Regulatory harmonization and alliances to foster vaccination

Developing Country Vaccine Manufacturers Network 14th AGM

7-9 October 2013, Hanoi

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WHO/HIS/EMP/TSN

World Health Organization

Outline

- Regulatory harmonization - or regulatory convergence?
  - Platforms to promote regulatory convergence
  - AVAREF
- Common standards for vaccines
  - Development of WHO written and measurement standards
  - Implementation of recently adopted WHO standards
- Alliances to promote vaccination
  - Network of WHO Collaborating Centers for standardization and evaluation of vaccines
  - Regulatory science agenda for vaccines

Harmonization or convergence?

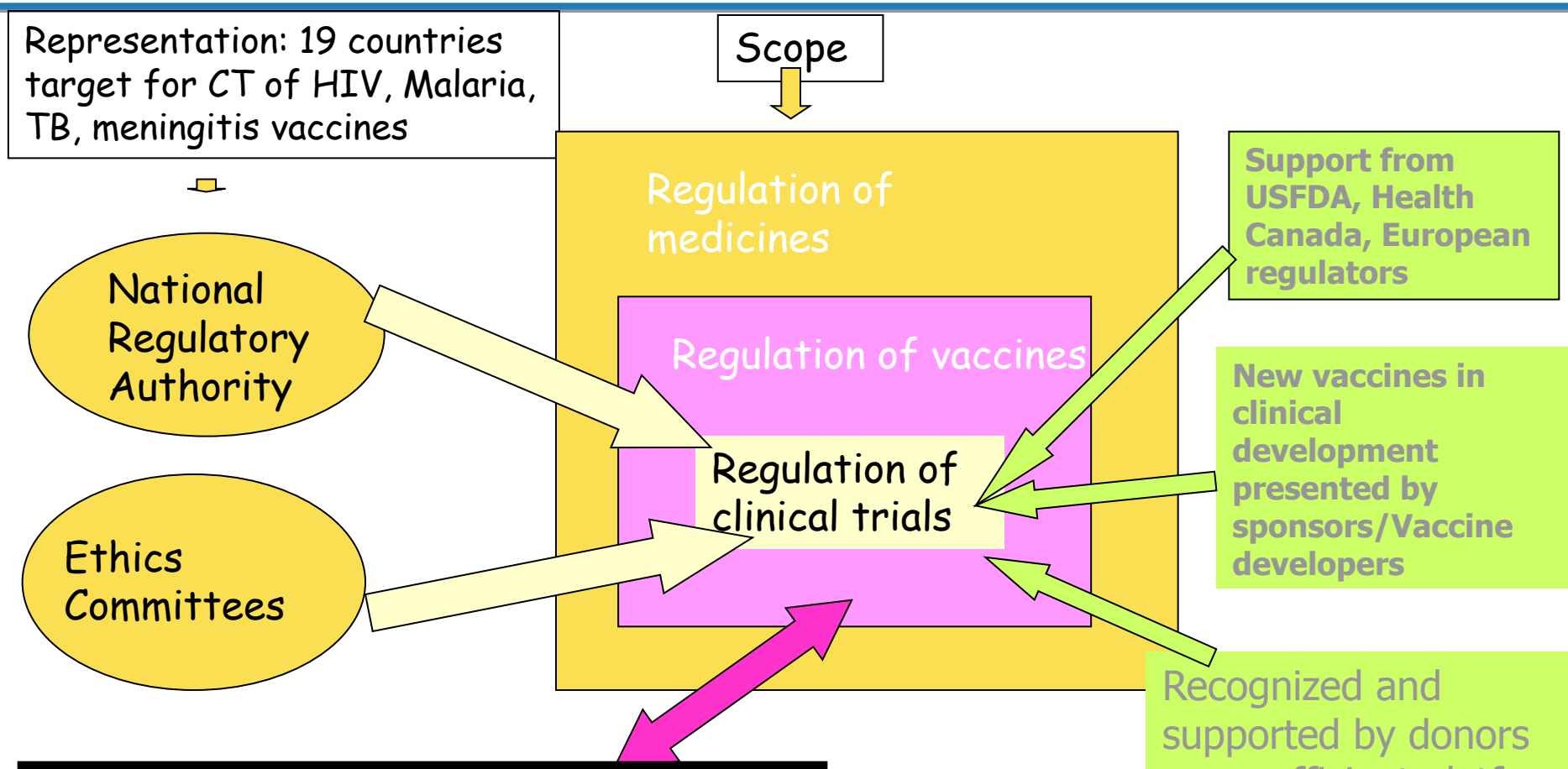
- Regulatory harmonization initiatives
  - European Medicines Agency
  - ASEAN
  - APEC
  - East African Community
  - Many others
- Regulatory convergence
  - Current direction of thinking by regulators
    - Soon to be published US Institute of Medicine report
  - Same decisions are reached without a legally-binding obligation to do so

Platforms to promote regulatory convergence

- Leveraging decisions of others
  - Expedited review procedure for prequalified vaccines
    - See Nora Dellepiane's presentation at this meeting
- Joint reviews
  - Article 58 process of EMA
  - Clinical trail applications for multi-country CTs
    - AVAREF
- Common standards
  - WHO standardization processes
  - WHO prequalification

AVAREF-African Vaccine Regulatory Forum

An informal network approach to regulation of clinical trials in Africa



Informal structure allows rapid and dynamic response as per needs identified

Currently working on formalization process

WHO norms and standards for biologicals

Global written standards

www.who.int/biologicals

Global measurement standards

Regulatory science agenda

1) Standardization of assays
2) Further development and refinement of QC tests
3) Scientific basis for setting specifications

Reference preparations for vaccines and biotherapeutics

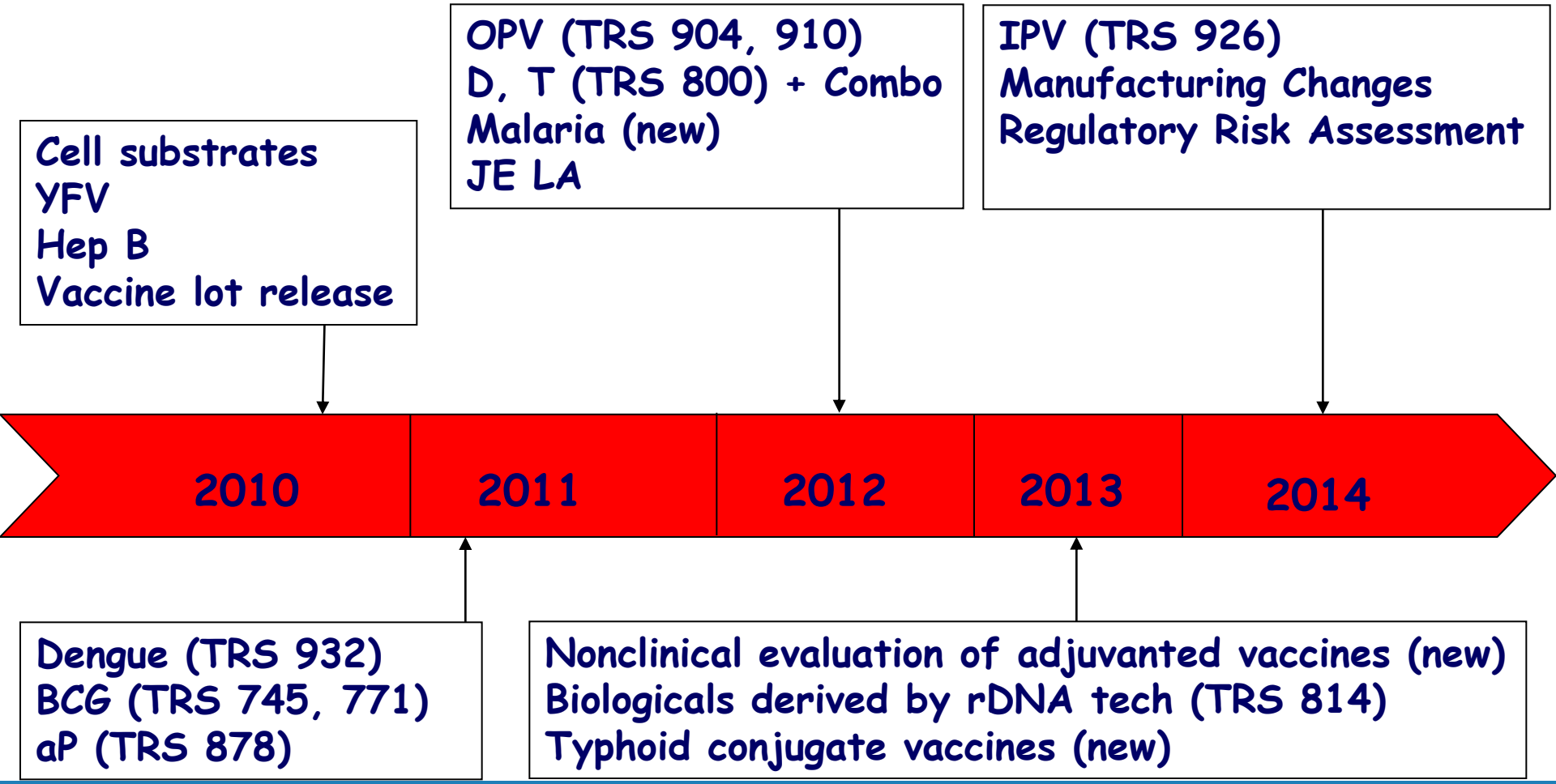
Measurement standards:
essential elements for development, licensing and lot release

WHO Written Standards for Vaccines

- Technical specifications that help define safe and efficacious vaccines
- Intended to be scientific and advisory in nature
- Starting point for setting national requirements as well as a basis for vaccine prequalification
- Guidance for NRAs and manufacturers on international regulatory expectations for the production and quality assurance of vaccines, stability, non-clinical and clinical evaluation of vaccines
- Facilitating international convergence of vaccine licensure
- Living documents revised in response to scientific advances

Evolving concept: from quality specifications to scientific principles for the entire regulatory oversight

Development of written standards ECBS 2010 - 2014



New reference preparations from WHO

International Standards adopted by ECBS 2012

- Anti HPV -18 serum - **1st International Standard**
- Diphtheria antitoxin, Human- **1st International Standard**
- Antibody to influenza H1N1 pdm virus – **2nd International Standard**
- BCG Moreau – **Reference Reagent**
- Endotoxin- **3rd International Standard**

Proposed new International Standards for consideration by ECBS 2013

- Trivalent inactivated polio vaccine (TIPV) for D antigen assay

Proposed new projects for consideration by ECBS 2013

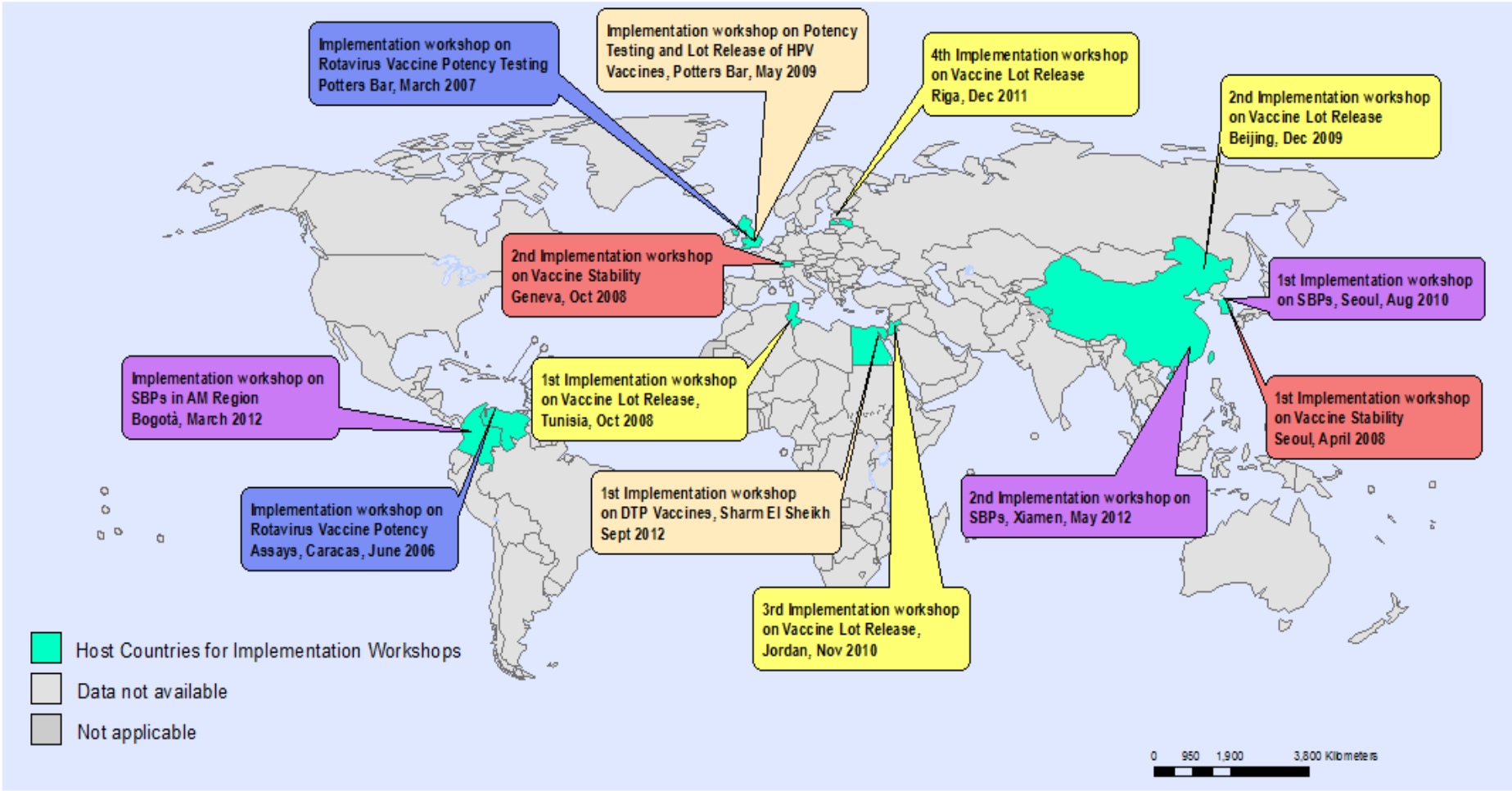
- Replacement standards for: Diphtheria toxoid for flocculation assay; High and Low Mutant Reference Virus for MAPREC assay of poliovirus type 2

New standards for Typhoid Vi polysaccharide; Meningococcal Serogroup A polysaccharide

Selected topics for implementation workshops

1. Stability evaluation of vaccines
2. Standardization of biotherapeutic products
3. Vaccine lot release
4. Combined vaccines based on DTP
5. Regulatory Risk Assessment

Implementation of selected written standards - 2008-2012



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Data Source: World Health Organization

World Health Organization

Stability evaluation of vaccines: WHO Guidelines

- WHO Guidelines on Stability Evaluation of Vaccines: Oct 2006

http://www.who.int/biologicals/vaccines/stability_of_vaccines_ref_mats/en/index.html

- Implementation workshops:
  - WHO/ IABS workshop – Oct 2008
  - Regional workshops
    - Hosted and co-organized by Korea FDA – April 08
    - Bi-regional workshop: Bangkok, 30 Jan – 1 Feb 2013

- Concept of regional implementation
  - NRAs and NCLs involved as well as manufacturers (DCVMN, IFPMA)
  - Case studies focused on the need in the region in question
  - Opportunity for further developments in specific areas

Constraints at NRAs in SEA & WP in Implementing Stability Guidelines

- Limited human resources dedicated to evaluating vaccine stability, there for lack of experts with comprehensive understanding and knowledge of stability issues
- Limited experiences in reviewing stability report based on statistical modeling
- Limited access to statistical experts (in-house or academic) who are knowledgeable to study design & analysis of vaccine stability
- Others
  - Lacking appropriate analytical assay methods
  - Complex decision making process
  - Rigidity in changing legislation

Emerging Issues Relating to Vaccine Stability Guidelines

- Regulatory consideration for evaluation of vaccines for use in a Controlled Temperature Chain (stand-alone or annexed to VacStabGLs?)
  - Definition of terms to be introduced: e.g. CTC, temperature cycling, stability budget, peak temperature indicator, VVMs
  - Algorithm to help assess the need for clinical trials
  - Standardized labeling
- Standardized format (or protocol) for stability report in filing Label Variations for shelf-life, lot release specifications, CTC studies, and others (can be annexed to VacStabGLs)
  - A Report Format is available in ASEAN guidelines for Drug Product

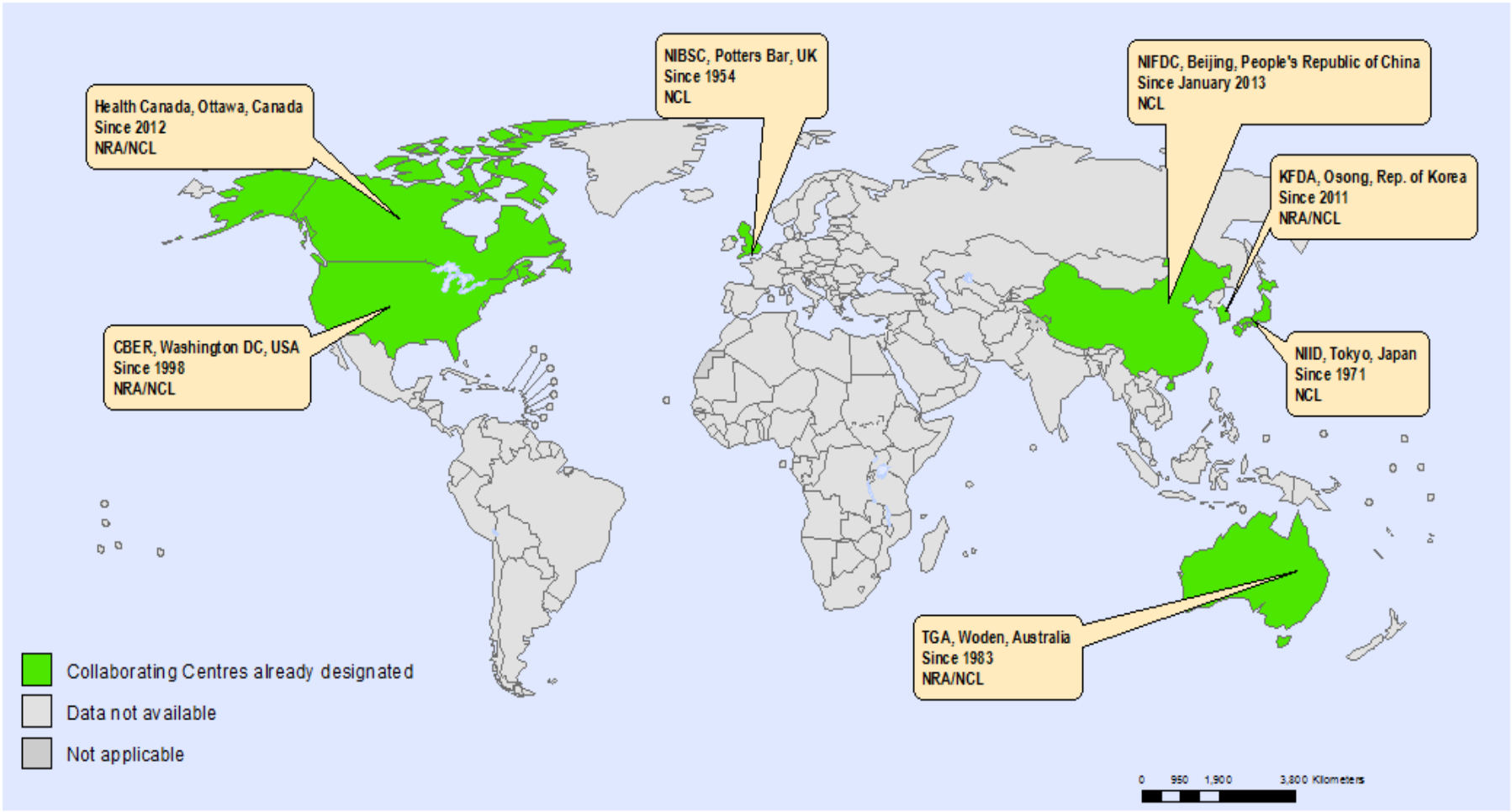
Regulatory Risk Assessment

- Scientific principles for evaluating risk in the case of an adventitious agent found in an already licensed vaccine
- Case studies in preparation (PCV in rotavirus vaccine, RT in MMR, SV40 in polio vaccines, bacteriophage in live viral vaccines)
  - Narrative part
  - Table with step by step review of the evidence
- Informal consultation with regulators, manufacturers and other experts: 30-31 May 2013, Lijiang, China
- Review of examples for publication and/or Guidelines

Implementation workshops and next steps

- Opportunity to discuss all issues in a forum of regulators, manufacturers and other experts
- Outcomes:
  - Current: Meeting report with the summary of the lectures, case studies and the outcomes of the discussion
  - Future: E-learning tools to assist with the implementation of guiding principles into regulatory and manufacturers' practice
- Technical support to NRAs and NCLs - identify areas where assistance is needed
- Challenges:
  - Timely nomination of the suitable participants (ie representatives of NRAs/ NCs)
  - Funds
  - Organizational and technical support by the host institution

WHO Collaborating Centres for Standardization and Regulatory Evaluation of Vaccines



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Network of CCs: 2013-2014

- Increasing demand for technical assistance from Member States
- Better coordination of WHO technical assistance
- Growing complexity of reviewing scientific evidence for regulatory purpose, especially for novel vaccines
- Plan for additional CCs in 2013-2014:
  - Division of Virology, Paul Erhlich Institute, Germany
  - Thai NCL
  - Indonesian NRA
- Link between CCs network and various expert groups, regional regulatory networks and other relevant bodies/ associations

Regulatory science

A Global Regulatory Science Agenda for Vaccines

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- Laboratory-based regulatory science

- correlates of immunity;
- correlates of safety;
- improved product characterization
- improved potency assays

- Science to develop regulatory processes

- innovative clinical trial designs;
- tools to assist the benefit-risk decision-making process;
- novel pharmacovigilance methodologies

Examples of how regulatory science has contributed to improved access to vaccines

- MAPREC and transgenic mouse tests for evaluation of OPV
- Development and use of alternative potency evaluations for pandemic H1N1 vaccines
- Defining international consensus values for serological correlates of immunity for pneumococcal conjugate vaccines

Expected outcomes from a regulatory science agenda

- New regulatory tools are developed to improve access to products of assured quality
- Linkages are established with science and technology communities to nurture regulatory innovations
- Spread of regulatory science expertise and the benefits of regulatory science to the less-well-resourced countries

Further information and contact

Biological standardization website:

www.who.int/biologicals

Immunization website: www.who.int/immunization

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