

Attendees: Adriansjah Azhari (AA), Apoorv Kumar (AK), Benoit Hayman (BH), Bernadette Hendrickx (BNH), Marcos Freire (MF), Martin Reers (MR), Meei-Yun Lin (ML), Parag Nagarkar (PN), Ping Zhao (PZ), Valeria Brizzio (VB), Rajinder Suri (RS) (left at 12:15), Rosane Cuber (RC), Sonia Villasenor (SV), Sunil Gairola (SG), Thien Do (TD), Sonia Pagliusi (SP).

DCVMN COVID-19 Committee at 12.00 CET and finished at 13:02 CET

AA chaired the meeting and welcomed the participants. AA introduced topics for discussion.

PN, Global Regulatory Head at Serum Institute of India since 2019, introduced himself and identified that the challenges in vaccine regulatory pathways:

1.1 In initial stages

- Some developing countries find difficulties to conduct clinical trials in the local population, e.g. performing a full immune-bridging evaluation of the results before authorizing the use of a vaccine. Thus, the need for an accelerated regulatory pathway.
- He suggested creating rolling submissions (which many countries have been using), an emergency use authorization or a special import license, and conditional marketing authorization, to name a few options.
- Many regulators are not confident to take a first decision and prefer to rely on other developed countries' regulations approval, before kickstart their studies and approvals.

1.2 Post-approval changes/ Life-cycle management of COVID-19 vaccines

- For example, DS/DP site addition, scale up and shelf-life extension are concerning factors.
- Regulators must be based on Science and Risk approaches for a rapid increase of manufacturing capacity for COVID-19, such as streamlining stability test requirement based on data or alternative process validation approaches; thus, concurrent validation; decoupling DS and DP validation; and/or continuous process verification could facilitate approvals.

PN clarified that National Control Laboratories (NCLs) usually test vaccines but in this COVID-19 situation there is burden on releasing a COVID-19 vaccine urgently.

- The availability of well-standardized and qualified reagents is also a pressuring issue for various NCLs. In order to overcome these challenges, countries should establish a number of National Drug Testing Laboratories and also reduce testing when viable.
- An international collaboration agreement may facilitate importation requirements, repeated testing and enable a global agreement on tests/specifications per vaccine.

Availability of Raw Materials/ Excipient/Consumables

- Under an emergency situation, several vaccine manufacturers experience shortage or limited supplies of raw materials/media and consumables. A solution may be using alternative media/raw materials upon a regulatory framework support.

Regulatory Convergence on Assessment Report & GMP

It is extremely important to have mutual Reliance on Assessment Report and GMP audit inspection report of other regulatory body/agency for helping each other's validation towards an easy entry of new COVID-19 vaccine candidates. As a suggestion, regulators may publish Public Assessment Report (PAR)/ Assessment report as part of assessment for COVID-19 vaccine that provides basis of approval and data that has been reviewed as part of regulatory approval.

Additional Challenges/Concerns – Next steps

regulatory guidance is urgently needed for the next generation COVID-19 vaccine candidates that are in earlier stages of developments, for CMC, Clinical (Immuno-bridge/CoP) and overall submission approach. Another improvement is the standardization across labs/immunoassays, such as using the WHO International Standard.

Clinical Drop Out from Clinical Trials

PN showed concern of drop-out in unvaccinated volunteers participating in clinical trial as there are other vaccines already available to the general public. AA added that shelf-life is the main challenge that manufacturers of COVID-19 have been facing nowadays and questioned PN if there are guidelines in this regard. PN responded negatively. RS asked if there are any challenges foreseen on the Collaborative Registration Procedure. PN answered that they haven't applied CRP for COVID-19 but during this phase WHO EUL has played a key role, based on which some local regulatory agencies have shortened their timelines and given a faster approval.

SP inquired about the vaccine booster as WHO already addressed this point at SAGE, but also mentioned that manufacturers can provide data to support (or not) policy but it is difficult to establish it. PN said that a large population needs urgently of 1st dose. BNH commented that WHO has stated that the priority is the vaccination availability but boosting it is not a current focus. Elderly and individuals with chronic diseases are the target group, so she does not foresee a boost for the general population. She added that many experts don't know how to tackle the mutated virus, and some think COVID-19 may disappear in the long term. Boosting may be ongoing in some European countries, where populations are older, but the primary vaccination is the current concern; however, many people are not rushing for it. SP added that SAGE recommended the boost of inactivated vaccines and for the population over 60. BNH replied that we must consider that not all vaccines have high efficacy; SP invited MF to confirm if elderly from 65 years and older are receiving a third shot.

MF mentioned that it depends on the number of doses each country/state has available and the priority to vaccinate everyone with at least a second dose. Bio-Manguinhos/Fiocruz is producing around a twenty million doses/month. The Brazilian government understands everyone must be vaccinated with a third dose, although there are few groups refusing to get vaccinated but, fortunately, it is not a big part of the population, such as in Europe or the US.

BNH asked MF the coverage rate of vaccination in Brazil. MF responded that yesterday, for a second dose, was more than 100 million (ca. around 50%). For a single dose, it was around 70%. SG commented that policymakers concern on who should take the decision of a 3rd dose, as there are many uncertainties on the shelf-life, length of protection and many others factors. In India, the third dose will be applied only after 100% of the population is vaccinated with a second dose. SP shared her understanding that immunogenicity waning is the first criteria for a third dose, focusing on people with other diseases, and profiling the breakthrough of infection in vaccinated people. BNH said each country has to try to get 75-80% of people with a single shot at least. There has been a rapid waning and enormous difference on vaccine's immunogenicity so it is difficult to start with standardized recommendations. An overall surveillance will be able to teach us how to proceed with the vaccination. Europe already ordered doses for a fourth shot, this is underlying the rapid loss of immunogenicity; this is a real problem. There are technical, budget, practical and regulatory problems.

VB shared a snapshot on the vaccination landscape: up to October 12th, 6.56 billion of doses have been administered, representing 21.65 million doses/day, less in comparison to July, when there was an average of 40 million doses/day. So far, 47.7% of the global population have received at least one dose and 2.5% of individuals from low-income countries have received at least one dose. The largest number of doses are administered in China, over 2 billion, followed by India with 961 billion, USA with 403 million, and Brazil with 249 million of doses. There are some countries with more than 80% of people vaccinated with at least one dose – UAE, Portugal, Chile, Spain, and Singapore). Other countries still have a way to go, such as Ethiopia or Nigeria, with an average of 2% of the population.

VB showed data on the percentage of people willing to get vaccinated against COVID-19, from September 15th, 2021. On the top, Spain with 80% of people vaccinated, 13% unvaccinated and not willing. SP asked VB about the acceptability from people to being vaccinated in developing countries, as she only presented the willingness from those located in developed countries. VB answered she doesn't know, because she took the data from "Our World Data", which based its research on the Imperial College London – located in a developed country. Lastly, the general

tracker she pointed vaccines approved and are being used. A new DNA vaccine was approved for Emergency Use in India by Zydus, and Protein subunit by Medigen.

SP highlighted the fact that billions of doses administered actually reflect the manufacturing capacity of the countries, with 2.2 billion doses used in China are made there, as well as nearly 1 billion in India. However, most vaccines administered in Brazil and Indonesia are from China. Concerning Brazil's vaccine, Bio-Manguinhos is filling with drug substances imported from China. MF confirmed SP statement adding that Fiocruz will start soon to produce API.

AA said that the contribution from developing countries is beyond their vaccine production capacity. PN emphasized COVID-19 vaccines must not be produced under the cost of other vaccines and diseases. MF said to be also proud of DCVMN because of its outstanding capacity to respond to the pandemic, manufacturers have been preparing since a long time, in increasing DCVMs technologies and facilities to produce multiple vaccines.

AK noted that over the months of July & August WHO, CEPI and COVAX concentrated the focus on technology transfer Hubs in the world. South Africa has been a case of success with the first mRNA vaccine technology agreement by Biovac – Pfizer/BioNTech. African Vaccine Manufacturing Initiative (AVMI) coordinated the Vaccine Security in Africa Webinar to prospect the next steps for Africa to become self-sufficient in the production of vaccines for COVID-19 and other primary immunization schemes.

He added that the UNICEF and HOPE Consortium have partnered in order to bridge supply chain gaps and more importantly to support 21 nations within the continent of Africa with ultra-cold chain freezers; addressing the manufacturing, but also the supply chain constraints across the globe and how their partnerships are keen to support that.

AP shared one specific slide in which WHO presented at the AVMI, on how to expand vaccine production. They focused on three specific lines of execution: (i) Fill-Finish, (ii) Bilateral Technology Transfer and (iii) Multilateral Technology Transfer – Technology Hub Model. SP added that PAHO awarded Bio-Manguinhos and Sinergium to developing mRNA-based vaccines. She mentioned that the PAHO's approach in Latin America is different to Biovac/Pfizer, because the latter is a filling agreement, while PAHO aims to support LA with drug substance and ingredients. VB complemented that Sinergium is producing Astra Zeneca's drug substances but they are also investing in the mRNA Hub. It is unclear for the group if the Biovac Hub includes technology transfer for the drug substance. SP suggested to contact somebody from the AVMI to provide a presentation on the short-term/long-term future.

BH presented the results of a survey to assess the effectiveness of the COVID Committee in achieving its objectives and the efficiency of the committees' meetings. In total there were 7 anonymous survey respondents, 6 of whom represent organizations engaged in COVID-19 vaccine development while all respondents' respective organizations have engaged in licensing agreements or a joint venture for COVID-19 vaccines. Respondents agreed that the committee was achieving its objectives, yet there is clear margin for improvement. Particularly, two areas lacking were "discussing solutions provided by stakeholder organizations" and "evaluating prime COVID-19 vaccine candidates". Five of seven respondents stated there are benefits of the COVID-19 Committee citing the usefulness of the geographic overview of COVID-19 vaccines and players, and the opportunity to share international experiences and share best practices. To improve the quality of future meetings respondents highlighted the following topics that should be addressed: clinical trials and efficacy studies, the vaccine landscape, regulatory requirements and tech transfers. The responders agree to the frequency to remain monthly, with the expectation that the quality of meetings will improve.

AA informed the next meeting will be held on November 11th.

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Adriansjah Azhari

Chair DCVMN COVID-19 Committee, October 18th, 2021

Notes taken by T. Lacerda (based on recording), edited by SP and SV