

# Second 3Rs WG Meeting Teleconference

2<sup>nd</sup> July, 2020

Developing Countries Vaccine Manufacturers  
Network International

# Agenda

1. 3Rs WG next project
2. PSPT Project
3. Updates on the training opportunities that will be available within 2020 (MAT, DT, etc.)
4. 3Rs DCVMN Paper
5. AOB
6. Important COVID19 Information

# 1. 3Rs WG next project

**ACTION: identify the next 3Rs Project for the 3Rs WG**

It should involve as many DCVM members as possible.

WHO/NC3Rs new project aimed to enable manufacturers, regulators, and national control laboratories to apply the latest non-animal testing approaches and strategies to support faster access to vaccines globally:

<https://www.nc3rs.org.uk/news/new-project-reduce-animal-use-batch-release-and-quality-control-testing-biologicals>

Based on the NC3Rs' strong track record in working with manufacturers, regulators, and academics we have been asked by the WHO to carry out an independent and comprehensive review of their guidelines for biologics to determine:

1. Which animal tests are recommended for the batch release testing of biologics and vaccines.
2. What 3Rs principles are already encouraged, what opportunities exist for better implementation of 3Rs principles and alternative test methods within those guidelines, and to make recommendations to WHO on how this could be best achieved.
3. What barriers exist in different regions which may hinder the adoption of 3Rs approaches by manufacturers, national regulatory authorities, and control laboratories that are responsible for the testing and release of biologicals.

It is estimated that the review will cover approximately 60 guidelines and will highlight the extent to which animal tests are recommended for quality control testing within general and vaccine specific guidelines. These tests include, but are not limited to, studies in rabbits to assess the potential of a product to increase body temperature, and rodent challenge and immunogenicity potency assays.

The project was approved by the WHO Expert Committee on Biological Standardization (ECBS) in 2019 and has received funding of £370,000 from the Bill & Melinda Gates Foundation. It is estimated that the project will take three years to complete and is being overseen by an expert international working group who will work with the NC3Rs to review the guidelines and develop the recommendations that will be submitted to the ECBS for their approval and implementation.

# 1. 3Rs WG next project

- RPT replacement with MAT – interest in rFC as well?
- Rabies (BSP148 ongoing)
- DT (is it a priority? – EDQM strategy on rationalizing toxicity testing requirements: <https://www.edqm.eu/en/news/european-pharmacopoeia-tetanus-vaccines-rationalising-toxicity-testing-requirements>)

At its 165th session (November 2019), the European Pharmacopoeia (Ph. Eur.) Commission adopted 16 revised monographs on tetanus vaccines, following a re-assessment of toxicity testing requirements. The revisions include the suppression of three tests and the harmonisation, as far as possible, of the Ph. Eur.'s toxicity testing requirements for tetanus vaccines for human and veterinary use.

The *Test for specific toxicity* of tetanus vaccines for human use and the *Test for residual toxicity* of tetanus vaccines for veterinary use (using guinea pigs), both carried out on the final lot, have been deleted. The tests were considered redundant because a more sensitive test (*Test for absence of toxin*) is performed routinely at an earlier stage of the process. The revised monographs emphasise the need to validate the detoxification process to demonstrate that the toxoid is stably detoxified.

The *Test for irreversibility* of tetanus toxoid (using guinea pigs) has also been removed. This decision is based on data on the stability of tetanus toxoid and the fact that tetanus toxin was shown to lose neurotoxic activity under the conditions of the storage test at 37°C. The more sensitive *Test for absence of toxin* is carried out on non-incubated purified toxoid.

The Ph. Eur. Commission is committed to phasing out the use of animal tests by continuously reviewing in vivo tests described in Ph. Eur. texts and applying, whenever possible, the 3Rs principles set out in the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS No. 123). The re-assessment of toxicity testing requirements for tetanus vaccines and the decision to delete three animal tests is an illustration of this commitment.

The revised monographs will be published in Ph. Eur. Supplement 10.3 and become effective on 1 January 2021.

# 1. 3Rs WG next project

- aP – Replacement of HIST with CHO cells assay (limited to some members)
- Others?

## 2. PSPT Project

- DCVMN/NIIMBL signature expected end of July
- Consortium Agreement MoU – first 3 signatures (2 companies, 1 NCL)
- Steering Group Selected
- Coating Antigen – Eurofins quote + BioLyo Technology quote under review



### 3. Updates on the training

- 3Rs general e-learning module (DCVMN Moodle) by Prof. Coenraad Hendriksen NOW AVAILABLE: <https://moodle.dcvmn.net/course/view.php?id=22> – **ACTION: please get the certificate!**
- MAT – webinar/e-learning course and video (pending signature MoU with ISS, Italy) – Q3
- DT alternative methods (pending signature MoU with ISS, Italy) – Q3
- Acellular Pertussis – e-learning module and webinar in preparation

# 4. 3Rs DCVMN Paper

**ACTION: Select WG members/DCVM members to contribute to the text**

Outline:

## 1. Introduction

- Concept of 3Rs and short history
- Advancements in the field – examples of recent successful changes (the majority EU-regulation based; India = waiver and deletion of Abnormal Toxicity Test; introduction of Bacterial Endotoxin Test for all human vaccines, replacing the rabbit pyrogen test)
- DCVMN's rationale for the engagement in the promotion for the 3Rs implementation: DCVMN strategy and activities for the promotion of 3Rs in testing and new manufacturing platforms.

## 2. Opportunities

- Strategy – very briefly: introduce dedicated working group and activities
- Testing Activities:
  - PSPT – contribution from ISS(TBC)
  - DT – as above (TBC)
  - aP – ?
  - MAT – contribution from ISS (TBC)
  - Summary table with the 3Rs opportunities already implemented by DCVMN Members – data to be collected through the 3Rs WG

# 4. 3Rs DCVMN Paper

## 3. New manufacturing technologies

- Mammalian cell culture:
    - Rabies, switch from animal based manufacturing to cell-based, etc.
    - JE VERO Cells platform
  - Non-mamalian cell culture:
    - Baculovirus platforms
    - E.coli based systems
    - ....
  - Yeast based platforms:
    - Hansenula polimorphica
    - Saccharomyces cerevisiae
    - Picchia pastoris
    - ....
  - DNA and RNA
  - Conjugation platforms
  - ....
4. Discussion: feasibility and priorities (working group here)
5. Conclusion – go back to DCVMN strategy and way forward.

# 5. AoB/ Key updates and events about 3Rs

Any updates from your countries?

Pharmacopoeias' update?

Industry/Regulators meetings?

Conferences?

# 6. Important COVID19 Information

- EDQM provides COVID-19 vaccine developers with free access to quality standards applicable in Europe:  
<https://www.edqm.eu/en/news/edqm-provides-covid-19-vaccine-developers-free-access-quality-standards-applicable-europe>
- EMA and Korean Ministry of Food and Drug Safety to share confidential COVID-19 information:  
<https://www.ema.europa.eu/en/news/ema-korean-ministry-food-drug-safety-share-confidential-covid-19-information>
- World Congress on Alternative Methods – Maastricht, The Netherland: COVID19 and 3Rs webinars – August 25-26, 2020 :  
<http://wc11maastricht.org/webinar/>

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