

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

**ENGAGING WITH THE
PHARMACEUTICAL
INDUSTRY FOR COVID-19
VACCINE SAFETY
SURVEILLANCE**

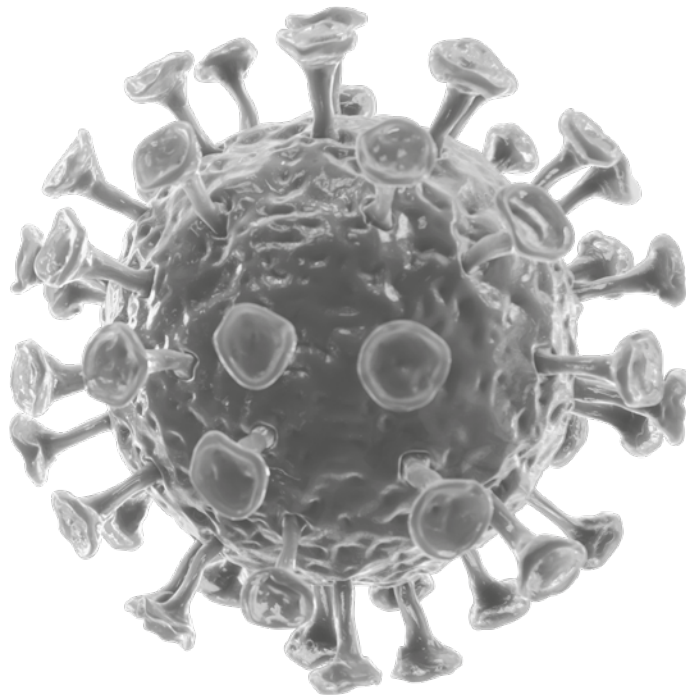


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Contents

Key points	iv
1. Introduction	1
2. Legal provisions and guidelines regarding COVID-19 vaccine safety	1
3. Risk management plans	3
3.1 Format and components of RMPs for COVID-19 vaccines	3
3.2 Routine pharmacovigilance plan as part of the RMP	4
3.3 Additional pharmacovigilance activities	5
3.4 Specific considerations under different scenarios	5
Scenario 1: COVID-19 vaccines submitted for WHO prequalification or emergency use listing	5
Scenario 2: COVID-19 vaccines not submitted for WHO prequalification or emergency use listing	6
4. Oversight	7
5. Data sharing	8
6. Training	9
7. Funding	10

Key points

- The pharmaceutical industry plays a critical role in the accelerated development of vaccines and therapeutics
- They also have an essential role in verifying the safety of COVID-19 vaccines through vaccine safety surveillance activities described in risk management plans for licensed vaccines particularly via periodic safety update reports
- Vaccine manufacturers are encouraged to adopt existing formats for risk management plans, which contain essential elements, such as a safety specification section, pharmacovigilance activities, risk minimization activities, and evaluation of the effectiveness of the risk minimization measures
- Both routine and additional pharmacovigilance activities, which are integrated in the RMP, contribute to the maintenance of a positive benefit-risk balance for a vaccine
- There should be global, regional and national oversight of the RMPs for COVID-19 vaccines
- National regulatory agencies (NRAs) and the WHO prequalification team should consider making data sharing a condition of marketing authorization or prequalification for COVID-19 vaccines during the pandemic, particularly in countries
- Effective data flow should be established between NRAs or the WHO prequalification team and the vaccine manufacturer while respecting data security and patient privacy
- Training to enhance pharmacovigilance competencies and to enable regional coordination should be coordinated and existing training materials and programmes should be leveraged as much as possible

01 Introduction

The private sector plays an essential role in the development and introduction of vaccines, as well as in on-going pharmacovigilance activities to ensure efficacy, quality and safety throughout the vaccines' life cycle. Under the current pandemic, it plays a critical role in accelerated development of vaccines and therapeutics. Although diverse players make up the private sector, this module will focus on the vaccine manufacturers¹ and their role in ensuring the safety of COVID-19 vaccines through pharmacovigilance activities, as described in risk management plans and more specifically in providing periodic safety update reports (PSURs).

02 Legal provisions and guidelines regarding COVID-19 vaccine safety

In countries where the regulatory authority is a member² or an observer of the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (ICH), ICH technical guidelines and requirements will guide the vaccine manufacturers in meeting their obligations for COVID-19 vaccine registration and continued monitoring of safety when the vaccine is on the market. Two ICH guidelines set out common standards for pharmacovigilance activities to ensure the safety of new drugs and those already on the market: *ICH E2E Pharmacovigilance Planning*,³ and *ICH E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)*.⁴

¹ For the purpose of this document, manufacturer also means marketing authorization holder.

² ICH Members & Observers. Available at: <https://www.ich.org/page/members-observers>. Accessed 25 October 2020.

³ ICH E2E Guideline: Pharmacovigilance Planning 2004. Available at: https://database.ich.org/sites/default/files/E2E_Guideline.pdf. Accessed 25 October 2020.

⁴ ICH E2C(R2) Guideline: Periodic Benefit-Risk Evaluation Report (PBRER) 2012. Available from: https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf. Accessed 25 October 2020.

All national regulatory authorities (NRAs) are encouraged to follow ICH guidelines. However, in settings where ICH guidelines have not yet been implemented, existing legislation governing pharmacovigilance should be interpreted under the COVID-19 pandemic situation, to provide clear guidance and directives on pharmacovigilance requirements to the vaccine manufacturers. A risk management plan (RMP) is a key document in the marketing authorization submission dossier. The RMP describes the current knowledge about the benefits and the risks of the vaccine or medicinal product, providing key information on plans for studies and other activities to gain more data on missing information, more knowledge about the safety profile of the product, and plans for risks minimization. Depending on their complexity, some RMPs may require special measures for their implementation, especially in low- and middle-income countries (LMICs). Hence there is a need to coordinate efforts by stakeholders and partners at national, regional, and global levels and the following key considerations should be included in specific directives and guidelines for COVID-19 vaccine safety:

- specific conditions when relevant authorities might request the vaccine manufacturer to provide a regional annex to the RMP, to reflect local situations such as epidemiological characteristics, medical practice, ethnicity, limitations of logistics and regional health and regulatory systems;
- requirements for PSURs/periodic benefit risk evaluation reports (PBRERs);
- specifications of routine and additional pharmacovigilance activities to be carried out during the pandemic as well as the periodicity for updating safety information. These activities may include:
 - monthly safety summaries in addition to routine PSURs;
 - post-authorization safety studies;
 - the establishment of sentinel sites, as part of an active surveillance system for COVID-19 vaccine safety; and
 - provision of educational materials and implementation of tracking system of vaccine administered e.g., barcode stickers.
- requirements for the vaccine manufacturer launching a COVID-19 vaccine in a country to designate a qualified person responsible for pharmacovigilance (QPPV) (or a global QPPV for international vaccine manufacturers) for monitoring its safety; and to clearly present the contact information and qualifications of the QPPV.

Risk management plans

The short timelines under which COVID-19 vaccines are being developed and ultimately deployed present challenges for guaranteeing their safety. Lessons learnt and best practices from past pandemics, such as those from 2009 H1N1 pandemic⁵, should be used to guide current procedures for the safety of COVID-19 vaccines.

As with the H1N1 vaccines, more information about the immunogenicity, effectiveness, and safety of COVID-19 vaccines will only become available during their use in the field. Hence, the risk management plan for COVID-19 vaccines will be an evolving document and should be amended when new significant information, such as a change in the profile of adverse events, results from safety studies, changes in benefit-risk balance, becomes available.

3.1 Format and components of RMPs for COVID-19 vaccines

The vaccine manufacturer is encouraged to adopt existing formats, such as the European Union RMP format, which contain essential elements such as a safety specification section, pharmacovigilance activities, risk minimization activities, and evaluation of the effectiveness of the risk minimization measures.⁶ RMPs in alternative formats, such as a global or core RMP, are also acceptable provided they contain the essential elements mentioned above.

In addition, when requested, a region-specific annex (referred to as a regional annex hereafter) to the core RMP that takes into consideration additional context specific to the region where the vaccines are to be deployed, should be provided. Similar annexes are routinely implemented by certain regulatory authorities to ensure adaptation to local context, e.g. Australia-specific annex required by the Australian Government Therapeutic Goods Administration (TGA)⁷. In general, the regional annex for COVID-19 vaccines in the RMPs should highlight any differences in safety concerns in the regions where the COVID-19 vaccines are launched, e.g., differences in the frequency, severity or nature of safety concerns, resulting from differences in the epidemiology of COVID-19 and the target population. It should also confirm that the pharmacovigilance (PV) and risk minimization activities are compatible with the safety concerns specified.

⁵ CHMP Recommendations for the pharmacovigilance plan as part of the risk management plan to be submitted with the marketing authorisation application for a pandemic influenza vaccine adopted by CHMP in November 2006. Revision 1.1 adopted by CHMP on 24 September 2009 (EMA/359381/2009).

⁶ Guideline on good pharmacovigilance practices (GVP) Module V – risk management systems (Rev 2). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf. Accessed 25 October 2020.

⁷ Risk management plan for medicines and biologicals– Australia-Specific Annex. Available from: <https://www.tga.gov.au/book-page/risk-management-plan-australia-specific-annex>. Accessed 4 October 2020.

3.2 Routine pharmacovigilance plan as part of the RMP

Both routine and additional PV activities contribute to the maintenance of a positive benefit-risk balance for a vaccine. They form part of the RMP, along with further PV measures that are appropriate for the evaluation of efficacy and safety of vaccines.

For COVID-19 vaccines, as part of routine PV activities, the vaccine manufacturer should describe in the RMP:

- specific activities for the collection, compilation, assessment, and reporting of adverse reactions to the NRA
- format, content and periodicity of the PSURs/PBRERs
- other requirements defined in the regional annex.

Challenges related to restrictions during the pandemic (e.g. due to social distancing or limited medical resources) or to the volume of reports of adverse events following immunization (AEFIs) to be processed (e.g., associated with a mass vaccination campaign) should be considered and reflected in the planning document. The reporting patterns following mass vaccination campaigns during a pandemic are likely to differ qualitatively from routine reporting, and this needs to be taken into account when performing the analyses.

During the pandemic, the usual 6-month reporting cycle may be too long for the assessment of COVID-19 vaccine safety because it is expected that there will be high levels of exposure within a short period of time. Therefore, it is recommended that monthly safety summaries are provided focusing on adverse events of special interest (AESIs), at a minimum. The monthly safety summaries are intended to complement the regular 6-monthly PSURs for COVID-19 vaccines during the pandemic period and should include:

- a summary of vaccine distribution (number of doses, locality of distribution, etc.);
- global numbers (with country of origin) and analyses of AESIs reported in individuals following immunization, following the Brighton Collaboration recommendations for COVID-19 vaccines;⁸ and
- numbers of deaths and relevant case histories, including observed over expected analyses.

In addition to the monthly safety summaries, a 6-monthly cumulative PSUR/PBRER should be submitted following the PBRER ICH E2C (R2) format³. This provides a cumulative overview of all available information which provides the vaccine's overall benefit-risk profile. Following the first 6-month report, and as experience with the vaccine evolves, the periodicity of the monthly summaries and of the PSURs/PBRERs should be reviewed by the regulator.

⁸ Brighton Collaboration Safety Platform for Emergency vAccines (SPEAC) Project (WHO slide deck presentation by Robert T Chen, Scientific Director Brighton Collaboration). Available from: https://www.dcvmn.net/IMG/pdf/8_cepispeac_presentation_bob_chen.pdf. Accessed 7 October 2020.

3.3 Additional pharmacovigilance activities

If ongoing or planned clinical trials or routine activities will not provide sufficient data for the complete characterization of important identified and potential risks, then additional PV activities, such as post-authorization safety studies (PASSs) should be considered and reflected in the RMP ([Guideline on good pharmacovigilance practices \(GVP\) Module V; Risk management plan for medicines and biologicals– Australia](#)). If an observational study is proposed, it should be on a cohort of individuals who have comparable ethnic and geographic origins and appropriate study protocols that are specifically designed for LMICs should be used.

The pandemic COVID-19 pharmacovigilance plan will terminate when national competent authorities decide that it is no longer necessary.

3.4 Specific considerations under different scenarios

The NRA should provide clear guidance on PV requirements for different scenarios, as many different COVID-19 vaccines are likely to be introduced to the market, through different channels. For example, the NRA should specify conditions and types of AEFIs and AESIs that should be included in the monthly safety summaries for each vaccine type. Penalties and sanctions for non-compliance should also be clearly defined and communicated. Two possible scenarios, depending on if the vaccine has been submitted for WHO prequalification (PQ) or emergency use listing (EUL) are described below.

Scenario 1: COVID-19 vaccines submitted for WHO prequalification or emergency use listing

Vaccines submitted for WHO PQ or EUL are likely to be developed by established companies who have submitted well-defined RMPs for stringent review by regulatory authorities. However, the vaccines can be introduced outside of the country where they were originally authorized, in countries where additional activities may be required. In this case, WHO PQ could request that an annex is included in the original RMP to cover any additional considerations and PV activities in the country where the vaccine will be introduced. As far as possible, a regional annex will be the preferred option, valid for all countries in a specific region (e.g., for the WHO African region).

The details of the monthly safety summaries and any PASS will be agreed as part of the WHO PQ / EUL procedure. The vaccine manufacturer will be responsible for compiling and submitting the monthly summaries and PSURs/PBRER to the local competent authority and WHO PQ.

Planned PASSs should be carried out by the vaccine manufacturer or its local representatives or distributors. Ideally, multi-country collaborative PASSs could be considered, with the PASS implemented in selected, representative sites across a few countries in a region. Study

sites should be selected in countries with the best capacity,⁹ or with previous experience of participating in PASSs.

When available, PASS protocols such as those developed by WHO, should be used when such studies are to be conducted in LMICs.

Scenario 2: COVID-19 vaccines not submitted for WHO prequalification or emergency use listing

This scenario may include smaller companies that implement COVID-19 vaccines in LMICs. In this case, the vaccines may not have undergone stringent review for authorization by a regulatory authority. In this scenario, regional and coordinated approaches will be critical to ensure the safety monitoring of these COVID-19 vaccines. Additional considerations in this scenario include the following:

- the smaller vaccine manufacturers may consider collaborating with other manufacturers to prepare a common RMP for the region where the vaccine will be introduced;
- regional or global cooperation and coordination should be adopted, wherever feasible, and may include:
 - joint review of RMPs through regulatory reliance or works-sharing (more information in the [regulatory reliance module](#));
 - leveraging existing regional networks, such as, the African Vaccine Regulatory Forum (AVAREF), the Western Pacific Regional Alliance of NRAs (WPRA) and the Pan American Network for Drug Regulatory Harmonization (PANDRH);
 - supporting multi-country safety studies to evaluate the real-world safety profile of the vaccines, especially in populations not represented in clinical trials, such as children and pregnant women;
- training to be provided to the smaller vaccine manufacturers on:
 - common core RMP components and any region-specific requirements;
 - regulatory obligations for vaccine PV for the region, including review of PSURs and analysis of AEFIs.

⁹ WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. Available from: http://www.who.int/medicines/regulation/benchmarking_tool/en/. Accessed 25 October 2020.

04 Oversight

Oversight should be at different levels:

- at the national level, the NRA is responsible for providing clear guidance on the PV requirements for COVID-19 vaccines as described previously and should also:
 - provide input to WHO PQ on RMP assessments, to help define special considerations or annexes for the RMPs;
 - contribute to establishing criteria for PASS study site selection;
 - provide oversight for study implementation, including study sites inspections;
 - provide clear guidance to the vaccine manufacturer on requirements for routine communication of study findings, monthly safety summaries, and ad hoc communications for any urgent emerging issues;
 - implement a coordinated routine communication plan with stakeholders such as the national immunization programme or expanded programme for immunization (NIP/EPI) and the vaccine manufacturer; and
 - ensure that a national committee is ready to review any national PASS data as they become available.
- at the regional level, a regional review committee with scientific and regulatory expertise should be established to:
 - participate in WHO PQ assessments of RMP for COVID-19 vaccines, to bring the regional-specific perspectives to the review;
 - advise when a regional annex to the RMP would be justified;
 - develop and communicate clear guidance on criteria for study site selection in multi-country collaborative PASSs in the region for vaccine manufacturers;
 - review results from multi-country collaborative PASSs in the region;
- at the international level, an international review committee should be established to:
 - review PASS protocols;
 - review and analyse multi-country study data across continents;
 - provide support to the WHO PQ team for the analyses of RMPs and PSURs/PBRERs.

05

Data sharing

Data sharing is essential for generating reliable evidence on the safety of COVID-19 vaccines which will facilitate timely regulatory actions and effective public health interventions. Spontaneous AEFI reporting systems, active surveillance systems for AESIs, and PASSs are all important sources of data. To be successful at sharing data in a timely manner, while respecting data security and patient privacy, close collaboration between national stakeholders, such as the NRA and the EPI or NIP is critical.

Effective data flow needs to be established between the NRA and the WHO global database of individual case safety reports, [Vigibase](#), and between the NRA and the vaccine manufacturer. In countries where current legislation does not mandate data sharing, NRAs should consider making data sharing a condition of marketing authorization. Alternatively, a data sharing agreement or memorandum of understanding could be established between the vaccine manufacturer and the NRA. Similarly, the WHO PQ programme should consider making data sharing a condition of inclusion of a vaccine on the EUL.

Data sharing and data sharing platforms are discussed in detail in the [module on data sharing](#). In the context of coordinated regional review of RMPs and evaluation of multi-country PASSs, a data-sharing platform is critical for:

- enabling data pooling from multi-country sites to facilitate meaningful interpretation;
- enabling review committees to review PASS outcomes; and
- identifying patterns and safety issues of regional importance.

Training

Many training needs to enhance pharmacovigilance competencies and to enable regional coordination have been identified:

Training needs	Training Target				Potential training providers
	<i>NRA/PV review staff</i>	<i>National AEFI Committee</i>	<i>Regional Review Committee</i>	<i>Vaccine manufacturer / subsidiary</i>	
Legislation and legal obligations for pharmacovigilance	✓			✓*	DCVMN*, IFPMA*, ISoP, NRA
RMP review: common core elements, regional annex, PSUR core elements	✓		✓		WHO, NRA
Ethics review of study protocols	✓	✓	✓		CIOMS, WHO
Review of safety study outcomes		✓	✓		WHO, GACVS, AACVS
Pharmacovigilance for vaccine safety	✓			✓*	DCVMN*, IFPMA*

* Training to manufacturer/subsidiary to be provided by DCVMN, IFPMA.

AACVS: African Advisory Committee on Vaccine Safety; CIOMS: Council for International Organizations of Medical Sciences; DCVMN: Developing Countries Vaccine Manufacturers Network; GACVS: Global Advisory Committee on Vaccine Safety; IFPMA: International Federation of Pharmaceutical Manufacturers and Associations; ISoP: International Society of Pharmacovigilance; NRA: national regulatory authority; WHO: World Health Organization

In LMICs, vaccine manufacturers may also require training to understand NRA's requirements and how to compile, summarize and analyse data from COVID-19 vaccine safety studies.

Coordination will be critical for the efficient provision of all levels of training. Existing training materials and programmes should be leveraged as much as possible. Stringent regulatory authorities can contribute their technical expertise to help LMICs strengthen their regulatory systems. It is equally critical to ensure that designated QPPVs and local subsidiaries of large vaccine manufacturers can set up efficient in-country PV systems. Existing networks, such as DCVMN (Developing Countries Vaccine Manufacturers Network) and IFPMA (International Federation of Pharmaceutical Manufacturers and Associations) could play a key role in coordinating and delivering training to the vaccine manufacturers in anticipation of the introduction of COVID-19 vaccines, as they have a good understanding of the needs and capacity of these companies.¹⁰

¹⁰ Hartmann K, Pagliusi S, Precioso A. Landscape analysis of pharmacovigilance and related practices among 34 vaccine manufacturers' from emerging countries. *Vaccine*. 2020;38(34):5490-7. doi: 10.1016/j.vaccine.2020.06.016.

07

Funding

Post-authorization safety studies, carried out by the vaccine manufactures, may be supported financially through COVAX, the vaccine pillar of the ACT Accelerator. Training could be co-funded by several stakeholders. GAVI, the Vaccine Alliance, and WHO could potentially provide funding to train the NRAs, with stringent regulatory authorities potentially providing technical expertise or financial support or both. Industry networks such as DCVMN and IFPMA should support the training needs of vaccine manufacturers by providing funding and scientific expertise. Funding needs for monitoring systems, and platforms for data sharing between the NRAs or the WHO PQ team and vaccine manufacturers at the regional level are discussed in the module on data sharing.

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