COVID-19 Vaccines: Safety Surveillance Manual

Module: Regulatory reliance and work-sharing

Contents

Abbreviations

AACVS	African Advisory Committee on Vaccine Safety
ACE	Angiotensin-converting enzyme
ADEM	Acute disseminated encephalomyelitis
ADRs	Adverse drug reactions
AEFI	Adverse event following immunization
AESI	Adverse event of special interest
ARDS	Acute respiratory distress syndrome
AVSS	Active vaccine safety surveillance
CEM	Cohort event monitoring
CEPI	Coalition for Epidemic Preparedness Innovations
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	Coronavirus disease 2019
DCVMN	Developing Countries Vaccine Manufactures Network
DL	Data linkage
DNA	Deoxyribonucleic acid
EH	e-Health
EPI	Expanded programme on immunization
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barré syndrome
GVAP	Global vaccine action plan
HCW	Health care worker
ICD	International classification of diseases
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
ISoP	International Society of Pharmacovigilance
ISRR	Immunization stress-related response
MAH	Marketing authorization holder
MedDRA	Medical dictionary for regulatory activities
MH	m-Health
MoH	Ministry of Health
mRNA	Messenger RNA
NIP	National Immunization Programme
NITAG	National Immunization Technical Advisory Group
NRA	National regulatory authority
PBRER	Periodic benefit-risk evaluation report
PHEIC	Public health emergency of international concern
PLSS	Post-licensure safety studies
PSUR	Product safety update report
PV	Pharmacovigilance
QPPV	Qualified person responsible for pharmacovigilance
RITAG	Regional Immunization Technical Advisory Groups
RMP	Risk management plan
RNA	Ribonucleic acid
SAGE	Strategic Advisory Group of Experts (for immunization)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SKG	Significant knowledge gap
SIA	Supplementary immunization activities
SS	Sentinel surveillance
TGA	Therapeutic Goods Administration (Australian Ministry of Health)
VAED	Vaccine-associated enhanced disease
VLP	Virus-like particles
VPD	Vaccine preventable disease
WHO	World Health Organization

Glossary

Adjuvant	A pharmacological or immunological agent added to a vaccine to improve its immune response.
Adverse event following immunization (AEFI): general definition	Any untoward medical event that follows immunization and that does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.
• AEFI by cause: coincidental events	• An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety.
• AEFI by cause: immunization anxiety-related reaction	• An AEFI arising from anxiety about the immunization (see immunization stress related responses).
• AEFI by cause: immunization error-related reaction	• An AEFI that is caused by inappropriate vaccine handling, prescribing or administration, that, therefore, is preventable.
• AEFI by cause: vaccine product-related reaction	• An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product, whether the active component or one of the other components of the vaccine (e.g. adjuvant, preservative or stabilizer).
• AEFI by cause: vaccine-quality defect-related reaction	• An AEFI that is caused or precipitated by a vaccine due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.
Adverse event of special interest (AESI)	A preidentified and predefined medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further specific studies.
Causal association	A cause-and-effect relationship between a causative (risk) factor and an outcome. Causally-associated events are also temporally associated (i.e. they occur after vaccine administration), but events that are temporally associated may not necessarily be causally associated.
Causality assessment	In the context of vaccine AEFI surveillance, a systematic review of data about the AEFI case(s) to determine the likelihood of a causal association between the event and the vaccine(s) received.
Cluster	Two or more cases of the same or similar events related in time, geography (place), and/or vaccine administered. AEFI clusters are usually associated with a particular supplier/provider, health facility, and/or a vial of vaccine or a batch of vaccines.
Contraindication	A situation where a particular treatment or procedure, such as vaccination with a particular vaccine, must not be administered for safety reasons. Contraindications can be permanent (absolute), such as known severe allergies to a vaccine component, or temporary (relative), such as an acute/severe febrile illness.
Immunity	The ability of the human body to tolerate the presence of material 'indigenous' to the human 'body' (self) and to eliminate 'foreign' (non-self) material. This discriminatory ability provides protection from infectious diseases since most microbes are identified as foreign material by the immune system.
Immunization	Immunization is the process whereby a person is made immune or resistant to an infection, typically by the administration of a vaccine. Vaccines stimulate the body's own immune system to protect the person against subsequent infection

Immunization safety	The process of ensuring the safety of all aspects of immunization, including vaccine quality, adverse event surveillance, vaccine storage and handling, vaccine administration, disposal of sharps and management of waste.
Immunization safety surveillance	A system for ensuring immunization safety through detecting, reporting, investigating, and responding to AEFI.
Immunization stress related responses (ISRR)	Stress response to immunization that may manifest just prior to, during, or after immunization.
Injection safety	The public health practices and policies dealing with various aspects of the use of injections (including adequate supply, administration and waste disposal) so that the provider and recipient are not exposed to avoidable risks of adverse events (e.g. transmission of infective pathogens) and creation of dangerous waste is prevented. All injections, irrespective of their purpose, are covered by this term (see definition of safe injection practices).
Mass vaccination campaign	Mass vaccination campaigns involve administration of vaccine doses to a large population over a short period of time.
Non-serious AEFI	An event that is not 'serious' and does not pose a potential risk to the health of the recipient. Non-serious AEFIs should also be carefully monitored because they may signal a potentially larger problem with the vaccine or vaccination or have an impact on the vaccination acceptability; in general.
Risk management plan (RMP)	A risk management plan is a document that describes the current knowledge about the safety and efficacy of a medicinal product. The RMP provides key information on plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine or vaccine. It also describes measures to be undertaken to prevent or minimise risks associated with the use of the product in patients.
Safe injection practice	Practices that ensure that the process of injection carries the minimum of risk, regardless of the reason for the injection or the product injected.
Serious AEFI	An event that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Any medical event that requires intervention to prevent one of the outcomes above may also be considered as serious.
Severe vaccine reaction	Vaccine reactions can be mild, moderate or severe. Severe reactions may include both serious and non-serious reactions.
Signal (safety signal)	Information (from one or more sources) that suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify verification.
Surveillance	The continual, systematic collection of data that are analysed and disseminated to enable decision-making and action to protect the health of populations.
Trigger event	A medical incident following immunization that stimulates a response, usually a case investigation.
SAGE Values Framework	Values Framework, developed by WHO's SAGE, offers guidance globally on the allocation of COVID-19 vaccines between countries, and guidance nationally on the prioritization of groups for vaccination within countries while COVID-19 vaccine supply is limited
Vaccine	A biological preparation that elicits immunity to a particular disease. In addition to the antigen, it can contain multiple components, such as adjuvants, preservatives, stabilizers, each of which may have specific safety implications.

Vaccine-associated enhanced disease (VAED)	Vaccine-associated enhanced diseases are modified and severe presentations of clinical infections affecting individuals exposed to a wild-type pathogen after having received a prior vaccine against the same pathogen.
Vaccine pharmacovigilance	The science and activities relating to the detection, assessment, understanding and communication of AEFI and other vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or vaccination.
Vaccination failure	Vaccination failure can be defined based on clinical endpoints or immunological criteria, where correlates or surrogate markers for disease protection exist. Primary failure (e.g. lack of sero-conversion or sero-protection) needs to be distinguished from secondary failure (waning immunity). Vaccination failure can be due to (i) failure to vaccinate, i.e. an indicated vaccine was not administered appropriately for any reason or (ii) because the vaccine did not produce its intended effect
Vaccine reaction	An event caused or precipitated by the active component or one of the other components of the vaccine. It may also relate to a vaccine quality defect.
Vaccine safety	The process that maintains the highest efficacy of, and lowest adverse reaction to, a vaccine by addressing its production, storage and handling. Vaccine safety is a part of immunization safety.

1. Definition of regulatory reliance

Regulatory reliance is defined in the WHO draft guideline on good reliance practice standards[1] 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.*".

Reliance can involve increasing degrees of recognition between NRAs, from independent decisions by NRAs (no reliance) to mutual recognition (full reliance) (Figure 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.

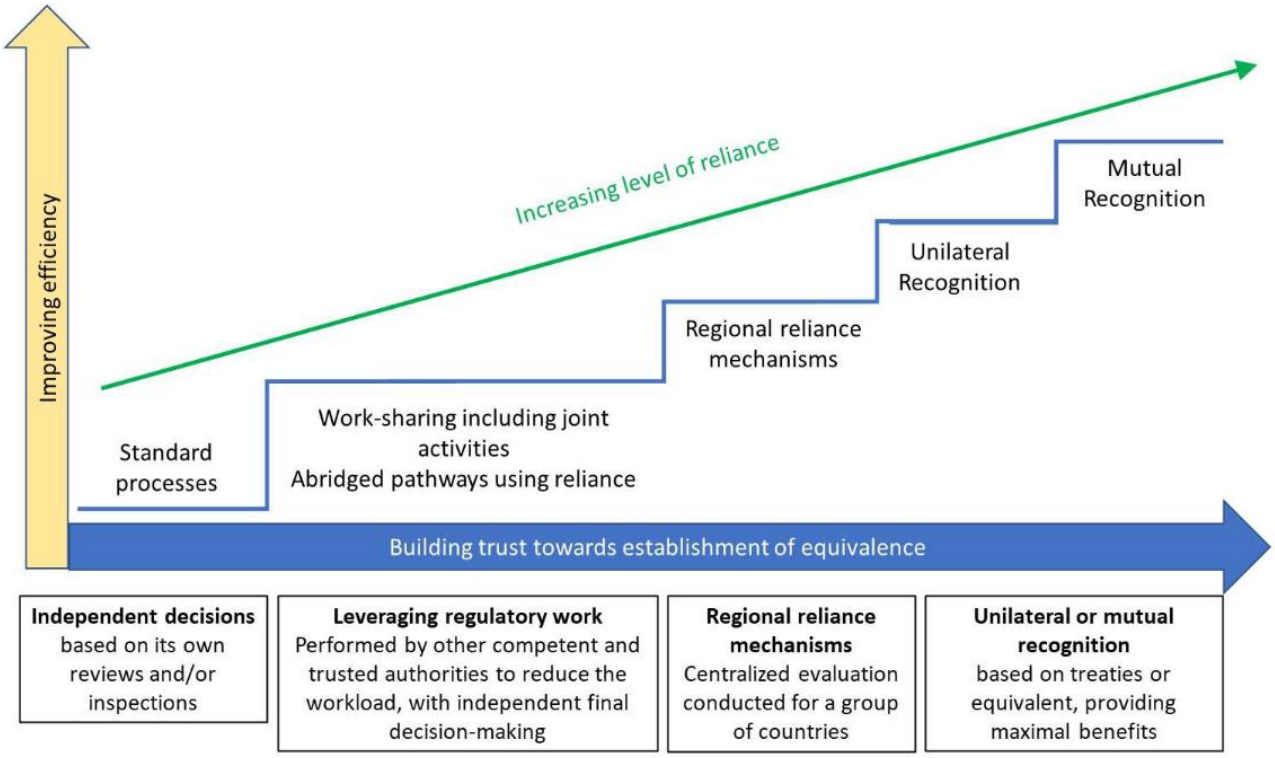

Figure 1: Key concepts of reliance

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,

[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_Reliance_Practices.pdf?ua=1. Accessed 26 October 2020. [NOTE: The GRelP document has been adopted at the 55th ECSPP (12-16 October 2020) and will be published in the TRS. Reference to be revised].

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 required 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.[1] It is particularly important to note that reliance does not mean a decrease in evidentiary standards 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.

2. Definition of work-sharing

Work-sharing is defined in the WHO draft guideline on good reliance practice standards[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.".

3. 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.[1] Several of them are presented in the WHO working document. Some examples of its application in pharmacovigilance are presented here.

3.1. 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 WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC). 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 the region share and use safety data on products of mutual interest and for products that are specific for their region/groups of countries.

In Europe, the EU pharmaceutical legislation, under Regulation Article 57 of (EC)726/2004, requires that all marketing authorization holders (MAHs) for medicines in the European Union (EU) and the European Economic Area (EEA) submit and update a standard set of information on authorized medicines to the European Medicines Agency (EMA)[3]. 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.

3.2. Product-specific activities

Under the Article 58 of Regulation (EC)726/2004 procedure, also known as EU Medicines4All, 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 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.

4. 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 monitoring of safety issues and implement risk minimization measures.

[2] WHO Programme for International Drug Monitoring. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/National_PV_Centres_Map/en/ (Accessed 03 October 2020).

[3] EMA. 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.

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[4]. 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[5]. CARICOM member states also submit in-country adverse reaction reports to VigiBase thereby leveraging the regional capacity for post-market surveillance.

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.

4.1. 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. Other activities where regulatory reliance can be considered to support safety and pharmacovigilance after the introduction of COVID-19 vaccines are listed in Appendix, along with a summary of existing institutions, organizations, and initiatives at national, regional, and global levels that could support or facilitate this reliance.

4.1.1. Example 1: Risk management plans developed at regional and WHO prequalification levels

Reliance for the review of risk management plans (RMP) submitted by MAHs 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 MAH and accelerate patient access to COVID-19 vaccines. Existing formats with essential section, such as safety specification, pharmacovigilance activities, risk minimization activities, and evaluating effectiveness of risk minimization measures could be considered, e.g., the EU format of RMP,[6]. The RMP should be accompanied by a regional annex that takes into consideration the specific context of the region where the vaccines will be being deployed. If country-specific characteristics exist that are significantly different from the regional characteristics and these could impact the safety profile of the COVID-19 vaccines, the NRA should request they are included in the RMP by the MAH.

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

[4] 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.
[5] 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.
[6] EMA 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 04 October 2020.

the reference LMIC could participate as assessors for the WHO prequalification/emergency use listing of COVID19 vaccines, to review the RMPs submitted by applicants to the WHO prequalification process. This would facilitate reliance for the countries represented on the WHO prequalification process. A good example is the East African Community (EAC)'s Medicines Regulatory Harmonization (MRH) initiative[7]. Within the EAC-MRH, each national regulatory authority has one regional technical offer who specialize in different areas, e.g. Kenya leads pharmacovigilance, Burundi, leads clinical trials and Uganda leads joint GMP inspections.

4.1.2. Example 2: Post-licensure safety study (PLSS) protocol template

PLSSs will address issues of missing information, identified in the RMP, compare safety profiles and highlight differences in special populations such as ethnic groups, pregnant women, children and the elderly, and those with chronic conditions. A protocol template with design options should be developed by the MAH and agreed with the reference national/regional regulatory authority to facilitate implementation of multi-country PLSSs. This template could be used for the development of country-specific protocols following the site selection. In addition, information sheets for PLSS participants could be developed at the regional level to provide consistent messaging and transparency about COVID-19 vaccines.

4.1.3. 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. The activities that could be carried out through work-sharing include (see Table 1 for other potential activities):

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

4.1.4. 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.[8] The reliance approach could be used for 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.

[7] 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

[8] 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 04 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 taken from another NRA, such as:

- management of national data on adverse events of special interest (AESIs) and disease epidemiology in specific populations;
- spontaneous reporting systems, assessment of adverse drug reactions reported nationally and in VigiBase;
- 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.

4.2. Specific considerations under different scenarios for COVID19 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.

4.2.1. Scenario 1: Introduction of a new COVID-19 vaccine for the first time

If a new COVID-19 vaccine is introduced to 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 it suitable for PV work-sharing, and any unique features of each country that could impact the safety profile of the vaccine, such as ethnicity, epidemiological characteristics, medical practice, and health and regulatory framework. Joint reviews of submissions related to drug safety, e.g. PSURs and RMPs, could be carried out collaboratively by the target countries through an agreement on the collaborative approach, e.g. joint assessment with a representative from each country, or shared review of different sections/modules by participating NRAs. If a unique local characteristic could impact the safety profile of the new vaccine being introduced, the NRA should request that PV plans that take into account local characteristics, are submitted by the MAH.

4.2.2. 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 based by a reference regulatory authority using stringent regulatory requirements or the WHO prequalification emergency list programme, the country can rely on:

- the assessment from the reference regulatory authority for marketing authorization decisions;
- the assessment of updated safety information from the reference regulatory authority during the pandemic, based on the interim simplified (iS)-PSUR, which will be submitted more frequently than standard PSURs;

- 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 impact 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 MAH.

5. Appendix: Regulatory reliance and work-sharing

Essential requirements, along the product life cycle, for vaccine safety and pharmacovigilance where regulatory reliance should/can be considered, along with existing institutions, organizations, and/or initiatives at national, regional, and global levels, that would support or facilitate this approach.

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	Regional	National
PHASE: prior to licensing				
Clinical trials protocol, critical safety endpoints, registry	Possible to develop master protocol for multi-country trials	**Brighton Collab** (L) **CIOMS** WG VI 2005, WG VII (DSUR) 2006 (S) **WHO** (Solidarity Trials, ECBS guidance) (L)	**WHO** (S) (AVAREF) **HPRA** (L) scientific advice/protocol assistance/assessment of centralised EU applications	**Butantan** On-going (BRA) (L) **TGA** (Therapeutic Goods Administration, Australia (L) **HPRA** (L)
Risk Management Plans	Standard format of RMP can be adopted; region-specific annex can be developed to address local context	**CDC** **CIOMS** WG IX (2014) (S) **WHO PQ** (L)	**CDC** **EMA** (EU) Regulatory approval of RMPs of vaccines centrally authorized in the EU (L) **HPRA** (S) **WHO** (S) (AVAREF)/RO	**Butantan** On-going (BRA) (L) **CDC** (USA) **TGA** (AUS) (L) **HPRA (S)**

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	**Regional**	**National**
Identify AESI, priority criteria and background rate	Normally performed at national level	**Brighton Collab (L)** **CIOMS**/WHO Working Group on vaccine PV (2012) (S) **UMC** (MIS-C case definition) (S) **WHO** (S) (GACVS)	**EMA** Provision of AESI list (continuously updated), background rates provided by EMA funded project ACCESS (EU) (L) **HPRA** (S) **WHO** (S) thru RO to adopt/background rates	**Butantan** On-going (BRA) (L) **CDC** (USA) **TGA** (AUS) (L) **HPRA** (S) **WHO/CO** (S) to adopt
Templates for benefit-risk evaluation per vaccine product (e.g. using Brighton Collaboration Benefit-Risk Assessment of Vaccines by Technology (BRAVATO))	Standard templates should be developed and adopted internationally	**Brighton Collab** (L) **WHO** (S) (GACVS, ECBS endorsements/advice	**HPRA (L)** **WHO** (S) thru RO to adopt/implement	**Butantan** On-going (BRA) (S) **TGA** (AUS) (L) **WHO** (S) to adopt/implement thru WCO

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	**Regional**	**National**
Data sources and networks to study background AESI rates	Normally performed at national level	**Brighton Collab (S)** **WHO (L)** with guidance on data sources, methods	**EMA** Provided by EMA funded project ACCESS, available data sources and establish a network for vaccines monitoring for studying safety, effectiveness and coverage (EU) (L) **HPRA** (S) **WHO** (S) thru RO to adopt/train	**Butantan** On-going (BRA) (S) **CDC** (USA) **TGA (AUS) (L)** **WHO** (S) thru WCO to implement/estimate background rates
PV requirements for pandemic preparedness (checklists, guidance)	Standard checklists and guidance should be developed and adopted internationally	**Brighton Collab** (S) **WHO (L),** to prepare checklists, guidance	**EMA** GVP guidance applies, EU network COVID-19 vaccines monitoring preparedness plan in preparation (L) **HPRA** (S) **WHO** (L) through RO, to promote, train	**Butantan** On-going (BRA) (S) **TGA** (AUS) (L) **HPRA** (L) **WHO** (L) through WCO, to apply, determine preparedness

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	**Regional**	**National**
Contribution to strategies on injury-compensation policies		**Brighton Collab** (S) **WHO** (S) through COVAX Task Force on liability, indemnification and compensation	**WHO** (S) through RO, with AEFI regional data	**WHO/WCO** (S) with AEFI national data
PHASE: licensing				
Safety specification per vaccine product	Joint review, through work-sharing of RMPs at the regional level should be considered	**WHO/PQ & R&D** (S)	**EMA** – Regulatory approval for vaccines centrally authorized in the EU (L) **HPRA** (S)	**Butantan** Planned (BRA) (S) **TGA** (AUS) (L)
Pharmacovigilance plan per vaccine product	Joint review, through work-sharing of RMPs at the regional level should be considered	**WHO/PQ** (S)	**EMA** Regulatory approval for vaccines centrally authorized in the EU (L) **HPRA** (S) **WHO/RO** (S) through platforms such as AVAREF	**Butantan** Planned (BRA) (L) **CDC** (USA) **TGA** (AUS) (L)

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	**Regional**	**National**
Risk minimization plan per product with annex by country	Joint review, through work-sharing of RMPs at the regional level should be considered	**WHO/PQ** (S)	**EMA** Regulatory approval for vaccines centrally authorized in the EU (L) **HPRA** (S) **WHO/RO** (S) through platforms such as AVAREF	**Butantan** Planned (BRA) (L) **TGA** (AUS) (L)
PHASE: early post-licensing/general use: active vaccine safety surveillance (AVSS)				
Establishment of preferred design and standard study protocol	Possible to develop a master protocol for multi-country studies, the implementation of which can be tailored to sites in-country	**Brighton Collab** (S) **CDC** **CIOMS (L)** **WHO (S) (**work with CIOMS, to develop guidance**)**	**CDC** **EMA** For studies included in the RMP as category 1 and 2 in vaccines centrally authorized in the EU (L) **WHO/RO** (S), to train	**Butantan** On-going (BRA) (L) **CDC** (USA) **TGA** (AUS) (S) **WHO/CO (S)**, to train, implement AVSS

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	**Regional**	**National**
Decision on number, size, location and responsible investigator of AVSS	Same as above	**Brighton Collab** (L) **WHO (S)**, coordinate	**EMA** - For studies included in RMP as category 1 & 2 vaccines centrally authorized in EU (L) **WHO/RO** (S), to identify participating countries and study sites	**Butantan** Planned (BRA) (L) **TGA** (AUS) (S) **WHO/CO**, to coordinate with MoH/EPI
Establishment of a global office to coordinate operations of local safety follow-up studies and data streams	Same as above	**Brighton Collab** (S) **WHO** (L)	**WHO/RO** (L)	**Butantan** Planned (BRA) (L) **TGA** (AUS) (S) **WHO/CO** (L)
Ethical clearance for collecting personal and clinical information in countries	Normally performed at national level	Brighton Collab (S) CIOMS/WHO International ethical guidelines for health-related research (2016) (S)		**Butantan** Planned (BRA) (L) **TGA** (AUS) (S)

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	Regional	National
Develop information material for vaccine recipients taking part in AVSS	Possible to share at regional level for multi-country studies			**Butantan** Planned (BRA) (L) **CDC** (USA) **TGA** (AUS) (S)
Software for recording of vaccine details and contact details of recipient	Normally performed at national level	**Brighton Collab** (S) **WHO/IVB?** (S)		**Butantan** Planned (BRA) (L) **CDC** (USA) **TGA** (AUS) (S)
Training of staff to carry out follow-up interviews	Joint regional training can be conducted by organizations such as GAVI			**Butantan** Planned (BRA) (L) **CDC** (USA) **TGA** (AUS) (S)
Software (E2b) for recording of AEFIs by investigator	Recording and transmission of AEFI are normally performed at national level	**Brighton Collab** (L) **WHO/UMC** (S) by participating in ICH	**WHO/RO (S)**, to adopt E2b standards/bridge with EPI	**Butantan** On-going (BRA) (L) **CDC** (USA) **TGA** (AUS) (L) **WHO/UMC (S), to implement E2b compatible tools**

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	Regional	National
Communication facilities for transmission of collected data to national, regional and global data analysis centre	Data transmission is normally performed at national level	**UMC** (S) **WHO** (S)	**WHO/RO** (S)	**Butantan** On-going (BRA) (L) **TGA** (AUS) (L) **WHO/CO** (S)
Statistical package for near real-time screening for AESI reports	Normally performed at national level if systems and competency exist	**Brighton Collab** (S)	**EMA** in the EU using the Eudravigilance database	**Butantan** On-going (BRA) (L) **CDC** (USA) **TGA** (AUS) (L)
Establishment of safety data review committees with Standard Operating Procedures for their activities	Work-sharing possible at regional and global level	**WHO** (S) through guidance docs, facilitating joint reviews between groups of countries	**WHO/RO (S)** by convening platforms and supporting joint reviews	**Butantan** Planned (BRA) (L) **CDC** (USA) **TGA** (AUS) (L) **WHO/CO (S)** to train/implement committees

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	**Regional**	**National**
Establishment of communications policy and plan for interaction with regulatory authorities, the scientific community, media and the public	Normally performed at national level	**CDC** **WHO** (L) to develop guidance	**CDC** **HPRA** (S) (Chair at Vx Working Party) **WHO/RO (S)** to adopt	**Butantan** On-going (BRA) (L) **CDC** (USA) **TGA** (AUS) (L) **HPRA** (S) (through national cross-organizational teams on Vx) **WHO/CO** (S) to implement
PHASE: early post-licensing/general use: passive vaccine safety surveillance				
Establishing centres for management of the safe introduction of Covid-19 vaccines with relevant competencies and resources	Normally performed at national level	**Brighton Collab** (S) **UMC** support/training to NRA (S) **HPRA** (S) **WHO** (L) through PIDM and GVSI	**HPRA (S)** **WHO/RO (L)** Training and coordination between countries in regions	**HPRA (L)** **UMC** (S) **TGA** (AUS) (L) **WHO/CO** (L) in liaising between NRA and EPI in country

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	**Regional**	**National**
Information material developed for target groups, explaining the different routes for AEFI reporting and what to report	Normally performed at national level	**UMC** (S) **HPRA** (S) **WHO/HQ** (L) with guidance, training	**HPRA (S)** **WHO/RO** (S) with coordination in region, training	**TGA** (AUS) (L) **HPRA** (L) **WHO/CO** (S) with implementation in countries
AEFI Reporting tools developed / made available (paper based, phone, e-mail, web, reporting-apps)	A number of tools available globally, e.g. VigiFlow	**Brighton Collab** (L) **UMC** (L) **HPRA** (S) **WHO (S)** by coordinating	**HPRA (S)** **WHO/RO** (S) by advocating, training	**UMC** (S) **TGA** (AUS) (L) **HPRA** (L) **WHO/CO (S)** in implementing, feedback on tools
Systems for confirmation/ acknowledgement of receipt of AEFI reports	Normally performed at national level	**HPRA** (S)	**HPRA** (S)	**Butantan** On-going (BRA) (S) **CDC** (USA) **TGA** (AUS) (L) **HPRA** (L)
Pooling of data through the different reporting routes	Can be shared at regional and global level	**UMC** (L) **HPRA** (S) **WHO (S)** by coordinating	**HPRA (S)** **WHO/RO** (S) by convening/facilitating platforms for data sharing/pooling	**Butantan** On-going (BRA) (L) **CDC** (USA) **TGA** (AUS) (L) **HPRA (L)**

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	**Regional**	**National**
Reconciling data from AVSS and the spontaneous reporting systems		**UMC** (S)		**Butantan** On-going (BRA) (L) **CDC (USA)** **TGA** (AUS) (L)
Vaccine safety expert panels for continuous review of safety data	Work-sharing at regional level and global level possible	**Brighton Collab** (L) **CIOMS** WG X (2016) (S) **UMC** (L) **HPRA** (S) **WHO** (L) GACVS	**EMA**– Signal detection for vaccines that are centrally authorised in the EU (L) **HPRA** (S) **WHO/RO** (S) in establishing regional committees	**Butantan** Planned (BRA) (S) **CDC (USA)** **TGA** (AUS) (L) **HPRA** (L) **WHO/CO** (S) in establishing/training etc
Collating distribution statistics by product and geographic region with batch numbers	Normally performed at national level	**HPRA** (S) **WHO** (IVB) S	**EMA** -In collaboration with ECDC and member states in the EU (L) **HPRA** (S)	**Butantan** On-going (BRA) (L) **TGA** (AUS) (L) **HPRA** (L)

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	**Regional**	**National**
Communications policy and plan	Normally performed at national level	**CIOMS** Guide to Vaccine Safety Communication (2018) (S) **HPRA** (S)	**EMA** – Communications at EU level (L) **HPRA** (S)	**Butantan** On-going (BRA) (L) **CDC** (USA) **TGA** (AUS) (L) HPRA (L)
PHASE: late stage activities following general use				
Verification and characterization of identified new safety signals/clusters.		**Brighton Collab** (S) **CIOMS** WG VIII (2010) (S) **UMC** (L) **HPRA** (S) **WHO** (GACVS) (L)	**EMA** – Signal management for vaccines centrally authorised in the EU (L) **HPRA** (S)	**Butantan** On-going (BRA) (L) **CDC** (USA) **TGA** (AUS) (L) **HPRA** (L)
Additional verification/signal characterization studies		**Brighton Collab** (S) **HPRA** (S) **WHO** GACVS (L)	**EMA** - As part of signal management for vaccines centrally authorised in the EU (L) **HPRA** (S)	**Butantan** On-going (BRA) (L) **CDC** (USA) **TGA** (AUS) (L) **HPRA** (L)

Requirements for COVID-19 vaccine safety/PV	Considerations for regulatory reliance	Existing vaccine safety initiatives/organizations		
		Global	**Regional**	**National**
Publication of results (scientific journal, general media)		**Brighton Collab** (S) **UMC** (L) **HPRA** (S) **WHO** GACVS (L)	**EMA** Publication of the outcome of signals assessed by PRAC and the regulatory actions to be taken by the MAH (L) **HPRA** (S)	**Butantan** Planned (BRA) (L) **CDC** (USA) **TGA** (AUS) (L) **HPRA** (L)
Updating of Summary of Product Characteristics (product labelling) based on outcome of study. PHASE: periodic reporting by MAH	Reliance can be implemented using decisions from reference NRA	**Brighton Collab** (S) **HPRA** (S) **WHO/PQ** (S)	**EMA**– For the SmPC and PL of vaccines centrally authorised in the EU (L) **HPRA** (S)	**Butantan** Planned (BRA) (L) **TGA** (AUS) (L) **HPRA** (L)
Periodic Benefit Risk Evaluation Report (PBRER); legislations, guidelines, records, etc.	Work-sharing can be considered for joint review of PBRER where appropriate	**Brighton Collab** (S) **HPRA** (S) **WHO PQ and** GACVS (S)	**EMA** For vaccines centrally authorised in the EU (L) **HPRA** (S)	**Butantan** On-going (BRA) (L) **TGA** (AUS) (L)

Note: The list of existing institutions, organizations, and/or initiatives and their activities that support COVID-19 vaccine safety is generated from responses to a survey conducted by the WHO. As more responses are received, the list will be refined and updated. [List of acronyms to be added]

L: leading role for a specific requirement; S: supporting role for a specific requirement.