EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The application of the 3Rs in regulatory testing of veterinary medicinal products

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Areas to cover

- Legislative background
- CVMP/CHMP joint ad hoc expert group on the application of the 3Rs (JEG 3Rs)
- Interactions with other groups
  - EURL ECVAM
  - EDQM
  - VICH
  - EPAA

Legislative Background

In formulating and implementing the Union's agriculture, fisheries, transport, internal market, research and technological development and space policies, the Union and the ***Member States shall, since animals are sentient beings, pay full regard to the welfare requirements of animals,*** *while respecting the legislative or administrative provisions and customs of the Member States relating in particular to religious rites, cultural traditions and regional heritage*

Treaty on the Functioning of the European Union

Legislative Background

- Directive 2009/9/EC amending Directive 2001/82/EC states that:

  "Member States shall ensure that all experiments on animals are conducted in accordance with Council Directive 86/609/EEC"
- Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes was based on the European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes, adopted the same year.
- Directive 86/609/EEC has now been replaced by Directive 2010/63/EU on the Protection of animals used for scientific purposes

Directive 2010/63/EU on Protection of animals used for scientific purposes

Replaces and strengthens previous rules (Directive 86/609/EEC) and formally places the principle of the 3Rs in legislation. In particular:

- MSs shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, not entailing the use of a live animal, is recognised under the legislation of the Union
- If it is necessary to use animals, the method which to the greatest extent reduces the number of animals; uses animals with the lowest capacity to experience pain, suffering, distress or lasting harm; causes the least pain, suffering, distress or lasting harm and is most likely to provide satisfactory results, shall be selected
- Foresees greater involvement of regulators and MS in validation of 3Rs methods
- Came into full effect on 1 Jan 2013

Directive 2010/63/EU on Protection of animals used for scientific purposes

Note that EMA is not responsible for implementation of the Directive. However, in line with the Agency's stated commitment to the 3Rs we will provide support for the Directive's implementation in whatever way we can.

Joint CVMP/CHMP ad hoc expert group on the application of the 3Rs in the regulatory testing of medicinal products (JEG 3Rs)

- Created in 2010/2011 to

  provide advice and recommendations to CVMP and CHMP on all matters relating to the use of animals in the testing of medicines for regulatory purposes

- Membership:
  - experts from existing WPs for which animal testing is relevant: SWP-H&V, IWP, QWP, BWP, VWP, EWP-V
  - 1 CVMP member
  - 1 expert nominated by CHMP
  - observers from EURL ECVAM and EDQM
  - Chair: Dr Sonja Beken, Vice Chair: Dr Ellen-Margrethe Vestergaard
- Meets for 2 one day meetings per year

JEG 3Rs – recent/ongoing activities

Communication & awareness:

- increased awareness and communication on 3Rs issues
  - within and between EMA working groups and between EMA working groups and NCAs
  - with key EU bodies working in 3Rs areas - EURL ECVAM, EDQM and DG Environment
  - with other EU (and non-EU) bodies working on 3Rs topics - European Partnership for Alternatives to Animal Testing (EPAA)
- creation of a dedicated forum from which to draw experts for participation in relevant external 3Rs activities and through which to provide advice in the 3Rs area

JEG 3Rs – recent/ongoing activities

Communication & awareness (continued):

- General statement on EMA webpage on EMA commitment to 3Rs
- General statement on EMA webpage on compliance with Directive 2010/63/EU in relation to batch release testing
- Plan to add a similar statement highlighting on compliance with Directive 2010/63/EU and the deletion of the need for Target Animal Batch Safety Testing

JEG 3Rs – Recent/ongoing activities

- Reviewing existing guidance with recommendations to WPs to consider revisions where appropriate
- Development of guidance relating to gaining acceptance for 3Rs testing paradigms
- Pilot project to review batch testing requirements for individual products and highlight possible shortcomings directly to MAHs
- PARERE – development of comments on the preliminary regulatory relevance of methods proposed for entry into the EURL ECVAM validation programme

JEG 3Rs – the future

- Original mandate was for 2 years – now ending
- A proposal to extend mandate by further 2 years will be presented to the EMA Management Board at its March 2013 meeting.
- If approved, a work plan for the next 2 years will be published. Likely to focus on 3 areas:
  - compliance of existing animal testing guidance with 3Rs principles and the development of guidance relating to the acceptance of 3Rs testing paradigms
  - 3Rs issues related to batch release testing
  - supporting implementation of Directive 2010/63/EU

Interactions with other groups – EURL ECVAM

- Set up in 1991 by the European Commission to promote alternative methods, their validation and acceptance as requested by Directive 86/609/EEC
- Directive 2010/63/EU established EURL ECVAM as the European Reference Laboratory for Alternatives to Animal Testing
- Duties (Annex VII) include:
  - Coordinating and promoting development and use of 3Rs approaches
  - Coordinating the validation of alternative approaches

In relation to these aims EURL ECVAM set up the PARERE/ESTAF network to obtain views of stakeholders on relevance of possible alternative methods. JEG 3Rs contributes to PARERE and EURL ECVAM is represented on JEG 3Rs

Interactions with other groups – EDQM

- Ph Eur Commission continually revises general texts and monographs, re-evaluating relevance of animal tests and including alternatives where appropriate
- Biological Standardisation Programme aims to validate new pharmacopoeial methods with a focus on 3Rs and establish Ph Eur reference preparations
- Last year the Ph Eur Commission adopted the deletion of the TABST for all veterinary vaccines
- Ph Eur Commission Expert Groups are considering need to further amend monographs in light of Directive 2010/63/EU
- EDQM is represented in JEG 3Rs and EMA working parties are represented in Ph Eur expert groups

Interactions with other groups – VICH

- VICH develops harmonised data requirements which, in itself, contributes to the reduction of animal testing
- VICH guidance is used in areas other than just the EU, USA and Japan
- The VICH Organisational Charter specifies that Expert Working Groups have a responsibility to consider 3Rs by encouraging the use of validated alternative methods
- Wherever possible VICH refers to OECD test guidelines, the development of which also consider 3Rs issues

Interactions with other groups – VICH

VICH is directly involved in efforts to avoid unnecessary batch safety testing for veterinary vaccines:

- the possibility to waive TABST has existed in EU since 2004 but has not been widely implemented.
- One of main reasons for this is that the tests would still need to be performed for countries outside EU
- In 2011 VICH GL50 on the harmonisation of criteria to waive TABST for inactivated veterinary vaccines was published for consultation
- The progression of the 3Rs approach in the batch safety testing of veterinary vaccines is now being discussed at VICH with a view to widening the scope of VICH GL 50.

Interactions with other groups – European Partnership for Alternatives to Animal Testing

- EPAA is a collaboration between Commission, EU trade associations and companies from 7 industrial sectors with aim to accelerate development, validation and acceptance of alternatives

  Divided into 3 platforms:

  - Platform on science
  - Platform on 3Rs in regulation
  - Platform on Communication & Dissemination

  EMA involved with platform 2, and particularly:

  - Project on the consistency approach for QC of vaccines (2 JEG 3Rs members and both observers involved)
  - A project encouraging international acceptance of alternative testing methods for QC of vaccines and other biologicals

Summing up

- EMA is committed to implementation of 3Rs wherever possible, as are its stakeholders
- Directive 2010/63/EU has provided a renewed impetus for activity in the 3Rs arena
- EMA, through the JEG 3Rs and other European and international bodies will seek to support implementation of the new directive