should be presented showing that they do not have an impact on performance of the method and that validity criteria are met. If an impact is observed this should be evaluated and any revision to validity and/or acceptance criteria should be supported by appropriate validation data.
5	The laboratory did not participate in the collaborative study and intends to test a product that was not included in the study.	The method must be successfully transferred to the testing laboratory (for example by testing reference and or control materials, if available, used in the collaborative study to confirm adequate method performance within the new laboratory). If modifications are introduced to the test protocol data should be presented showing that they do not have an impact on performance of the method and that validity criteria are met. Data should be presented showing that the method is suitable for testing the product in question and that there is no impact on method performance or validity criteria. If an impact is observed this should be evaluated and any revision to validity and/or acceptance criteria should be supported by appropriate validation data.

References

[1] 5.2.14. Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccine, Pharmeuropa, *2016* 28(2), *Pages 1–4 (to be replaced by reference to Ph.Eur. 9th Edition).*

[2] P. Castle, Reference standards for vaccine-producing laboratories, Rev. sci. tech. Off. Int. Epiz., 1998, 17 (2), 585-591.