DCVMN 3Rs Working Group Meeting Minutes – July 20thth, 2021

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

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

Sunil Gairola (SG) welcomed all participants and introduced the agenda for the Q3 session. SG thanked speakers for their willingness to share case studies from Biological E and Indian Immunological Limited. SG stated that the case studies will address single dilution assays, implemented 3R methodologies and highlight the immense saving of animals when *in vivo* methods are replaced by *in vitro* methods. SG encouraged other members to share successful case studies to further educate the group and push 3R efforts.

Laura Viviani (LV) proposed a joint workshop(s) with the RAWG to delve in depth in case studies, regulatory challenges faced by replacement/alternative methods and the way forward. Workshop(s) will be planned before the end of the year. LV summarized the barriers to the 3Rs implementation as they have been identified in conferences in the last 10 years. She invited the group to check whether those are still in place or not. Those could be further explored during the next workshop(s).

- Limited expertise.
- Lack of business case to adequately inform relevant managers (QA, RA and production) of advantages.
- Hesitation due to the absence of regulatory/pharmacopoeia acceptance and guidance on 3Rs methods.
- Regulator's hesitation on new methods.
- Lack of global harmonization of release requirements.
- Difficulties in in-house validation of the new methods.
- Need for establishment of new working Standard materials.
- Reagent's availability.
- How to apply the alternative methodologies to evaluate vaccine stability.

2. **Deletion of abnormal toxicity test**

LV reminded and informed 3RWG members of the multi-stakeholder (WHO, EDQM FDA etc.) workshop organized by AFSA and EFPIA in collaboration with IABS: *Accelerating Global Deletion of the Abnormal Toxicity Test. Planning common next steps* to which the DCVMN companies are invited to join on the 14th of October 2021 at 12:30 CEST via Zoom. If any members would like to participate in a special country specific session to share their experience, they are to contact LV as the registration link soon to be shared by organizers.

3. 3R Case studies

Please find all presentations on the DCVMN 3R section. All presentations have been approved for internal distribution amongst DCVMN 3RWG members by presenters.

Indian Immunological Limited Case Study Q&A – Mahesh D (MD)

SG thanked MD for his presentation. MD explained that due to the confidentiality restrictions the data generation for each of the presented vaccines and their subsequent replacement tests could not be shared. However, within the context of *in vitro* vs *in vivo* the compilation of data the first steps taken is the establishment of the correlation using the regular assays. Using statistical software to analyze the correlation of the batch release assays (*in vitro* and *in vivo*) if a correlation of >60% was recorded these results were seen as significant and a comparison could be made between both methods. Additionally, subpotent batch testing was also

conducted to ensure both methods can distinguish the failed batches and to determine limitations of each technique. SG thanked MD for his explanation and followed by asking if in the future more data can be shared to provide a more comprehensive presentation. Zebun Nahar (ZB) raised a question regarding the number batches tested for this validation. MD explained that Indian Immunological Limited tested a minimum of 30 batches as this is minimum number to establish statistical significancy. Pradip Das (PD) added that Biological E for the Hepatitis B the *in vitro* technique was adopted in 2017 for both monovalent and pentavalent vaccines and no animal studies are now conducted except for stability studies. Similarly, to Indian Immunological Limited 30 batches are used when carrying out this validation. After sharing with CDSCO a full waiver (of the *in vivo* test) was given but for stability testing both *in vivo* and *in vitro* data is needed.

Biological E Case Study Single Dilution Method for DTP – Pradip Das (PD)

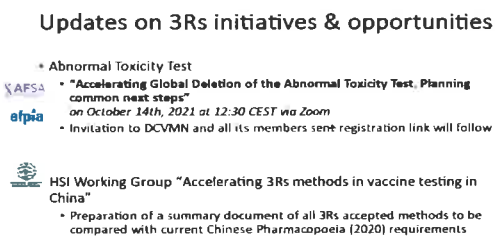
SG thanked PD for his comprehensive presentation. SG requested that given the complexity and expertise in understanding the guidelines for the Single Dilution Method, a workshop based on the Biological E presentation would be beneficial in the future. SG reiterated that while the single dilution is applicable for the batch release testing it is not applicable for the stability assay. Additionally, a concern for manufacturers producing high valency vaccines would be that the dose-response validation would have to be redone for each combination of vaccines in accordance with WHO (minimum 10-20 batches multi-dilution assay should be considered to meet the single dilution assay requirement) and EDQM recommendation. Yet for batch release testing regulators can be convinced with the small amount of data generated to move toward single dilution assays but this would not be applicable to stability testing assays which are non-quantitative.

LV confirmed the request that the DCVMN can hold a workshop solely focused on single dilution assays inviting all other DCVMN working groups as this would be relevant to the whole network a separate workshop focused on Hepatitis B can also be arranged to delve deeper with the work from Immunological India limited.

4. DCVMN updates

LV updated group on the status of the Pertussis Serological potency study (see previous minutes) currently 10/11 labs are entering the testing phase.

LV updated the WG regarding the new draft of 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 but if case studies can be shared it would be appreciated. Publication will take place before the end of 2021 therefore volunteers are invited to contact Laura Viviani ASAP.



dcvmn
Developing Countries Vaccine Manufacturers Network

Updates on 3Rs initiatives & opportunities

- NC3Rs: Reviewing animal use requirements in WHO biologics guidelines – opportunities for the 3Rs – https://nc3rs.org.uk/review-animal-use-requirements-who-biologics-guidelines
  - Survey to manufacturers is going to be distributed soon within all DCVMN
- World Congress on Alternative to Animal testing
  - 23 August – 2 September – online - https://www.wc11maastricht.org/
  - S21 dedicated to ATT deletion

LV stated that the NC3Rs project is of high importance as DCVMN would like to have the full membership complete the survey so that information can be collected globally addressing what changes are needed in regulation at NRA and WHO guidance in implementation of 3Rs. DCVMN will host a webinar with NC3Rs and WHO in September further discussing the aspects of the project. LV finally updated the 3RWG to register to the World congress on alternative animal testing a cross industry event that is held every 2 years.

Closing remarks

SG stressed the importance of the NC3Rs project given the WHO engagement and publication to the ECBS which will open the door to dialogue with your NRA. SG also asked both presenters if the presentations can be shared confirmation to be given offline.

Actions

- Set up RAWG and 3RWG workshop
- Set up 2 workshops with all DCVMN WGs
  - Single dilution assay workshop
  - Hepatitis B invitro test workshop
- Share 3R survey report with 3RWG members
- **Volunteers to co-author 3R survey report to contact L. Viviani**
- Case study presentations to be shared with 3RWG
- Webinar with NC3R and WHO to be scheduled in September

DCVMN will send out doodle for the next 3Rs WG meeting, taking place by TEAMS on in Q4.

The meeting was adjourned 14:05 CET.

Dr. Sunil Gairola
Serum Institute of India Pvt. Ltd.
Chair of the 3Rs WG