3RsWP – past & future activities. 3Rs in veterinary vaccines.

3Rs implementation in veterinary vaccine batch-release testing: Current state-of-the-art and future opportunities

Workshop – November 16th, 2022
Hotel Pullman Brussels Centre Midi, Place Victor Horta 1, 1060 Brussels and remote

Presented by Sonja Beken and Elisabeth Balks, 3RsWP

The Directive is firmly based on the principle of the Three Rs, to replace, reduce and refine the use of animals used for scientific purposes (article 4).

There is a legal obligation to replace the use of animals when new non-animal methods become available (article 13).

The EU Directive is unique in the world because it sets as its ultimate goal the full replacement of use of animals for scientific purposes.


Data and knowledge sharing: PARERE and other mechanisms

Increased efficiency of assessing substances by grouping

One substance – One assessment, see ‘ONE – Health, Environment, Society - Conference’, June 2022 Brussels

3Rs in R&D of medicines EMA and 3Rs

ALURES statistical database and open-access database on non-technical summaries of authorised projects

IMI and H2020/Horizon Europe and European Research Council

EURL-ECVAM reviews on NAMs in biomedical research

Training programmes on 3Rs

EPAA as means for collaboration

https://3rs-campaign.org

3RsWP – past & future activities. 3Rs in veterinary vaccines.

Competent Parliamentary Committee: N.A.
Animal use in the EU

10.4 million animals used in 28 Member States incl Norway (2019)
Publicly accessible version of the ALURES Statistical EU Database on animal use
https://ec.europa.eu/environment/chemicals/lab_animals/alures_en.htm

Regulatory use:

<table>
<thead>
<tr>
<th>Legislation</th>
<th>Quality control (incl batch safety and potency testing)</th>
<th>Toxicity and other safety testing including pharmacology</th>
<th>Other efficacy and tolerance testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legislation on medicinal products for human use</td>
<td>715,652</td>
<td>313,083</td>
<td>64,195</td>
</tr>
<tr>
<td>Legislation on medicinal products for veterinary use and their residues</td>
<td>240,853</td>
<td>43,532</td>
<td>31,960</td>
</tr>
<tr>
<td>Medical devices legislation</td>
<td>2,496</td>
<td>49,735</td>
<td>1,332</td>
</tr>
<tr>
<td>Industrial chemicals legislation</td>
<td>6</td>
<td>153,640</td>
<td>457</td>
</tr>
<tr>
<td>Plant protection product legislation</td>
<td>180</td>
<td>68,036</td>
<td>647</td>
</tr>
<tr>
<td>Biocides legislation</td>
<td>260</td>
<td>1,905</td>
<td>552</td>
</tr>
<tr>
<td>Food legislation including food contact material</td>
<td>161</td>
<td>36,520</td>
<td>30</td>
</tr>
<tr>
<td>Feed legislation including legislation for the safety of target animals, workers and environment</td>
<td>19</td>
<td>7,092</td>
<td>9,351</td>
</tr>
<tr>
<td>Other legislation</td>
<td>648</td>
<td>40,992</td>
<td>188</td>
</tr>
<tr>
<td>Total</td>
<td>960,212</td>
<td>719,855</td>
<td>100,712</td>
</tr>
</tbody>
</table>

2019

<table>
<thead>
<tr>
<th>Type of use</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch potency testing</td>
<td>744,710</td>
</tr>
<tr>
<td>Batch safety testing</td>
<td>150,977</td>
</tr>
<tr>
<td>Other quality controls</td>
<td>33,613</td>
</tr>
<tr>
<td>Pyrogenicity testing</td>
<td>30,912</td>
</tr>
<tr>
<td>Total</td>
<td>960,212</td>
</tr>
</tbody>
</table>

Table 18: Quality control related uses by type of use

2 3RsWP – past & future activities. 3Rs in veterinary vaccines.

Classified as internal/staff & contractors by the European Medicines Agency
3 Rs – past & future activities. 3Rs in veterinary vaccines.


NEW
Start of CHMP/CVMP Joint 3Rs Working Party - Q3 2022


3RsWP – past & future activities. 3Rs in veterinary vaccines.
Guideline on the principles of regulatory acceptance of 3Rs testing approaches


**Regulatory acceptance**:  
- Incorporation of a new 3R testing approach into a regulatory testing guideline  
- On a case-by-case basis: acceptance by regulatory authorities of new approaches not (yet) incorporated in testing guidelines but used for regulatory decision making

**Criteria for regulatory acceptance**  
- Defined test methodology (protocol, endpoints)  
- Relevance within a particular context of use (including accuracy)  
- Context of use (including limitations).  
- Reliability/robustness  
- Voluntary submission of data obtained by using a new 3Rs testing approach can be made in parallel with data generated using existing methods (safe harbour)

**Procedure**

Guideline on Qualification of Novel Methodologies for Drug Development (EMA/CHMP/SAWP/72894/2008 Rev. 1)


3RsWP – past & future activities. 3Rs in veterinary vaccines.
Retrospective: JEG3R and J3RsWG

• JEG3R 2010 -2016 (objectives achieved)

• Continued importance of developments in 3Rs ⇔ group maintained in a revised form (creation of a Working Group, J3RsWG).

• Smaller group composed of members from SWP-H/V, BWP, EWP, IWP; core group supported by four co-opted experts in the field of 3Rs. Other working parties of EMA scientific committees linked by nomination of non-core members

  • more focused on reacting to requests from CHMP/CVMP,
  • responding to public consultations of published guidance and reflection papers and preparing the final documents for adoption
  • continuing the scientific review of batch release tests for human and veterinary vaccines/biologicals for alignment with best practice in 3Rs.
  • complemented the work of other European bodies (EURL ECVAM, EDQM)
3RsWP (joint 3Rs working party of CHMP & CVMP)

- Strategic and visible WP to monitor and supervise the different 3Rs activities required to achieve the strategic goals in line with the EMA Regulatory Science strategy 2025 and the 3-year workplan of the NC domain.

- Multidisciplinary aspects of the 3Rs (H & V) into a restricted core group (WP) complemented by Operational Experts Groups (OEGs) and drafting groups (DGs) with targeted expertise (E) to support the main operational activities (A).

**WP core team**

- A1
- A2
- A3
- A4
- H+V
- A5

**Operational expert groups or drafting groups**

- A1 E1
- A1 E1
- E1 E1
- E1 E1

- A2 E2
- A2 E2
- E2 E2
- E2 E2

- A3 E3
- A3 E3
- E3 E3
- E3 E3

- Batch Release testing
- t.b.d.

**Experts (NCAs/academia)**

- E E E E E E
- E E E E E E
- E E E E E E
- E E E E E E
- E E E E E E
The 3RsWP (ii)

• Composition

<table>
<thead>
<tr>
<th>Name</th>
<th>Country</th>
<th>Institution</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sonja Beken (chair)</td>
<td>BE</td>
<td>FAGG AFMPS</td>
<td>Human MPs – Non-clinical</td>
</tr>
<tr>
<td>Sarah Adler-Flindt (Vice-chair)</td>
<td>DE</td>
<td>Federal Office of Consumer Protection and Food Safety</td>
<td>Veterinary MPs – Batch release</td>
</tr>
<tr>
<td>Peter Theunissen</td>
<td>NL</td>
<td>MEB</td>
<td>Human MPs – Non-clinical</td>
</tr>
<tr>
<td>Kathrine Just Andersen</td>
<td>DK</td>
<td>Danish Medicines Agency</td>
<td>Veterinary MPs – EWP-V, Non-clinical and clinical</td>
</tr>
<tr>
<td>Elisabeth Balks</td>
<td>DE</td>
<td>PEI</td>
<td>Veterinary MPs – Batch release</td>
</tr>
<tr>
<td>Camilla Svensson</td>
<td>SE</td>
<td>Swedish MPA</td>
<td>Human MPs – Non-clinical</td>
</tr>
</tbody>
</table>

• EMA support to 3RsWP
- Scientific secretariat: Stefano Ponzano (H-Division), Michael Empl (Vet-division)
- Administrative secretariat: Stavroula Tasiopoulou

• 3RsWP Web Page


• First meeting scheduled for November 2022

7 3RsWP – past & future activities. 3Rs in veterinary vaccines.

Classified as internal/staff & contractors by the European Medicines Agency
3RsWP - tasks

- Preparing, reviewing and updating guidelines and concept papers
- European and international co-operation
- Liaising with stakeholders such as pharmaceutical companies, animal welfare organisations and national competent authorities (NCAs)
- Providing training and workshops to assessors
- Providing product support on 3Rs-related issues when requested by EMA Committees, the Innovation Task Force and the Scientific Advice Working Party.

EMA will publish the 2022-24 work plan and provide information on the mandate, responsibilities and procedures of this working party as soon as available.
EMA’s Innovation Task Force and 3Rs

**Multidisciplinary**: scientific, regulatory & legal

**Dedicated forum for early dialogue** between regulatory and stakeholders (e.g. SMEs, academics, researchers, research and public-private funded consortia (e.g. IMI), pharmaceutical industry)

**Focus on emerging therapies, methodologies & technologies**

**NEW focus on regulatory acceptance of so-called new approach methodologies (NAMs) to replace the use of animals in the testing of medicines (3Rs)**

→ e.g., *in silico* modelling & novel *in vitro* assays (e.g. MPS technology)

**Objectives** are to encourage the development of NAMs and accelerate their integration in the regulatory framework for the development and evaluation of medicines

**Informal exchange** of information and provision of guidance *early* in the development process during briefing meetings

Discussion led by multidisciplinary experts from the Agency network, and EMA working parties & committees – **best available scientific expertise**

The briefing meetings are **free of charge**

Statement of the EMA position on the application of the 3Rs (replacement, reduction and refinement) in the regulatory testing of human and veterinary medicinal products

The European Medicines Agency (EMA) commits to the application of replacement, reduction and refinement (the 3Rs) of animal testing as detailed in Directive 2010/63/EU. To this end, a Joint ad hoc Expert Group (the JEG 3Rs) has been created in order to promote best practice in the implementation of the 3Rs in regulatory testing of medicinal products and to facilitate cooperation among other European groups working in the 3Rs area.

While significant progress has been achieved, there is still a need to increase the application of the 3Rs principles in order to further reduce the use of animals in research and development.
J3RWG on the Application of the 3Rs in Regulatory Testing of Medical Products

3R activities/guidance documents relevant for veterinary medicine (i)

• Recommendation to marketing authorisation holders, highlighting the need to ensure compliance with 3Rs methods described in the European Pharmacopoeia EMA/CHMP/CVMP/JEG-3Rs/252137/2012 (Applicable to all medicinal products regardless of type)

• Recommendation to marketing authorisation holders, highlighting recent measures in the veterinary field to promote reduction, refinement and replacement (3Rs) measures described in the European Pharmacopoeia EMA/CHMP/CVMP/3Rs/336802/2017 (Applicable to veterinary vaccines from 01/01/2017)
J3RsWG on the Application of the 3Rs in Regulatory Testing of Medical Products, biennial report 2016/2017

3R activities/guidance documents relevant for veterinary medicine (ii)

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

- 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)

- 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)

- Supporting CVMP input into VICH GL50 & GL55, waiver TABST, new draft LABST
J3RWG on the Application of the 3Rs in Regulatory Testing of Medical Products, report 2016/2017

3R activities/guidance documents relevant for veterinary medicine (iii)

• 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)

• Review of final product batch testing requirements (centralised authorized products)

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

• Collaboration with EC, other EU agencies and international organisations
Non-Clinical Domain Workplan 2022-2024 – reference to veterinary domain, batch release testing and 3RsWP

Tactical goals - Multidisciplinary collaboration

• In collaboration with the veterinary domain, perform a review of the most promising available 3Rs methodologies that could be considered for qualification, i.e. identify animal tests where the largest impact from a move to alternative/non-animal testing would apply.

• Establish a workflow for involvement of 3RsWP in the 3Rs ITF procedure.

• Collaborate with the veterinary domain and the human quality domain for the review of product batch testing requirements with regards to the application of the 3Rs in batch release testing of human vaccines and biotechnology derived pharmaceuticals and veterinary medicinal products.
Non-Clinical Domain Workplan 2022-2024 – reference to veterinary batch release testing and 3RsWP

Long term goals

- With the 3RsWP, ensure the follow-up of the application of the 3Rs in batch release testing of human vaccines and biotechnology derived pharmaceuticals and veterinary medicinal products.

Communication and stakeholder activities

- Organise annual 3RsWP brainstorming sessions on emerging 3Rs topics with interested parties and all relevant 3Rs stakeholders.

- Organise an EMA 3RsWP-led multistakeholder conference to showcase the achieved progress with regards to 3Rs in the field of human and veterinary medicinal products and to introduce the new 3RsWP and future workstreams.
## Examples of past/ongoing 3R (4R) activities

<table>
<thead>
<tr>
<th>Initiative</th>
<th>Example</th>
<th>Strategy</th>
<th>Level</th>
<th>Vet/Hum</th>
<th>Dissemination</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO/NC3R</td>
<td>WHO docs</td>
<td>Review</td>
<td>Guidance documents</td>
<td>V/H</td>
<td>Virtual/f2f (regional) events</td>
</tr>
<tr>
<td>EC/PPP</td>
<td>vac2vac</td>
<td>Consistency approach</td>
<td>Regulatory and method-based (platform technologies)</td>
<td>V/H</td>
<td>Virtual/f2f (regional) events, open access publications</td>
</tr>
<tr>
<td>EDQM (initially vet company)</td>
<td>BSP130</td>
<td>Model character (Clostridia)</td>
<td>Method based (in process)</td>
<td>V</td>
<td>Virtual/f2f (regional) events (recording available), open access publ.</td>
</tr>
<tr>
<td>EDQM</td>
<td>BSP168</td>
<td>Use of leftover test material; model character (?)</td>
<td>Replacement of reference antiserum</td>
<td>V</td>
<td>Tbd.</td>
</tr>
<tr>
<td>NCA/OMCL, Ph. Eur., VICH, WHO</td>
<td>Rev. to tox., ATT, TABST, LABST</td>
<td>Discontinue</td>
<td>In process/ final product</td>
<td>V/H</td>
<td>f2f events, publ.</td>
</tr>
<tr>
<td>NCA/OMCL</td>
<td>div. companies</td>
<td>Consultation</td>
<td>Pre-licensing, variations</td>
<td>V/H</td>
<td>(internal)</td>
</tr>
</tbody>
</table>

16 3RsWP – past & future activities. 3Rs in veterinary vaccines. Classified as internal/staff & contractors by the European Medicines Agency
Classified as internal/staff & contractors by the European Medicines Agency

WHO/NCR
Review of documents (H)

Vac2Vac, PPP
Regulatory and method based (V/H)

BSP168, EDQM
(Rabbit multicomponent Clostridia antiserum)
Use of leftover material; (replacement of reference material) (V)

BSP130, EDQM (C. septicum)
method based; in process/model character (V)

(Early) communication & interaction
(needs, plans ⇝ `pipeline´)

Resources
(human, technical, financial)

Common effort/expertise
(study & data evaluation)

Sustainability
(availability of reagents, data)

Outreach
(Dissemination of results; regulatory acceptance)

International harmonisation

Reversion to toxicity; ATT, TABST, Labst (V/H)

Resources (human, technical, financial)

Early communication & interaction
(needs, plans ⇝ ‘pipeline´)

Common effort/expertise
(study & data evaluation)

Sustainability
(availability of reagents, data)

Outreach
(Dissemination of results; regulatory acceptance)

International harmonisation

BSP168, EDQM
(Rabbit multicomponent Clostridia antiserum)
Use of leftover material; (replacement of reference material) (V)

BSP130, EDQM (C. septicum)
method based; in process/model character (V)

Early communication & interaction
(needs, plans ⇝ ‘pipeline´)

Resources
(human, technical, financial)

Common effort/expertise
(study & data evaluation)

Sustainability
(availability of reagents, data)

Outreach
(Dissemination of results; regulatory acceptance)

International harmonisation

Reversion to toxicity; ATT, TABST, Labst (V/H)

WHO/NCR
Review of documents (H)

Vac2Vac, PPP
Regulatory and method based (V/H)

BSP168, EDQM
(Rabbit multicomponent Clostridia antiserum)
Use of leftover material; (replacement of reference material) (V)

BSP130, EDQM (C. septicum)
method based; in process/model character (V)

(Early) communication & interaction
(needs, plans ⇝ ‘pipeline´)

Resources
(human, technical, financial)

Common effort/expertise
(study & data evaluation)

Sustainability
(availability of reagents, data)

Outreach
(Dissemination of results; regulatory acceptance)

International harmonisation

Reversion to toxicity; ATT, TABST, Labst (V/H)

WHO/NCR
Review of documents (H)

Vac2Vac, PPP
Regulatory and method based (V/H)

BSP168, EDQM
(Rabbit multicomponent Clostridia antiserum)
Use of leftover material; (replacement of reference material) (V)

BSP130, EDQM (C. septicum)
method based; in process/model character (V)
Take home messages

**Flexibility regarding guideline requirements:**
- impact on *Reduction* and *Refinement* of animal use
- based upon *scientific rationale*
- *scientific advice* (EMA Scientific Advice Working Party)

**Qualification of novel 3R testing approaches (*in vitro, in silico, ex vivo, …*):**
- (extent of) *qualification* criteria to be defined *in line with context of use*
- *early dialogue* with regulatory authorities is encouraged
- *Collaboration* is key to achieve progress towards regulatory acceptance of 3Rs methods

**ITF is EMA’s tool for informal early engagement and feedback**

**The European Regulatory Network is open to 3Rs**

**The new 3RsWP is the official 3Rs hub at the EMA**
Any questions? Suggestions welcome!

Further information

sonja.beken@fagg-afmps.be, elisabeth.balks@pei.de