

COVAX

CEPI



Workshop Report

COVAX Vaccine Safety Working Group Workshop on “COVID-19 *Vaccines Risk Management Planning: Stakeholders Experiences and Perspectives*”

April 28th, 2021

Meeting report prepared by
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Executive summary

On 28th April 2021, the COVAX Vaccine Safety Working Group hosted a workshop on “COVID-19 Vaccines Risk Management Planning: Stakeholders Experiences and Perspectives.” The main aim was to provide a platform to discuss, exchange, and share expectations regarding requirements as well as experiences and perspectives related to pharmacovigilance planning and risk management strategies.

Key points from the regulators’ experience and expectations included:

- COVID-19 has brought about significant challenges, but also opportunities in that numerous different countries across regions and settings are coming together to address common challenges and for collective learning.
- The World Health Organization (WHO) Good Reliance Practices document includes regulatory oversight of all medical products and addresses all regulatory functions as defined in the Global Benchmarking Tool.
- European Medicines Agency (EMA) guidance is based on European Union (EU) Good Pharmacovigilance Practices which includes specific recommendations on risk management for vaccines and biologicals. In addition, coreRMP19 guidance, which covers additional topics relevant to COVID-19 vaccines, has been developed and is now in the public domain.
- Pharmacovigilance activities for COVID-19 vaccines includes evaluation of monthly simplified periodic reports; risk management plan (RMP) evaluation; pharmacovigilance planning; publication of informative sheets, statistical reports, and information notes; survey on vaccinated people; adverse event following immunisation (AEFI) reception; AEFI evaluation and follow-up; and feedback of more significant cases.
- Safety monitoring of COVID-19 vaccines is key to characterising the full safety profile of the vaccine.
- It is important to maintain confidence and trust in vaccines.
- Collaboration between the National Regulatory Agency (NRA) and vaccine manufacturer/Marketing Authorisation Holders (MAHs) is critical.
- Adequate minimisation measures put in place in the RMP should be well implemented in conjunction with the NRA oversight.

Key points from industry experience and perspective included:

- Development of a core organisational risk management stance is considered strategically important and provides the ability to quickly mobilise for submissions.
- Both challenges (e.g., unknown requirements, implementation of pharmacovigilance in low- and middle- income countries [LMICs]) and opportunities (e.g., innovative methods for implementing requirements) have arisen from the pandemic situation.
- The RMP for COVID-19 vaccines is a “live” document that must be updated on an almost monthly basis.
- Global RMP must be managed according to the highest regulatory standards despite possible deviations in expectations of various regulators.
- Guidance from EMA, WHO, and other regulators is highly appreciated.
- Harmonisation of safety data with other vaccine manufacturers is needed.

The slideset from the meeting can be found here:

https://media.tghn.org/medialibrary/2021/05/Slide_set_VSWG_webinar_April28.pdf

Agenda

Time (PDT)	Session	Speaker
(2:30 pm CET)	Tech check	
(2:50 pm CET)	Attendees start to arrive	
(2:50 pm CET)	Platform and webinar dynamics slide & instructions	
3:00 pm CET	Workshop welcome	Katharina Hartmann (COVAX) Daniel Brousseau (COVAX)
3:00 pm CET	Introduction	Rogério Gaspar (WHO) Jakob Cramer (COVAX)
3:10 pm CET	Regulators' Experience and Expectations	
	Presenters: <ul style="list-style-type: none"> • Petra Doerr (WHO) • Emil Cochino (EMA) • Helaine Carneiro Capucho (Brazil) • Juan Roldan (Chile) • Mojisola Christianah Adeyeye (Nigeria) Joint Q&A	Moderator: Daniel Brousseau (COVAX) Q&A curator: Gabrielle Breugelmans (COVAX)
3:40 pm CET	Industry Experience & Perspective	
	Presenters: <ul style="list-style-type: none"> • Sarah Frise (AstraZeneca) • Jamie Wilkins (Pfizer) • Marc Ceuppens (J&J) • Polina Dombure (Gamelaya, Inpharmatis) • Jiayi Wang (Sinovac) 	Moderator: Katharina Hartmann (COVAX) Q&A curator: Gabrielle Breugelmans (COVAX)
4:10 pm CET	Round table	
	Panelists: <ul style="list-style-type: none"> • Petra Doerr (WHO) • Shanthi Pal (WHO) • Nora Dellepiane (former WHO PQ) • Emil Cochino (EMA) • Helaine Carneiro Capucho (Brazil) • Juan Roldan (Chile) • Mojisola Christianah Adeyeye (Nigeria) • Corinne Jouquelet-Royer (IFPMA) • Alexander Precioso (DCVMN) 	Moderator: Katharina Hartmann (COVAX) Q&A curator: Gabrielle Breugelmans (COVAX)
4:50 pm CET	Summary and Closure	Shanti Pal (WHO) Jakob Cramer (COVAX)
5:00 pm CET	End of meeting	

Welcome

Dr Katharina Hartmann and Dr Daniel Brasseur, COVAX, welcomed participants to the workshop. The aim of the workshop was to provide a platform to discuss, exchange, and share expectations regarding requirements as well as experiences and perspectives related to pharmacovigilance planning and risk management strategies. Specific objectives included:

- To inform COVID-19 vaccine developers and MAHs about the expectations of different regulatory agencies regarding pharmacovigilance planning, and to share experiences in assessing COVID-19 vaccine files and post-approval safety surveillance as well as challenges with routine/expected pharmacovigilance activities.
- To share experiences in obtaining RMP approval and post-approval challenges in implementation.
- To develop consensus on how to bridge expectations and “real world experience”, and how to improve efficiency and effectiveness of pharmacovigilance activities in the context of a pandemic.

Introduction

Dr Rogério Gaspar, WHO, and Dr Jakob Cramer, Coalition for Epidemic Preparedness Innovations (CEPI), set the context for the workshop.

Key points included:

- Conventional processes developed in a non-pandemic situation are now being used to deal with a pandemic and there is a need to align non-integrated processes in a comprehensive format. This is a challenge for all professionals involved (developers, regulatory agencies, institutions such as WHO etc.). Concepts from the past are being challenged, adapted, and deployed, but at the same time it is important to ensure that quality, safety, and efficacy are not compromised at any point.
- Lessons learnt from RMPs for the regulatory submission of first-generation vaccines will be important for those developing late-stage vaccines for example against variants. However, current discussions on strain changes, risk from variants, need for other platforms, and monovalent versus multivalent vaccines also need to be integrated.
- Risk management planning needs to integrate all current developments/discussions in a comprehensive, convergent format that allows for safe use of vaccines. It also needs collaboration between different regulatory authorities from regions and countries across the world.
- Safety surveillance, pharmacovigilance, and risk management planning are key post-vaccine rollout activities as very rare safety signals will not be detected pre-licensure during clinical development.
- RMPs are required by certain regulatory agencies but also for WHO prequalification.
- In a pandemic context it is important to harmonise global safety surveillance and RMP activities and to contribute respective data across platform technologies.

Regulators' experience and expectations

World Health Organization

Dr Petra Doerr summarised the WHO experience with COVID-19 vaccine safety planning.

Summary points included:

- The WHO has published WHO Good Reliance Practices which aims to highlight the importance of international cooperation to ensure the safety, quality, and efficacy/performance of locally used medical products and to make best use of available resources and expertise, avoid duplication, and concentrate regulatory efforts and resources where they are most needed.
- The WHO Good Reliance Practices document includes regulatory oversight of all medical products (i.e., medicines, vaccines, medical devices, blood and blood products) and addresses all regulatory functions as defined in the Global Benchmarking Tool.
- This high-level document ([9789240020900-eng.pdf \(who.int\)](#)) will be complemented in a second step by an interactive repository of practical examples of reliance and questions and answers documents.
- Reliance is the act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information in reaching its own decision.
- The following principles have been defined in the WHO Good Reliance Practices document: universality, sovereignty of decision-making, transparency, respect of national/regional legal basis, consistency, and competency.
- The application of reliance in Public Health Emergencies includes for authorisation, batch release, and vigilance.

European Medicines Agency

Dr Emil Cochino discussed EMA requirements for products authorised in the EU and experiences thus far with the first four full authorisations of COVID-19 vaccines and ongoing procedures.

Summary points included:

- EMA guidance is based on EU Good Pharmacovigilance Practices which includes specific recommendations on risk management for vaccines, biologicals, etc. In addition, coreRMP19 guidance, which covers additional topics relevant to COVID-19 vaccines, has been developed and is now in the public domain.
- coreRMP19 content includes for example list of adverse events of special interest (AESI) and how the follow-up of these events will happen, content and periodicity of monthly summary safety reports, traceability, and minimum requirements for post-authorisation safety studies (PASS).
- EMA provides early support for vaccine developers in terms of scientific advice and a dedicated Task Force (COVID-ETF).
- Rapid approval processes in the EU include rolling reviews, followed by an application for conditional marketing authorisation, the EMA opinion, and subsequent conditional marketing authorisation from the European Commission.
- EMA has improved their RMP assessment process based on their recent experiences.
- The COVID-19 pandemic has resulted in severe disruption to the work environment, travel, and medical access which has brought challenges for MAH staff fulfilling pharmacovigilance obligations; however, the EU Network has remained united and flexible. There has been frequent and early dialogue with vaccine manufacturers, and unprecedented transparency measures have been put in place to enhance the communication and ensure confidence in the vaccine and assessment process.
- EMA has gained some experience of post-marketing data assessment through the monthly summary safety report and has raised signals, identified topics for further investigation, and provided a forum for discussion of emerging safety concerns.

ANVISA, Brazil

Dr Helaine Carneiro Capucho summarised the Brazilian experience with regards to pharmacovigilance.

Summary points included:

- Pharmacovigilance of COVID-19 vaccines is challenging as COVID-19 is a new disease and technology has been developed in record time. There is a greater need for surveillance given the short life cycle for vaccine development and the quick and large-scale distribution.
- Four COVID-19 vaccines have at present been authorised by ANVISA; two emergency use authorisation (EUA; Sinovac/Butantan, Jansen) and two registration (Oxford/AstraZeneca/Fiocruz, Pfizer).
- In the pre-marketing phase of the Brazilian pharmacovigilance process, RMPs sent by companies that want to register their product in Brazil are evaluated. The RMP is an important document in the submission dossier for the registration process.
- In the post-marketing phase of the Brazilian pharmacovigilance process, the executive summary of adverse events, benefit-risk assessment reports, and notifications are evaluated, and signal detections and international alerts issued by other institutions monitored.
- There is no single system for the notification of adverse post-immunisation events in Brazil. Health professionals can report directly to the Ministry of Health, and companies directly to ANVISA.
- Communicating risks is considered important and ANVISA have thus published several documents to guide the general public and health professionals with a focus on patient safety and clarifying doubts about vaccines risks.
- The challenge is to integrate systems used in Brazil to analyse causality quickly and communicate risks without reducing adherence to vaccination. However, with challenge comes opportunity. The need for greater vigilance is a global movement and there is increased use of information technology, greater involvement of the population, and more dissemination of health information.

Instituto de Salud Publica de Chile, Chile

Dr Juan Roldan discussed experiences with pharmacovigilance planning/risk management plans and engaging stakeholders in Chile.

Summary points included:

- COVID-19 vaccines in Chile have been authorised for provisional use (similar to emergency authorisation in other countries). This mechanism authorises an entity (i.e., company or government) to import a specific quantity of product if shortage of supplies can be demonstrated, which is the case in the COVID-19 pandemic. The government of Chile is the only provider of COVID-19 vaccine for the population.
- The meetings to evaluate the authorisations of COVID-19 vaccines were streamed for transparency and to generate trust in the population. Pharmacovigilance was an important component of these evaluations.
- Pharmacovigilance activities for COVID-19 vaccines includes several activities: evaluation of monthly simplified periodic reports; RMP evaluation; pharmacovigilance planning; publication of informative sheets, statistical reports, and information notes;

survey on vaccinated people; AEFI reception; AEFI evaluation and follow-up; and feedback of more significant cases.

- Validated information in the form of technical datasheets, informative notes, and a guide for the pharmacovigilance process in pandemic times for health professionals has been disseminated to counteract the circulation of misinformation via social networks.
- The Chilean pharmacovigilance strategy for COVID-19 vaccines has strengths, limitations, and challenges.

National Agency for Food and Drug Administration and Control, Nigeria

Professor Mojisola Christianah Adeyeye presented the Nigerian perspective on risk management planning.

Summary points included:

- The structure of the RMP in Nigeria includes a product overview, safety specification, pharmacovigilance plan, plans for PASS, risk minimisation measures (including evaluation of the effectiveness of risk minimisation measures), summary of RMP, and annexes.
- There is need to focus pharmacovigilance planning in the following areas: specific activities for collection, compilation, assessment, and reporting of AEFI to the NRA; monthly safety summaries in addition to routine periodic safety update reports (PSURs); PASS; the establishment of sentinel sites, as part of active surveillance system for COVID-19 vaccine safety; and provision of educational materials and implementation of technology-driven tracking system of vaccine administered (e.g., barcode stickers).
- PASS should be considered and reflected in the RMP if planned clinical trials and routine activities do not provide enough information for the complete characterisation of important identified and potential risks.
- Examples of NAFDAC activities include general awareness education on use of COVID-related commodities, debunking unproven claims for COVID-19 cures, guidance for some regulatory processes and outcomes such as COVID-related clinical trials, training of Traceability Technical Working Group, development of in-country track and trace plan, Vaccine Committee review of COVID vaccine dossiers, and monitoring of AEFIs.
- Capacity strengthening, electronic data collection tools, online platforms for direct adverse drug reactions reporting alongside local, national, and international stakeholder engagement is critical towards strengthening systems for pharmacovigilance in Nigeria.
- Safety monitoring of COVID-19 vaccines is key to characterising the full safety profile of the vaccine.
- Collaboration between the NRA and vaccine manufacturer/MAHs is critical.
- Adequate minimisation measures put in place in the RMP should be well implemented in conjunction with the NRA oversight.

Industry experience and perspective

AstraZeneca and Pfizer

Dr Sarah Frise, Astra Zeneca, and Dr Jamie Wilkins, Pfizer, shared their experience and perspective of filing an RMP with the WHO.

Key points included:

- Prior to filing an RMP with WHO, both companies had substantial experience with the large regulators. Both Pfizer and AstraZeneca have filed RMPs with the Medicines and

Healthcare Products Regulatory Agency and EMA, and these included additional items such as routine descriptive pharmacovigilance, traceability, complex signal detection methods, monthly summary reports, and numerous PASS studies.

- A pharmacovigilance plan, which is normally optional, was a requirement for Pfizer's vaccine application to the US Food and Drug Administration.
- The RMP for submission to WHO was based on the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2) template plus a regional annex to address any specific requests from the WHO.
- Development of a core organisational risk management stance is considered strategically important by both companies in terms of such a large-scale regulatory process.
- The core organisational risk management stance includes a core organisational stance on information contained within major regulatory risk management documents and the organisational position on elements to include in core risk management documents versus appropriate information for an addendum and provides the ability to quickly mobilise for submissions.
- Both challenges (e.g., unknown requirements, implementation of pharmacovigilance in LMICs) and opportunities (e.g., innovative methods for implementing requirements) have arisen from the pandemic situation.

Janssen

Dr Marc Ceuppens shared the Janssen experience in terms of risk management planning.

Key points included:

- Janssen uses a core risk management plan based on the European template, which is widely acceptable in other countries. The Core RMP version 2.0 also includes additional guidance provided by EMA as part of the strengthening of RMPs for COVID-19 vaccines. This core RMP has supported the development of an EU-RMP, US pharmacovigilance plan, and meet local country requirements.
- The development of the RMP as well as vaccine was accelerated. The RMP was developed in parallel with Phase 3 trial conduct.
- Challenges faced during RMP development include the need for product specific exposure data to enable evaluation of any signal that arises, need for reliable background incidence for AESI, meeting multiple country expectations, PASS set-up and roll-out, and assessing effectiveness risk minimisation tools (i.e., monitoring and reporting AEFIs through local surveillance).

Gamelaya/Inpharmatis

Dr Polina Dombure, Inpharmatis, discussed the success and challenges of RMP preparation for Sputnik V (Gam-Covid-Vac).

Key points included:

- Sputnik V is a collaboration between The Gameleya National Center of Epidemiology and Microbiology (i.e., vaccine developer), Russian Direct Investment Fund (i.e., authorised for production and distribution outside of Russia), and Inpharmatis (i.e., global pharmacovigilance for Sputnik V).
- Unlike other companies represented at this workshop (i.e., Pfizer, Astra Zeneca), Inpharmatis did not have global pharmacovigilance operations already in place and had to set up a global pharmacovigilance system and implement it compliantly.
- Interim analyses of the Phase 3 trial in adults showed that the Sputnik V vaccine is 91.6% effective (21 days after the first dose) in preventing symptomatic COVID-19 cases,

induces a robust humoral and cellular immune response, and has a good safety profile. More than eight million doses of Sputnik V have been administered to the public, and the vaccine has EUA in 62 countries.

- RMP development was associated with the following challenges: market entry from the Russian Federation; Eurasian Union GVP requirements are very similar to European GVP requirements; numerous ongoing clinical trials around the world, including with another vaccine; numerous EUAs in the world; numerous Contract Manufacturing Organisations (CMOs) around the world for Sputnik V; data derived from other vaccines / Pharmacovigilance Risk Assessment Committee (PRAC) recommendations should be considered (e.g., thrombosis events); and new information received daily from the market requiring urgent processing, centralisation, analysis, and conclusions requiring urgent RMP update, and different RMP or RMP-like expectations (format, frequency) globally.
- The RMP for COVID-19 vaccines is a “live” document that must be updated on an almost monthly basis.
- Global RMP must be managed according to the highest regulatory standards despite possible deviations in expectations of various regulators.
- Safety profile and measures for risk management must be reviewed on a daily basis and the RMP is not the best document for the management of this task.
- Guidance from EMA, WHO, and other regulators is highly appreciated.
- Harmonisation of safety data with other vaccine manufacturers is needed.

Sinovac

Dr Jiayi Wang shared the Sinovac experience of risk management planning.

Key points included:

- Sinovac COVID-19 vaccine obtained Conditional Marketing Authorization in China on 5th February 2021 and has subsequently obtained EUA in many countries/regions worldwide.
- Sinovac is in the process of answering the Second List of Questions focusing on RMP for Emergency Use Listing (EUL).
- Sinovac has submitted a RMP to EMA to obtain an EU marketing authorisation.
- The main post-approval challenge is AEFI collection in countries/regions outside China, particularly in those with an immature pharmacovigilance system.

Round table

Petra Doerr (WHO), Shanthi Pal (WHO), Emil Cochino (EMA), Helaine Carneiro Capucho (Brazil), Juan Roldan (Chile), Mojisola Christianah Adeyeye (Nigeria), Corinne Jouquelet-Royer (IFPMA), Alexander Precioso (DCVMN)

- *Are there any examples or success stories of how focus on reliance principles as is related to ongoing vigilance is happening in practice, maybe helping to reduce a number of similar safety questions or requests to a single MAH?*
 - An RMP assessment was facilitated by the reliance of the NRAs on the EUL assessment of the RMP and the issuing of EUA of the COVID-19 vaccines. In addition, this was facilitated by explanatory sessions (organised by the WHO headquarters in collaboration with the regional offices) with the NRAs to explain the decision making around the EUL including the RMP. The annex of the Good Reliance Practice document includes further examples, including from pharmacovigilance.

- *Is there a consideration by regulators in the international arena to accept the summary periodic safety update reports in the form of the monthly safety reports requested by the EMA?*
 - Defining one single template for monthly summary safety reports is difficult as the requirements have evolved from month to month and from one product to another. EMA has sections and minimum requirements described in general terms and this will be updated in version 2 of the core RMP guidance; however, this is still evolving. Thus, having an EU baseline requirement that others around the world could align to is unlikely.
- *In LMICs where GAVI will be distributing the vaccines and safety data will be collected by the WHO, what is the mechanism of the safety data collection if a sponsor proposes to use specific questionnaires for enhanced data collection of AESIs from spontaneous reports? WHO does mention forms for data collection in the post-marketing setting – can the clinical staff be trained on the additional sponsor-specific AESI questionnaires as well?*
 - WHO has developed three options to aid data collection on events of special interest, including a protocol/template for cohort event monitoring, a protocol/template for sentinel site based surveillance (currently being considered to monitor thrombosis with thrombocytopenia syndrome [TTS] with the adenovirus vector vaccine platform), and support for a data repository.
- *Can COVAX and WHO provide leadership to ensure global deployment of a universal pharmacovigilance system accompanying vaccine development?*
 - The WHO guidance contained in the global vaccine safety surveillance manual is underpinned by the 3S (Smart Safety Surveillance) principles.
 - There is a general approach to strengthening regulatory systems that is applied by WHO using the global benchmarking tool, which includes vigilance as one of the regulatory functions.
- *Is there a difference between the Sinovac and Sinopharm vaccines?*
 - These are both vero cell inactivated COVID-19 vaccines but from different Chinese companies.
- *Have there been any cases of TTS among the eight million people who have received the Gameleya Sputnik V vaccine?*
 - WHO is not aware of any such cases but suggested confirming with colleagues from the Gameleya Institute.
- *To what extent will artificial intelligence be used to screen for signals?*
 - The COVID-19 pandemic has ignited the need for innovation on an unprecedented scale. Thus, Pfizer has ongoing artificial intelligence initiatives and is developing and actively deploying other technological approaches.
- *How well are efforts to ensure traceability being implemented in the EU or elsewhere?*
 - Nigeria has successfully used track and trace to monitor the COVID-19 vaccine supply chain and distribution within the country.
 - Some European Member States are using electronic means to scan codes and add data to the patient records, which appears to be working well. Misspelling of the brand name appears in the vigilance data however this has not had a significant

impact. Very few (<10%) batch numbers provided with ADRs are valid batch numbers.

Summary and closure

Dr Shanti Pal, WHO, and Dr Jakob Cramer, CEPI, thanked attendees for their participation in the workshop.

Closing remarks included:

- COVID-19 has brought about significant challenges, but also opportunities in that numerous different countries across regions and settings are coming together to address common challenges and for collective learning.
- A major challenge is for developers in LMICs to meet their pharmacovigilance obligations. Regulators in LMIC are also challenged by not having the resources to guide or oversee the obligations from the developers in their setting. It is important to assess how the relevant stakeholders can be helped and what kind of resources and capacity building would be needed.
- It is important to maintain confidence and trust in vaccines.
- The need for continued discussions with WHO was highlighted.