Participants: Sebastian Comellas (SC)-Sinergium, Rajinder Suri (RS)-DCVMN, AbdulAziz Hamid Almutairi (AA)-Arabio, Chozhavel Rajanathan T M (ChR)-Zydus, Cleber Gomes (CG)-Butantan, Harsh Jogdand (JG), Manish Mahajan (MM), Monique Cruz (MC)-Fiocruz, Pei-Yin Lim (PYL)-Hilleman Labs, Pieter Neels (PN), Sameer Naik (SN), Subhodeep Chakraborty (SCh)-Zydus, Sunil Goel (SG), Prerna Kumar (PK) -DCVMN, Sonia Villaseñor (SV)-DCVMN.

RS welcomed the participants and started a round of introductions. He emphasized that whatever is decided in this workshop shall be executed on time, in excellence and must be something innovative for the benefit of all the member companies.

PN gave a presentation on **Adaptive Design Clinical Trials**, which are defined as "a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial". This includes modifying an ongoing clinical trial in accordance with predetermined rules, based on data from interim analyses.
Protocols can become more complex and can delay times for study start; however, time can be gained by having a seamless continuation between phase I and phase II, e.g., selecting the dose of the antigen and the adjuvant at the same time.
Challenges include the control of chance of erroneous conclusions. It is important that all adaptations are completely specified to ensure trial integrity. Most adaptive design trials work on dose definition.
Experienced people are required (especially good biostatisticians) and clear discussions with regulators before submission of the CTA. Adapted design can require larger arms, but it gives flexibility, it saves money and is also more ethical, because you can decide not to expose people to the wrong dose.

Controlled Human Infectious Models (CHIM). These are human challenge trials. For challenge trials there is one important criterium; the researcher should be the first volunteer in the trial; otherwise, it is questionable.
In CHIM trials, the benefit-risk balance should be very carefully evaluated. CHIM trials could be ethical, provided that you have a good protocol, the patient is well informed, and that all has been done to avoid adverse events. The right dose needs to be defined, provided that we know enough about the disease.
For the production of challenge strain, it shall comply GMP, however, some strains e.g. Schistosomiasis, are produced in animals, thus there cannot be GMP compliance.
NRAs shall be involved with clear discussions.
There is a need for CHIM trials, because in early development it is nice to see if the new product works, and also to convince investors, CHIM data is important. In addition, in case field trials are not possible, CHIM trials could replace field trials.
The major pitfall of CHIM is extrapolation of data, because CHIM is a highly controlled CTA. Other elements need to be discussed are the infection route, the strain comparability, cross protection and be aware of timelines, including the setup of the production process (6-9 months). Consider acceptability of immune bridging in the absence of a Correlate of Protection/Surrogate of Protection.

Real World Evidence. Kaat Bollaerts (KB) gave a presentation on Real World Evidence (RWE), which is the clinical evidence about the use and potential benefits or risks of a medical product, derived from analysis of Real World Data (RWD); which is patient health status and/or the delivery of health care routinely collected from a variety of sources.
Nowadays more studies include a dichotomization of clinical trials and observational studies. Traditional RCTs and RWD/RWE are complementary, and the use of RWE/RWE and speed up medicine development and support post marketing safety and effectiveness monitoring.
A discussion was held in relation to how to control the quality of the RWD. KB mentioned that the data need to undergo validation studies with different sources of data; also use some statistical techniques

or methodological approaches, try to draw some conclusions. Validation of data is a shared responsibility of all stakeholders. The main challenge is then not collecting the data itself but the quality of the data, as it is not always collected with the same rigor as in clinical trials.
Other challenge, in Developing Countries is the availability of the data as it is not as digitalized as in Europe or USA. Hospital networks are a good source in these cases.
One example shared, was COVIDRIVE, which is a network of hospitals in Europe that collect data with an electronic case report form. This was started to be used during COVID for evaluating COVID-19 vaccines. It has been used also for regulatory commitments for post-marketing vaccine effectiveness. They also do monitoring and source verification.
CB shared that ANVISA ANVISA has published in September the Guide No. 64/23 (Best practices for Real World Data studies). The guide does not make clear the use for biological products, but the understanding is that it is possible. Gold standard are still clinical trials. ANVISA is open for discussion. It has only been used for the approval of use of COVID-19 vaccines in children.
PN added that Real World Evidence is the complement of CHIM trials in order to get vaccines on the market, which are very difficult to get into the market, and to create post-authorization data. Brazil is taking the lead in the use of RWE. It is important to do it, especially for safety. But it is a long process. It needs a collaboration between companies, intermediates like P-95 analyzing information, control, validation; and the NRAs.
SG added that regarding the generation of data, the first important thing is to have a good PV system in place. The second point is that NRA won't allow a product into the market only with the patients, but until we have the approval and the product of the market, we are not able to generate RWD. Lastly, once the product is on the market, the RWD can be used for Post Approval Changes, but this needs to be taken care carefully.

Next Generation Sequencing (NGS).
In this session we had the participation of Koen Brusselsmans (KB), ScienSano, NRA Belgium and Gibran Horemheb Rubio Quintanares (GRQ), PEI NRA Germany.
PN gave an introduction on NGS. He mentioned ICH Guideline Q5A (R2) on viral safety evaluation of biotechnological products derived from cell lines of human or animal origin will soon be updated with NGS. KB clarified that the draft is already available online on the EMA website.
NGS is a technology for determining the sequence of DNA or RNA to study genetic variation associated with diseases or other biological phenomena. NGS enables interrogation of hundreds to thousands of genes at one time in multiple samples to identify adventitious agents. Studies can be performed quickly and cost-effectively. It could replace a number of time consuming and costly viral detection assays.
KB gave an introduction on regulatory aspects of NGS. He gave reference of several guidelines that state that NGS is acceptable, either to complement or to replace the existing virus screen methods. Although, for method validation, sometimes the information is a bit limited.
Companies have been proposing NGS, mainly for 4 different purposes:
1. As a supplementary test in addition to all the classic methods.
2. To replace specifically the *in vivo* virus screening tests for starting materials
3. To replace also the *in vitro* virus tests in specific cells and or also specific PCR tests. This is more challenging
4. To replace the virus screening of the crude harvest.
It is important to note that the method needs to be validated. Sensitivity needs to be evaluated. Comparison with classic *in vivo* screening methods is recommended, and also to compare with literature, but no head-to-head comparison.
GRQ spoke about NGS for Adventitious Virus Detection. They allow to have a broad spectrum and a high sensitivity. However, there are some challenges, one is the huge variety of types of viruses, which makes

it difficult to have a solution that works for every type of viruses. Another challenge is the 8 different types of genomes of the viruses, so the solutions that work well for one, e.g. DNA may not work well for RNA and so on. Therefore, we need to consider what we are intended to find (inside viral particle in the supernatant, or free genomes, integrated, episomal, transcripts, etc).
Finally, he clarified that NGS is a technology that allows establishing a method that include 10 steps.
For the validation process, it is necessary to validate the whole process, and if there is a change in one of the tests, it needs to be validated that it does not affect the final result.
For the broad spectrum, they are working with WHO to develop a validating panel which will include 7 different viruses (porcine circovirus, Mammalian orthoreovirus, RSV, Epstein Barr, Feline Leukemia, Coronavirus, Mice minute virus) and it will include representatives from the different structures of the viruses and for the genomes. Ideally it would be available by mid-spring 2024.

ChR shared Zydus's experience on the use the NGS platform for testing of Adventitious virus. Zydus decided to explore the technology for their virus bank and cell line screening. The challenges faced were mainly the virus type- the extract procedure has to be robust and broad enough to encompass all types of viruses; the Sample matrix- depending on what within the vaccine manufacturing process has to be tested, the physicochemical properties of the viruses in combination with the sample matrix becomes more complicated; and the computer system validation is required. They shared a case study for the viral seed characterization of MR vaccine as per WHO guidelines with 15 different viruses.
They used EP-2022 and IP-2022; however, these still do not have information about NGS as it is still in a very early stage. There is limited knowledge of the platform on its sensitivity and on the procedural methodologies; so the question is how DCVMN companies are going to adopt this methodology in an easy way, this needs to be discussed and taken forward.
KB shared that indeed validation is very tricky because of the lack of experience, even for regulators. He recommended Zydus to search for scientific advice, especially in the early phase. In terms of references viruses, regulators would favor WHO to make the model viruses available ASAP so to have it standardized panel of model viruses that can be used worldwide by different companies.
In terms of correlation, KB clarified that regulators do not expect manufacturers to perform side-by-side analyses, certainly not versus the *in vivo* screening methods; rather a sensitivity analysis and do some comparative analysis based on what you have available from your experience, literature. But take in consideration that regulators from other regions may think differently. For *in vitro* testing it is less difficult to perform side-by-side validation.
GRQ also answered some of the questions posed by Zydus.

SN presented the experience of Serum Institute of India in the use of NGS for Adventitious Agent Detection. SN emphasized on the sensitivity, speed and reproducibility of the method as well as it is 3Rs compliant. He shared the challenges faced and the solutions found. Important things to consider is that there needs to be a case-by-case defined work flow.
They did a dry lab validation by constructing genome sequences that were deliberately introduced into the data set and were subjected into the bioinformatics analysis to check if these sequences were being detected into the bioinformatic spike line. They detected a 100% alignment. They tested the reproducibility of these analyses. Samples were also tested using classical methods.
He shared that SII was able to develop the Ebola vaccine in 100 days, mostly thanks to the NGS for Adventitious Agent Detection.
KB recommended that when they perform validation of these kind of methods with novel viruses, do not introduce the viruses into their production facilities. He suggested for smaller companies who do not have the means to make these validations, to work together with other pharmaceutical companies or subcontractors.

GRQ added that the internal control should be very well selected. It should be a virus that you are not expecting in your sample. Also, for the databases, RBDB is one of the most curated ones for viruses and it is in constant curation and revalidation. He also suggested the members to be cautious when testing for transcripts, because there are two types of cells (susceptible and permissible). If you have B cells infected but not permissive, there will be no transcription detected even though the cell may be infected. Then the risk comes when introducing them into the human, as we have susceptible and permissible cells, it could create a problem.

Post-Approval Changes (PACs)

SC made a quick review of the WHO Technical Report Series (TRS) 993-Annex 4 and a review of the PAC situation in Latam. SC shared the results of the publication made in 2020. The situation has not changed since then. Only Mexico has adopted the WHO PAC guideline, so the situation is complex; each country NRA has a different way to evaluate vaccines and PACs. Argentina will adopt EMA PAC regulation.

RS invited the WG members to think about the way forward. During COVID, many regulatory flexibilities were executed and implemented. He suggested to synthesize this information, consolidate it, analyze it, structure it, and put it in a very meaningful way which can then show what changed during COVID that can be extrapolated to other the vaccines, or PACs; and what cannot be done because it is only for emergencies. And then, out of it, bring out something very meaningful to publish. This should be the recommendation to the regulators from the manufacturers. And we will use that effectively with the regulators in the next forum that we are going to organize. We can deploy a medical writer, but we need to give him the information. We need to set the goal and then the means will come.

SC suggested to go together with PAHO or directly with the NRA's; however, many of the NRA's in Latam are not open to receive manufacturers.

RS suggested to define the objectives as clearly as possible and divide roles and responsibilities, with support of companies already supplying all over the world, like SII or SK Bio, and with the support of experts. Create a roadmap.

CG and MC presented the PAC situation in Brazil. A timeline was presented with the evolution of post-approval legislation and since 2020 ANVISA issued a new legislation RDC 413/200 and IN 65/2020 which gives a post-approval legislation closer to the ICH and WHO Guidelines. The classification of the changes is based on the potential effect of the quality change and on the potential impact on the safety or efficacy of the product. The main issue faced by manufacturers is the long time for ANVISA to analyze the changes. During the pandemic, ANVISA issued many resolutions that reduced the timelines for licensing, especially for products involving COVID-19, but for other products and PACs, the timelines increased to up to 18 months, depending on the prioritization. ANVISA is still conservative in reliance on PACs already approved by reference NRAs. ANVISA has announced that by 2025 they will adopt the CTD format. ANVISA will also implement ICH 12 (Technical and Regulatory considerations for pharmaceutical product lifecycle management).

AA shared the assessment of PAC in Middle East. Most authorities have adopted TRS 993 Annex 4. However, the time period for evaluation is widely differentiated. There is lack of PAC regulation in most countries NRA. There is low reliance between NRAs, and there is high variability in the expertise level of the NRAs to evaluate PACs. Most NRAs rely on SaudiFDA.

In general terms in the world, the NRAs do not rely on what WHO or other agencies say. They prefer to do the review on their own. RS added that this is even related to the revenue they get. If they stop doing these activities, they will receive less revenue, and will lose regulatory force.

RS and PN suggested the manufacturers to give all the information they have, not to lie nor hide any information, and be very polite, in order to build confidence and reliance of the NRA on the manufacturer.

SCh presented the PAC situation on Asia and Africa. India has the Central Drugs Standard Control Organization (CDSCO), part of the NRA. Ther PAC guideline is PAC/1108. For manufacturers it is important to have a fast approval and also see the category of variations to leverage so that supportive documents are accepted in the different countries where the vaccine is supplied. This is a big burden for manufacturers.
SCh made a comparison between the different classifications of the PAC used in several countries and the timelines for approval, including India, Srilanka, Philippines, Malasya, Tanzania, South Africa and Egypt. The classification criteria and timelines are different in each country. Some adopt TRS 993 Annex 4 and others have their own guidelines.
RS suggested him to consolidate this information in one slide with the different nomenclatures, and then on a second slide about WHO. Include only countries that are directly linked with DCVMN where we want to bring attention.

SC made a proposal to improve the situation in Latam, which is to approach María Luz Pombo in PAHO or any other person to promote the regional adoption of TRS 993 Annex 4. The issue is that some NRA do not have enough resources, knowledge and expertise to meet the timelines defined.
RS suggested to create a table with one column with observations, one with the real challenges (duplication of guidelines) and with the solution e.g. training. Prepare one slide for WHO, one for PAHO and one for NRAs. The best is to approach now but first refine the issues, list the priorities (only 2 or 3), synthetize max. 4 slides, communicate effectively with focus approach. We need to bring all this people in one single platform and discuss (not complain) request them to harmonize (categories and timelines). This could be DCVMN or WHO platform or create a new one and invite NRAs and regulators. Best practices need to be communicated with regulators. RS can guide a person who can push through this.
Analyze the impact of having harmonization, is it only nomenclature, what is the impact for NRA and for manufacturer, likewise, the timelines. We can leverage CRP.

The Regulatory WG members made a SWOT analysis of the Regulatory activities in DCVMN.

Strenghts	**Weaknesses**
1- The DCVMN is a very important stakeholder in the vaccine world. 2- Knowledge of the regulatory context in different countries and regions. 3- We have people who have hands on experience with dealing with different products, NRAs, PAC who can contribute with their experience 4- DCVMN has unique capability to holding training and teams can find relevant topics to participate in. 5- 78 PQd products being supplied to >170 countries 6- Five of eight PQd C-19 Vaccines supplying >60% of global production	1- Low interaction (o no interaction) and communication between multifunctional teams (PV, Reg, CD). 2- Lack of consolidated database within the network (language could be a barrier) 3- Lack of milestones (break bigger task in smaller tasks) 4- We do not have a refined approach to communicate to agencies
Opportunities	**Threats**
1- We are getting in touch with various NRAs like PAHO, WHO, IFPMA, EU, whose experiences may	1- Regulatory guidelines defined based on the reality of companies in developed countries.

be taken in consideration 2- Post COVID-19 flexibilities/Openness offered by regulators) 3- Advancement in digital technology facilitating ease of submission 4- AI could be an important tool to improve management 5- Novel manufacturing Technologies meeting specifications of standardization, validation and reproducibility Leading to capacity enhancement and shrinking timelines enabling better Regulatory compliance. 6- Flexibility of implementing rolling reviews like during COVID-19/PHEIC. 7- 3R and NGS 8- Registration of platform Technologies using Design of Experiment tier Regulatory approach. 9- Good reliance practices	2- Some agencies are very conservative; they are not open to changes. 3- NRA or WHO may not accept our proposals, in that case we need to redefine our strategy 4- Unexpected long timelines for Developing Countries NRAs to review PAC 5- Complexity of vaccine manufacturing and Regulatory pathway leading to very high-cost burden.

The conclusions and deliverables obtained from the workshop were:

1- Framing our Objectives for further discussion with WHO and others:

a. NRAs to harmonize the categories of post approval changes in accordance with TRS 993 Annex 4

b. NRAs to be in alignment of timelines for approval of each category of change

c. Propagation of GReP by Developing Countries NRAs for acceptance of PACs approved by other functional NRAs

Action plan

- Prepare slides with information. RC: Subhodeep- End Jan 2024
- DCVMN to engage in regional discussions with NRAs. (Ask members for contact details) with regional online workshops
- Finalize e-learning module of PACs – January 2024 – RC Sebastian Comellas
- Make an in-person workshop (2 days) on NGS open to all members with live demo (BMGF has a Project in NGS). Could be a collaboration with IABS and DCMVN. Focused on replacing in-vivo tests. Invite multiple vendors and investigate to include practical sessions at FDA (A. Khan) during this workshop. RC- P. Neels, e.g. Q4 2024
- Approach regulators of DCVM countries to convey the importance of implementing NGS. Decide if we invite some of them to the workshop. Send a survey to members on how they can DCVMN approach their NRA.

RS thanked the mind openness of the participants, and ended by saying “whatever mind can conceive, you can achieve”. He invited the participants to leverage the strengths and mitigate the weaknesses. He thanked specially the contribution and commitment of PN.

Sebastian Comellas

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