EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 June 2014
CHMP/CVMP/JEG-3Rs/94304/2014
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary use (CVMP)

Concept paper on transferring quality control methods validated in collaborative trials to a product/laboratory specific context

Agreed by JEG 3Rs	March 2014
Agreed by BWP	May 2014
Agreed by IWP	May 2014
Adopted by CVMP for release for consultation	5 June 2014
Adopted by CHMP for release for consultation	26 June 2014
Start of public consultation	18 July 2014
End of consultation (deadline for comments)	31 October 2014

Comments should be provided using this template. The completed comments form should be sent to JEG-3Rs@ema.europa.eu

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1. Introduction

Demonstration of scientific validity is a necessary condition for regulatory acceptance of any test method, including 3R (replacement, reduction, refinement) testing approaches. The demonstration of scientific validity is a lengthy process typically involving demonstration of proof of concept, transferability of the method across laboratories and large scale collaborative studies to demonstrate that the method is fit for its intended purpose for a range of medicinal products. Successful completion of these steps may culminate in the integration of the method into a recognised regulatory framework such as a European Pharmacopoeia (Ph. Eur.) monograph, WHO guidance or EMA guidance.

Before a method that has undergone the above process can be used for development and quality control purposes a final hurdle must be overcome: the validity of the method must be demonstrated within the hands of the individual laboratories proposing to use it and for the purpose of testing of the specific medicinal products on which it will be used. Those laboratories involved in large collaborative studies will have already generated a substantial body of data on the functioning of the method. This concept paper proposes the development of guidance on how these data can be used to support laboratory and product specific validation of 3Rs methods in order to facilitate implementation of such methods for product specific testing. The paper would also provide guidance on how published data from the collaborative study can be used to support in-house validation for other laboratories not involved in the collaborative work.

2. Problem statement

Ph. Eur. monographs and other official regulatory publications make reference to numerous methods that are, in principle, acceptable from a regulatory point of view. Many such methods represent an improvement, from a 3Rs perspective, over older, 'standard' methods. However, in order to gain acceptance for use in development and quality control testing of an individual medicinal product such a method must first be demonstrated to function appropriately in each individual laboratory in which it will be used and for each specific medicinal product that it will be used to test (product specific validation). Guidance on the requirements for this final stage of the validation process is currently lacking.

3. Discussion (on the problem statement)

The Ph. Eur. Commission, at its session in June 2013, approved a proposal from the Ph. Eur. group of experts 15 to elaborate guidance to facilitate the introduction of 3Rs compliant assays. This guidance would focus on the required data and rationale for the introduction of an alternative method, without necessarily having to demonstrate that the new method correlates with the existing pharmacopoeial method. The process should involve collaboration between relevant Ph. Eur. and EMA expert groups to provide a comprehensive guidance document that would ultimately be included in the Ph. Eur. In another development the Official Control Authority Batch Release / Veterinary Batch Release Network (OCABR/VBRN) has prepared new and revised documents to highlight 3Rs concerns during method validation and for maintaining competence in testing as relevant to the EU Official Medicines Control Laboratories (OMCL) network.

The Ph. Eur. monographs (and other relevant regulatory publications) already include a number of 3Rs relevant methods that have been validated in large collaborative studies (like those run by the EDQM Biological Standardisation Programme) and it is hoped that the measures described in the preceding paragraph will facilitate the validation of further 3Rs methods.

However, even once a method has been included in the Ph. Eur. (or other official regulatory publication) the validity of the method must be demonstrated within each specific laboratory planning to use it, and for each specific medicinal product for which it is planned to be used. Only then can the method be routinely used. This need for laboratory/product specific validation is perceived as an obstacle to the implementation of methods that have the potential to replace, reduce and refine routine *in vivo* tests.

In practice, laboratories that participate in large collaborative studies that lead to the inclusion of methods in regulatory texts will gain valuable experience with the method. It should be possible to take advantage of this experience in order to facilitate the process of gaining laboratory and product specific validation. It should also be possible to benefit from the ground work laid in the collaborative study to facilitate implementation of the method in other laboratories.

This concept paper proposes the development of guidance that will clarify the criteria to be met in order to achieve laboratory/product specific validation and describe the level of validation that will be required for laboratories and medicinal products included in large collaborative studies.

4. Recommendation

The JEG 3Rs, BWP and IWP recommend the development of guidance that will clarify the level of validation that will be required for individual medicinal products and laboratories wishing to use quality control tests that have already been validated in a large collaborative study. Such a guideline will have relevance both for medicinal products under development and for medicinal products already on the market. The guideline should be developed with input from EDQM and EURL ECVAM.

5. Proposed timetable

Release of concept paper for 3 months consultation:	18 July 2014
Deadline for receipt of comments:	31 October 2014
Discussion in working parties:	quarter 4 2014 – quarter 2 2015
Discussion of draft guideline at CXMP:	quarter 3 2015
Anticipated release of draft guideline for public consultation:	quarter 3 – 4 2015

6. Resource requirements for preparation

Input will be needed from the JEG 3Rs, BWP and IWP. In addition, the involvement of JEG 3Rs observers from EDQM and EURL ECVAM is foreseen.

7. Impact assessment (anticipated)

The guideline will improve implementation of validated 3Rs methods for development and quality control purposes and clarify the requirements for industry and assessors. It will encourage consistent regulatory criteria and decisions and will promote compliance with Directive 2010/63/EU. The guideline may also encourage the development of new 3Rs methods and participation in large scale collaborative studies.

8. Interested parties

Regulatory authorities for medicinal products for human and veterinary use, the human and veterinary pharmaceuticals industry, animal welfare bodies.

9. References to literature, guidelines, etc.

Directive 2010/63/EU of the European Parliament and of the Council, available at http://ec.europa.eu/environment/chemicals/lab_animals/home_en.htm