Minutes of the WHO- DCVMN Workshop on CRP for vaccines Geneva, 26th-27th September 2022

In-Person Attendees

WHO:

1. *Dr Rogerio Gaspar, Director- RPQ Co-Chair*
2. *Dr Hiiti Baran Sillo, Unit Head, Regulation and Safety, RPQ*
3. *Dr Samvel Azatyan Team Lead, RCN/REG/RPQ*
4. *Dr Carmen Rodriguez Hernandez, Team Lead,RPQ/PQT/VAX*
5. *Dr Joey Gouws, Team Lead GMP*
6. *Dr Olivier Lapujade, Clinical Assessment*

DCVMN:

1. *Mr. Rajinder Suri CEO-DCVMN Co-Chair*
2. *Dr. Sunil Gairola (representing SII)*
3. *Dr. Andrew Wong (representing Walwax)*
4. *Mr. Parag Nagarkar (representing DCVMN-RAWG)*
5. *Mr. Abulaziz Al-Motiri (representing Arabio)*
6. *Dr. Bernadette Hendrickx (Consultant-DCVMN),*
7. *Dr. Katharina Hartmann (Consultant-DCVMN),*
8. *Dr. Sonia Pagliusi (Executive Secretary-DCVMN),*
9. *Mr. Sivashen Cunden (Astt. Manager-DCVMN)*

Virtual Attendees

WHO: Dr Deus Mubangizi (Unit Head PQT/RPQ/MHP), Dr Mariana Roldao Santos (T.O. FPI) Nyasha Maregere (WHO FPI) Dr Ana Nogueira (WHO Consultant),

DCVMN: Beatriz Lucchesi (Butantan), Brandon Geldenhuys (Biovac), Chaiti Roy (Bharat Biotech), Chen Jun (Bravovax), Dr Do Tuan Dat (Vabiotech), Devi Sahoo (Indian Immunologicals), Hien Dang (Polyvac), Hongde Xie (Bravovax), Iris Qian Xie (CNBG), Jingjing Gao (CNBG LIBP), Li Yansonghe (Sinopharm SIBP), Linda Nesbitt (Biovac), Maria da Luz Leal (Bio-Manguinhos/Fiocruz), Paul Torkehagen (Medigen), Qiaoruo Xiong (CNBG), Rajendra Kasi (Zydus Cadila), Rosane Cuber (Bio-Manguinhos/Fiocruz), Sandra Cho (Butantan), Sebastian Comellas (Sinergium Biotech), Song Yanan (CCIBP), Sunday Kisoma (WHO FPI), Venkat Sivaramakrishnan (Bharat Biotech), Viska Indriani (Biofarma), Wenjuan Han (innovax), Yifan Wang (CNBG), Yiyuan Chen (BIBP)

IFPMA: Mic McGoldrick

Aims of WHO-DCVMN 2-day Workshop

1. WHO to provide overview of workshop objectives and agenda
2. WHO to share PQ vaccines programme and PQ assessment reports to enable CRP
3. WHO to present overview of CRP: Progress in implementation & identified challenges
4. DCVMN to share industry experiences and challenges with implementation of CRP
5. Identifying quick “wins” to improve operational procedures, and move with a sound-and-safe basis to CRP implementation in the first half of 2023
6. Co-design solutions and roadmap for equitable access to healthcare and quality medical products using CRP
7. Arrive on agreed actions and follow-up plan

1. Introduction

Dr. Rogerio greeted the participants and laid out the workshop’s aim, to codesign solutions for healthcare and for equitable access to quality medical products, also based on lessons learned from the pandemic that he shared:

a. Firstly, as demonstrated by COVID-19, vaccines can be developed in about one year, with high rate of success for several products introduced simultaneously globally, without compromising any international quality standards. It is expected that DCVMN associated companies will ensure continued supply of COVID-19 monovalent

vaccines, important in the primary vaccination programmes, while (omicron) variant-based vaccines are indicated for booster doses only.

b. Secondly, while the pipeline for novel COVID-19 monovalent vaccines needs to continue, availability of comparator for immune-bridging studies is a challenge, particularly of mRNA based vaccines. Hence, WHO is building a global health security agenda and reinforcing regional manufacturing, as an important strategic component of health for all, as to resolution 74.6 of WHA of 2021. In this context, a hub in South Africa serves as global tech transfer, where 10 to 15 countries will receive tech-transfer, with support from governments, despite regulatory challenges.
c. Other global transformational change includes to move 56 regulatory authorities towards WLA (WHO Listed Authorities) framework, according to maturity level bench-marking tool, in the coming five years, to enable expansion of manufacturing capacity, as to strategic directions discussed by WHO member states. A major lesson from the COVID crisis is that we can do better, streamlining regulatory approvals within a year, to avoid redundancy.

This meeting was aimed at identifying quick "wins" to improve operational procedures, and move with a sound-and-safe basis to CRP implementation in the second half of 2023, and improve global heath. Specifically, in the first half of 2023 many internal procedures will change to make countries reports available to accelerate vaccines' CRP, welcoming inputs from DCVMN on priorities in specific regulatory files, aligned with public health needs. Our goal is to have all regulatory-files and procedural issues resolved by the end of June 2023, and thus increase the number of vaccine CRPs to hundreds or thousands, particularly in LMICs, as it is the case for medicines.

2. *WHO PQ Vaccines programme and sharing of PQ assessment reports to enable CRP (Presenter: Ms. Carmen Rodriguez Hernandez)*

- In 2011-12 the principle of CRP was piloted and endorsed by ECBS in 2016 to be used for other vaccines and by several countries, on ad hoc basis.
- WHO identified the following challenges; 1) feedback from users (Manufacturers) ,2) outdated PQ reports and 3) competing priorities on available resources for PQ inspections and other core activities.
- To mitigate these challenges identification of country specific regulatory pathways and barriers are now being "mapped", to better define vaccines with public health benefits
- The way forward for CRP includes;1) preparedness to share reports, 2) questions from countries to be addressed directly by manufacturers, 3) that countries follow the reliance mechanism for variations of CRP registered vaccines, and 4) apply principles and criteria used for COVID EUL, used as road map for WHO assessment of vaccines during COVID PHE, exploring options for other vaccines registrations.

3. *Overview of Collaborative Registration Procedure: progress in implementation and identified challenges (Presenter: Dr. Sanvel Azatyan)*

- WHO reliance practices started in 2004, and rely on prequalification and on "stringent" regulatory approvals (SRAs). Reliance and recognition principles, avoid work duplication, reduce regulatory time, and enable assessing benefit-risk at local context.
- CRP work flow is as follows:
  I. PQ Vaccine CRP Registration request submitted from applicant / manufacturer, to target country NRA.
  II. Request is forwarded by the NRA to WHO or SRA requesting sharing the reports
  III. WHO or SRA shares the documentation confidentially with NRA, through secure electronic platform hosted by WHO.

IV. NRAs do desk assessment to achieve their national decisions, within a 90 days target, for marketing authorization, or not.

- WHO advocates and supports CRP applicants (DCVMN Members) with organized CRP meetings and regional training workshops with NRAs, including a CRP annual meeting for all stakeholders (next meeting in Dec 2022).

4. *Industry (DCVMN) experience with the implementation of CRP for vaccines prequalified by WHO and approved by SRAs (Presenter: Parag Nagarkar, Chair RAWG -DCVMN)*

- Captured from an internal survey conducted experience and challenges of CRP were captured from 36 respondents whom represented 26 member of the DCVMN.
- Challenges included:
  I. Countries requesting additional data or country specific documentation, e.g. local Risk Management Plans (RMPs), mock-up labelling and package inserts, samples for local testing, batch records, raw-data for stability studies, and facility inspection reports.
  II. Lack of WHO mechanisms to approve certain categories of variations as members observed countries refusing PACs approvals
  III. Unclear approval timelines as few members experienced CRPs which took over 90-day target.
  IV. Lack of visibility of information between WHO and NRA

DCVMN Suggestions for improvements:

1. Provide access to the manufacturers to the exchange of information and decisions taken between NRAs and WHO (web-portal) even if restricted
2. clarification needed on the process for handing queries
3. Validity of certificates provided by NRAs to be aligned with WHO PQ
4. list of vaccines registered under CRP to be published on WHO website (like PQ);
5. Ensure CRP considers PACS and reliance on WHO PACs, aligned to WHO 2015 guidance on reporting variations and documents;
6. ensure that for all CRP signatory countries the “global or regional dossiers” are accepted, e.g. CTDs or WHO CTD, rather than request country specific dossiers;
7. recognition and acceptance of WHO GMP certificate, instead of request redundant GMP inspections;
8. ensure that format of labels and SmPC/package insert should be identical to those products approved on WHO PQed documents (only translated to local language, if needed).
9. Having the contact of CRP focal points in specific countries available for applicants that intend to make submissions in specific countries, to facilitate communication ensure timely completion of CRP

Discussion on selected 4 main points presented by DCVMN

1. Validity of local certificate to be aligned with WHO-PQ

- Time validity of certificates have to follow local laws or regulations, and there is no legally binding manner to de-link the CRP, a voluntary process, and cannot supersede the local laws that may define the validity period to be respected.
- PQ vaccines have a validity based on risk-based approach, and can be revoked anytime, if issues arise.

2. Variations/PACs management in CRP

- CRP guidelines contain provision on variations, when variations on PQed vaccines are made, manufacturers responsibility is to immediately inform WHO, as well as inform directly the countries where the same product is registered.

- The new EPQS[1] database will generate notifications flagged to all parties or countries where the product is registered, and trigger approval of variations by relevant countries, but notification and submissions are required by most countries.

3. Differences in the Packaging & Labelling and to comments on GMP inspections

- It is challenging to ask countries to adopt PQ labels, that are not aligned with their own regulations.
- Regarding inspections, some NRAs request GMP reports, as the WHO GMP inspection report have a validity of 3 years, The NRAs are entitled to take or not that GMP report.

4. Central Country focal point for CRP (local level)

- Every CRP signatory has a focal point, though they are not necessarily aware of every detail nor are they decision makers these names are key as local NRA contacts.

Actions from the Workshop

1. DCVMN to participate in the six WHO CRP regional advocacy workshops in the first half of 2023 ensuring common vision to advance faster, for awareness. WHO to share Workshop schedule for participation.
2. WHO will facilitate several joint workshops with NRAs and manufacturers to achieve a common understanding of the changes being implemented for SRA to WLA within 5-year period
3. By mid-2023, to identify a public health impact vaccines and apply CRP in various countries for maximum impact.

Continued discussion on additional CRP topics and other relevant issues:

DCVMN perspective on CRP for older prequalified vaccines:

- This is a challenge, as NRAs are now requesting CTDs, which is resource intensive. From 2017 most products are in this format but prior to that mostly products are in the PSF format, (Product Summary File). Particularly, clinical trial data may not be available in the CTD format NRAs are used to see today.
- Further, many monovalent vaccines, have been replaced by combination vaccines, therefore monovalent products may no longer be a priority.
- WHO will continue to seek solutions but needs to prioritize public health issues that need attention, it may depend on product specific supply and demand balance, as well as volumes and programmatic context.
- On 18th of October there will be a stakeholders meeting e.g. WHO, UNICEF, Gavi, to discuss priorities.
- Regarding changes to CTD files already submitted for PQ, and amending the said CTDs, WHO is not yet accepting eCTD submissions, but the manufacturer could notify the PQ services of the changes, and share a copy for information and consideration.
- Alternatively, updates could also be submitted in the context of the evaluation process, e.g. as part of responses to related questions. In the near future, the e-CTD which is linked to EPQS to be completed in 2023, will enable online amendments/updates. Meanwhile there is a need to adapt to various files formats.

Extended CRP approval timelines

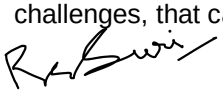
- In principle, the NRAs sign voluntary agreements with WHO, to use CRP, and commit to comply with the procedure. WHO tries to advocate and sensitize NRAs to remind of the procedure, and extended CRP process duration is rare.

[1] Electronic Pre-qualification System

- Joint assessments of a specific product are another reliance mechanism to leverage knowledge between NRAs, towards registration, mostly on a regional basis.
- NRAs sometimes have questions to fulfil national regulatory requirements, CRP is often not fully aligned with regulations in other countries, thus the discrepancy and delays in some assessments.
- Regulatory advancements to changing outdated regulatory requirements, is a long-term goal and WHO will implement benchmarking tools and reliance principles will help building a new regulatory culture.
- WHO rotation programme and global implementation programmes may also aid regulators to get acquainted with CRP and positively impact the approval timelines.
- Another issue impacting timelines, is vaccines PQ group does not currently recruit several experts from various streams. However, note that within the next 2 years, product prequalification and reviews will not be conducted by staff at WHO, but by experts from different countries, regions, backgrounds, skills and knowledge which may impact products in the CRP pipeline.

How can individual manufacturer support WHO in PQ and CRP?

- DCVMN to identify and communicate key countries which are priorities for adoption of CRP. Due to resource constraints the WHO vaccine team cannot support all and any CRP, but prioritize those with public health impact.
- Manufacturers to updating dossiers format to CTDs for example. As soon as the EPQS will be available with the e-CTD, there will be a period of transition, to determined based on consultation with manufacturers. However, it is not yet clear when the e-CTD will be launched.
- To accelerate CRP, it is essential to involve all stakeholders, early on, NRAs, procurement agencies and WHO PQ team. This includes pre-submission meetings to address specific challenges, that can well be conducted on a virtual and confidential manner.



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