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Developing Countries Vaccine Manufacturers Network

DCVMN 3Rs Working Group Meeting Minutes – May 11th, 2021

Attendees: Sunil Gairola (Serum Institute of India) *chair*, Pradip Kumar Das (Biological E) *co-chair*, Sunil Goel (Serum Institute of India),Deepak Mahajan (Panacea Biotec), Zebun Nahar (Incepta Vaccine), Irma Riyanti Hidayat (BioFarma), Shri T. Sekar (Pasteur Institute of India), Ganesh Dubey (Bharat), D. Mahesh (Indian Immunologicals), Leen Madhuri Valisetti (Indian Immunologicals), Adhir Chaubal (Indian Immunologicals), Lingyun Zhou (Shanghai Zerun Biotechnology), Laura Viviani (DCVMN), Sivashen Cunden (DCVMN), Tana McCauley (DCVMN), Sonia Pagliusi (DCVMN), Rajinder Suri (DCVMN), Prerna Kumar (DCVMN). Excused: Indrajeet Poredi (Bionet Asia), Li Yi (IMBCAMS), Jie Song (IMBCAMS), Patricia Carneiro (Butantan), Vu Tien Dung (Vabiotech), Hassan Ahmed (Amson), Taehyun Kim (LG-CHEM), Rajanathan Chozhavel (Zydus Cadila).

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1. **Brief introduction of participants and agenda**

   SG introduced and welcomed the new members; Jie Song, Head (Quality Control, IMBCAMS China), Lingyun Zhou (Department of Quality Research, Shanghai Zerun Biotechnology Co.,Ltd., China) and Patricia Carneiro (QC Manager, Butantan Institute, Brazil)

2. **Sharing case studies on successful 3Rs implementation**

   The 3R WG was invited to consider sharing positive and negative case studies on 3Rs implementation. SG explained that as part of the 3Rs WG initiative to move work forward identifying how the manufacturers in the group carried out the adoption of 3Rs for their products is crucial; the work which was done with NCLs and NRAs to gain approval, the timelines for 3Rs adoptions and the impacts (number of animals saved and costs saved etc.) These learnings from case studies will benefit the entire network and 3Rs efforts. Due to the number of animals required to produce DTP vaccines it is expected that there will be many examples of 3Rs adoption from the manufacturers who produce this combination. SG encourages sharing of the case studies and volunteered a case study from Serum institute. Examples of the 3Rs opportunities of interest include:

   Examples for Safety Tests
   - Abnormal Toxicity Test,
   - deletion of Specific Toxicity Test for Tetanus,
   - deletion of the pertussis irreversibility test and replacement of HIST with CHO-cell assays
   - Next Generation Sequencing (adventitious viruses/agents)

   Examples for Potency Tests
   - Serological assays
   - Single dilution
   - SRID, RIA, etc.
   - Antigen quantification
   - In vitro relative potency test

   LV called for volunteers from the WG who would like to present the case studies at the next WG call. Sunil Goel volunteered on behalf of the *Serum Institute of India* to update the group on the 3Rs methods presented during the DCVMN meeting in Hyderabad in 2019 to discuss the challenges that were faced and how they were overcome. PD volunteered on behalf of *Biological E* case studies on the adaption and implementation of single dilution assays (approved by the Indian NRA and WHO, 2020), abnormal toxicity tests no longer required by the Indian NRA, (similarly so for the specific toxicity test for diphtheria and tetanus) since 2016 but due to a statement released by the WHO to perform the abnormal toxicity on final bulk the tests are still performed, and a case study for Hepatitis B potency testing using ELISA based testing. LV asked PD that if the first case study could be on the adaption and implementation of single dilution assays since this could be a future project with the DCVMN provided the interest of other members in the group. SG updated PD on a 2019 WHO position paper (WHO TRS 1016, 2018) regarding the use of abnormal toxicity testing and that it is no longer required within pharmacopeia. PD stated while he is aware of the position paper Biological E have submitted to the WHO a variation letter. LV shared a 2020 publication on the topic (Dianliang Lei et al., Biologicals 2020) with WG. LV also informed WG that the NC3R are reviewing all the WHO Technical Report Series to identify tests that can be replaced or that are obsolete to report to the WHO NCBS for changing within the next 3 years, and DCVMN is engaged on this project (Dr. Zebun Nahar from Incepta, Bangladesh). D. Mahesh from *Indian Immunologicals* volunteered

to present relevant case studies at the next 3R WG call. LV thanked the volunteers and stated that the DCVMN will prepare a template to aid volunteers in the presenting their case studies.

SG provided an example of how the case studies may aid the other WG members as currently the abnormal toxicity testing is still required in China, Japan and Russia but with the evidence of its removal in Canada, Brazil, India the 3R WG may provide assistance with the Chinese NRA for its removal. LV informed the WG of a global event organized by AFSA and EFPIA tackling the removal of the abnormal toxicity test; she informed that Russia has begun reviewing the requirements for the abnormal toxicity test to minimize its use; and also, South Korea is considering the removal of the test. However, LV stated that the AFSA/EFPIA event aims to encourage manufacturers to join given that they will drive the changes in the future. PD stated that while manufacturers will drive the deletion if products are exported compliance with the regulatory requirements in destination country affects whether a test is also performed. Therefore, within the pharmacopeia these tests will also need to be removed but these changes take extended periods of time.
LV asked WG for approval that for the next WG Call that abnormal toxicity test deletion and single dilution assays be retained as standing agenda items. SG agreed but stated that to provide support to the members of the group that the challenges the WG members face in deletion / adoption of abnormal toxicity test and single dilution assays (potency) be shared so that those who have overcome similar issues may advise on implementation. LV in agreement and asked if members can be prepared for the next WG call.

3. Single dilution assay for DT vaccines

LV presented that could it be a next project for DCVMN members. Biological E to provide update on how this was done in India. The ISS/Italy will support this project if approved.

4. DCVMN updates

LV introduced the Pertussis Serological potency test which is an independent intra lab assessment of replacement ELISA methods to determining the potency of DTP vaccines to new members of the WG and updated working group on current activities. LV also updated the WG regarding the 3R survey report and asked the WG to volunteer as writers to the paper which will be published in the journal Biologicals. No confidential information will be shared but the paper will bring attention to the work the DCVMN 3R WG. Therefore, volunteers are invited to contact Laura Viviani.

4.1 Upcoming DCVMN trainings

I. MAT (Monocyte activation test)
   E-learning module (DCVMN moodle) based on the webinar given earlier in the year by the ISS will be published at the end of June.
II. Diphteria and Tetanus
   E-learning module (DCVMN moodle) from the ISS will be published at the end of Q3.
III. Statistical analysis of the stability testing
   E-learning module (DCVMN moodle) based on the webinar given earlier in the year published in June

4.2 Key publications of note to members

I. Characterisation of tetanus monoclonal antibodies as a first step towards the development of an *in vitro* vaccine potency immunoassay. https://doi.org/10.1016/j.biologicals.2021.04.002
II. Characterisation of diphtheria monoclonal antibodies as a first step towards the development of an *in vitro* vaccine potency immunoassay. https://doi.org/10.1016/j.biologicals.2020.12.002
III. Variability of *in vivo* potency tests of Diphtheria, Tetanus and acellular Pertussis (DTaP) vaccines. https://doi.org/10.1016/j.vaccine.2021.03.078

External Updates

- Abnormal Toxicity Test
  - Animal Free Safety Assessment Collaboration + EFPIA plans half a day discussion (first half of October) with industry and regulatory stakeholders to speed up deletion of the test
  - Invitation to DCVMN and all its members will come in the next weeks
- Rabies – replacement of NIH with ELISA
  - EDQM/EPAA BSP148 phase 2 started – protocol distributed, vaccines samples distribution
- Polio Vaccines – NGS to replace MAPRECT+Monkey NVT
  - PATH is looking for interested manufacturers to join FDA/NIBSC phase 2 international collaborative study. If interested contact Kutub Mahmood - kmahmood@path.org
- HSI Working Group "Accelerating 3Rs methods in vaccine testing in China"
  - Promotion of the WG activities at Symposium on Regulatory Science Issues Related to Vaccine R&D and Registration" (疫苗研发注册有关的监管科学问题座谈会), May 15th, 2021.

Closing remarks

RS supportive of the work that has been conducted the group and would like to have feedback from members how best to help them adopt/move forward with 3R opportunities and asks the group that to move forward sharing of information is strongly encouraged not only strategic but also how it has impacted business so long as the information shared is not confidential. SG agreed and suggested that as the topics will require more in-depth discussion only 2 items be to focus of the meetings. LV agreed and suggested that longer meetings maybe an option but will need to be decided with the larger group.

The meeting was adjourned 12:15 CET.

DCVMN will send out doodle for the next 3Rs WG meeting, taking place by TEAMS on in Q3.

Sunil Gairola
Chair of the 3Rs WG