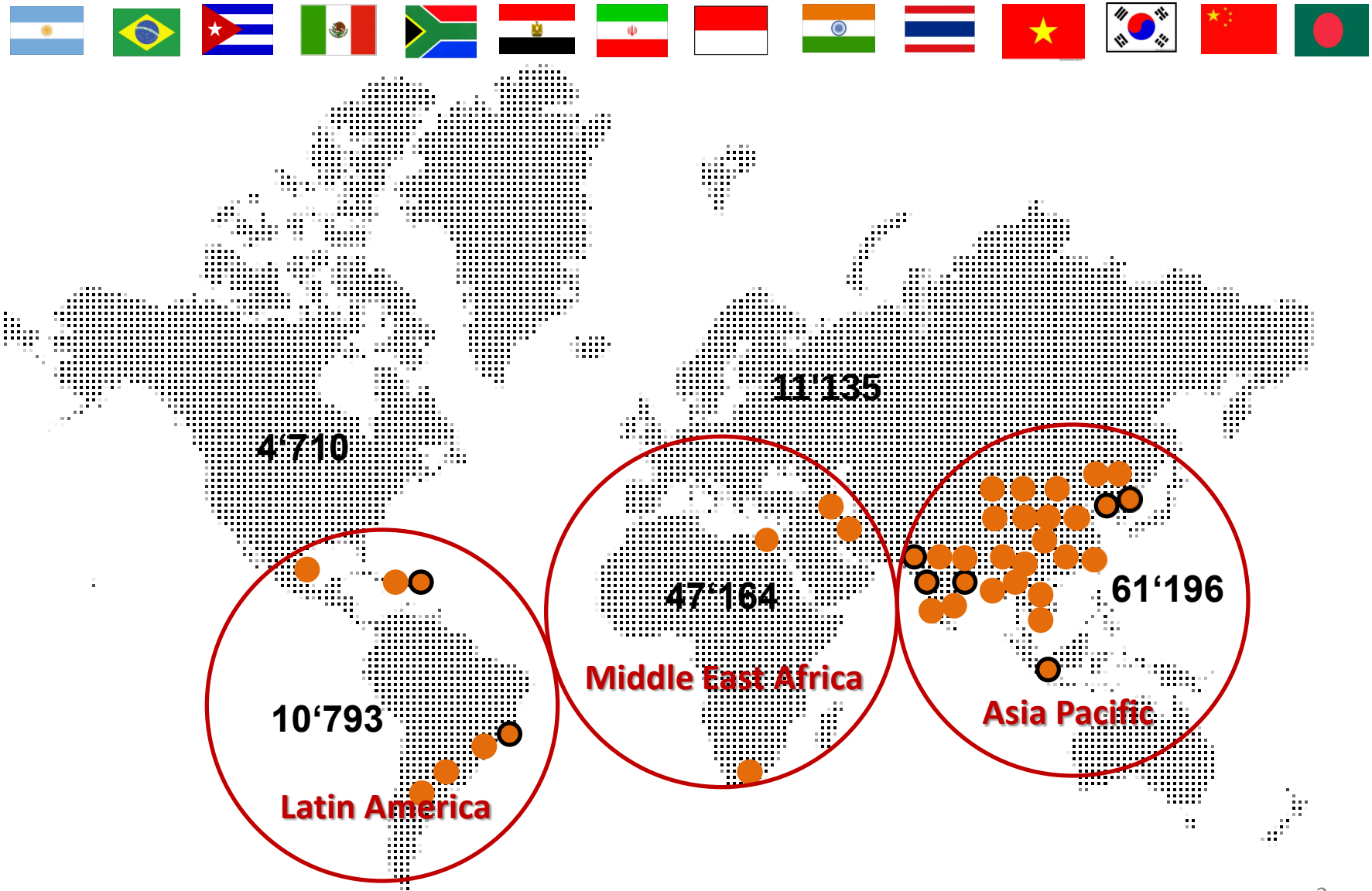
Product Summary File submissions

International Workshop on
Vaccine Quality Management Systems
Sonia Pagliusi
Mexico City, July 10-11th 2013

DCVMN
Connecting the world for a cause

- To protect people against known and emerging infectious diseases globally by enhancing the quality and increasing availability of vaccines produced in developing countries.

DCVMN: 39 manufacturers from 15 countries/territories and number of birth cohorts regionally



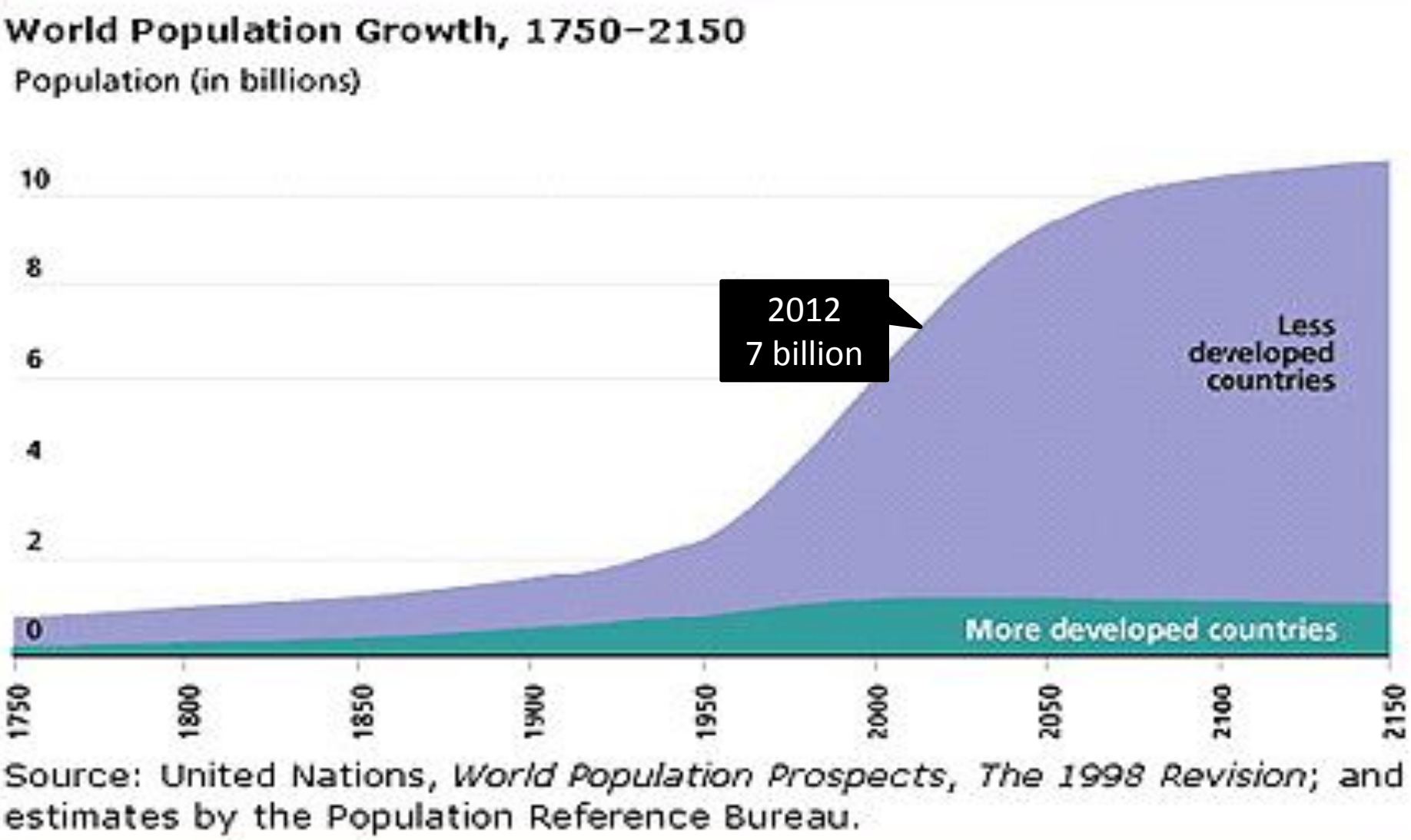
Members as of January 2013 Members with WHO PQ vaccines

Developing Countries

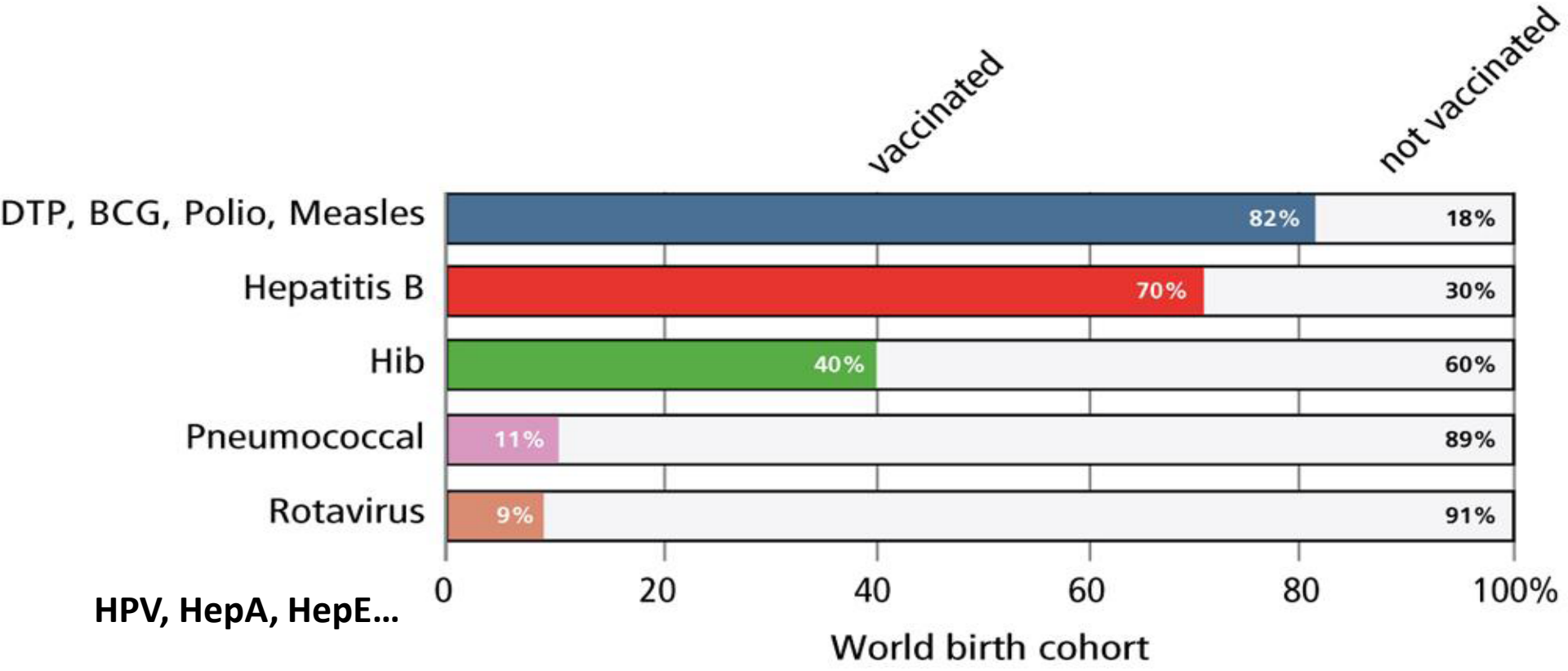
- developed economies
- developing economies (according to the IMF)
- graduating to developed economy

The World Bank classifies countries into four income groups. These are set each year on July 1.
Economies were divided according to 2011 GNI per capita using the following ranges of income:
Low income countries had GNI per capita of US$1,026 or less.
Lower middle income countries had GNI per capita between US$1,026 and US$4,036.
Upper middle income countries had GNI per capita between US$4,036 and US$12,476.
High income countries had GNI per capita above US$12,476.

Developing countries' people need vaccines



Global annual surviving infants cohort = 129 million* and other vaccines coverage



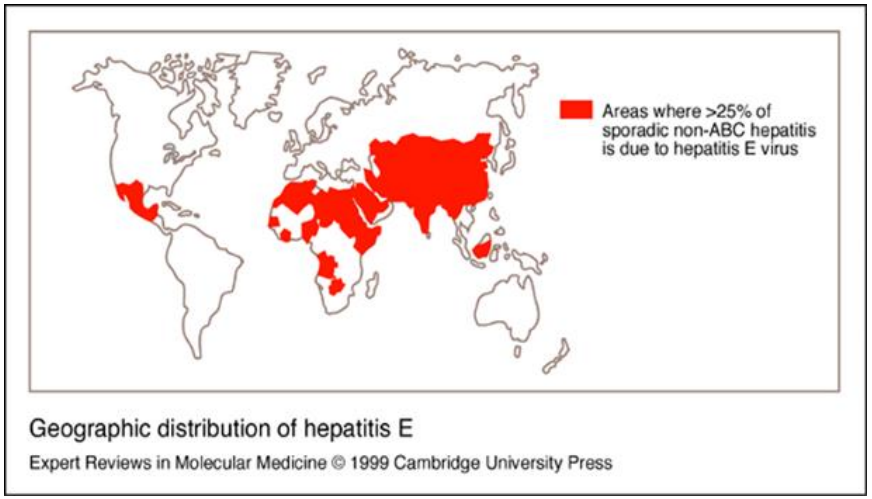
HPV, HepA, HepE…

* WHO/UNICEF http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm
Other sources: Johns Hopkins Bloomberg School of Public Health; UN,DESA, Population Division

DCVMs tackling regional infectious diseases

MenAfriVac™

Hepatitis E vaccine, Hecolin™



Geographic distribution of hepatitis E

Expert Reviews in Molecular Medicine © 1999 Cambridge University Press

Japanese encephalitis

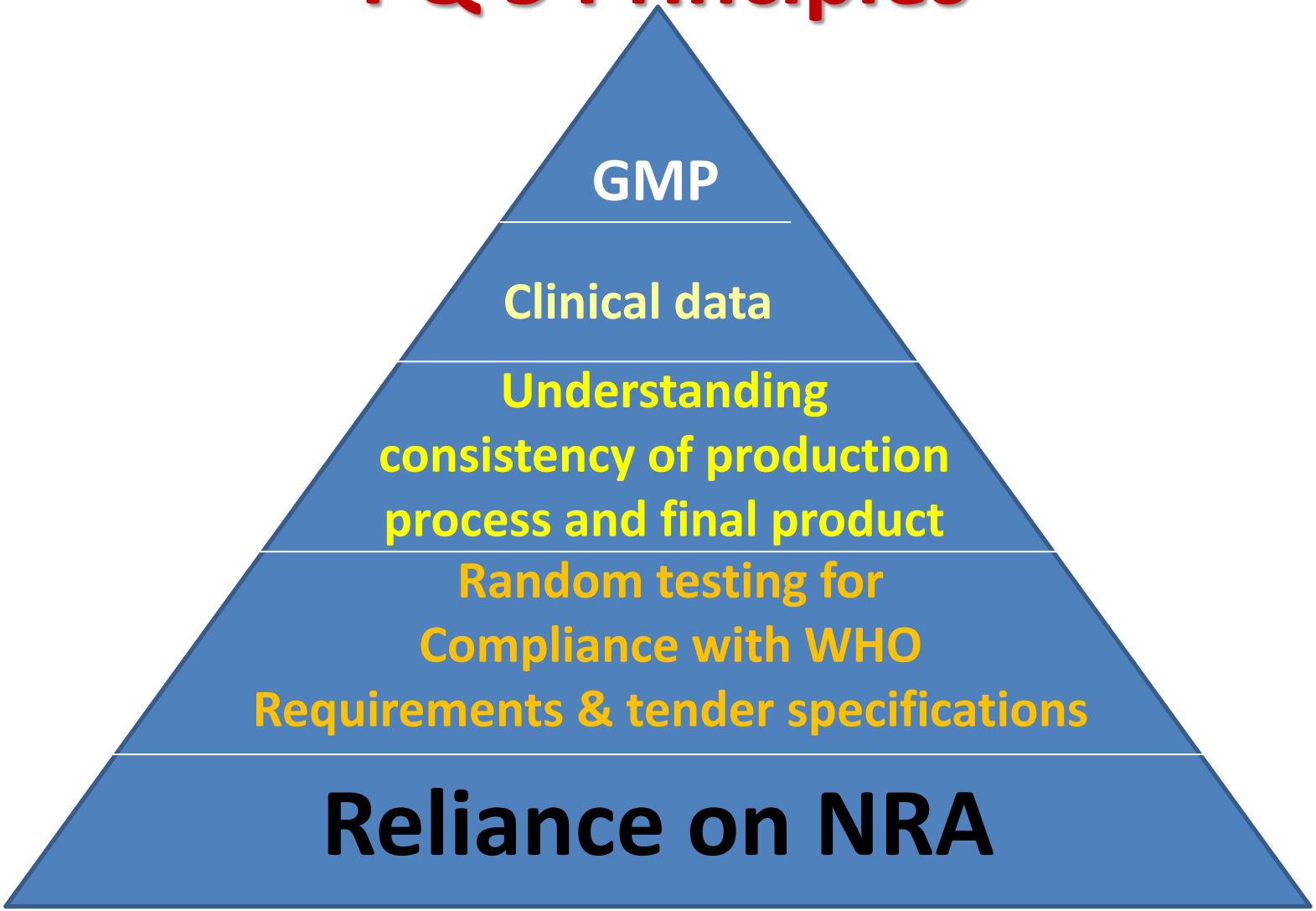
Yellow Fever Vaccines

Presentation outline

A. Requirements, format and remarks

B. Content and points to consider

PQ 5 Principles



http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/index.html

Pre-conditions for PQ evaluation

1. Vaccine is licensed/registered by the responsible NRA in manufacturing country

2. WHO guidelines/recommendations approved by ECBS are available/published

http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_manufacturers_guidance/en/index.html

3. Programmatic suitability

http://www.who.int/immunization_standards/vaccine_quality/ps_pq/en/index.html

* http://www.who.int/immunization_standards/vaccine_quality/priority_pq_vaccines_2013_14/en/index.html

Pre-conditions for PQ Evaluation (cont.)

4. Listed in the vaccine priority list (2013-2014)*:

High priority: Bivalent oral polio (bOPV1+3), trivalent oral polio (tOPV)
DTwP based pentavalent combination
(fully liquid DTwP-Hep B-Hib)
Diphtheria-tetanus-pertussis (DTwP)
Inactivated polio (IPV)
Measles-Rubella
Pneumococcal conjugate
Rotavirus, Yellow fever,

Middle priority: DTwP-Hep B-Hib-IPV, HepA, HPV, Flu, Typhoid conjugate, …

Low priority : Hepatitis E, Rabies, varicela, BCG, Typhoid non-conjugate, …

No priority: HepB, Hib, H1N1; DT, rubella,

* http://www.who.int/immunization_standards/vaccine_quality/priority_pq_vaccines_2013_14/en/index.html

Format requirements for product summary files (PSF)

1. The PSF shall be submitted in **two hard copies plus an electronic copy** or three hard copies with the covering letter specifying the vaccine presentations that the Company intends to prequalify;

2. The hard copies should be presented in ring binders (not as a spiral bounded document);

3. The PSF shall present subsequent linear page numbering from the front page (pag.1 of first volume) onwards, from first volume to the last volume, including annexure. Page numbers must be placed at the bottom right part of the page;

4. The Header/Footer shall include the name of the Company and of the Product, the Volume, the PSF Edition/Date, the Chapter number;

5. The Table of contents should be complete providing all the Subsections for each Chapter and refer to the pages of each;

6. The PSF shall present a Note to Reviewers (as deemed appropriate) to include relevant information that the manufacturer would like to emphasize or highlight such as absence of chapter subsections, absence of data, changes from the former PSF edition to the current PSF edition, etc.

http://www.who.int/immunization_standards/vaccine_quality/psf_format_april05.pdf

Format requirements for product summary files (PSF)

•Guideline for preparation of the product summary file for vaccine prequalification, WHO/IVB/06.16
http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.16_eng.pdf

•Environmental monitoring of clean rooms in vaccine manufacturing facilities , 2012
http://www.who.int/immunization_standards/vaccine_quality/env_monitoring_cleanrooms_final.pdf

Additional remarks

- Applications for prequalification of a vaccine usually requires the vaccine to have a marketing authorization from an NRA.
- The information provided is summarized and the review workload would be substantially less than in an usual clinical evaluation of a new drug application by a NRA.
- Reviewer needs to check and comment on whether the applicant has provided information as requested in the procedures document and viewed as satisfactory or whether additional data needs to be provided.
- Should additional information be requested, reviewer retains the data until the responses of the company have been provided and sent to reviewer and the evaluation is finalized.
- Reviewers can evaluate any independent expert clinical summary provided by the applicant, as to whether the supplied data supports the safety and efficacy of the vaccine.

Content of PSF

Details and clarification of the contents of the PSF chapter / sections (e.g. 600 pages plus annexes):

1. General Information (corporate history, products, sites, e.g. 20-30 pages)
2. Personnel (employees, contractors, qualifications, organigrams, training, health&hygiene; 20-30 pages)
3. Premises and Equipment (water, heat, ventilation, air-conditioning systems, blocks/zones surface; 100-150 pages)
4. Vaccine composition, presentations and schedules (components names/amounts in ug or IU, volume, stoppers, vials, sealing materials, labels; 20-30 pages)
5. Production (description of manufacturing processes/steps, e.g. seeds fermentation, clarification/filtration, detoxification, purification, conjugation, etc; ca. 100 pages)
6. Quality Control (results, ca. 100-200 pages)
7. Stability (results, ca. 50-100 pages)
8. Clinical experience (clinical study reports, ethical committee signatures, NRA approval, certificates/accreditations, etc, 20-30 pages)(Clinical study reports as annexes ca. 40 pages plus pharmacovigilance plan ca. 20 pages)
9. Production and distribution data (package format/size, shipping, vvm; 10-20 pages)
10. Update of Regulatory Authority Actions Relevant to the Product (20 pages)

http://whqlibdoc.who.int/hq/2006/WHO_IVB_06.16_eng.pdf

Key Documents

- The WHO prequalification procedure can be found at

http://www.who.int/immunization_standards/vaccine_quality/pq_revised_procedure_final_1may2012.pdf

- "Procedure for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies"

http://whqlibdoc.who.int/hq/2006/WHO_IVB_05.19_eng.pdf

- "Guidelines on clinical evaluation of vaccines: regulatory expectations"

http://whqlibdoc.who.int/trs/WHO_TRS_924.pdf

- "Guidelines on clinical considerations for evaluation of vaccines for prequalification", 2010

http://www.who.int/immunization_standards/vaccine_quality/clinical_considerations_oct10.pdf

- Position papers:

http://www.who.int/immunization/documents/positionpapers/en/

e.g. Meningitis http://www.who.int/immunization/wer7740meningococcal_Oct02_position_paper.pdf
Cholera http://www.who.int/wer/2010/wer8513.pdf
Hepatitis A http://www.who.int/wer/2012/wer8728_29.pdf
Influenza http://www.who.int/wer/2012/wer8747.pdf

Points to Consider to facilitate PQ

- Testing methods to be fully established and validated, reference materials available, company to transfer methodology to testing labs through WHO

- Compliance with WHO GMP for biological products

http://www.who.int/immunization_standards/vaccine_quality/guide_to_master_formulae_final_2012.pdf

- Cell banks characterization documentation

- Have established and strong QA and QMS system in place

- Proposed Pharmaco-vigilance system in place

- Feasibility of co-administration with other vaccines included in the national immunization programme

http://www.who.int/biologicals/publications/trs/areas/vaccines/gmp/WHO_TRS_822_A1.pdf

Additional 10 points to consider

1. Are the lot numbers of batches used in the trial detailed and what is the scale of production of these lots

2. Do the clinical trials demonstrate lot-to-lot consistency of the vaccine

3. Were clinical trials conducted according to GCP and was there ethical oversight of the trials

4. Is the data consistent with a WHO position paper on the vaccine.

These can be found at
http://www.who.int/immunization/documents/positionpapers/en/index.html

The applicability of the vaccine to the target population identified in these documents should be considered.

5. Is the schedule of vaccination used consistent with that required by the WHO

6. Are the serotypes included in the vaccine protective against those circulating in the recipient countries

7. Could the disease burden in the intended recipient countries impact on the dose of the vaccine required compared with that given in the clinical trial.

Additional 10 points to consider (cont.)

8. Is the concomitant immunization given in the trial consistent with that required in the recipient countries. Based on the above issues you should comment as to whether bridging studies should be conducted.

9. Do the clinical studies comply with WHO guidelines:

WHO TRS 924 (2004), Annex 1: WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations.

http://whqlibdoc.who.int/trs/WHO_TRS_924.pdf

WHO TRS 927 (2005), Annex 1: WHO Guidelines on Non-clinical Evaluation of Vaccines.

http://whqlibdoc.who.int/trs/WHO_TRS_927.eng.pdf

WHO TRS 850 (1995) Annex 3: Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products.

http://whqlibdoc.who.int/trs/WHO_TRS_850.eng.pdf

10. Do the studies comply with ICH guidelines:

http://www.ich.org/cache/compo/276-254-1.html

Vaccine specific guidelines

http://www.who.int/biologicals/vaccines/en/

Vaccine-specific standardization

- BCG (Tuberculosis)
- Cholera
- Dengue
- Diphtheria
- DNA vaccines
- Haemorrhagic fever
- Haemophilus influenzae (Hib)
- Hepatitis A
- Hepatitis B
- Human Papillomavirus (HPV)
- Influenza
- Japanese encephalitis (JE)
- Malaria
- Measles
- Meningococcal meningitis
- Mumps
- Pertussis
- Plant-derived vaccines
- Pneumococcus
- Poliomyelitis
- Rabies
- Rift Valley Fever
- Rotavirus
- Rubella
- Smallpox
- Synthetic peptide vaccines
- Tetanus
- Tick-borne encephalitis
- Typhoid fever
- Viral vector vaccines
- Varicella
- Yellow Fever

General topics and regulatory guidance

- Biotechnology and related topics
- Cell substrates
- WHO reference cell banks (RCBs)
- Clinical evaluation of vaccines
- Good Manufacturing Practices (GMP)
- Lot Release of Vaccines
- Non-clinical evaluation of vaccines
- Regulation and quality control of vaccines
- Stability of vaccines and reference preparations
- Sterility testing
- Thiomersal
- Transmissible Spongioform Encephalities (TSE)

Prequalification: information and guidance documents for vaccine manufacturers

- **Fees**

20 March 2006 - The cost of the activities required to assess the acceptability, in principle, of candidate vaccines for UN agency purchase are as follows:

- Screening fee: US$ 500.

Evaluation fee:

- US$ 25,000 for traditional vaccines and
- US$ 66,500 for combinations and novel vaccines (see Table 1).

- Annual fee: US$ 8,000 for traditional vaccines and US$ 14,000 for combinations and novel vaccines (see Table 19.

- The expenses related to the site audit will be charged on a cost recovery basis.

http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_manufacturers_guidance/en/index.html

List of Vaccines for PQ

Traditional vaccines

- BCG vaccine
- Diphtheria-Tetanus toxoids (DT-dT)
- Diphtheria-Tetanus-wPertussis
- (DTwP) vaccine
- Haemophilus influenzae type b vaccine
- Hepatitis B vaccine
- Influenza (without adjuvants or adjuvation with aluminium)
- IPV
- Measles vaccine
- **Measles-Rubella vaccine (MR)**
- Meningococcal A+C polysaccharide vaccine
- Meningococcal A+C +W polysaccharide vaccine
- Mumps vaccine
- Measles-Mumps-Rubella vaccine (MMR)
- OPV
- w Pertussis vaccine
- Rubella vaccine
- Rabies vaccine
- Tetanus Toxoid (TT) vaccine
- Yellow Fever vaccine
- Typhoid

Combinations and Novel vaccines

- DTwP-Hep B vaccine
- DTwP-Hib vaccine
- DTwP-IPV
- DTwP-HepB-Hib vaccine
- DTwP-IPV-Hep B vaccine
- DTwP-IPV-Hep B-Hib vaccine
- HPV
- Influenza (adjuvanted with adjuvants other than aluminium)
- **Meningococcal conjugate vaccine**
- Oral Cholera vaccine
- Other combinations
- Pneumococcal conjugate vaccine

Other possible candidate vaccines in the future, for example:

- DTaP vaccine and
- DTaP based combinations
- Japanese Encephalitis vaccine
- Malaria
- Dengue
- HIV
- TB

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www.DCVMN.org

Thank you

Q&A