WHO Good Reliance Practices
(and examples in pharmacovigilance and lot release)

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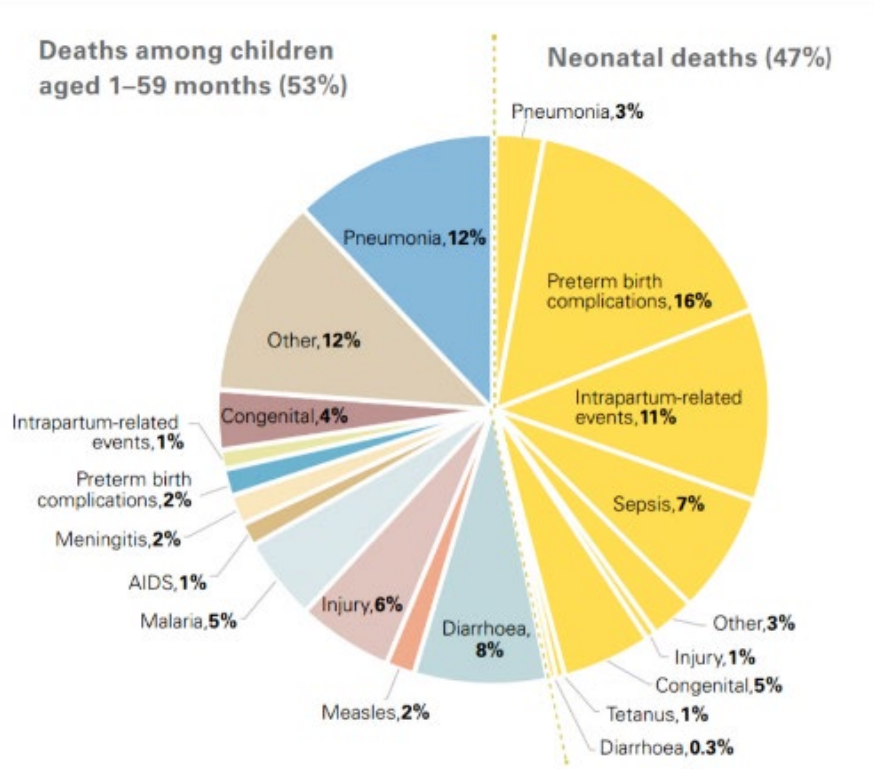
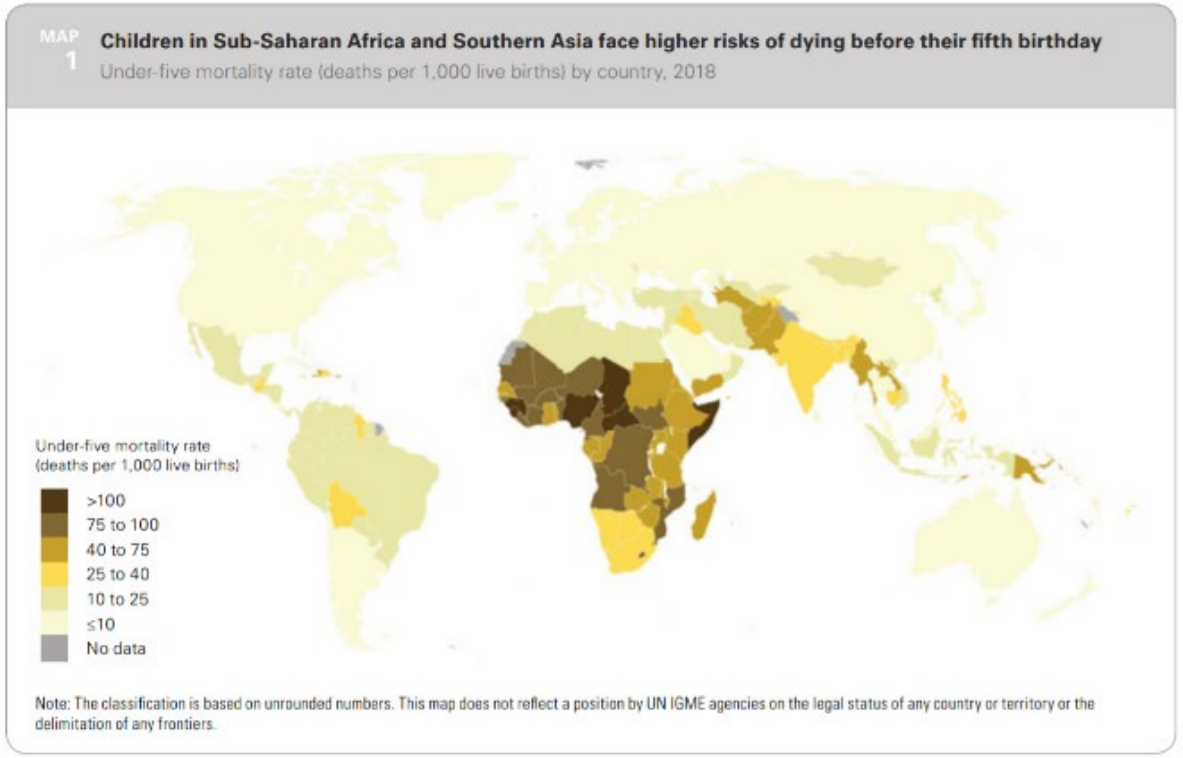
Infectious (preventable) diseases remain a leading cause of death among children under age 5



Global distribution of deaths among children **under age 5 by cause**, 2018



One child under age 15 died every five seconds in 2018

UN Inter-agency Group for Child Mortality Estimation

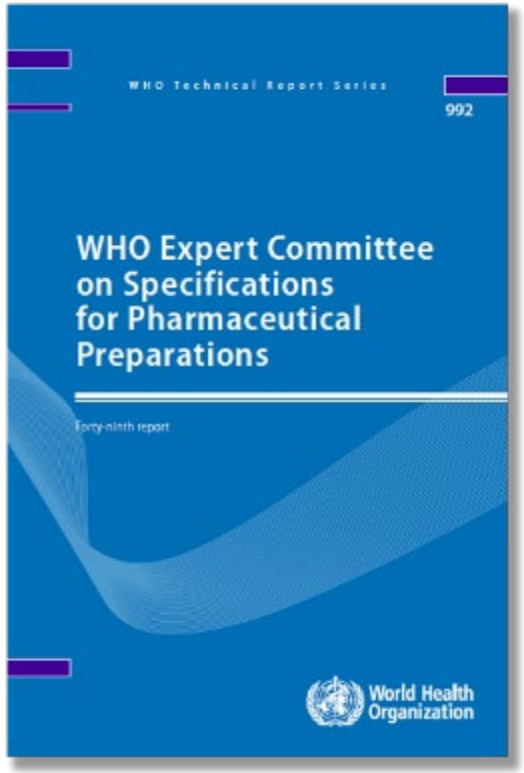
IGME

Access to medical products – global challenge

- WHO Constitution: "…the highest attainable standard of health is a fundamental right of every human being."
- Good health is impossible without access to medical products;
- Universal Health Coverage depends on the availability of quality-assured affordable health technologies in sufficient quantities;
- An estimated **two billion people have no access to essential medicines**, effectively shutting them off from the benefits of advances in modern science and medicine.
- Reasons for limited/insufficient access are numerous – including inadequate regulatory capacity and lack of collaboration and work sharing in medicines regulatory area between countries.

Globalization in medical products regulation (1)

- All medical products should be used in the countries **only after approval by the national or regional regulatory authority - in line with current international standards** (WHA Resolutions: WHA 67.20 (2014); WHA 67.21 (2014); WHA63.12 (2010)**;**
- There is no clear vision or policy about HOW to set up regulatory systems in times when it is unrealistic to manage all functions in one national setting for most regulators – due to **globalization of regulatory science**;
- New products are likely more complex and sophisticated – demanding advanced health systems and "quality use“.



Globalization in medical products regulation (2)

- Ability/need to assess and inspect all products coming to the markets:
  - Does repetitive assessments and inspections give any added value?
- How to build confidence in scientific assessments/ inspections carried out by other regulators?
- Are new products equally fit for all types of health systems and health providers available?
- Benefit/risk assessment taking into consideration health systems in which product is to be launched?
- What exact competencies are needed for regulators – to perform key regulatory functions?

Capacity to regulate medical products globally

- About **one third of NRAs glob**ally have limited capacity to perform core regulatory functions
- Regulatory capacity gap between different countries (low- and high-income) in terms of:
  - Human and financial resources;
  - Regulatory functions effectively performed;
  - Expertise available for fulfilling regulatory functions;
  - Availability of proper systematic training for regulators;
  - Applying quality management principles.

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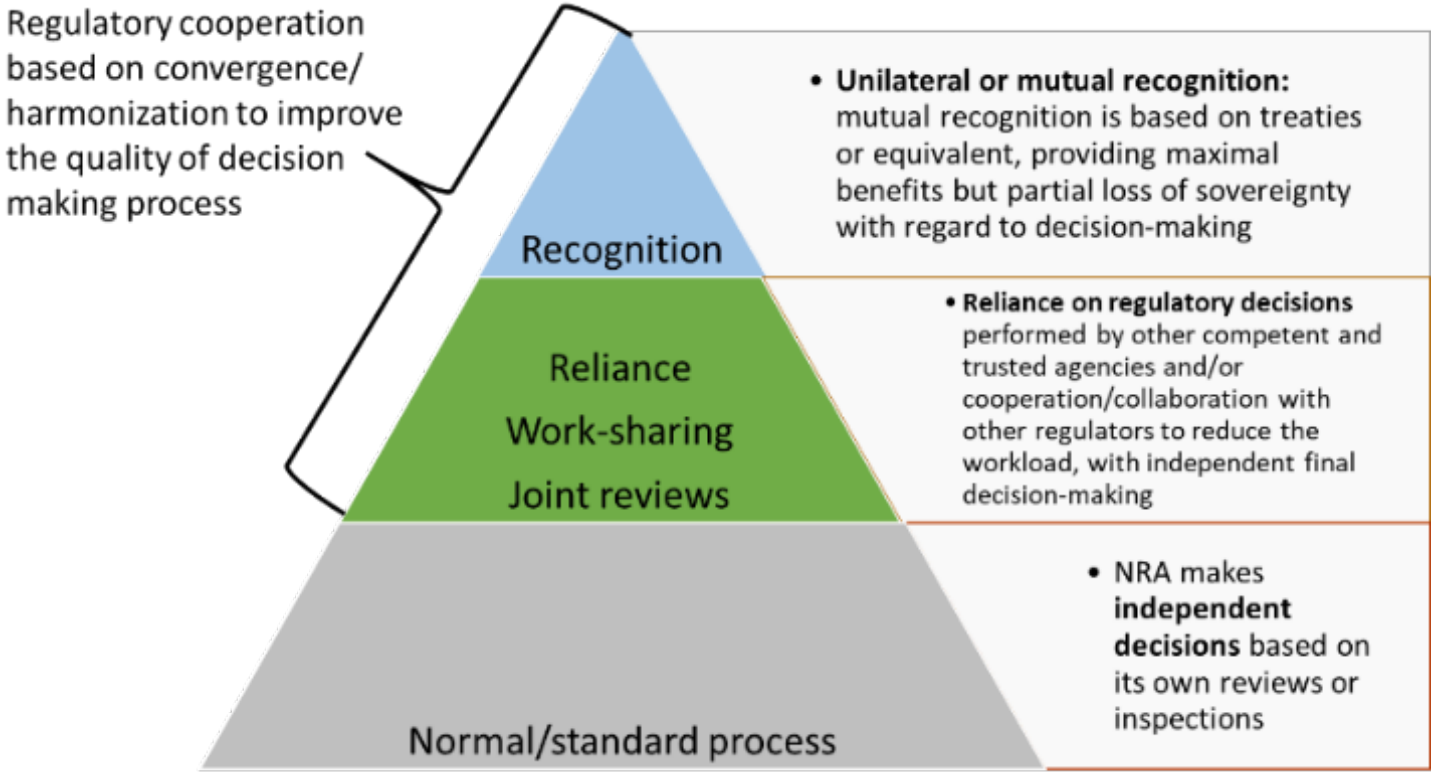
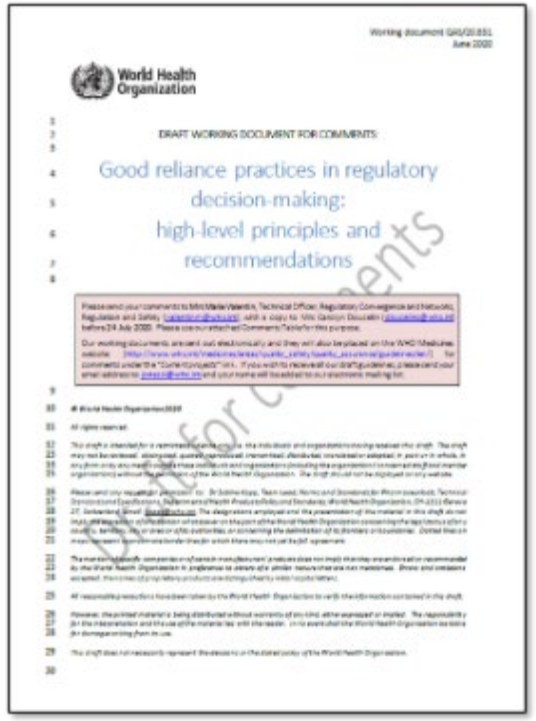
Options to facilitate good quality regulatory decisions – reliance in the focus

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DRAFT WORKING DOCUMENT FOR COMMENTS

Good reliance practices in regulatory decision-making: high-level principles and recommendations

Adopted by ECSPP, 15 October 2020

WHO Good Reliance Practices

Promote **a more efficient approach to regulation**, thereby improving **access to quality-assured, effective and safe medical products**

The act whereby the regulatory authority in one jurisdiction **may take into account and give significant weight to assessments performed by another regulatory authority or trusted institution**, or to any other authoritative information in reaching its own decision.

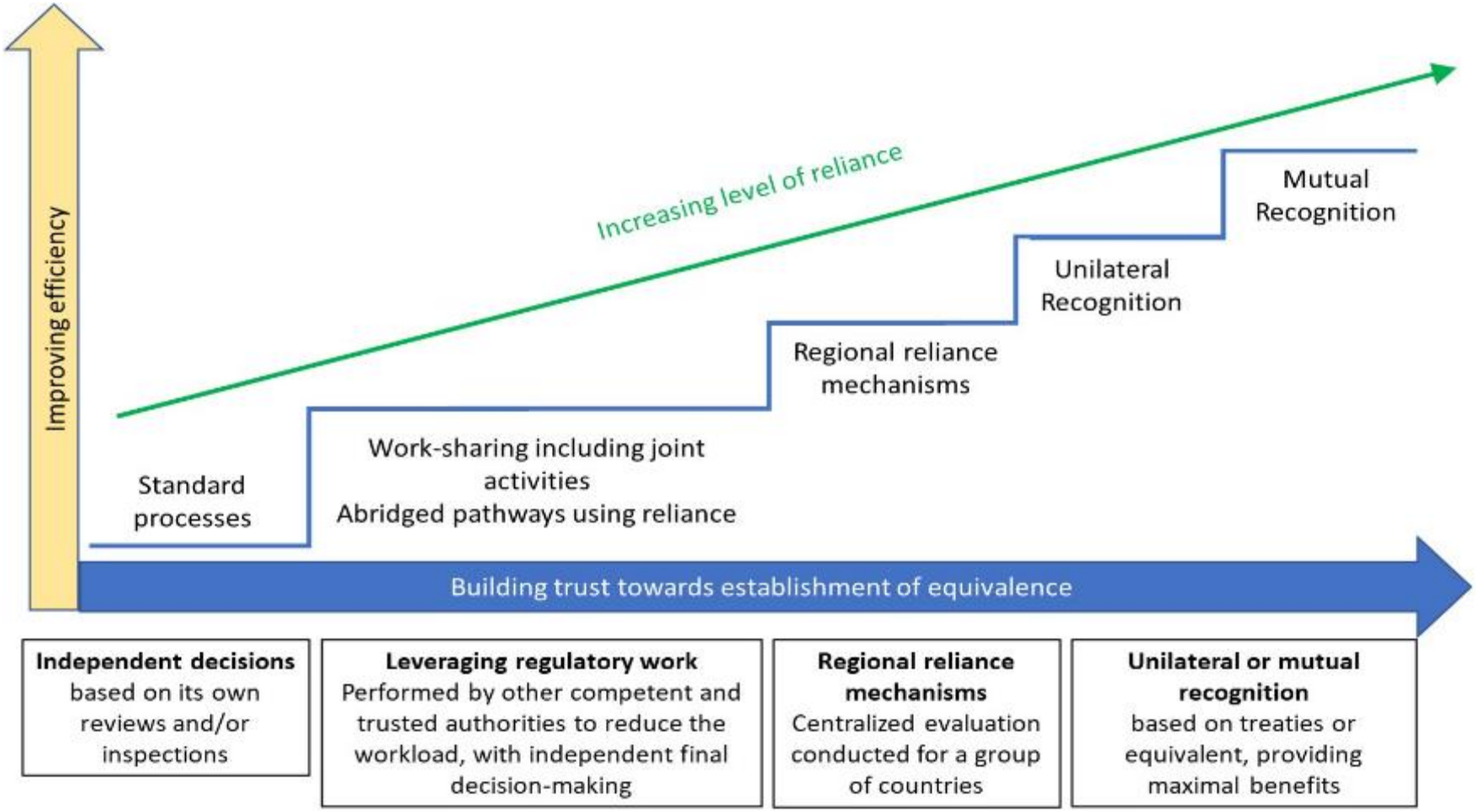
The relying authority **remains independent, responsible and accountable regarding the decisions taken**, even when it relies on the decisions, assessments and information of others.

WHO Good Reliance Practices - Scope

- Covers reliance activities in the field of **regulation of medical products** (i.e. medicines, vaccines, blood and blood products and medical devices including in vitro diagnostics)
- Addressing **all regulatory functions** as defined in the Global Benchmarking Tool (registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trials oversight, and NRA lot release) - spanning the full life cycle of a medical product.

The high-level document will be complemented in a second step by a repository of case studies, practice guides and examples of practical applications of GReIP

Facilitated registration based on reliance (2)



Regulatory information and knowledge could be transferred through facilitated pathways

MAIN PRINCIPLES:

- **Sharing information / expertise** (assessment, inspection and testing results or expertise) that serve as basis for authornational decisions – avoiding duplication.
- **Voluntary participation** – reference authorities, participating ities and manufacturers/sponsors

WHO PQ collaborative registration procedure

Vaccines: 2004

- Medicines: Started in 2012
- Diagnostics: Pilot 2019
- Vector control: Pilot 2020

**CRP-lite

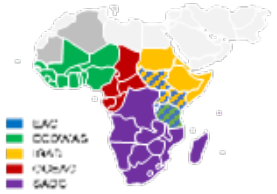
"SRA" collaborative registration procedure

Initiated in 2015

- European Medicines Agency (EMA)
- UK Medicines and Healthcare Products Regulatory Agency (MHRA)
- 20 African NRAs

Regional networks

African Medicines Regulatory Harmonization Project (AMRH)

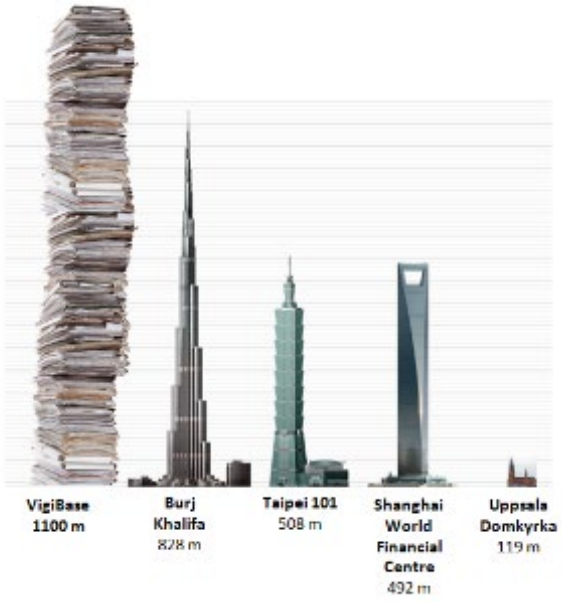


ASEAN SIAHR Project

Examples of Reliance in Pharmacovigilance

Reliance on Global PV Data

- Around 140 Member States report safety events to the WHO global database of individual case safety reports - ***VigiBase***;
- Member States rely on this resource (and thereby, on each other's data), to confirm or validate signals of adverse events;
- Regional pharmacovigilance databases, as a subset of *VigiBase*, can also help regulators from the region share and use safety data on products that are specific for their region/groups of countries.



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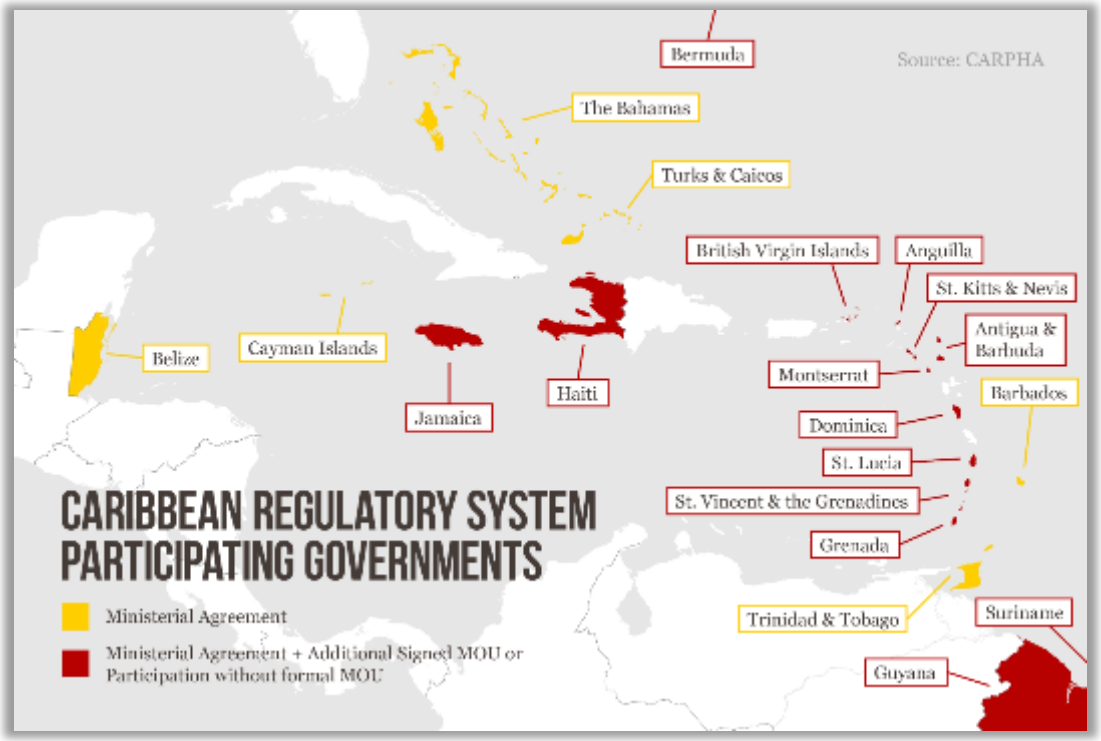
Reliance for product and MAH information

- Under **Article 57 of EU** pharmaceutical legislation:
  - manufacturers submit and update information on authorized medicines to EMA.
- Regulators of all EU Member States can access the information;
- This helps regulators to:
  - Identify the company's qualified person for pharmacovigilance (QPPV);
  - Submit coordinated enquiries to companies;
  - Organize joint PV inspections etc.

Article 58: Reliance on EMA scientific opinions by non-EU countries

- EMA provides scientific opinions on high priority medicines & vaccines for markets outside EU;
- The evaluations are carried out by EMA in cooperation with WHO and “target” non-EU NRAs;
- The relying regulatory authorities can use the risk management plan (RMP) proposed by EMA for specific products;
- But, benefit-risk assessment is focused on the intended non-EU population and indication(s);
- Procedure facilitates patient access to essential medicines ad vaccines in low- and middle-income countries (LMICs), especially for:
  - neglected diseases;
  - diseases such as HIV/AIDS, malaria and tuberculosis.

Regional reliance for PV



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- The Caribbean Regulatory System (CRS) provides an example of a regional reliance mechanism;
- Many small states in the Caribbean Community (CARICOM) submit in-country adverse reaction reports to *VigiBase* through CRS;
- Good example of leveraging the regional capacity for post-market surveillance.

Reliance in the context of WHO PQ process

- A group of countries, or a regional economic community could identify a reference country to join (and represent the region/ community in) the WHO PQ assessment process;
- For example, representatives from the reference LMIC could participate as assessors for the WHO PQ/EUL of COVID19 vaccine:
  - to review the Risk Management Plans and PV activities in the dossiers;
  - to ensure relevance of the PV plans for their region.
- All other countries in the region would then be able to rely on the WHO PQ decision;
- The reliance approach could be used also for PV inspections.
  - For WHO-prequalified products, WHO inspection outcomes would be used by all countries.

Examples of work-sharing in PV

Groups of countries coming together in a region to carry out:

- Joint review of periodic safety update reports/periodic benefit-risk evaluation reports (PSURs/PBRERs) on products of mutual interest;
- joint review of safety data from regional multi-centre studies; and
- collaborations between NRA and national immunization programme (NIP) for activities such as training, signal investigation, etc.

Batch release of vaccines: challenges

Vaccine lot release by the National Regulatory Authority (NRA) / National Control Laboratory (NCL) is a fundamental component of the vaccine regulation post-licensing.

Challenges:

- **Globalization** of vaccine industry: increasing number of production sites
- **Limited resources** of regulatory authorities (developed and developing countries) and laboratories
- **Duplication of efforts** through redundant testing and approval of variations
- **Non-compliances** in test outcomes by importing countries: delay in vaccine access, disruption of vaccine delivery
- Increasing number of **complex vaccines** (test and cost intensive) and against **new pathogens**

Batch release of vaccines: challenges (cont.)

- WHO recommends* that further release by the NRA/NCL of receiving countries **is not required** since these products will have already been released by the responsible NRA/NCL.
- **To support the implementation of this guidance**, in 2017 WHO launched a National Control Laboratory Network for Biologicals (WHO-NNB);
- WHO-NNB covers pre- and post- prequalification testing of biologicals by WHO contract laboratories;
- Aims to facilitate access to prequalified vaccines (or other biological products) **through RELIANCE on the batch release testing** performed by the respective Network Members.

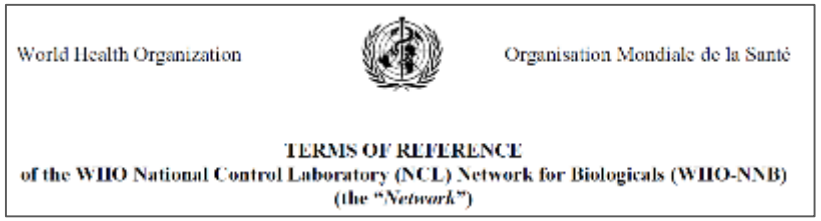
*__Guidelines for independent lot release of vaccines by regulatory authorities__. WHO Technical Report Series 978, Annex 2

WHO response to challenges: WHO-National Control Laboratory Network for Biologicals

Creation of a structure and infrastructure to make information available to others (receiving/importing countries)

WHO-NNB works towards effective use of globally available resources, which is only possible through building of confidence, harmonization of requirements, exchange of information, collaboration, reliance and recognition of regulatory decisions

WHO-National Control Laboratory Network for Biologicals (2017)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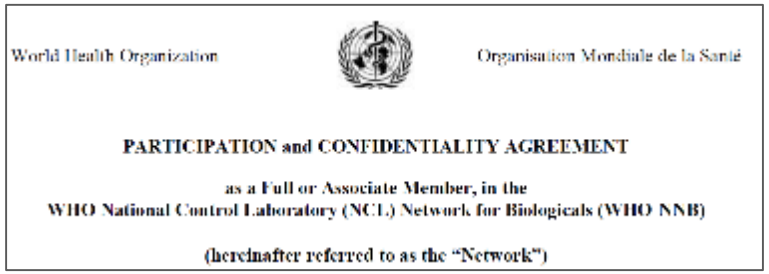
TERMS OF REFERENCE
of the WHO National Control Laboratory (NCL) Network for Biologicals (WHO-NNB)
(the "*Network*")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PARTICIPATION and CONFIDENTIALITY AGREEMENT

as a Full or Associate Member, in the
WHO National Control Laboratory (NCL) Network for Biologicals (WHO NNB)

(hereinafter referred to as the "Network")

The Network – platform and basis for reliance: Main objectives - Membership

- Aims to facilitate access to prequalified vaccines (or other biological product) through reliance on the batch release testing of the respective Network Members;
- Main objective is to share quality information in order to facilitate access to prequalified vaccines through recognition by recipient countries of the lot release decisions of the responsible NRA;
- Intention to build mutual confidence amongst members, reduce redundant testing, promote the development of common standards and facilitate the sharing of best practices.

Membership

There are two types of **Members** of the Network, as follows:

a) **Full Members**: this classification is eligible to NCLs from countries producing WHO-prequalified vaccines (or other biological medicinal products), and WHO-contracted NCLs; and

b) **Associate Members**: this classification is eligible to NCLs or NRAs in countries that are recipients of UN-procured vaccines (or other biological products).

The Network – platform and basis for reliance: what each partner brings to the Network - NRAs

Responsible NRAs/NCLs in producing countries have

- Best insight in vaccines and testing methods;
- Functional vaccine regulation including lab capacity;
- Batch release – part of the national regulation.

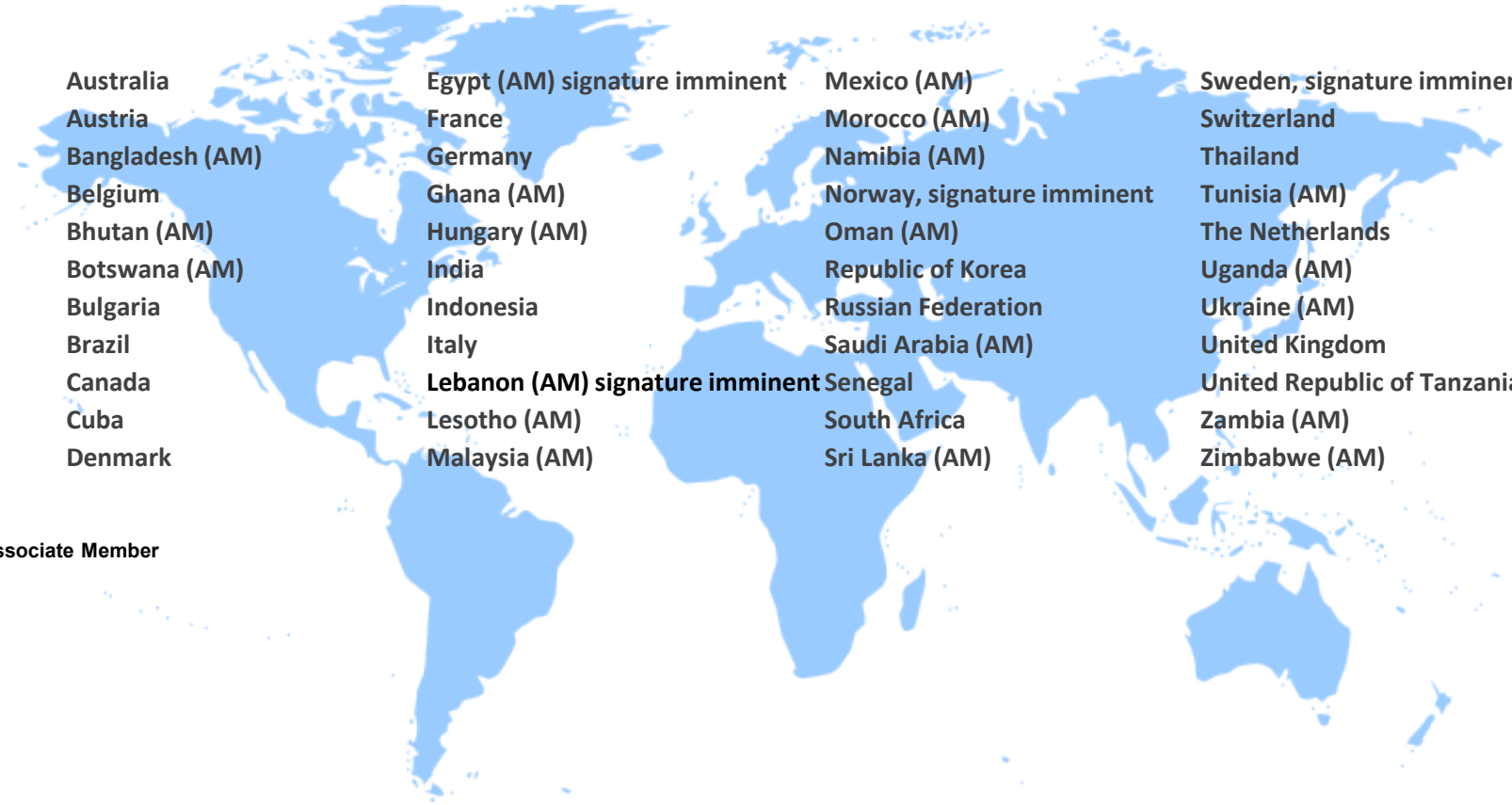
Expert hub which assures quality and safety of vaccines - 22 full Network members.

The Network – platform and basis for reliance: What each partner brings to the Network - WHO

- International mandate of **194 Member States** and WHA resolution 67.20 concerning regulatory networks;
- Existing expert hub of qualified NCLs testing for WHO;
- Reports on vaccine quality data = WHO test outcome (pre- and post-PQ);
- Reports on vaccine quality data through sharing of lot release data;
- Established Terms of Reference & Participation-Confidentiality Agreement;
- Secured electronic platform.

Information and service center which collects, contributes and distributes quality information in a secure and confidential setting

The Network – platform and basis for reliance: > 40 country members



Australia
Austria
Bangladesh (AM)
Belgium
Bhutan (AM)
Botswana (AM)
Bulgaria
Brazil
Canada
Cuba
Denmark
Egypt (AM) signature imminent
France
Germany
Ghana (AM)
Hungary (AM)
India
Indonesia
Italy
Lebanon (AM) signature imminent
Lesotho (AM)
Malaysia (AM)
Mexico (AM)
Morocco (AM)
Namibia (AM)
Norway, signature imminent
Oman (AM)
Republic of Korea
Russian Federation
Saudi Arabia (AM)
Senegal
South Africa
Sri Lanka (AM)
Sweden, signature imminent
Switzerland
Thailand
Tunisia (AM)
The Netherlands
Uganda (AM)
Ukraine (AM)
United Kingdom
United Republic of Tanzania (AM)
Zambia (AM)
Zimbabwe (AM)

AM: Associate Member

WHO responses to challenges: WHO test programme

- Harmonization of test methodologies (performance of feasibility studies, collaborative studies and hands-on training courses)
- Change in PQ procedure section 3.4 (endorsed by ECBS, meeting 2014):
  - Optimized logistics: Introduction direct shipments of vaccines to WHO test laboratories
  - Use of NCL of producing country (testing)
- Use of resources: lot release data gathered by the official national control laboratory (on consent of manufacturers) and technical know-how.

Summary/conclusions

- Timely access to medical products – never-ending challenge;
- All patients/consumers deserve access to quality assured medical products with positive benefit-risk characteristics – Universal Health Coverage;

Today's reality and demand:

- To generate quality national decisions regulators globally MUST collaborate and MUST take into consideration the information available from other regulatory authorities;
- Not using the outputs and outcomes from other (better resourced) regulatory authorities would only mean lost opportunity, duplication of efforts, increased regulatory burden and waste of scarce resources.

World Health Organization

www.who.int/medicines