9 November 2017
EMA/CHMP/CVMP/3Rs/83712/2017
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guidance for individual laboratories for transfer of quality control methods validated in collaborative trials with a view to implementing 3Rs' (EMA/CHMP/CVMP/3Rs/94436/2014)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Association of Veterinary Consultants (AVC)
2	IFAH-Europe
3	International Plasma Fractionation Association (IPFA)
4	IMI-VAC2VAC consortium
5	European Coalition to End Animal Experiments (ECEAE)
6	EFPIA - European Federation of Pharmaceutical Industries and Associations

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	Association of Veterinary Consultants (AVC) comment on EMA/CHMP/JEG-3Rs/94436/2014: At this stage this guidance is high level and would benefit from some real examples or further references to examples of 3Rs work (not necessarily from the regulatory field).	We are not in a position to give more detailed advice on the quantity of data. When more experience is gained it could be considered to update the Guideline with an annex giving examples.
2	IFAH-Europe has no comments to the draft Guidance for individual laboratories for transfer of quality control methods validated in collaborative trials with a view to implementing 3Rs (EMA/CHMP/CVMP/JEG-3Rs/94436/2014).	
3	On behalf of the International Plasma Fractionation Association (IPFA) I thank you for offering the opportunity to comment on the EMA Draft Guidance on Transfer of QC methods validated in collaborative trials -implementing 3Rs (EMA/CHMP/CVMP/JEG-3Rs/94436/2014). After consulting the IPFA member organisations, I can inform you that we have no comments on this document.	
4	THE IMA-VAC2VAC project partners welcome the possibility to comment on the draft Guideline. The Guideline will be of good support whenever in vivo tests are intended to be replaced by in vitro tests. It is recognised that currently no stakeholder has extensive	

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	experience in this field and therefore a Guideline cannot be based on sufficient data.	
5	The European Coalition to End Animal Experiments (ECEAE) warmly welcomes the creation of this guideline, which is aimed at improving the implementation of validated alternatives to quality control tests for regulatory testing of human and veterinary medicinal products. The purpose of the guideline is now clearer to us and we do agree that it helps address the problem statement given in the concept paper. The guideline provides a good overview of the purpose and scope of collaborative trials and the table helps a great deal to highlight various scenarios and the corresponding actions that should be taken to achieve acceptance of the method for each laboratory and each product. This is appreciated. We are also pleased that the table covers the scenarios whereby the product or laboratory was *not* involved in the collaborative trial. This is a possible scenario and now companies finding themselves in this position have some guidance. The title of the guidance however, therefore may prevent such companies from identifying that the guidance is relevant to them, which might be something to bear in mind. Scenario 1 in the Table, is it clear whether we are talking about the same active ingredient and/ or the same product? Scenario 3 is different product, similar active ingredient. Is a scenario missing (same active ingredient/different product?) - indeed this seems to be a common scenario from our experience, is it covered under Scenario	

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	1? Whilst we do appreciate the difficulty with giving advice on the quantity of data required in this area, we are concerned with the vagueness to the statements: "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." Is there a document (EurPh, (V)ICH, EMA) that could assist in answering the obvious question, 'what is appropriate validation data'? Similarly, with respect to the data required for demonstration of 'transfer': "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)." Is there a EurPh or (V)ICH or EMA document that can assist with determining the data needed to demonstrate adequate transfer?	Not accepted: the title refers to methods validated in collaborative trials, not laboratories/companies. We are not in a position to give more detailed advice on the quantity of data. When more experience is gained it could be considered to update the Guideline with an annex giving examples.
6	1. Waiving assays: not all alternatives to in vivo methods are replacement; some animal assay can be removed, eg General Safety Test 2. Additional objectives: Engagement of non-EU authorities and willingness for <u>international</u> recognition	Ad 1.Accepted. J3rsWG pays equal notice to all areas covered under the 3Rs concept, including refinement and reduction in addition to replacement. Ad 2.Accepted. Ongoing coordination in ICH and VICH. There are ongoing collaboration on addressing 3Rs at VICH and ICH. Examples include waiving the Target Animal batch Safety Test for live and inactivated vaccines adopted in May

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	3. Consideration for validation by non-EU authorities and acceptance by EU authorities	2017 (VICH GL50 [inactivated vaccines], VICH GL55 [live vaccines).
	4. Consistency approach: to be considered as the objective is not to replace one-to-one animal assays by non-animal assays, but to envisage another quality control system.	Ad 3.Accepted. In collaboration with EDQM and ECVAM. In accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes. The Ph.Eur is committed to the reduction of animal usage wherever possible in pharmacopoeial testing, and encourages those associated with its work to seek alternative procedures.
	5. Incentives to facilitate the QC changes with more accurate methods should be considered. Declaration rather than authorization should be sought.	Ad 4.Accepted. The consistency approach is incorporated into the 3Rs GL, Regulatory acceptance of 3R (replacement, reduction, refinement) testing approaches EMA/CHMP/CVMP/JEG-3Rs/450091/2012, effective from 01/01/2017. The Ph.Eur encourages animal-free approaches to be used by manufacturers including, for example, through the proof of consistency to avoid unnecessary tests in animals on intermediate stages of production or on the final product. Ad 5.Not accepted. The current regulatory framework requires QC changes to a Marketing Authorisation to be submitted as a variation and subject to authorisation.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
102-121	4	Comment: Lines 102-109 are very clear but lines 110 to 121 do not provide sufficiently clear guidance. The comparison with previous studies/data should not be so focussed as the new methods will probably target different endpoints, and the comparison will not be possible. Proposed change: <u>New methods targeting the same endpoints:</u> 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	Not accepted. The General text 5.2.14 (ref. [1]) gives guidance on substitution of in vivo test with in vitro tests and should be sufficient. Reference to 5.2.14 has been added to the sentence "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 [1]."

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		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. New methods targeting other endpoints: New methods will probably target different endpoints and comparison with the former tests will not be possible. Parallel testing of a sufficient amount of batches with both test (panels) to evaluate the equivalence of the endpoints chosen may be necessary.	
127-130	4	*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.* Comment: The replacement of tests performed on batches should always be made in the context of consistency.	Not accepted: There is no requirement to perform new clinical trials if the "original" clinical batches are not available. It is clearly stated that batches equivalent to batches proven to be safe and efficacious. This could well be batches manufactured by the approved manufacturing process for release, i.e. the batches are deemed safe and efficacious otherwise they would

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		Especially for existing products, it should be difficult to link the new test(s) with the batches used in clinical studies. The need for new clinical trials for existing products should be reconsidered. New studies should be declared as not necessary. One solution may be the use of the safe harbor testing. It should be stressed that the in vivo tests currently used for batch testing were never validated according to the present requirements. Therefore, it cannot be concluded that the established in vivo tests give confidence in the efficacy in the target species. Proposed change: 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. For products, where the batches used in clinical trials cannot be used for these studies on equivalence the repetition of clinical studies should be regarded as ultima ratio and should be avoided as far as possible. In any case, parallel testing of a sufficient amount of batches with both test (panels) to evaluate the equivalence should be sufficient.	not be release for clinical use. Such an approach would cover consistency in production.

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29	6	Comment: To include acceptance of alternative methods by all EU authorities. Laboratories can be challenged by some authorities having different level of expectations. Proposed change (if any): …to facilitate transfer and acceptance of the new methods….	Accepted
41	6	Comment: Strengthen the importance of involvement of non-EU authorities to facilitate international recognition Proposed change (if any): Engagement of international organizations should be encouraged in order to represent as many authorities as possible.	Not accepted. Although it is agreed that international harmonisation is of importance for introduction of alternative methods, it is not the scope of this guideline. The foot note to on page 41, indicate by examples, that there are international organisations in place that are involved in collaborative studies on validation of alternative methods.
71	6	Comment: Date of Directive 2010/63 is wrong Proposed change (if any): Directive 2010/63… on 22 Sept 2010	Accepted.
89	6	Comment: If the collaborative initiative is not under the leadership of EU, or not with the participation of EU authorities, how can implementation of replacement method be accelerated?	Noted. It is not a prerequisite that the initiative is under EU leadership. See lines 89-11. The rate of implementation of any new 3Rs method will be dependent on a number of factors that are outside the scope of the GL. We are not in a

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			position to give more detailed advice. When more experience is gained it could be considered to update the Guideline with an annex giving examples of best practice for implementation.
92	6	Comment: There is not always correlation between animal and non-animal methods. How to manage effectively the replacement and its acceptance?	Accepted. Reference is given to 5.2.14. Substitution of in vivo method(s) by in vitro method(s) for the quality control of vaccine, Ph.Eur. 9th Edition.
122	6	Comment: QC testings are repeated by OMCLs. If animal method for one product has been replaced, there should be an obligation for the authority to use the alternative test. The transfer should be effective to OMCLs	Accepted. The guideline is applicable to both OMCLs and Manufacturers performing quality control testing.