DCVMN INTERNATIONAL
Developing Countries Vaccine Manufacturers Network International

# Joint Working Group Workshop

## 15th and 16th February 2024

## The Lalit, New Delhi

**Participants:**

Bhargav Reddy (BR), Chetanraj Bhamare (CB), Devang Patel (DP), Mahesh Babu (MB), Manish A. Mahajan (MM), Mayra Moura de Oliveira (MO), Monica de Camargo (MC), Pradip Das (PD), Ramakanth K (RK), Rini Mulia (RM), Sunil Goel (SG), Subhodeep Chakraborty (SCh), Vastal Desai (VaD), Vipul Doshi (ViD), Viska Indriani (VI), Alexander Precioso (AP), Rajinder Suri (RS), Katharina Hartmann (KH), Pieter Neels (PN), Sonia Villasenor (SV), Prerna Kumar (PK) **Virtual:** Patricia Mouta (PM)

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RS welcomed the participants and invited them to discuss in depth and focus on real-life issues and challenges that companies are facing, and find how to address and mitigate, having a common thread that could benefit at large all manufacturers. He suggested not to have any block in their minds as unattainable. He shared his experience with the regulators few days back and said they are willing to listen, cooperate and support, provided we bring to them real-life issues. WHO is very open and willing to help. The contribution of DCVMN manufacturers is being recognized amongst all international organizations. They are all ready to listen. He thanked the presence of AP and the support of CEPI to the PV initiatives and gave the floor to ViD who chaired the meeting.

The group made a round of introductions.

The group expressed the following needs/challenges and possible solutions:

- Enhance the collaboration amongst the 3 areas within the companies. (VI)
    - The 3 departments i.e Regulatory, Clinical & PV, could have periodic meetings and give a forecast of the goals and plans, and what are the documentation expectations so that the Benefit-Risk assessment can be properly integrated. (DP)
- To strengthen the capacity building of each of the three departments propose list of documents to be generated for approaching the regulators. (VI)
- In most cases the challenge is to get the real time data to do the Benefit-risk assessment. (KH)
- Another challenge is to access data and also, the procedure for collecting the documentation required to submit. (ViD)
    - The best suggestion is to collaborate with the respective agencies. (ViD)
    - Some ways to help for the data collection are the PPP (Public-Private Partnerships); but in some countries it is difficult to convince the regulators that this data is good (PN)
    - To consider the role of the National Immunization Program, so manufacturers find ways to bring them around the table and find ways for data sharing for the benefit-risk assessment (AP)
- In Developing Countries there is underreporting, so it is difficult to extrapolate data from one country to another. (DP)
    - To work as a country level, because in some countries there are regulatory variations and to take a collaborative approach. (ViD)
- Even in some developed countries, medical doctors do not share PV passive surveillance reports with the authority, so the best would be to go for Active Surveillance programs. (PN)
- AVSS is good, but it is needed to train the physicians to know what are the unexpected and unaware events to be reported. Safety culture is what we need to cultivate. (KH)
- RMP and AVSS are interconnected. We need to set a pathway to reach the goal (SCh)
    - Find a way to promote the management of electronic patient files and safety

investigations and anonymize data in Developing Countries. (PN)
  - The best source to provide the data are the AEFI institutions and not the private practitioners. Training is a very important tool. (SG)
  - To collect the mobile number of the persons rather than emails in order to make a good follow up. (CB)

**Clinical/Medical Affairs Discussion**

The group discussed the clinical expectations from the Regulatory which included several points. (Refer to slides)

- CHIM studies could cover most of the points expressed in the slide. (SG)
  - To implement CHIM studies needs to have a Benefit-Risk assessment. In PV, an adverse event has a temporal relationship but when it becomes causal, it fills our labels of adverse events temporal related; this should be included in the benefit-risk analysis. The template of EMA includes different elements that should be considered. (PN)

RM presented the vaccine life cycle in the clinical development. She also expressed the main barriers or challenges faced in the Clinical trials:

- Lack of ability to design the clinical trial dossier.
- Need of collaboration between regulatory and manufacturers to fast track the process of the clinical trials while fulfilling all the requirements.
- Need to standardize the documents and protocols.
- Need of having a training for doing the statistical analysis.
- Poor acceptance of Adaptive Clinical Trial design by regulators (MM)
- Recruitment and retention of participants in the clinical trials (MM)
  - A possible solution to that is to decentralize the clinical trials.
- Vaccine hesitancy affects reporting, recruitment and retention.

- In terms of facilitating clinical development one area of learning is the use of AI and machine learning. (MM)
  - This is not for regulators; it is more for manufacturers to generate reasonable data to present the dossier in a shorter time. (ViD)
  - AI is not yet ready to understand all the terms. (PN)

***Adaptive Clinical Design***- The protocol needs to describe a situation where the protocol might be changed; most of the adaptive design is about dosing. It allows to make phase 1 and phase 2 in one protocol, and based on decisions on the data that come in. Benefit Risk is a dynamic process that starts when you get the first data, and all adverse events temporally related need to be added to it. Every PSUR should have Benefit-Risk. This needs to have a multidisciplinary team Regulatory & Clinal and Pharmacovigilance. (PN)

- It is important to have training in PSUR. (KH)
- There is need to have good understanding on the adaptive clinical trial first and then to create a proposal to regulators; create a pathway to get it done, more knowledge is required on preparation of the protocol, subject size and how much flexibility should be there, we can take further discussion to get this adaptive trial active rolling. (SCh)
- Some arguments academics used 15 years ago to convince EMA and FDA regulators is this is time reducing in the development and thus benefit for the population. (PN)
- Go for advice with the regulators and put on the table what you have, explain to them what you are doing and going through discussion with them. (PN)

- DCVMN to bring regulators together, from Developing Countries and also have regulators from EMA and FDA. In these type of forums regulators tend to be more open as there is no pressure. There is capacity building. (PN)
- To prepare a roadmap, have a structure prepared that what should be the adaptive clinical design, and then through this platform or through the NRAs, we can promote this adaptive design. The WHO guideline the TRS 1004 Annex 9 does not talk about adaptive clinical design. (SCh)
- Sometimes the regulators are not the experts. It would be good to create a panel of experts to help the regulators. DCVMN could help on more insight of the proposals. (CB)
- Strong training is needed for the member companies including statistical models, epidemiology. (MM)
- To write a white paper to show that adaptive clinical design is not only a pandemic issue, it should become an order of the day. (MM)

RS advised that although regulators are open, they are not very flexible about routine clinical trials. Their main concern is safety and they need complete data from phase 1, 2 and 3.

- He suggested to adapt COVID-19 examples from different countries and create a position paper that says that the same kind of adaptive trial can be emulated in certain situations which require fast track approval **without compromising** the safety and efficacy and quality of the trial; and fully supported with the statistical model able to extrapolate e.g. the statistically significant cohort and what changes are needed.
- DCVMN can support hiring a statistician of international repute to model different trials already conducted and based on that propose what is possible. Keep in mind that it is always the decision of the regulator not of the industry. Use a scientific approach.
- To draw a kind of flow chart with the timelines and roadblocks that are creating unwarranted delays and how to cut down, and then you have a neat presentation for the regulators

PN shared 2 proposals of expert statisticians. He mentioned that if we desire to make a meta-analysis, this should be mentioned in the protocol beforehand, otherwise it will be labelled as post hoc analysis and regulators do not like this. He suggested to prepare the questions in advance. KH added that here it comes to relevance to have an integrated safety database.

Real World Evidence (RWE)- is good to have but it depends on the quality and source of the data. (PN)

- It is important to impart training to the physicians on what are the parameters to take more in consideration. (DP)

AP said that vaccine hesitancy brings the awareness of how preparedness is important. All Clinical Development programs should spend time in preparedness mostly in vaccines in new platforms.

- To prepare a publication on what are the best cases brought from the COVID pandemic scenario in terms of Clinical development, Pharmacovigilance, Regulatory and how can we adapt to other vaccines. (MM)
- In order to diminish vaccine hesitancy, we should emphasize on the benefit of the EPI program. Governments need to do that through interventional publicity. DCVMN platform could be of help to raise the awareness, rather than doing it on the manufacturers themselves, as it could be seen as publicity. (SG)
    - DCVMN has created an L&D working Group that is working in raising the public awareness and reduce misinformation and disinformation and thus vaccine hesitancy. The WG is looking for the right methods to counter vaccine hesitancy and create vaccine awareness, by using the right kind of people who are credible. Only right information will be disseminated by DCVMN without any propaganda to any of our members, we will

go through public opinion, not private. (RS)
- Healthcare professionals have high influence over people's decisions. (MO)

**Regulatory Discussion**

SCh presented the registration overview in India and the role of the Central Licensing Authority (CLA) and the State Licensing Authority (SLA).

SCh also presented a summary of the discussion the Reg WG had in Singapore in November 24-25 2023 on Post Approval Changes (PACs) where it was concluded that there are different levels of changes for different authorities and differences with respect to the WHO guideline TRS 993, Annex 4. So even there, the question comes on whether manufacturers shall follow the TRS 993 or version 7 of PQ vaccines.

- RS suggested to list down the 3 key points mentioned in the slide, the differentiation, how many countries are we talking about. What are the problems, what are the challenges, what are the differentiations.

RS reminded that WHO has 193 members and cannot be aligned with every NRA, so the best is to follow NRA guideline and convince WHO of the notifiable change, unless it is something very drastic.

SCh also presented the challenges for PACs.

- RS suggested to better structure the challenges, clearly segmented, pertaining to NRA, WHO, etc. in a table and then propose a mitigation by industry, by DCVMN in the next column and have this prepared before approaching the regulator. The third column should be the benefit to the Patient (not to the Industry). e.g. time to market reduces so the accessibility of the product to the patient is much faster; equitable distribution of the vaccine.
- RS will have a meeting with WHO in the next few months, we should be ready for that meeting.
- Keep in mind that the NRAs are sovereign, WHO can give recommendations, but cannot compel them to follow. We cannot push the NRAs to change guidelines. We need to bring the regulators together in one forum and explain them.

SCh presented the gaps and challenges like lack of Pharmacopeia harmonization, PAC management challenge due to lack of harmonized guideline. WHO-PQ limited window for submission (only three). Extended timeline due to limited resource availability with regulators. Requirement to bridging clinical trials in some countries. RS requested to add at least one example of each challenge.

SCh presented the regulatory proposals to streamline functions.:

1. Collaborative Registration Procedure (CRP) by sharing information on Assessments, Inspection Report and Testing Report. This will have the benefit of reliance and recognition to avoid duplications, reduce regulatory burden, ensure timely access to quality assured product, easier post-registration maintenance. This is already been applied for medicinal products; there are agreements between WHO and some NRA so that information has to be shared from NRAs to the respective countries as required to have the timeline count down so that they have limited window for review. For vaccines though CRP pathway is available but not actively functioning, this needs to be proposed.
2. SCh made a specific proposal based on 4 points
    1. Harmonization
    2. Good Reliance Practices (GreIP)
    3. WHO National control Lab Network for Biologics (WHO-NNB)
    4. Mutual Recognition Agreement (MRAs)

PN pointed out that mutual recognition means that that the NRAs involves also politicians because it involves the change of law.

SG shared that there is the WHO NCL network wherein WHO focuses and ensures that if a batch product has been manufactured by a PQd manufacturer with at qualified NRA, the product exported should not be re-tested. They should rely on the data of the country of manufacture, and in case needed ask for raw data.
AP asked if this kind of challenges are also being faced by HIC manufacturers. SG said these topics are being discussed by IFPMA.
PN pointed out that there is no willingness of the European or American regulators to trust the Indian, Chinese or other DC NRAs.
RS suggested them to start listing what is achievable in 1 or 2-years time.
RS mentioned that he will soon have a meeting with DG WHO so asked the members

- To list out few key points of relevance at high level that can be communicated in an informal discussion, particularly pertaining to pandemic: what have we learnt, something that can be done, pertaining to WHO. Be concrete with topics that are bothering us today and can be resolved by the decision makers. ASAP.

**Pharmacovigilance discussion**

PM presented the PV situation in Brazil. Then she explained about the interaction between Regulatory, PV and Clinical Development and the challenges faced, which include the communication between the 3 areas, as sometimes it is not efficient.

- There is a need of integrating PV in all stages of the vaccine, and to receive complete documentation from other areas. Consider that the Risk Management Plant and the PSUR are dynamic documents.
- PV shall be involved in all stages of the product development and life cycle. (KH)
- Good Pharmacovigilance Practices require an appropriate PV system, it depends on the vaccines produced and other factors like collection processing and reporting of safety data, continuous signal detection and Benefit-risk analysis, Timely communication and Quality management of PV procedures.
- Challenge: There are many different regulations in PV across different countries. Even though some countries try to adopt the ICH guidelines, the majority of them do not. (KH)

KH presented on the Management in Clinical Trials and the importance of having a multidisciplinary Vaccine Safety Management Team and the key activities of PV involved and then the in the safety management in post-licensure. The main issues in emerging countries include no or minimal legal framework enforcing PV, management benefit-risk assessment. No or limited data sharing with manufacturers; no common understanding of vaccine safety.

- To assess the PV system maturity in the members, so in an anonymized manner we can know what is the level of maturity of DCVMN members. And then establish an action plan and a target for 1-, 2- or 3-years time, to help mature the manufacturers PV level. (RS)

AP said CEPI is engaged in supporting LMIC countries to raise their PV maturity level. He offered CEPI's support individual companies by evaluating their maturity level and help them get a higher maturity level.
PM emphasized it is important for companies and all areas to do self-inspections and to do Quality Assurance.

The group also discussed about the importance of assessing the quality of the data received.

VI presented to the participants the AVSS project from the PV WG, and its 4 different phases. On Phase IV, companies will submit a protocol summary which will be reviewed by experts to receive feedback. The project will close in May 2024.
KH said that the main challenge for most companies is to establish the research question.
PN suggested the group to set the bar high, following EMA and to come out with clear protocols to be put into their RMP.
CB suggested to follow up on PPP which could save burdens to the manufacturers. KH said the INCLEN proposal would be a very useful tool.
AP added that CEPI is willing to support the capacity building, strengthening pharmacovigilance activities, which includes somehow AVSS projects and strategy. They are already working on a proposal that came through DCVMN. It's an AVSS project that will generate data that will benefit many of the companies of the network, having in mind that CEPI needs to fund projects that are aligned with CEPI's mission and main strategic objectives. AP offered the participants to reach out to him anytime that any has any idea or potential project to address vaccine safety. He is focal person to discuss PV things within CEPI.

- To prepare a nice presentation with the benefits that this project gets, while focusing with the risk the benefit, in the same line, have an Action Plan also for this active vaccine surveillance projects. (SCh)
- To club AVSS and the PM's study, with dynamics to meet an objective so that there won't be any need to have a two separate studies. (DP). Keep in mind that Phase 4 studies are not the same as PMs.

SCh gave an overview of the Regulatory context pre- and post-pandemic COVID-19. WHO EUL gave a context of reliance amongst authorities, upon certain conditions. Lessons learnt included that during emergency the adaptive trial was accepted and should include pre-specified criteria for adding or removing vaccine candidate or dosing regimen. There was also a reliance amongst NRA NCLs in order to avoid repetition of testing.
After discussion, what manufacturers expect post-Covid is: Rather than pressurizing regulators, we can suggest to maintain what they have agreed during the pandemic based on the science (ViD):

- The acceptance of adaptive clinical designs.
- QC analyses are done only once instead of repeating several times when reaching other markets. Also predictive analysis. (WHO networking laboratories)
- Look at another pandemic-like situation vaccines like Ebola, Nipah, Chikungunya, Dengue.
- To work on a position paper on the best learnings we had and those which can be used as a ready-made documents for the NRAs, and maybe WHO to further endorse it that if there are conditions of interest. Like the diseases of interest mentioned above. (MM). AP suggested to consider also outbreak situations and not only pandemic.
- To add parallel testing, so that while the tests are running at the manufacturer's end. Manufacturers can submit it through the National Control Laboratory parallelly and it can be released only after satisfactory outcome of the testing. (SG) This is already done for some vaccines during outbreaks, but not for all, and it is not a regular procedure. (PD)

The working groups teams established the objectives for 2024 as follows:

| Sr. No. | OBJECTIVE | DELIVERABLES | RC | TIMELINES |
|---|---|---|---|---|
| 1 | To upgrade the skills of DCVMN members staff by training them on Basics of Adaptive Clinical Trial Design, Statistics and Methodologies for Designing Adaptative Clinical Trial Protocol | Writing Adaptive Clinical Trial Protocol | Fernanda Castro (Chair) | **Start Date:** 15th Feb. 2024 **End Date:** 31st Dec. 2024 |
| 2 | To issue a Position paper / Systematic Review on Adaptive Clinical Trial Design | Sharing practices across the globe which can be adopted for early access of vaccines | Manish Mahajan | **Start Date:** 15th Feb. 2024 **End Date:** Submission of Manuscript 31st Dec. 2024 |
| 3 | To seek clarity from WHO Team on WHO variation guideline i.e. "Guidance on Variation to a Prequalified Vaccine, V.7 July 2015" & "TRS 993,Annex-4" | To contact Dr. Carmen | RWG Subhodeep | 2 Months: **Start Date-** 17.02.2024- 17.04.2024 |
| 4 | EUL for newer vaccines meant for outbreaks or Pandemic situation eg. Ebola, Dengue, Zika, Nipah etc. By evaluating the information already available at various platform like that of CEPI, GAVI & WHO. | To create regulatory pathway. | RWG | 7 Months **Start Date-** 17.02.2024- 17.09.2024) |
| 5 | To propose Pharmacopoeial Harmonization of Indian Pharmacopoeia in line with EP/BP for individual vaccine monograph. | To prepare benefit-risk analysis | RWG Subhodeep | 10 Months **Start Date-** 17.02.2024- 31.12.2024 |
| 6 | To propose activation of DCVRN (Developing Countries Vaccine Regulators Network) on the similar line of WHO NCL Networking. | To showcase the benefit-risk analysis | RWG Subhodeep | 10 Months **Start Date-** 17.02.2024- 31.12.2024) |
| 7 | To collaborate with Medical/ Clinical Team on Adaptive Clinical Trail Design | To support paper publication. | RWG Subhodeep | 7 Months **Start Date-** 17.02.2024- 17.09.2024 |
| 8 | To assess the PV system maturity of company and support the improvement of the PV system maturity | • Circulate the existing PV maturity matrix to all the manufactures to assess their maturity (Survey)<br>• Identification on the specific areas to improve the maturity level of PV system<br>• Compare PV maturity with the landscape analysis performed in 2020 to define the improvement done in the focus areas to be supported by training and workshops | • Sonia V<br>• Patricia M<br>• Viska I | **Start Date:** 01.03.2024 **End date:** 30.04.2024 **Start Date:** 01.05.2024 **End Date:** 01.06.2024 **Start Date:** 02.06.2024 **End Date:** 30.09.2024 |

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|---|---|---|---|---|
| 9 | To set up/Improve effective processes between the 3 areas (PV/CD/REG) to ensure the product safety life cycle | • Develop policies and best practices to support companies to set up/improve process flows and communication between PV/CD/REG (Policy document, SOPs, Wis including PV/CD/REG)<br>• Workshops with the 3 groups (PV/CD/REG) – best to be face to face 2 times/year – (the safety sections needed in the various documents, MAA, safety variations, RSI management, AVSS) | • Patricia<br>• Devang P | **Start Date:** 26.02.2024 **End date:** 31.08.2024<br>**Start Date:** 01.09.2024 **End Date:** 30.09.2026 |

RS closed the meeting by thanking the participation of all the members, considering this meeting as the best meeting we have had in the last 3 years with so much teamwork. He reminded the participants that it is their moral responsibility to take the action plan and reach the deliverables set and reassured them that from DCVMN side, whatever is required to be done for this joint working group, DCVMN will provide, whether it is a speaker, a writer, an analyst, a statistician, whatever kind of help or support they are looking for, he will generate funds.

**End of minutes**

**Notes taken by SV**
**16 February '24**

**Vipul Doshi**
**Chair of Regulatory Working Group –DCVMN'**