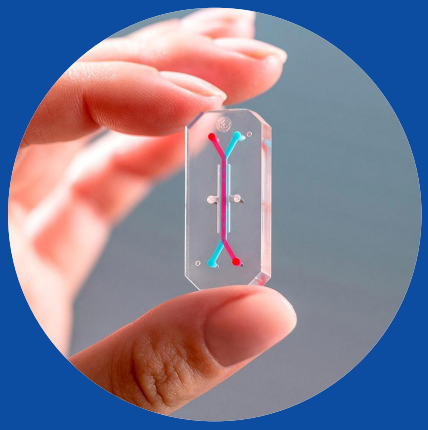
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Joint CVMP/CHMP Working group on the Application of the 3Rs in Regulatory Testing of Medical Products

Biennial report 2016/2017



Executive summary

This report is aimed at informing pharmaceutical companies and the public of the EMA activities in relation to "3Rs" (replacement, reduction, refinement) during 2016 and 2017. The report summarises the recommendations developed and the organisational structure enabling the development of such guidance. It also looks into the future with details about a new mandate to continue providing advice and recommendations to the Committee for Medicinal Products for Veterinary Use (CVMP) and Committee for Medicinal Products for Human Use (CHMP) on all matters relating to the use of animals and the application of the '3Rs' principles in the testing of medicines for regulatory purposes.

In the reporting period, the working group established for this purpose reviewed animal tests included in product release specifications for centrally authorised veterinary vaccines and human vaccines/biologicals to ensure best practice in 3Rs is applied to the methodology for conducting any *in vivo* tests. Where potential opportunities for improving compliance with best practice in 3Rs have been identified, the relevant Marketing Authorisation Holders were notified. At the same time, the group consulted with stakeholders on guidance and other 3Rs initiatives and provided expert input on 3Rs regulatory issues associated with medicinal products.

The period 2018 – 2019 poses some specific challenges resulting from Brexit and the associated move of the Agency to Amsterdam. Inevitably the focus will be on core-business activities during the period of transition. However, the 3Rs will continue to be addressed, not least through the continued endeavour of the working parties and committees to implement the 3Rs principles without putting public health and animal welfare at risk.

Introduction

The Joint CHMP/CVMP Expert Group on 3Rs (JEG 3Rs) had been active since October 2010 with a mandate to provide advice and recommendations to the CVMP and CHMP on all matters relating to the use of animals in regulatory testing of medicinal products.

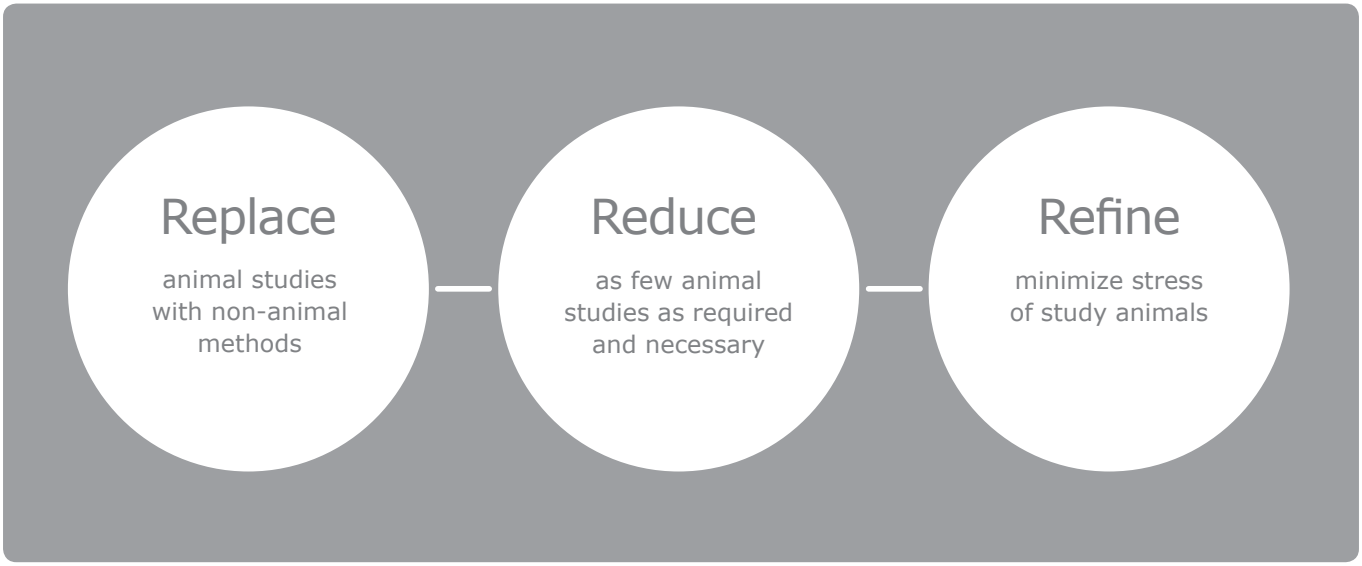
At the end of 2016, it was broadly recognised that the current JEG 3Rs had achieved its objectives in the previous 3 years. However, the importance of retaining a central group for coordination of 3Rs activities, with links to the relevant working parties of EMA scientific committees, was acknowledged and a proposal to renew the mandate for 2017–2019 under a new composition was supported. The mandate for the new **Joint CVMP/CHMP Working Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products (J3RsWG)** was endorsed by CVMP and CHMP, based on recommendations from the EMA's Medicines Leadership Team (MLT).

Like most scientific groups at the Agency, the J3RsWG will operate in line with a yearly work plan and reporting, which will facilitate periodic review of the new working group to monitor its progress and assess whether any adjustment to its mandate is required.

The new J3RsWG is a smaller group than the JEG 3Rs, and composed of members from those working parties of EMA scientific committees where animal tests form a significant component of the regulatory activity. The J3RsWG is comprised of "core members" from the CHMP Safety Working Party (SWP-H), CHMP Biologicals Working Party (BWP), CVMP Safety Working Party (SWP-V), CVMP Efficacy Working Party (EWP), and CVMP Immunologicals Working Party (IWP). The core members are supported by four co-opted experts in the field of 3Rs in their respective disciplines.

Other working parties of EMA scientific committees are linked to J3RsWG by the nomination of non-core members: CHMP Vaccines Working Party (VWP), CHMP Biosimilar medicinal products working party (BMWP) and the joint CHMP/CVMP Quality Working Party (QWP). The European Commission (EC), the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the European Union Reference Laboratory for alternatives to animal testing (EURL ECVAM) are observers to the group to establish strong links with other European institutions involved in 3Rs.

The new J3RsWG is focused on acting as a consultative group for requests from CHMP/CVMP, finalising guidance documents following public consultations, and continuing the scientific review of batch release tests for human and veterinary vaccines/biologicals for alignment with best practice in 3Rs.



3Rs guidance documents

Regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches (EMA/CHMP/CVMP/JEG-3Rs/450091/2012)

This guideline describes the process for submission and evaluation of a proposal for regulatory acceptance of 3Rs testing approaches for use in the development and quality control during production of human and veterinary medicinal products. It also presents the scientific and technical criteria for validation of 3Rs testing approaches and explains the pathways for regulatory acceptance of 3Rs testing approaches.

The guideline was adopted in 2016 and has been in force since 1 January 2017.

Reflection paper providing an overview of the current regulatory testing requirements for medicinal products for human use and opportunities for implementation of the 3Rs (EMA/CHMP/CVMP/JEG-3Rs/742466/2015)

This reflection paper was developed as a complement to the guideline on Regulatory acceptance of 3Rs testing approaches (see above) and provides an overview of the main animal tests required for the regulatory testing of medicinal products for human use. It includes information on opportunities for limiting animal testing that can already be implemented, where appropriate, as well as information on opportunities that may become available in the future. It is expected that the document stimulates further requests for CHMP advice on the regulatory acceptance of new 3Rs approaches and may decrease the use of obsolete methods.

The public consultation ended on 31 May 2017 and the final reflection paper is scheduled for publication in Q1 2018.

Reflection paper providing an overview of the current regulatory testing requirements for medicinal products for veterinary use and opportunities for implementation of the 3Rs (EMA/CHMP/CVMP/JEG-3Rs/164002/2016)

This reflection paper was developed as a complement to the guideline on Regulatory acceptance of 3Rs testing approaches (see above) and provides an overview of the main animal tests required for the regulatory testing of medicinal products for veterinary use. It includes information on opportunities for limiting animal testing that can already be implemented, where appropriate, as well as information on opportunities that may become available in the future. It is expected that the document stimulates further requests for CVMP advice on the regulatory acceptance of new 3Rs approaches.

The public consultation ended on 31 October 2016 and the final reflection paper is scheduled for publication in Q1 2018.

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)

This guidance aims to facilitate transfer of the new methods validated in collaborative 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.

The guidance was adopted and published in November 2017.

Supporting CVMP input into VICH guidelines

J3RsWG is informed of developments at the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) on 3Rs related issues that cover regulatory testing in the development and testing of veterinary vaccines and safety of veterinary residues in food for human consumption.

For relevant topic areas, the J3RsWG position is conveyed to the appropriate CVMP working party for consideration before CVMP endorses the EU position in preparation for discussions at VICH. J3RsWG has considered and commented on:

- VICH guidelines on target animal batch safety testing:
  - » VICH GL50 on Harmonisation of criteria to waive target animal batch safety testing for inactivated vaccines for veterinary use, and
  - » VICH GL55 on Harmonisation of criteria to waive target animal batch safety testing for live vaccines for veterinary use

The guidelines were adopted in June 2017 and will come into effect in May 2018.

- New draft VICH guideline on Harmonisation of criteria to waive laboratory animal batch safety testing for vaccines for veterinary use

Other activities

Report on actions taken in the review and update of EMA guidelines to implement best practice with regard to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products (EMA/CHMP/CVMP/JEG-3Rs/677407/2015)

CHMP and CVMP have undertaken a review and update of EMA guidelines to implement best practice with regard to 3Rs (replacement, reduction and refinement) in regulatory testing of medicinal products. The purpose of this review was not to reconsider established testing requirements, but to ensure that EMA guidelines did not make reference to animal tests that are no longer considered appropriate.

The published report is to provide a summary of the work undertaken and the guidelines that have been or will be updated as a result of the review.

The public consultation ended on 31 October 2016 and the final report is scheduled for publication in Q1 2018.

Review of final product batch testing requirements

J3RsWG continues to review animal tests included in product release specifications for centrally authorised veterinary vaccines and human vaccines/biologicals to check compliance with current Ph.Eur monographs and to ensure best practice in 3Rs is applied to the methodology for conducting any *in vivo* test.

The review of batch data is a multidisciplinary task involving IWP, BWP, VWP and QWP. Any product specific recommendations are made directly to marketing authorisation holders with endorsement from either CHMP or CVMP. In 2016 one variation was submitted to amend a batch potency assay for a veterinary vaccine as a consequence of a letter from the JEG 3Rs highlighting an issue with respect to best practice in 3Rs.

CVMP position statement on the ethical use of animals in the development, manufacture and testing of veterinary medicines

In December 2017 J3RsWG published a CVMP position statement on the ethical use of animals in the development, manufacture and testing of human and veterinary medicines following a number of ethical and animal welfare issues identified in third regions for products subsequently marketed in the EEA. The statement clarified that, in respect of medicines and veterinary medicines intended for supply in the EEA, the use of animals for the manufacture, or for any control tests for batch release is expected to conform to EU ethical and animal welfare standards.

Collaboration with EC, other EU agencies and international organisations

J3RsWG works closely with EDQM on the progress of 3Rs topics in the Ph.Eur. Significant developments in 3Rs communicated by EDQM are included on the EMA website to ensure the issues are communicated as widely as possible to all stakeholders, including academia, where many innovative approaches on 3Rs originate.

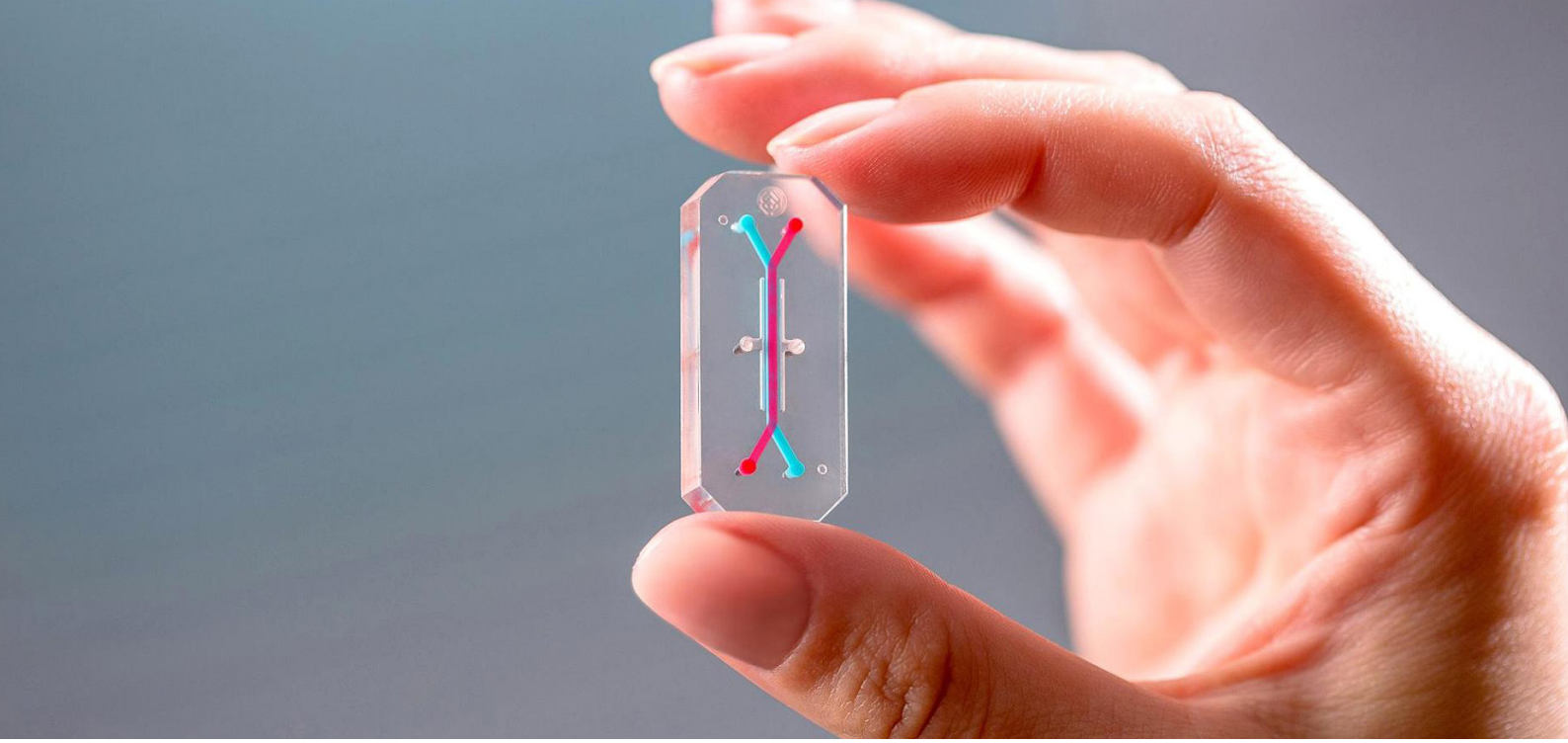
J3RsWG and the relevant CVMP WPs have provided comments on the following documents relating to 3Rs:

- A European Chemical Agency (ECHA) report on the current status of regulatory acceptability of non-animal approaches (published in November 2017): In this report ECHA reviews the current regulatory acceptability of non-animal approaches in the context of REACH (Registration, Evaluation, Authorisation & restriction of Chemicals), BPR (Biocidal Products Regulation) and CLP (Classification, Labelling and Packaging), with a focus on information requirements and data sets describing investigations in vertebrate animals.

- A draft European Food Safety Authority (EFSA) reflection on interpretation of some aspects related to genotoxicity assessment providing responses to provide advice on the: (1) the suitability of the unscheduled DNA synthesis *in vivo* assay to follow-up positive results in *in vitro* gene mutation tests; (2) the adequacy to demonstrate target tissue exposure in *in vivo* studies, particularly in the Mammalian Erythrocyte Micronucleus test; (3) the use of data in a weight of evidence approach to conclude on the genotoxic potential of substances and the consequent setting of health-based guidance values; published for consultation in 2017

- A draft OECD guidance document on good *in vitro* method practices (GIVIMP) for the development and implementation of *in vitro* methods for regulatory use in human safety assessment; published for consultation in 2016

J3RsWG also maintains close links with ECVAM's Network for Preliminary Assessment of Regulatory Relevance (PARERE).



Objectives for 2018 and beyond

The tasks of the new J3RsWG remain relatively unchanged with a focus in the following areas:

(1) Finalisation and adoption of reflection papers and guidelines under development on 3Rs

(2) Evaluation of 3Rs issues related to batch release testing for veterinary immunologicals and human vaccines & biologicals

(3) Support and promotion of the implementation of Directive 2010/63/EU for the use of 3Rs principles (best practices), including 3Rs training for regulators

(4) Agency platform for 3Rs-related issues

In 2018/2019, 3Rs activities may be impacted by Agency business continuity considerations in light of Brexit and the relocation of the Agency.

European Medicines Agency

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 www.ema.europa.eu/contact

www.ema.europa.eu

EMA/CHMP/CVMP/3Rs/502136/2017
Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)