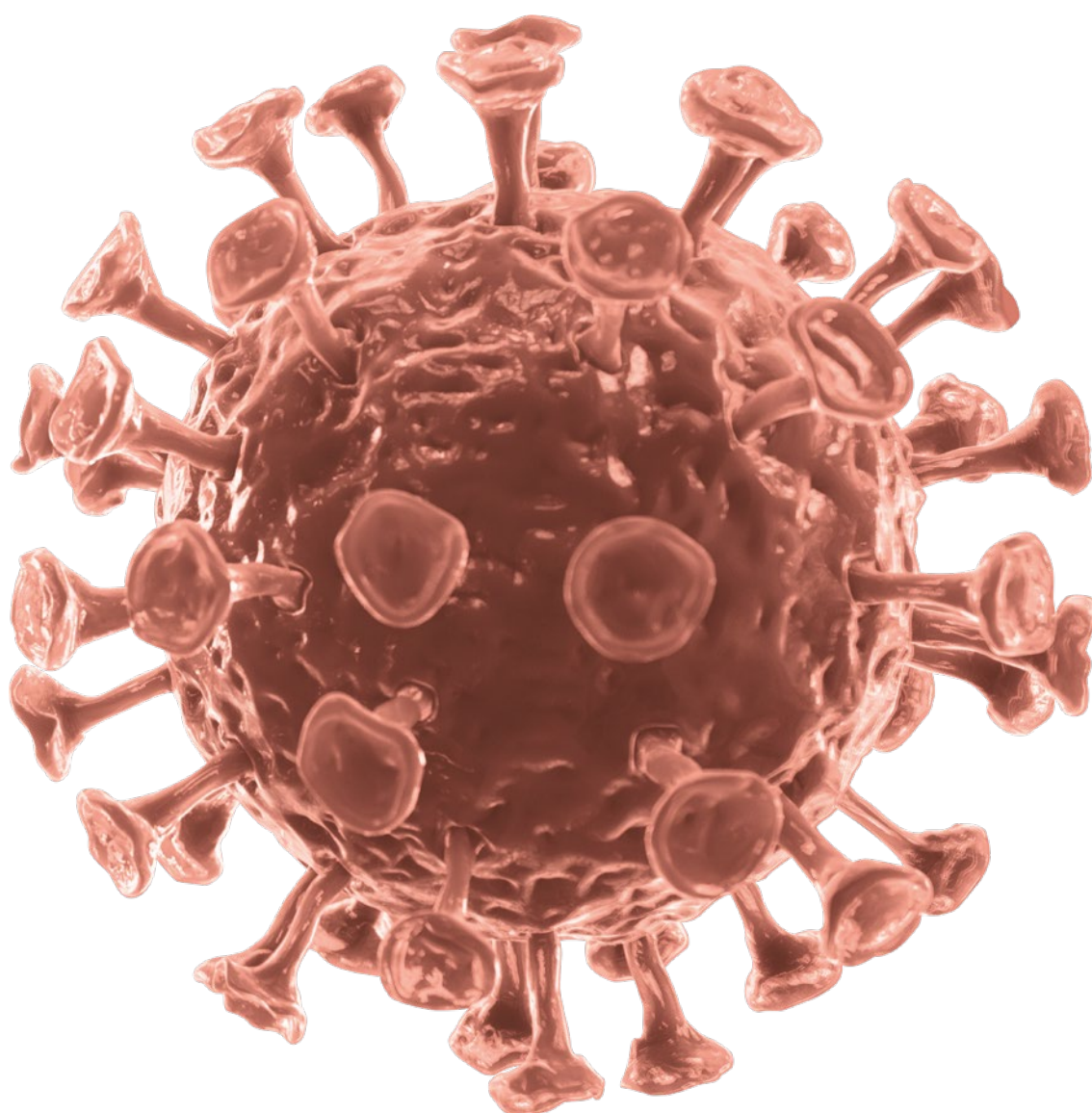


COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL

**REGULATORY RELIANCE
AND WORK-SHARING**

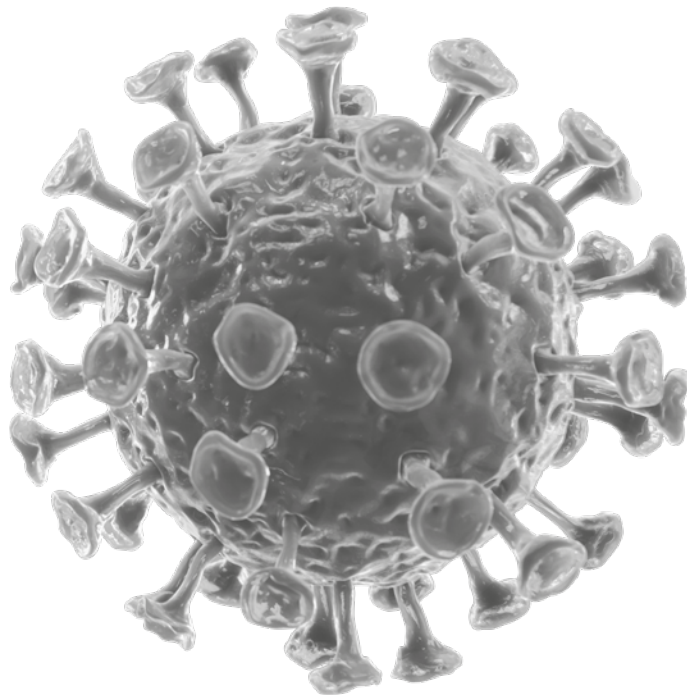


**World Health
Organization**

COVID-19 VACCINES:

**SAFETY
SURVEILLANCE
MANUAL**

**REGULATORY RELIANCE
AND WORK-SHARING**



**World Health
Organization**

Covid-19 vaccines: safety surveillance manual

ISBN 978-92-4-001828-0 (electronic version)

ISBN 978-92-4-001829-7 (print version)

© World Health Organization 2020

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (<http://www.wipo.int/amc/en/mediation/rules/>).

Suggested citation. Covid-19 vaccines: safety surveillance manual. Geneva: World Health Organization; 2020. Licence: [CC BY-NC-SA 3.0 IGO](#).

Cataloguing-in-Publication (CIP) data. CIP data are available at <http://apps.who.int/iris>.

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Design and Layout: Agence Gardeners

Contents

Key points	iv
1. Introduction	1
1.1 Definition of regulatory reliance	1
1.2 Definition of work-sharing	2
2. Examples of regulatory reliance in pharmacovigilance	3
2.1 Processes, tools, and methods	3
2.2 Product-specific activities	4
3. Regulatory reliance for COVID-19 vaccines	4
3.1 Pharmacovigilance for COVID-19 vaccines	5
3.1.1 Example 1: Review of risk management plans at regional and WHO prequalification levels	5
3.1.2 Example 2: Post-authorization safety study protocol template	6
3.1.3 Example 3: Regulatory review through work-sharing	6
3.1.4 Example 4: Pharmacovigilance inspections	6
3.2 Specific considerations under different scenarios for COVID-19 vaccine introduction	7
3.2.1 Scenario 1: First introduction of a new COVID-19 vaccine	7
3.2.2 Scenario 2: Introduction of a COVID-19 vaccine that has already been introduced elsewhere	8

Key points

- Levels of regulatory reliance between national regulatory authorities (NRAs) can range from independent decisions by NRAs (no reliance) to mutual recognition (full reliance).
- Work-sharing is a process by which NRAs of two or more jurisdictions share activities to accomplish specific regulatory tasks.
- Reliance and work-sharing are important for countries with limited regulatory capacity.
- Regulatory reliance can be used for various regulatory activities across the product life cycle, including post-authorization pharmacovigilance activities, and lead to increased efficiency and improvement to regulatory capacity.
- In the context of the current COVID-19 pandemic, regulatory reliance should be considered wherever possible, to improve regulatory efficiency, thereby facilitating timely access to COVID-19 vaccines, as well as effective monitoring of safety issues and implementation of risk minimization measures.
- Work-sharing at the regional level will be an important mechanism to perform regulatory oversight effectively and will require identifying the similarities between the countries that would make them suitable for pharmacovigilance work-sharing.
- Activities that could be shared include review of risk management plans, common template for post-authorization safety studies (PASSs), joint review of post-authorization safety data and pharmacovigilance inspections.

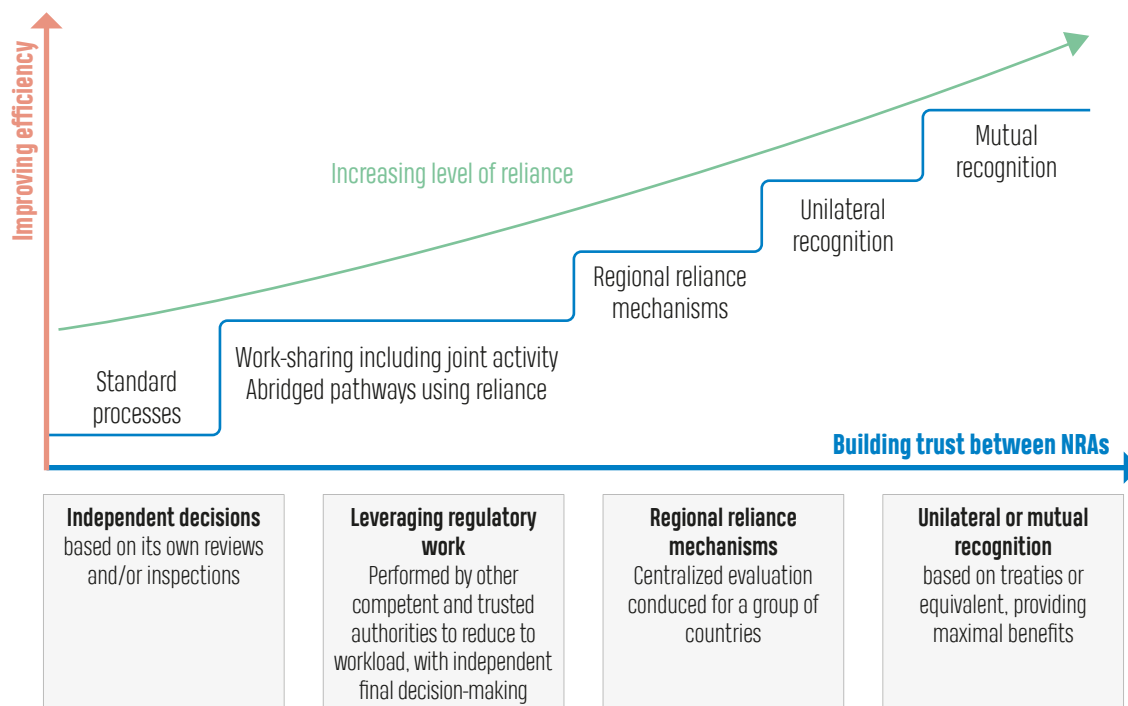
01 Introduction

1.1 Definition of regulatory reliance

Regulatory reliance is defined in the WHO draft guideline on good reliance practice standards¹ as “the act whereby the national regulatory authority (NRA) in one jurisdiction may take into account and give significant weight to assessments performed by another NRA or trusted institution, or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable regarding the decisions taken, even when it relies on the decisions and information of others.”.

The levels of reliance between NRAs can range from independent decisions by NRAs (no reliance) to mutual recognition (full reliance) (**Fig 1**). Recognition is a formalized process for reliance, based on legal provisions whereby one regulatory authority recognizes the decisions of a reference regulatory authority, without additional regulatory assessment. Recognition may be unilateral or mutual and several NRAs may participate in the same recognition agreement.

Fig 1: Schematic representation of increasing levels of regulatory reliance and the increasing benefits from this process



¹ WHO Working document QAS/20.851/Rev.1, August 2020. Available from: https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_Rev_1_Good_Reliability_Practices.pdf?ua=1. Accessed 26 October 2020. [NOTE: The GRelP document has been adopted at the 55th ECSP (12-16 October 2020) and will be published in the TRS. Reference to be revised].

While regulatory reliance is widely used for initial authorization of medical products, it is equally important to consider reliance for pharmacovigilance and other post-marketing activities. It is useful to distinguish between two types of activities:

1. Reliance on processes, tools and methods developed by others. This involves regulatory authorities adopting common processes and standards, e.g. templates for safety reporting, templates for study protocols and reports, signal detection methods, platforms for epidemiological studies.
2. Reliance on product-specific regulatory activities. These activities can cover the entire life cycle of the product. Product-specific reliance may include participation in a joint assessment committee for marketing authorization approval and variations and for safety assessments. Also, it can include reliance on product information approved by another NRA or reliance on the assessment of post-authorization safety study protocols and results by others. This level of reliance requires assurance that the products concerned are the same or are sufficiently similar in terms of composition, indications, conditions of use, etc.

The decision to practice reliance should take into consideration the context and characteristics of the national health and regulatory system, the availability of an authority that the NRA can rely on, and how reliance can complement existing capacities to drive efficiencies and optimization of resources. The general principles under which reliance should operate are discussed in the WHO working document for good reliance practice ([WHO working document QAS/20.851/Rev.1](#)). It is particularly important to note that reliance does not mean a decrease in level or quality of evidence for safety and efficacy or lowering of the quality of regulatory activities. It should be viewed as a more efficient form of regulatory oversight that is based on constructive regional and international collaboration.

1.2 Definition of work-sharing

Work-sharing is defined in the WHO draft guideline on good reliance practice standards ([WHO working document QAS/20.851/Rev.1](#)) as *"a process by which NRAs of two or more jurisdictions share activities to accomplish specific regulatory tasks. The opportunities for work-sharing include, but are not limited to:*

- *jointly assessing applications for authorization of clinical trials;*
- *marketing authorizations or good practices inspections;*
- *joint work in the post-marketing surveillance of medical product quality and safety;*
- *joint development of technical guidelines or regulatory standards, and collaboration on information platforms and technology.*

Work-sharing also entails the exchange of information consistent with the provisions of existing agreements and compliant with each agency's or institution's legislative framework for sharing such information with other NRAs."

02 Examples of regulatory reliance in pharmacovigilance

Regulatory reliance approaches have been applied for various regulatory activities across the product life cycle and have led to increased efficiency and improvements to regulatory capacity (WHO working document QAS/20.851/Rev.1). Several of them are presented in the WHO working document. Some examples of its application in pharmacovigilance are presented here.

2.1 Processes, tools, and methods

Around 140 Member States participate in the WHO Programme for International Drug Monitoring (PIDM)² and contribute to the WHO global database of individual case safety reports, [VigiBase](#), developed and maintained by the Uppsala Monitoring Centre (UMC), which is the WHO Collaborating Centre for International Drug Monitoring. Member States share their safety data, rely on this resource (and thereby, on each other's data) as a single point of pharmacovigilance information, to confirm or validate signals of adverse events with medical products. Regional pharmacovigilance databases, already available as a subset of VigiBase, can also help regulators from specific regions to share and use safety data on products of mutual interest and for products that are specific for their region/groups of countries.

In Europe, under Article 57 of Regulation (EC)726/2004 of the European Union (EU) pharmaceutical legislation, manufacturers³ of medicines in the EU and the European Economic Area (EEA) are required to submit and update a standard set of information on authorized medicines to the European Medicines Agency (EMA).⁴ This information enables the regulators of all EU Member States to access the same information on the characteristics of authorized medicinal products and identify the company's qualified person for pharmacovigilance (QPPV), which facilitates coordinated enquiries from regulators to companies, and the organization of other regulatory functions such as joint pharmacovigilance inspections.

2 World Health Organization. Programme for International Drug Monitoring. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/National_PV_Centres_Map/en/. Accessed 3 October 2020.

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

4 European Medicines Agency. Data submission of authorised medicines (Article 57). Available from: <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/data-medicines-iso-idmp-standards/data-submission-authorised-medicines-article-57#:~:text=All%20holders%20of%20marketing%20authorisations,information%20up%2Dto%2Ddate>. Accessed 01 October 2020.

2.2 Product-specific activities

Under the Article 58 of Regulation (EC)726/2004 procedure, the EMA provides scientific opinions on high priority medicines, including vaccines, that are intended exclusively for markets outside of the EU. The evaluations are carried out in cooperation with WHO and relevant 'target' non-EU NRAs. The same rigour and standards required for marketing authorization in the EU are applied, while the benefit-risk assessment is focused on the intended non-EU population and indication(s). The relying regulatory authorities can use the risk management plan (RMP) proposed by EMA for specific products and adapt it for relevance, feasibility, and implementation for use in their own countries. Hence, regulatory decisions for licensing and post-authorization requirements are taken by the regulators where the medicines or vaccines will be used. The Article 58 procedure facilitates patient access to essential medicines in low- and middle-income countries (LMICs), including improved treatment options for unmet medical needs and diseases of major public health interest, which include vaccines used in the WHO Expanded Programme on Immunization (EPI), medicines for protection against diseases such as HIV/AIDS, malaria and tuberculosis.

03

Regulatory reliance for COVID-19 vaccines

In the context of the current COVID-19 pandemic, regulatory reliance should be considered wherever possible, to improve regulatory efficiency, thereby facilitating timely access to COVID-19 vaccines, as well as effectively monitor safety issues and implement risk minimization measures.

Reliance is important for countries with limited regulatory capacity. Thus, for LMICs, a regional approach should be considered and implemented, especially in regions where the countries share common cultural values, languages, and health care system models.⁵ The Caribbean Regulatory System (CRS) provides an example of a regional reliance mechanism, where many small states in the Caribbean Community (CARICOM) that lack the resources and capacity to provide full regulatory oversight of medical products rely on the CRS for marketing authorization processes.⁶ CARICOM member states also submit in-country adverse reaction reports to [VigiBase](#) thereby leveraging the regional capacity for post-market surveillance.

⁵ Preston C, Chahal HS, Porrás A, Cargill L, Hinds M, Olowokure B, et al. Regionalization as an approach to regulatory systems strengthening: a case study in CARICOM member states. *Rev Panam Salud Publica*. 2016;39(5):262-268.

⁶ Preston C, Freitas Dias M, Peña J, Pombo ML, Porrás A. Addressing the challenges of regulatory systems strengthening in small states. *BMJ Glob Health*. 2020;5(2):e001912. doi: 10.1136/bmjgh-2019-001912.

Some regional reliance mechanisms involve the regional decisions being made for the participating members (e.g. EU processes), while in others they serve as the basis of consideration and the participating members make their own regulatory decisions (e.g. CRS, the Gulf Health Council (GHC)). Ideally, the application of reliance should be anchored in the regional strategy, with detailed procedures and integrated processes to avoid discrepancies in reliance decision and to be able to justify diverging decisions.

3.1 Pharmacovigilance for COVID-19 vaccines

Reliance for product-specific activities and for processes, tools and methods can be implemented for pharmacovigilance of COVID-19 vaccines. Examples of four specific aspects of pharmacovigilance, where reliance approaches can be implemented, are described below.

3.1.1 Example 1: Review of risk management plans at regional and WHO prequalification levels

Reliance for the review of risk management plans (RMP) submitted by vaccine manufacturers using a common format could be agreed with regional regulatory authorities or with the WHO prequalification programme to facilitate their assessment and the decision-making on the need and methods for additional pharmacovigilance or risk minimization activities. This process could also reduce the regulatory burden for the vaccine manufacturer and accelerate patient access to COVID-19 vaccines. Existing formats with essential sections, such as safety specification, pharmacovigilance activities, risk minimization activities, and evaluating effectiveness of risk minimization measures could be considered, e.g. the EU RMP format.⁷ If justified, the RMP should be accompanied by a regional annex that takes into consideration the specific context of the region where the vaccine(s) will be deployed. If country-specific characteristics exist that are significantly different from the regional characteristics and this could have an impact on the safety profile of the COVID-19 vaccine(s), the NRA should request that the vaccine manufacturer includes the regional annex in the RMP.

Practically, a group of countries, or an economic community could identify a reference country to lead the assessments of RMPs or pharmacovigilance documents. For example, representatives from the reference LMIC could participate as assessors for the WHO prequalification/emergency use listing of COVID-19 vaccines, to review the RMPs submitted by applicants to the WHO prequalification process. This would facilitate reliance for the countries represented in the WHO prequalification process. A good example is the East African Community (EAC)'s Medicines Regulatory Harmonization (MRH) initiative.⁸ Within the EAC-MRH, each national regulatory authority has the lead on one regulatory aspect, e.g. Kenya leads pharmacovigilance, Burundi leads clinical trials and Uganda leads joint GMP inspections.

⁷ European Medicines Agency. 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 4 October 2020.

⁸ Arik M, Bamenyekanye E, Fimbo A, Kabatende J, Kijo AS, Simai B, et al. (2020) Optimizing the East African Community's Medicines Regulatory Harmonization initiative in 2020–2022: a roadmap for the future. *PLoS Med* 17(8): e1003129. <https://doi.org/10.1371/journal.pmed.1003129>.

3.1.2 Example 2: Post-authorization safety study protocol template

Post-authorization safety studies (PASS) may be required to address issues that are specific to LMICs, either identified in the RMP or at the time of RMP-assessment, for example, to compare safety profiles and highlight differences in specific populations, such as ethnic groups. Where possible, protocol templates specifically developed for LMICs should be used by the vaccine manufacturer and agreed with the reference national or regional regulatory authorities to facilitate implementation of multi-country PASS. This template could be used for the development of country-specific protocols following study site selection. In addition, information sheets for PASS participants could be developed at the regional level to provide consistent messaging and transparency about COVID-19 vaccines.

3.1.3 Example 3: Regulatory review through work-sharing

Pharmacovigilance of COVID-19 vaccines could be conducted by a regional regulatory system or by a group of NRAs. Work-sharing at the regional level should be adopted wherever feasible in countries with limited regulatory resources and capacity. In this context, a regional review committee should be established to facilitate cooperation and coordination, as well as oversee the process in reaching valid regulatory decisions that will serve as a reference for relying NRAs. Activities that could be carried out through work-sharing include:

- joint review of periodic safety update reports/periodic benefit-risk evaluation reports (PSURs/PBRERs);
- joint review of safety data from regional multi-centre studies; and
- collaborations between NRA and national immunization programme (NIP) or EPI staff on activities such as signal investigation, calculation of AEFI rates (i.e., obtaining denominator data on doses delivered or administered).

3.1.4 Example 4: Pharmacovigilance inspections

Mutual recognition agreements have been developed by NRAs in different regions to enable regulatory authorities to rely on each other's inspection outcomes, thus avoiding duplication of efforts and making best use of resources. The Pharmaceutical Inspection Co-operation Scheme (PIC/S), a non-binding co-operative arrangement between regulators, has issued guidance on inspection reliance that outlines a process for remote (desk-top) assessment of GMP compliance.⁹ The reliance approach could be used for pharmacovigilance (PV) inspections. For COVID-19 vaccines where mutual recognition agreements exist, the reliance approach could be used also for PV inspections. For WHO prequalified emergency use listed vaccines, WHO inspection outcomes should be used.

⁹ PIC/S Guidance: GMP inspection Reliance. Available from: https://picscheme.org/users_uploads/news_news_documents/PI_048_1_Guidance_on_GMP_Inspection_Reliance_1.pdf. Accessed 4 October 2020.

As reliance is increasingly used for PV, especially during public health emergencies such as the current COVID-19 pandemic, it is important to specify PV activities that should be performed at the national level (and not through reliance on another NRA), such as:

- management of national data on adverse events of special interest (AESIs) and disease epidemiology in specific populations;
- national spontaneous reporting systems, assessment of AEFIs and adverse drug reactions reported nationally, and reporting to [VigiBase](#);
- risk communication to the public and to health care workers;
- information on the distribution system and statistics on vaccine exposure; and
- some risk minimization measures specific to the national context.

3.2 Specific considerations under different scenarios for COVID-19 vaccine introduction

As it is likely that several different COVID-19 vaccines will be introduced in different parts of the world, with a phased roll-out plan targeting initially front-line health care workers and other vulnerable populations, two likely scenarios should be considered for regulatory reliance for vaccine safety and PV activities.

3.2.1 Scenario 1: First introduction of a new COVID-19 vaccine

If a new COVID-19 vaccine is introduced in a group of LMICs with limited PV capacity, work-sharing at the regional level will be an important mechanism to carry out regulatory oversight effectively. In this case, it will be important to identify the similarities between the countries that would make them suitable for PV work-sharing. It will also be important to identify any unique features of each country that could have an impact on the safety profile of the vaccine, such as ethnicity, epidemiological characteristics, medical practice, and health and regulatory framework. Joint reviews of submissions related to COVID-19 vaccine safety, e.g. PSURs and RMPs, could be carried out collaboratively by the target countries through an agreement on a collaborative approach, e.g. joint assessment with a representative from each country, or shared review of different sections or modules by participating NRAs. If a unique local characteristic could have an impact on the safety profile of the new vaccine being introduced, the NRA should ask the vaccine manufacturer to reflect these characteristics in their PV plans.

3.2.2 Scenario 2: Introduction of a COVID-19 vaccine that has already been introduced elsewhere

If the COVID-19 vaccine being introduced into a particular country has already been introduced in other countries, and the vaccine was authorized by a reference regulatory authority using stringent regulatory requirements or the WHO prequalification emergency use listing programme, the country could rely on:

- the assessment from the reference regulatory authority for marketing authorization decisions;
- batch release by the reference regulatory authority;
- the assessment of updated safety information from the reference regulatory authority during the pandemic;
- safety signals from the phase 1 roll-out to health care workers and vulnerable populations that have been identified in the reference country(ies); and
- assessments of the effectiveness of the risk minimization measures made by the reference regulatory authority.

Routine surveillance may be sufficient to monitor the safety of the new COVID-19 vaccine being introduced in the relying country, unless there are significant differences between the local populations and the population of the reference country that could have an impact on the safety profile of the COVID-19 vaccine. If this is the case, the relying NRA should request that PV plans, specific to the local context, are submitted by the vaccine manufacturer.

COVID-19 VACCINES:

SAFETY SURVEILLANCE MANUAL