



Overview of the legal framework for Pharmacovigilance

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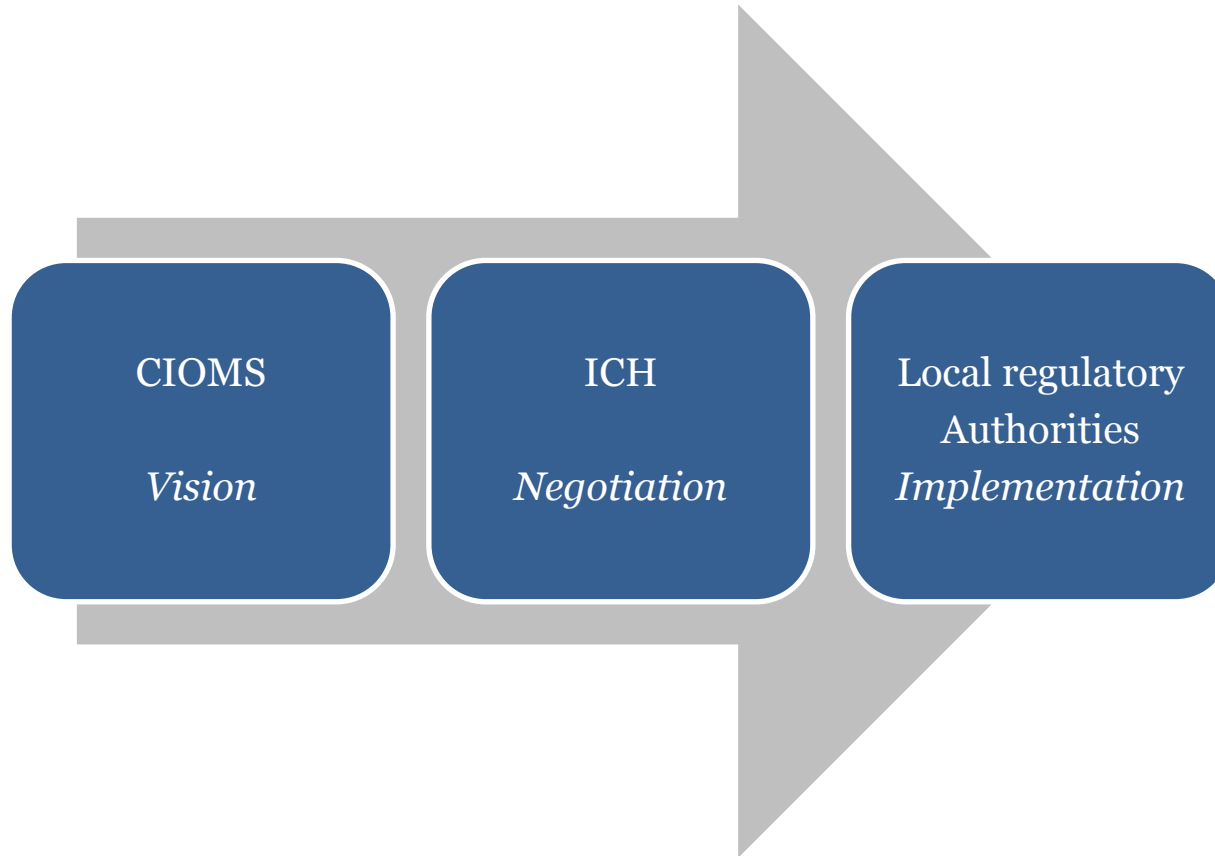
Overview of the legal framework

- **Overview of regulatory framework**
 - CIOMS
 - ICH
 - Legal framework in the EU
 - Legal framework in the US
 - WHO
 - China
- **Compliance with Pharmacovigilance Regulations**



CIOMS & ICH

From CIOMS to regulations





Council for International Organisations of Medical Sciences (CIOMS)

- The **Council for International Organizations of Medical Sciences (CIOMS)** is an [international nongovernmental organization](#) established jointly by [WHO](#) and [UNESCO](#) in 1949.
- CIOMS serves the scientific interests of the international biomedical community in general and has been active in promulgating guidelines for the ethical conduct of research, among other activities.



Council for International Organisations of Medical Sciences (CIOMS)

- **International members** (e.g International Society of Internal Medicine, International Society of Pharmacovigilance)
- **National members** (e.g Czech Medical Association; Korean Academy of Medical Sciences)
- **Associate members** (e.g Good Clinical Practice (GCP) – Alliance; National Fund for Scientific Research (NSFR))



Council for International Organisations of Medical Sciences (CIOMS)

CIOMS Working groups

A broad range of drug safety topics has been covered by CIOMS via working groups. Senior scientists from regulatory authorities, pharmaceutical industry and academia have joined together in order to develop consensus guidelines within areas such as international reporting of adverse drug reactions (CIOMS I reporting form), periodic drug safety update summaries and development safety update report, core clinical safety information on drugs, terminology of ADRs, standardised MedDRA queries and pharmacogenetics. There have also been joint working groups together with WHO covering drug development research and pharmacovigilance in resource-poor countries and vaccine pharmacovigilance.



Council for International Organisations of Medical Sciences (CIOMS)

CIOMS Working groups – some examples

- CIOMS I - Expedited reporting of individual ADRs (1990)
- CIOMS IA - Harmonisation of data elements and fields for Electronic reporting of individual ADRs (1995)
- CIOMS II - Periodic Safety Updates (1992)
- CIOMS III - Core Clinical Safety Information (1995)
- CIOMS IV - Benefit/Risk Evaluation (1998)
- CIOMS V - Good Case Management and Reporting Practices (2001)
- CIOMS VI - Surveillance and Assessment of Drug Safety Data from Clinical Trials



Council for International Organisations of Medical Sciences (CIOMS)

- CIOMS VII – Development Safety Update Reports
- CIOMS VIII – Signal Detection
- CIOMS IX – Risk Minimisation
- CIOMS X – Meta Analysis
- MedDRA (SMQs)
- Vaccine Pharmacovigilance
- Vaccine Safety



Council for International Organisations of Medical Sciences (CIOMS)

Main achievements

- Common format for the international reporting of suspected serious post-marketing reports
- Introduced concepts of:
 - ✓ Health Care Professional
 - ✓ Valid report
 - ✓ Seriousness
 - ✓ Relatedness
 - ✓ Expectedness



ICH – International Council for Harmonisation

Objectives of ICH

- ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered
- To bring together regulatory authorities from three regions (EU, USA, Japan) with experts from pharmaceutical industry
- To discuss scientific and technical aspects of product registration, leading to harmonisation to reduce duplicative effort during the development of new medicines



ICH – International Council for Harmonisation

- Provide forum for constructive dialogue
- Identify areas where modifications in technical requirements/greater mutual acceptance of R&D procedures could lead to more economical use of resources without compromising safety
- Recommend practical ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for registration



ICH – International Council for Harmonisation

Co-sponsors of ICH

- European Commission
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Ministry of Health, Labour and Welfare (MLHW), Japan
- Japan Pharmaceutical Manufacturers Association (JPMA)
- Food and Drug Administration (FDA), USA
- Pharmaceutical Research and Manufacturers of America (PhRMA)



ICH – International Council for Harmonisation

ICH Products

- Safety guidelines
- **Efficacy** guidelines (E2A – E2F Pharmacovigilance)
- Quality guidelines
- **Multidisciplinary** guidelines



ICH – International Council for Harmonisation

Safety Guidelines

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years



ICH – International Council for Harmonisation

Efficacy Guidelines

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.



ICH – International Council for Harmonisation

Efficacy Guidelines (E2A – E2F Pharmacovigilance)

- E2A: Clinical Safety Data Management: Definitions and standards for Expedited Reporting
- E2B(R3): Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
- E2B (R3) IWG: Implementation: Electronic Transmission of ICSRs
- E2C (R2): Periodic Benefit-Risk Evaluation Report (PBRER)
- E2C (R2) Q&As: Questions and Answers PBRER



ICH – International Council for Harmonisation

Efficacy Guidelines (E2A – E2F Pharmacovigilance)

- E2D: Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting
- E2E: Pharmacovigilance Planning
- E2F: Development Safety Update Report (DSUR)



ICH – International Council for Harmonisation

Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.



ICH – International Council for Harmonisation

Multidisciplinary guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI)



ICH – International Council for Harmonisation

Multidisciplinary guidelines

- M1: MedDRA terminology
- M2: Electronic transmission Standards
- M3: Nonclinical Safety Studies
- M4: Common Technical Documents
- M5: Data Elements and Standards for Drug Dictionaries
- ...



EEA – Regulatory Framework

- In October 2001, the Commission published its proposals to amend the body of legislation covering the EU medicines regulatory regime ([Regulation 2309/93](#) and [Directive 2001/83/EC](#))
- The **Regulation** applies to products that have been registered under the “Centralised” process and is immediately binding in all member states
- The **Directive** is relevant for products registered under mutual recognition or national procedures but requires endorsement via national legislation



EEA – Regulatory Framework

The agreed texts were adopted by the Council and the European parliament on 31 March 2004 as:

- [Regulation \(EC\) 726/2004](#) – Community Procedures for the authorisation and supervision of Medicinal Products for Human use and establishing a European Medicines Agency (amending Regulation 2309/93)
- [Directive 2004/27/EC](#) on the Community Code relating to Medicinal Products for Human use (amending Directive [2001/83/EC](#))



EEA – Regulatory Framework

Recent changes – 2012 & 2013

- [Directive 2010/84/EU & Regulation \(EU\) 1235/2010](#) amending the pharmacovigilance sections of [Directive 2001/83/EC & Regulation \(EC\) 726/2004](#)
- [Implementing Regulation \(EU\) 520/2012](#) - Performance of PV activities
- [Guidelines on Good Pharmacovigilance Practices \(GVP\)](#)



EEA – Regulatory Framework

GVP Modules

- I - Pharmacovigilance Systems and their Quality Systems
- II: Pharmacovigilance System Master File
- III: Pharmacovigilance Inspections
- IV: Pharmacovigilance Audits
- V: Risk Management Systems
- VI: Management and Reporting of ADRs
- VII: Periodic Safety Update Reports
- VIII: Post Authorisation Safety Studies (PASS)
- IX: Signal Management
- X: Additional Monitoring



EEA – Regulatory Framework

GVP Modules con't

- XV: Safety Communication
- XVI: Risk Minimisation measures tools & effectiveness indicators
- Annex I: Definitions
- Annex II: Templates
- Annex III: Other PV guidance
 - Guideline on the exposure to medicinal products during pregnancy
 - Guideline on conduct of PV activities for medicines used by paediatric population
 - Note for guidance EV Human – Processing of safety messages and individual case safety reports (ICSRs)
- Annex IV
 - ICH technical documents
- Annex V: Abbreviations



EEA – Regulatory Framework

GVP Modules – con't

Population specific Modules

- P I: Vaccines for prophylaxis against infectious diseases
- P II: Biological medicinal products

Other planned modules

- P III: Pregnancy and breast-feeding
- P IV: Geriatric population

All Modules are subject to ongoing reviews with public consultations



EEA – Regulatory Framework

PRAC – Pharmacovigilance Risk Assessment Committee

TASKS:

- Create and maintain EURD list (PSURs)
- Assess PV data (PSURs & RMPs)
- Assess & endorse/object to PASS if in more than 1 member state
- Establish a list of products for additional monitoring (black triangle)

39 voting members

- Appointed by each Member state (total 31)
- Appointed by European Commission
 - 6: relevant expertise
 - 1 representing patient organisations
 - 1 representing health care professionals



USA – Regulatory Framework

Law:

A legislative act of government that declares, commands, or prohibits something. Laws are usually written in general terms.

Regulation:

A rule issued by a government agency that has the force of law. Regulations interpret and add detail to a law, but cannot supersede it.

Guideline:

An interpretive document that represents current government thinking on a scientific topic. Guidelines are not binding on the public or government



USA – Regulatory Framework

Basic Definitions

- **Investigational New Drug (IND)**
 - An application that is required by the FDA before testing any new drug in humans.
- **New Drug Application (NDA)**
 - An application submitted by a manufacturer to the FDA for approval to market a new drug for human use in the USA.
- **Product Licence Application**
 - Similar to a NDA, but for biological products, including vaccines



USA – Regulatory Framework

The *Code of Federal Regulations* (**CFR**) contains general and permanent rules published in the *US Federal Register* (the Government's daily newspaper) by the Federal Government

- The CFR is divided into 50 titles representing broad areas subject to Federal regulations
 - Each title is divided into chapters that usually bear the name of the issuing agency
 - Each chapter is further subdivided into parts covering specific regulatory areas
 - Large parts may be subdivided into subparts.
 - All parts are organized in sections, and most citations to the CFR will be provided at the section level



USA – Regulatory Framework

Regulations that govern safety reporting to the FDA are found in **Title 21 of the CFR**

- 21 CFR 201: Labeling
- 21 CFR 211.198: Complaint Files
- 21 CFR 310.305: Records & reports concerning adverse drug experiences on marketed prescription drugs for human use without approved NDAs
- **21 CFR 312.32**: IND Safety Reports
- **21 CFR 312.33**: IND Annual Reports
- **21 CFR 314.80**: Post-marketing reporting of adverse drug experiences (applicable to all medicinal products with a marketing license)
- **21 CFR 600.80**: Post-marketing Reporting of Adverse Experiences (applicable to licensed biological products, including vaccines)



China – main regulations

- The Drug Administration Law of the People's Republic of China (1984, revised 2001)
- Regulation for the Administration of Adverse Drug Reaction Reporting and monitoring (1999; revised 2004 and 2010)



China – ADR monitoring

> 400 ADR centers in prefectures

→ > 30 provincial centers

→ 1 national center

- Timelines:

- New / serious 15days

- Death timely ≤ 15 days

- Other ≤ 30 days



China- Vaccines PV

- National AEFI information system since 2011, > 100,000 reports in 2013
- Involvement CDC in ADR monitoring (division of AEFIs in National Immunisation Program)



China - AEFI specific reporting requirements

Time since immunization	Type AEFI
Within 24 hours	anaphylactic shock, allergic reactions without shock (hives, rash, laryngeal edema, etc.), toxic shock syndrome, syncope, hysteria, etc.
Within 5 days	fever (axillary temperature 38.6°C), angioedema, systemic purulent infection (toxemia, septicemia, sepsis), redness and swelling in the injection site (diameter $>2.5\text{cm}$), scleroma (diameter $>2.5\text{cm}$), localized purulent infection (localized abscess, lymphangitis and lymphadenitis, cellulitis), etc.
Within 15 days	measles-like or scarlet fever rash, Henoch-Schönlein purpura, localized allergic necrosis reaction (Arthus' reaction), febrile convulsion, epilepsy, polyneuritis, encephalopathy, encephalitis and meningitis, etc.
Within 6 weeks	thrombocytopenic purpura, Guillain-Barre syndrome, vaccine associated paralytic polio, etc.
Within 3 months	brachial plexus neuritis, sterile abscess in the injection site, etc.
1-12 months	after BCG lymphadenitis or lymphangitis, osteomyelitis, systemic disseminated BCG infection, etc.
Any time	other serious AEFI suspected to be caused by vaccination



China - specificities

- Investigation of special reports: deaths, severe disabilities, clusters, AEFI of significant public health concern
- Includes causality assessment experts panels at local and national level
- AEFIs classification:
 - Adverse reactions
 - common reaction
 - rare reaction
 - Vaccine Quality Event
 - Program Error
 - Coincidental event
 - Psychogenic reaction



WHO prequalification requirements for vaccine safety monitoring



Vaccine prequalification (PQ)

- A service provided to UN purchasing agencies
 - UNICEF
 - PAHO's Revolving Fund
- Prequalification is often a requirement when vaccines are procured independently by countries
- Components of the evaluation
 - Quality assessment
 - **Clinical assessment**
 - Laboratory testing
 - Site audit
 - *Also:* Programmatic suitability



Conditions for PQ evaluation

- **Vaccine is licensed/registered by the responsible national regulatory authority (NRA) of the exporting country**
 - **Scientific opinion by EMA accepted**
- Continued regulatory oversight by NRA is required as well as
- communication with WHO about potential problems with the
- vaccine

- **WHO (regulatory) guidelines/recommendations available**
 - **Technical Report Series (TRS) documents**
 - **SAGE (if available)**
- **Vaccine listed in the vaccine priority list**
 - **http://www.who.int/immunization_standards/vaccine_quality/pq_priorities/en/index.html**



PQ Clinical Review

- Summary of Clinical Development plan
- • Clinical trial overview
- • Clinical summary with interpretation of the safety and efficacy data of all studies (pre- and post-licensure) and
- relevance to support worldwide use
- • Independent clinical expert report
- • Pharmacovigilance plan
- • Safety Studies
- • Clinical claims of the product insert



Post PQ activities

Commitments from the manufacturer

- Report variations to WHO
- Report serious AEFI
- Provide regular updates of safety profile
- Inform of WHO of problems that may impact the quality, safety, efficacy or timely supply of product



Post PQ activities: WHO

- Variations
- Annual Report evaluation
- Reassessment
- Targeted testing program
- Monitoring/Investigation of vaccine quality and cold chain complaints
- Monitoring/investigation of Adverse Events following immunization (AEFI)
- Collaborative National Registration
- Technical Review of tenders for UNICEF



Prequalified Vaccine Annual Reports (PQVAR)

- A summary of variations to the product that have been implemented since the previous annual report
- Supporting documents (including NRA approval)
- Testing results from the ongoing stability programme
- Production and distribution data.
- GMP inspections list (since the previous annual report).
- A summary update on implementation of post-PQ
- commitments
- Periodic Safety Update Report (electronic data only).



PSURs and Vaccine Prequalification

- PSURs can be received by WHO Vaccine PQ Secretariat in two situations:
 - Before prequalification
 - In case of new applications for PQ of vaccines already marketed for more than a year
 - After prequalification
 - PSURs should be submitted annually as part of the Prequalification Vaccine Annual Review (PQVAR) documentation

BOTH SITUATIONS APPLICABLE TO CHINA!



PSUR format

- No specific format required
 - The format required by the National Regulatory Authority (NRA) of reference is accepted by WHO
- Content is what matters
- ICH format is accepted



PSUR evaluators

- WHO staff member and /or
- External expert(s) contracted by WHO
 - Two for the clinical evaluation of a new application of a vaccine for PQ
 - PSUR evaluation is just one component
 - Usually one in case of annual review of novel vaccines
 - PSUR evaluation is the sole purpose
 - External experts have to
 - sign a Confidentiality Agreement
 - fill in and sign a Declaration of Interests



Evaluation of the PSUR - 1

1. Background information on the vaccine product
 - 1.1 Composition of the vaccine
 - 1.2 Recommended schedules and routes of administration
 - 1.3 Marketing authorization status



Evaluation of the PSUR - 2

2. Presentation of PSUR(s)

2.1 General information

2.2 Serious unlisted adverse events

2.3 Non-serious unlisted reported adverse events

2.4 Serious and non-serious listed events

2.5 Medically unconfirmed cases

2.6 Clustering

2.7 Other safety information

3. Overall safety evaluation, conclusions and recommendations



Additional considerations -

1

- All dosage forms, formulations and indications for a given vaccine should be covered in one PSUR
- Within a single PSUR separate presentations of data may be appropriate for different
 - dosage forms
 - indications
 - populations (e.g. children vs. adults)
 - schedules (e.g. age at administration, booster dose)
 - and routes of administration



Additional considerations - 2

- For combination vaccines a separate PSUR is required even when its individual components, alone or in combination, are marketed individually
 - e.g. measles-mumps-rubella vaccine, measles-rubella vaccine, measles vaccine etc...produced by the same manufacturer



The other (non-regulated) roles of WHO in vaccine PV

- The Global Vaccine Safety Blueprint
- Stimulate/support AEFI reporting systems
- Stimulate/support AEFI review systems
- **Global Advisory Committee on Vaccine Safety (GACVS)**
- **WHO Programme for International Drug Monitoring**
- And much more



Blueprint vision and goals

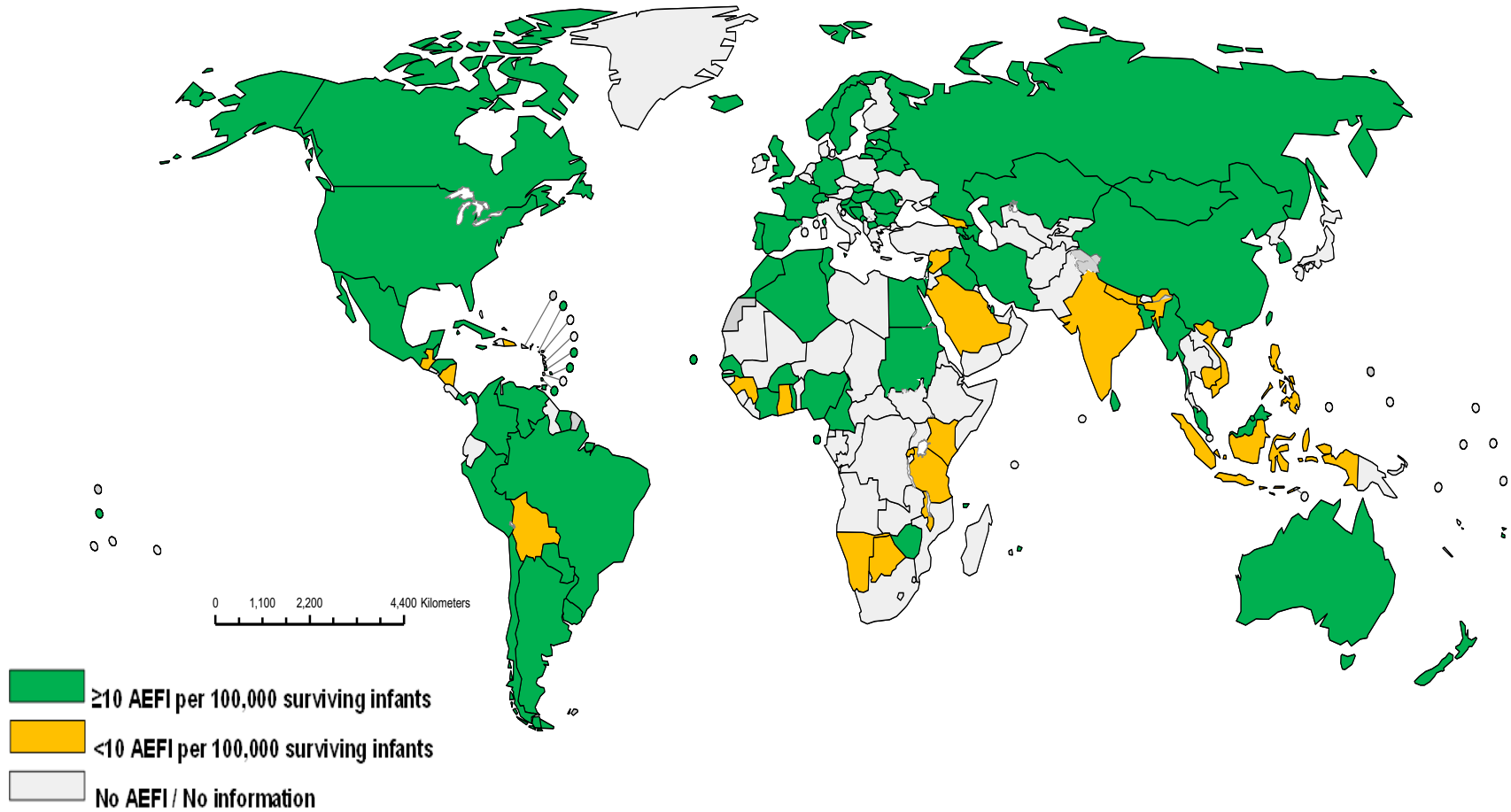
VISION

Effective vaccine pharmacovigilance systems are established in all countries

3 main goals

- ✦ To assist low- and middle-income countries to have at least minimal capacity for vaccine safety activities;
- ✦ To enhance capacity for vaccine safety assessment in countries that
 - introduce newly developed vaccines,
 - introduce vaccines in settings with novel characteristics or
 - both manufacture and use prequalified vaccines;
- ✦ To establish a global vaccine safety support structure.

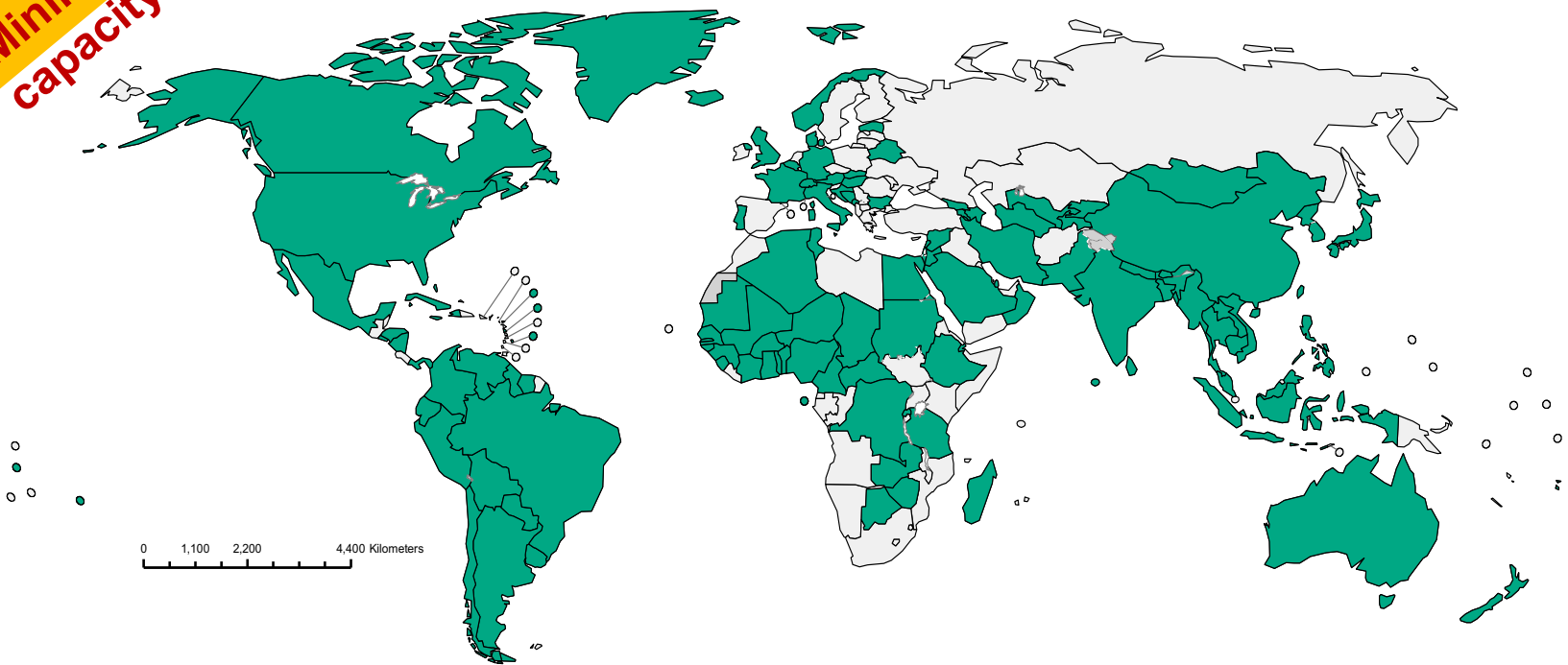
AEFI reports 2015





Member States with a Vaccine Adverse Events Review Committee in 2015

Minimal capacity



- 118 Member States or 61%
- No / No data
- Not applicable

Source: WHO/UNICEF coverage estimates 2015 revision.
Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization
Date of slide: 13 October 2016

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization 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 lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2016. All rights reserved



GACVS: Global analysis and response

- GACVS reviews safety issues raised by:
 - IVB and other WHO departments
 - Member states
 - Literature or research (pre- and post-publication)
 - Meetings, conferences
 - Committee members
- WHO/QSS/EMP serves as point of contact for bringing issues forward to GACVS
- Countries are encouraged to bring serious safety issues from national perspective to attention of WHO for possible GACVS review



WHO Programme for International Drug Monitoring



WHO Collaborating
Centre since 1978

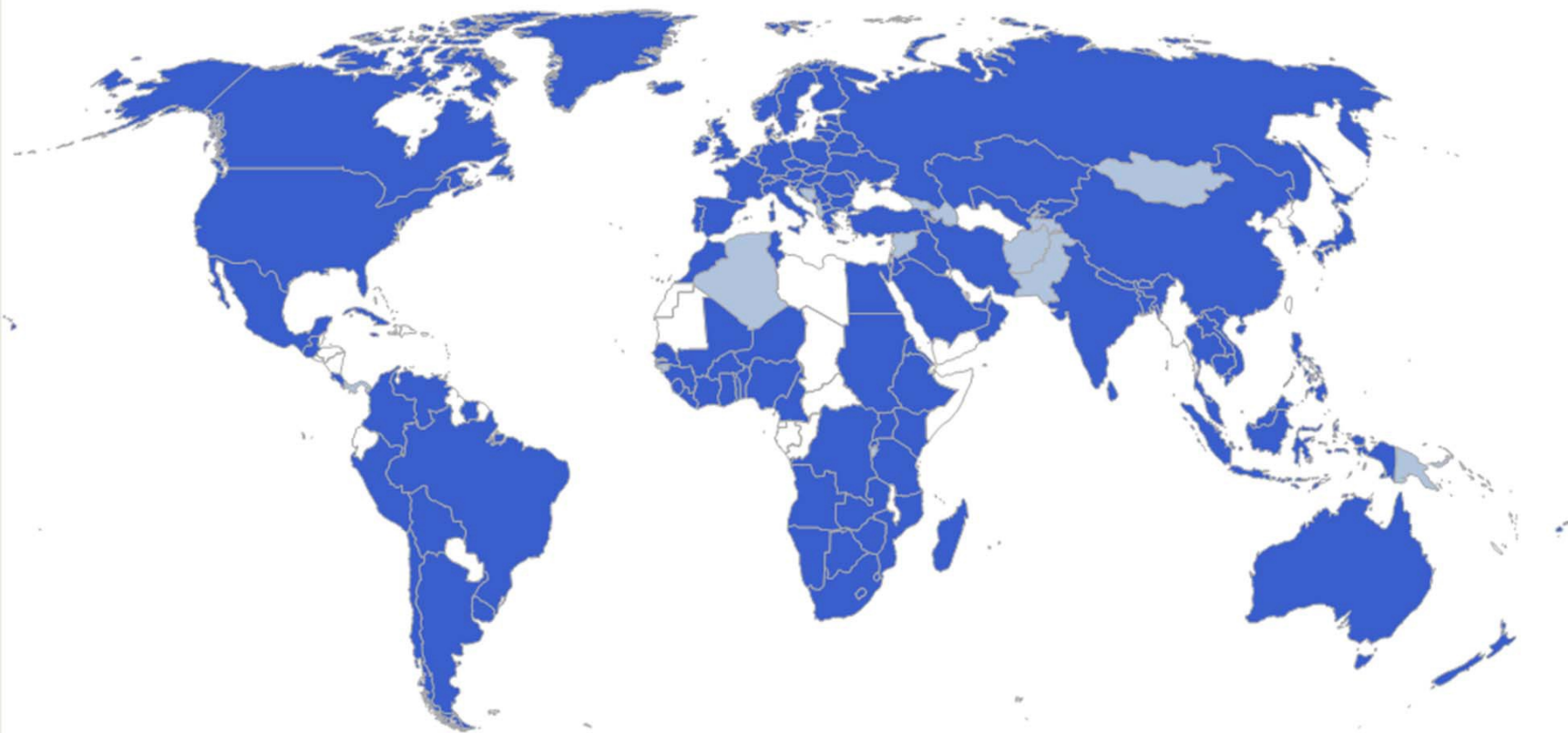
Functions include:

- Global database of “ADRs” from National Pharmacovigilance Centers (drugs, vaccines, herbals)
- Signal detection and signal strengthening
- Harmonization and standardization:
 - Definition of terminologies (events, reaction, signal)
 - WHO Adverse Reaction Terminology (WHO-ART)
 - WHO Drug Dictionary
- Forum for national centers to share experience



WHO Programme for International Drug Monitoring

As of August 2015



Full Member



Associate Member



And much more is being done by WHO on vaccine PV

- Vaccine Adverse Event Information Management System (VAEIMS)
- AEFI filed investigation simulation exercises
- Vaccine safety communication
- Vaccine Safety Net website (> 100 Mi visits/month)
- CIOMS involvement
- Regional/Local training (incl China)
- IS surveillance
- AEF_I surveillance India
- Global vaccine safety collaboration on active surveillance using databases