Introduction to the 3Rs initiative: Objectives and expected outcomes of the meeting

DCVMN Workshop on

Chemical Manufacturing and Controls to

foster implementation of vaccine release test methods aimed at reducing animal use (3Rs)

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Good science and good animal welfare go hand in hand.

- If an animal is suffering stress or pain it could affect the results of the research, hence it makes good scientific sense to house animals in the best possible conditions and make sure they get the best possible care from skilled and experienced carers.

- What animals need is not always the same as what people think they need, so scientists are studying which environments different animals prefer.

The guiding principles underpinning the humane use of animals in scientific research are called the three Rs.

- ✓ **Replace** the use of animals with alternative techniques, or avoid the use of animals altogether.
- ✓ **Reduce** the number of animals used to a minimum, to obtain information from fewer animals or more information from the same number of animals.
- ✓ **Refine** the way experiments are carried out, to make sure animals suffer as little as possible. This includes better housing and improvements to procedures which minimise pain and suffering and/or improve animal welfare.

Vaccines are biological products

- ✓ Biological products are generally large, complex molecules.
- ✓ They may be produced through biotechnology in a living system, such as a microorganism, plant cell, or animal cell, and are often more difficult to characterize than small molecule drugs.
- ✓ Vaccines are biological products normally evaluated for efficacy in CT during development and estimated through a potency test during routine production and release.
- ✓ The potency test is aimed at evaluating in an animal model the capacity of the lot under test to induce a protective response in the animals comparable to that shown to be efficacious during the CT.
- ✓ Other tests such as absence of toxicity, lack of reversion, viral inactivation, etc also require the use of laboratory animals.

Potency tests

- ✓ Potency tests generally compare a test vaccine against a reference vaccine with assigned value
- ✓ Potency tests generally require large quantity of animals in order to reduce the inherent variability of the test (biological test)
- ✓ In most cases they require a challenge with either the wild virus, or toxin or live bacteria; which causes suffering to the animals
- ✓ The comparison (ratio) between the protective response of the test vaccine (ED50) and that of the reference vaccine multiplied by the assigned value of the reference gives the potency of the test vaccine, which is supposed to

  be higher than an established minimum value

Change in paradigm

- ✓ Moving from a concept in which each lot is unique to a concept where each lot is part of a series where consistency in production is what is important.
- ✓ The specifications of the product are defined during CT and are those which render a safe and efficacious vaccine
- ✓ All subsequently produced lots in the series are expected to be “similar” to the clinical lots

The consistency concept allows to move away from the traditional potency testing approach

- ✓ For older vaccines, the replacement of methods is not easy, but not impossible, and we will see some of the options during this workshop
- ✓ Newer vaccines are developed according to the new paradigm with the aim of obtaining an effective product, as shown in CT, which can be consistently manufactured during its whole lifecycle,
  - ✓ Using in vitro, immunochemical or other types of tests and avoiding the use of animals to the maximum extent possible

Replacement of in-vivo tests by in-vitro tests in rabies vaccine

Test	Potency	Animal model	Duration of Test (days)	Number of animals per lot	Annual consumption
Rabies harvest titration	MIT (i.c. challenge method)	Mice	14	18	13824
		Mice	14	174	16704
Amplification test		Mice	14	20	1920
Identity test (Pooled harvest)					
3 R alternative					
	Potency	Model	Duration Test (days)		
Tests on harvests	(FAT)	In vitro using BHK cells	4 days	NA	

Animal reduction by 32448/annum.

Source: Serum Institute of India Pvt.Ltd.

Background: DCVMN 3 Rs meeting

- ✓ Strong commitment from many producers and regulators to abide by the 3Rs for vaccine testing
- ✓ Some vaccines have been prioritized for the development of replacement, refinement or reduction testing methods, including TT, DT, DTP and associated combos and rabies vaccine
- ✓ Many big pharma producers and some DCVMN producers have made significant progress in using alternative methods
- ✓ Some pharmacopoeias have accepted many of the proposed alternatives
- ✓ DCVMN is committed to support its members to facilitate the path towards the use of alternative testing methods

Objectives: DCVMN 3 Rs meeting

- ✓ To discuss the concept of 3Rs
- ✓ To launch a laboratory testing initiative supported by BMGF as part of the new grant to DCVMN - the new inititiative focuses on 3Rs testing methods
- ✓ To present and discuss available alternative methods for testing TT, DT, DTP and rabies vaccines
- ✓ To encourage other DCVMN members to start working on the development and validation of alternative testing methods

Expected outcome: DCVMN 3 Rs meeting

To establish a DCVMN working group that will focus its activities on supporting each other and other members to advance the 3Rs initiative by:

- ✓ Organizing workshops on vaccine testing, especially using alternative tests
- ✓ Facilitating access to training as required
- ✓ Exchanging information to assist each other in establishment and validation of the methods
- ✓ Fostering participation in regional and international collaborative studies
- ✓ Interacting with pharmacopoeias to foster acceptance of alternative methods
- ✓ Interacting with WHO and other 3Rs stakeholders as needed

THANK YOU

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