1st Coordination meeting Clinical/Medical Affairs Working Group

Tuesday 22nd March 2022, started at 1 pm and adjourned at 2.15 pm CET

Participants: Dr. Pieter Neels (**PN**) (consultant), Dr. Alexander Precioso (**AP**) (Butantan), Dr. Ravindra Mittal (**RM**) (Zydus), Dr. Daniela Lazzarini (DL) (Sinergium), Mr. Xu Long (XL) (Bravovax), Dr. Devi Sahoo (DS) (Indian Immunologicals), Dr. Sai Krishna (SK) (Indian Immunologiocals), Dr. Richard Chawana (RC) (Biovac), Mr Rajinder Suri (RS) (DCVMN), Ms. Prerna Kumar (PK) (DCVMN), Ms. Sonia Villasenor (SV) (DCVMN), Dr. Sonia Pagliusi (SP)(DCVMN).

Dr. A. Precioso (AP), Chair of the WG welcomed the participants to the 1st meeting of the Clinical Development & Medical Affairs Working Group, and invited participants to introduce themselves.

AP introduced the Terms of reference for the WG, previously shared with all in advance, and opened the discussion on the seven objectives, i.e. assessing capacity to develop Benefit-Risk approaches for clinical and medical activities of member companies, through surveys, trainings on methodologies within clinical trials, help to identify and link clinical and medical activities within companies, in the context of product life cycle and pharmacovigilance. RS suggested to restructure the text by including activities under 3 objectives, which was then edited accordingly. AP then discussed the focus on SOPs and periodic GCP training, inviting comments of the participants. PN suggested to add pharmacovigilance to the list of SOPs, as phase IV trials have evolved to effectiveness and safety studies of new vaccines. AP added that DCVMN has an established Pharmacovigilance (PV) working group, and asked as to whether the groups should create an environment to collaborate on these SOPs. RM reiterated that a PV working group is already established with ongoing activities, and there may raise a risk of duplicating the work in two places. RS suggested to integrate the activities of Clinical/Medical WG with PV, to co-develop projects/SOPs, for members to interact. SP suggested to avoid confusion and overlapping with existing activities. PN suggested to focus on benefit-risk assessment, as opposed to other PV activities such as safety monitoring, signal detection and causality evaluation. RM suggested post-marketing to be added as part of SOPs. AP agreed on the need to collaborate with other DCVMN WG, as a strategic point, as co-development/coordinated work between WG would be important. SP suggested that the clinical/Medical WG develops SOPs in consultation with the PV working group, though sharing of draft documents for comments. RS stressed that it is critical that work is defined by the expert consultant, PN, and working together hand-in-hand/should-to-shoulder with different groups, towards a new culture. AP agreed that this will create an environment where different groups work together. RM and PN agreed to enable the co-development of SOPs for post-marketing activities. RC observed that SOPs are function of clinical departments, thus it may be prudent to mention that this would be developed in case these would not be available. This would be a first step, to identify which SOPs are available. RM added that perhaps not all companies have the same type/level of clinical department activities, as many may outsource trials to CROs. AP acknowledged the interesting discussion and edits made to the draft terms of reference, and invited participants to move to the next agenda point.

PN provided a presentation on "Benefit-Risk approaches", indicating that in the past regulators experience has been based on mistakes, errors, scandals[1], that focused mainly on pharmacovigilance adverse events risk-averse approaches; the new approach is focusing on risk awareness and benefits. Further, societies have shifted towards concerns of individual adverse events, overseeing the health benefits at community level on the long-term, e.g. small pox vaccination.[2] The challenge is to provide safe vaccines that are thoroughly tested within a short time to address epidemics and

[1] E.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1383764/ ; https://pubmed.ncbi.nlm.nih.gov/24056737/
[2] E.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1069029/ ; https://www.sciencedirect.com/topics/medicine-and-dentistry/smallpox-vaccine

pandemics, e.g. COVID-19 vaccines. He elaborated on two examples of medicines (sulphanilamide and thalidomide) among others, that illustrate regulatory actions in the past[3]. Thereafter regulatory guidelines provided guidance to avoid such mishappens[4]. Hence, it is now important to recognize benefit-risk analysis as an accurate assessment of vaccines, based on prevention of mortality, hospitalization, disease or infection, as possible. In this context, surrogate endpoints and correlates of protection are helpful to assess benefit-risk of vaccines, and guidance on methodology on how to balance benefit & risk is now openly available[5]. The benefit-risk assessment of HPV vaccines, in measuring surrogate endpoints to register such cancer vaccines (rather than the cancer itself), was illustrated, while being mindful of uncertainties.

AP acknowledged the presenter and commented on the need for local baseline data to define accurate benefit-risk evaluations, and added that benefit-risk needs to be well communicated. PN agreed that active communication is crucial, such as through open webinars, in addition to making all vaccine materials openly accessible online. Regarding baseline information, PN commented that in COVID-19 vaccination context, surveillance for breakthrough or enhanced disease events shall be well monitored, as related to benefit-risk, which could be age or gender specific. AP invited participants to consider including communication plan for this group activities/training. RM endorsed the importance of broad communication plan. DL mentioned that sometimes neither physicians nor patients know how to report adverse events in real-world situations, thus neglect to report vaccine adverse events. PN suggested to conduct post authorization safety studies (PASS) and to invest in computer information of follow up, using proper coding. AP added that immunization programme structures differ among countries, and immunization stakeholders, should be involved to achieve good surveillance, not only industry. PN stressed the importance for industry to monitor serious adverse events, in order to document and quantify rare adverse events, to show that vaccines are safe, in general. AP reiterated the importance of this WG discussions.

RM invited the group to focus on outputs, such as SOPs. RS suggested to set up specific and quantitative objectives to be achieved. RM proposed to reflect and complement as relevant.

Upon AP invitation, participants approved the ToRs. Sai Krishna suggested to add selection of diagnostic labs, which PA suggested to include under clinical trials item, which was agreed by all.

AP proposed next WG meeting to be hybrid, e.g. face-to-face respecting international travel requirements and virtual, for those unable to travel. RS suggested exploring Singapore as venue. Dates to be suggested by AP and RM, around end-May or early-June, enabling to use available DCVMN budget for such meetings. AP closed the meeting acknowledging the interest and availability of all participants.

Notes taken by Dr. S.Pagliusi, for comments from participants by 01st April 2022.

Approved by Alexander B Precioso Date: April 1st, 2022.
Dr. Alexander Precioso, Chair of the DCVMN CDMA WG

[3] E.g. https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/elixir-sulfanilamide ; https://pubmed.ncbi.nlm.nih.gov/21507989/

[4] https://database.ich.org/sites/default/files/E2CR2_Q%26As_Q%26As.pdf

[5] https://www.ema.europa.eu/en/about-us/what-we-do/regulatory-science-research/benefit-risk-methodology