



Briefing on Vaccine Prequalification for DCVMN manufacturers

Webinar 23 April 2014



The PQ process mission, vision, objectives and stakeholders

**Briefing on Vaccine Prequalification for
DCVMN manufacturers**

Webinar 23 April 2014



WHO Goal for vaccines regulation

Ensure that "100%" of vaccines used in all national immunization programmes are of assured quality

Definition of "Vaccines of Assured quality"

- ✓ **National Regulatory Authority (NRA)** independent from vaccine manufacturer & procurement system
- ✓ **NRA is functional** (*system + 6, 4 or 3 regulatory functions implemented*)
- ✓ **No unresolved reported problem with vaccine**

WHO guidance by Experts Committee on Standardization of Biologicals (ECBS) recommendations on safety, efficacy and quality issued in WHO Technical Report Series (TRS)



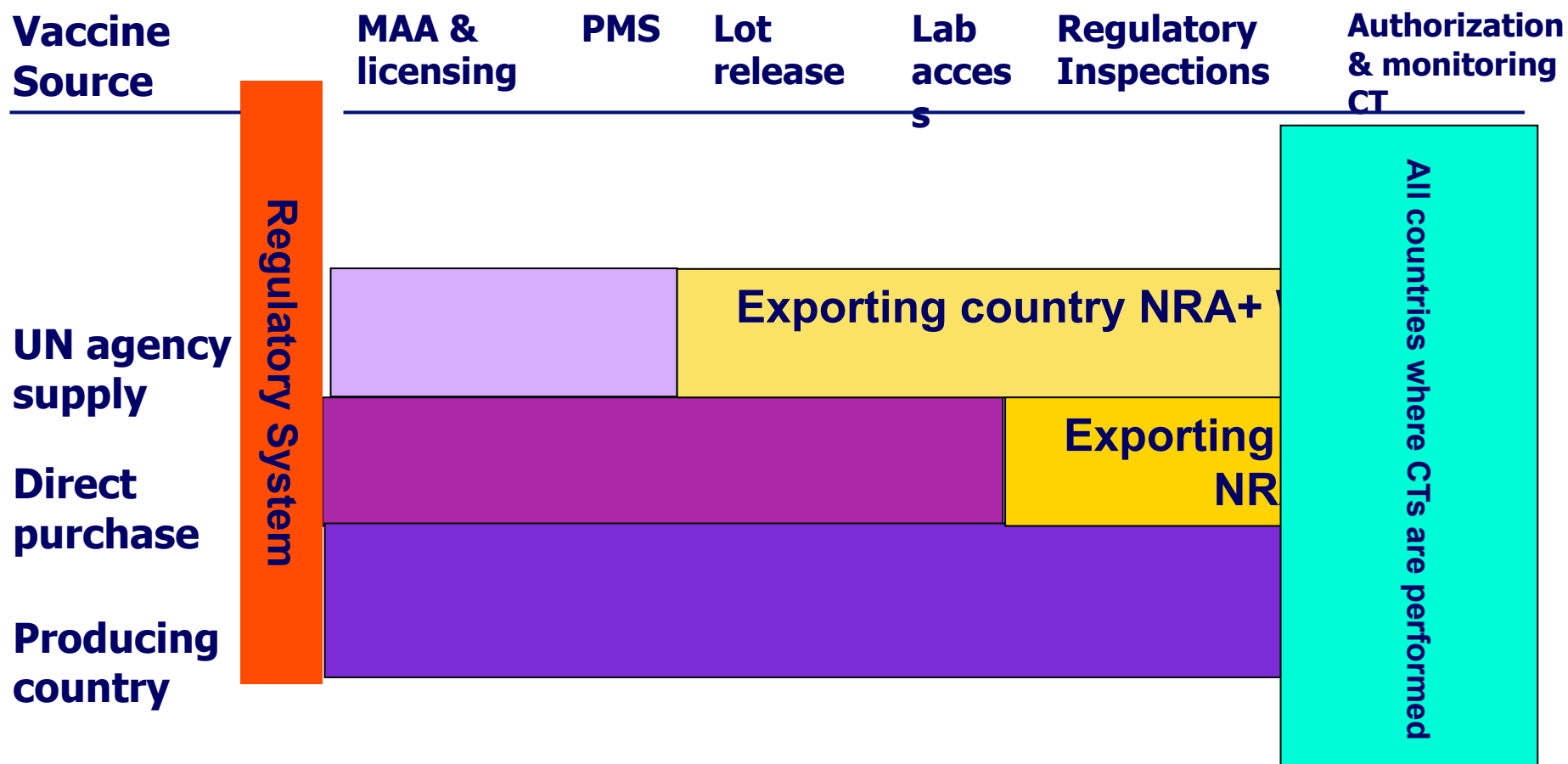
WHO concept of Vaccine Regulation

National Regulatory System : Governance

+ six regulatory functions

- 1. Marketing Authorization (MA) and Licensing Activities**
- 2. Post-marketing activities including surveillance of Adverse Events Following Immunization (AEFI)**
- 3. NRA Lot Release**
- 4. Laboratory access**
- 5. Regulatory Inspections**
- 6. Authorization/Approval of Clinical Trials**

Required functions according to vaccine source



Prequalification: The term

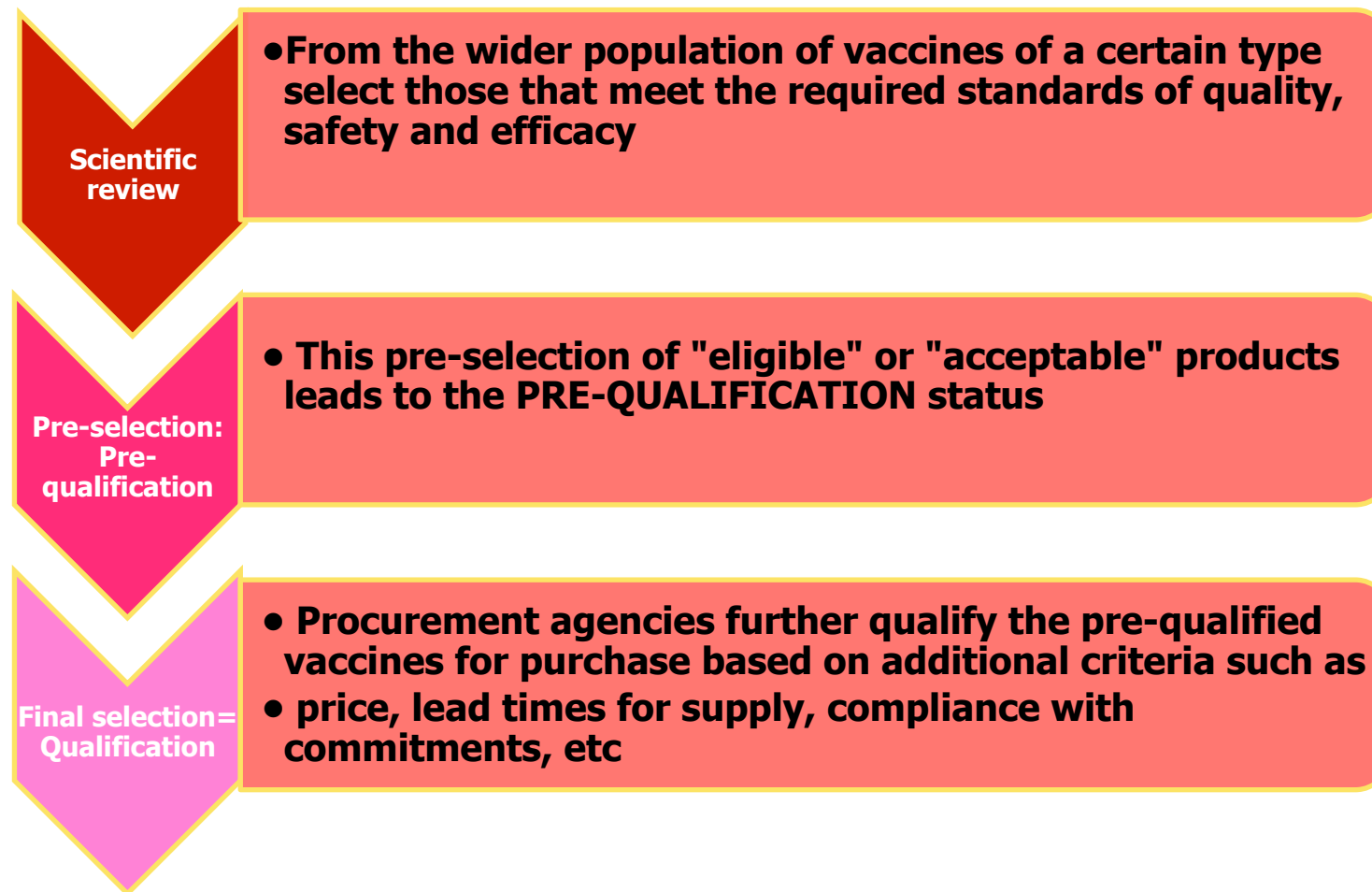
Where does the Pre-qualification term come from?

What does it mean?

It is a procurement term

It means limiting a global public tender to fewer than the total universe of possible suppliers.

Prequalification



Prequalification team Mission

Facilitate access to adequate supply of high quality vaccines to member countries



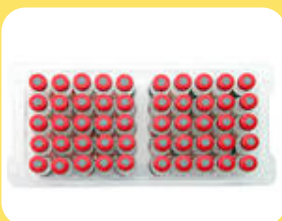
Means to accomplish the mission



Provide advice to UN agencies on the quality, safety and efficacy of vaccines for purchase



By assessing the acceptability, in principle, of vaccines for purchase by United Nations Agencies: Vaccines Prequalification Program



By continuous monitoring of quality and compliance with the established specifications

Vision



Objectives of the Vaccines PQ program

MAIN

Ensure supply of vaccines of assured Quality through UN agencies

Vaccines supplied meet WHO Recommendations issued by ECBS for quality, safety and efficacy and UN

Tender specifications

Vaccines supplied meet the needs of

the NIPs (programmatically suitable,

compatible with the current immunization schedules)

SECONDARY

Replaces regulatory oversight in receiving countries except for Marketing authorization and post-marketing surveillance

Used as a reference of quality by many countries that procure vaccines directly

Secure the supply base for vaccines by exploring alternative/additional sources

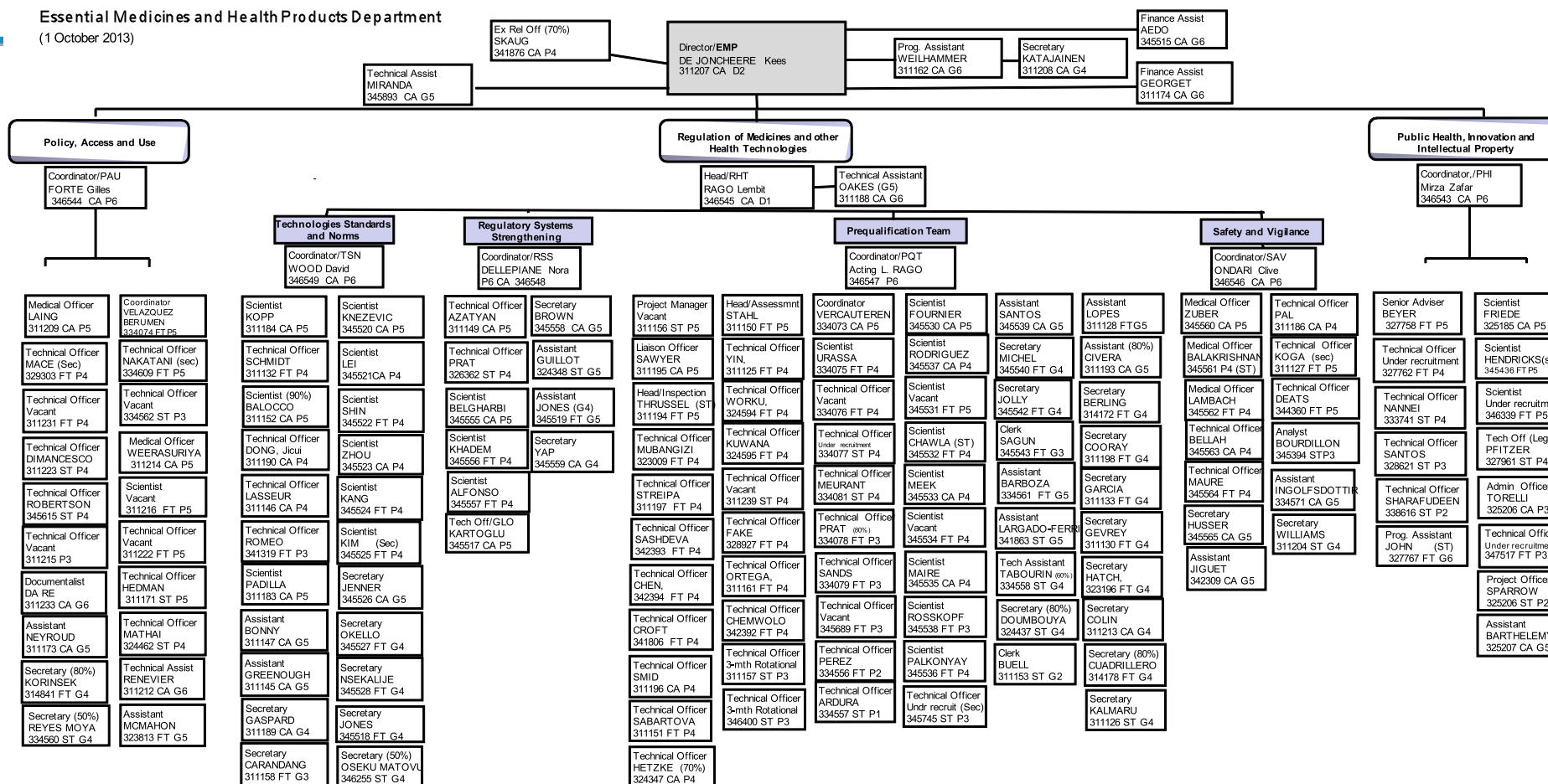
Prequalification stakeholders

- ☐ **Manufacturers and manufacturers' associations**
- ☐ **NRAs in producing countries and NRAs in receiving countries**
- ☐ **UN purchasing agencies**
- ☐ **GAVI**
- ☐ **Other purchasing agencies (MSF, DANIDA, JICS)**
- ☐ **Countries procuring vaccines directly**
- ☐ **Donors**
- ☐ **Immunization programmes**
- ☐ **Programmes for vaccine preventable diseases**

New structure at HQ for PQ

Essential Medicines and Health Products Department

(1 October 2013)

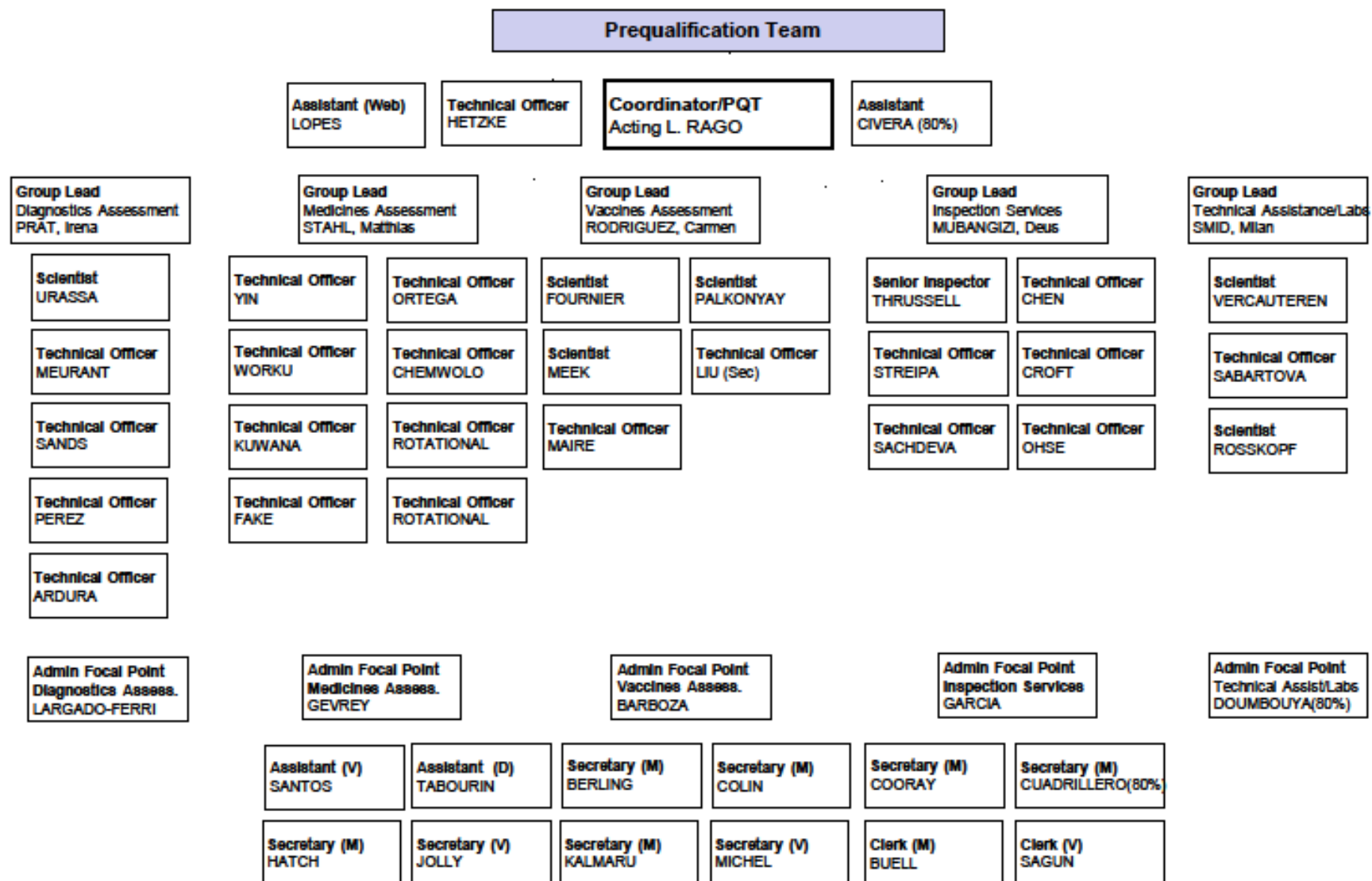


HIS/EMP/PQT



World Health Organization

- Policy, Access and Use (Coordinator Gilles Forte) addresses the issue of access to medicines and other health technologies (e.g. selection of essential medicines and technologies, pricing and supply, rational use of medicines/technologies, and controlled medicines)
- Public health, Innovation and Intellectual property (Coordinator Zafar Mirza) coordinates WHO's work on the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI), on transfer of technology and local production of medicines, vaccines and other technologies.
- Regulation of Medicines and other Health Technologies (Head of Unit Lembit Rago) comprises four teams, focusing each on a specific regulatory function:
 - Technologies' Norms and standards (Coordinator David Wood) concentrates on core normative work, notably through providing secretariat support to the Expert Committees on Specifications on Pharmaceutical Preparations and on Biological Standardization, the International Pharmacopeia, and the work on International Nonproprietary Names (INN).
 - Regulatory systems strengthening (Coordinator Nora Dellepiane del Rey Tolve) covers the work on National Regulatory Authority (NRA) assessment, technical support to regulatory authorities and the facilitation of regulatory harmonization initiatives.
 - Prequalification of medicines, vaccines, diagnostics and devices—Lembit Rago as acting coordinator—is in charge of prequalification of priority health products for international procurement.
 - Safety and Vigilance (Coordinator Clive Ondari) is concerned with pharmacovigilance and vaccine safety, acts as focal point for interactions with the Uppsala WHO Collaborating Center, and is in charge of the Secretariat function to assist the Member State mechanism on substandard/spurious/falsely-labeled/falsified/counterfeit (SSFFC) medical products.



Thank You



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



Quality aspects during Prequalification of vaccines

**Briefing on Vaccine Prequalification for
DCVMN manufacturers**

Webinar 23 April 2014

Pharmaceuticals Vs Vaccines

- **Pharmaceuticals**

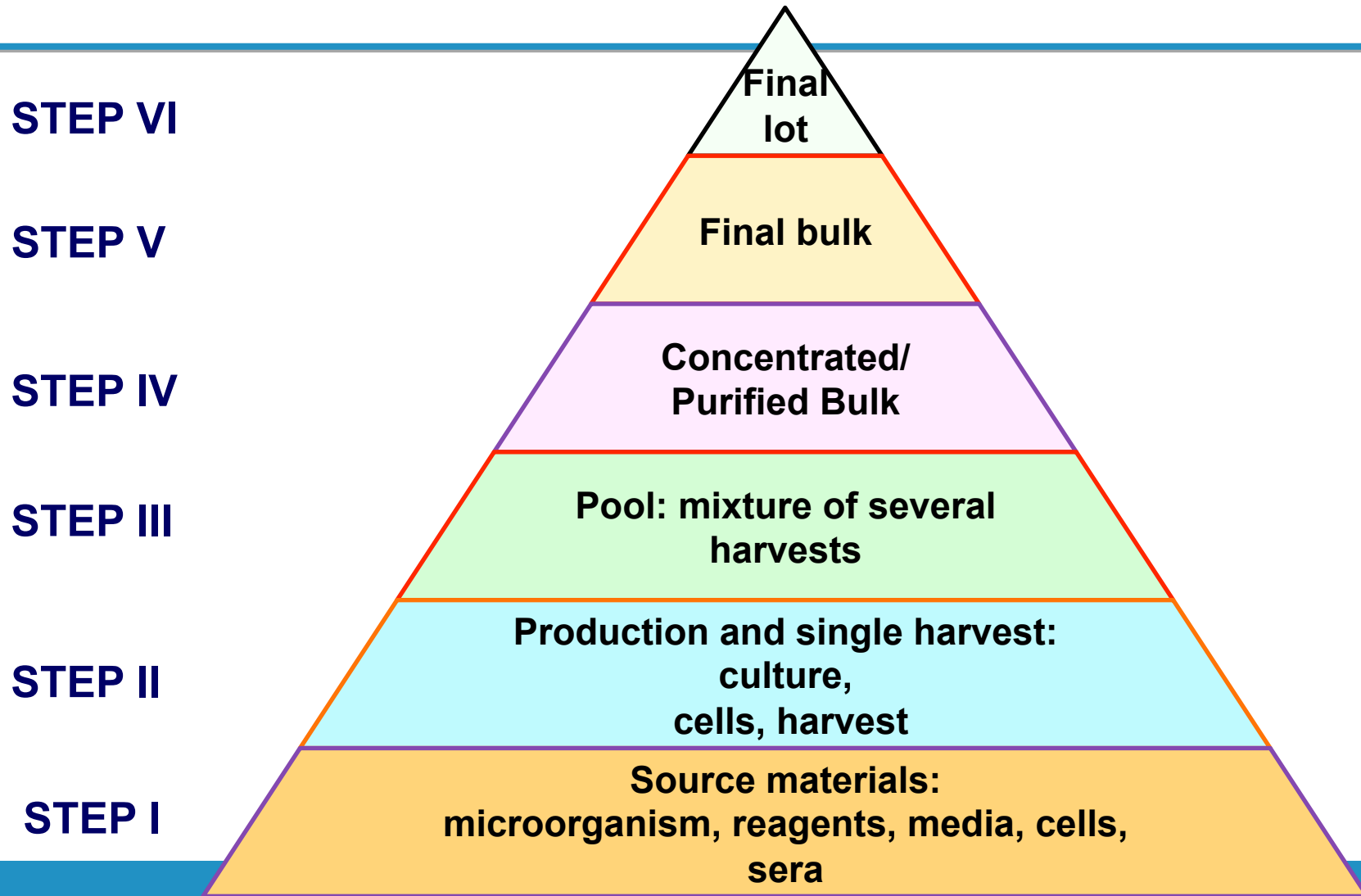
Produced and controlled using physicochemical methodologies

- **Vaccines**

Quality considerations

- **Raw materials**
- **Manufacturing processes**
- **Quality control methodologies**

Generic vaccine production steps



Each vaccine is an unique product

- **Different strains of bacteria or viruses can be used by different manufacturers for the same vaccine (eg Measles: Schwartz or Edmonston Zagreb)**
- **One company may make their vaccine in many bottles, and another may make the same vaccine in a single large fermentation tank.**
- **The same virus may be grown in one type of cell by company A and in a different cell by Company B.**
- **The same vaccine from one company may not use the same stabilizers or preservatives as another company.**

Quality Relationships

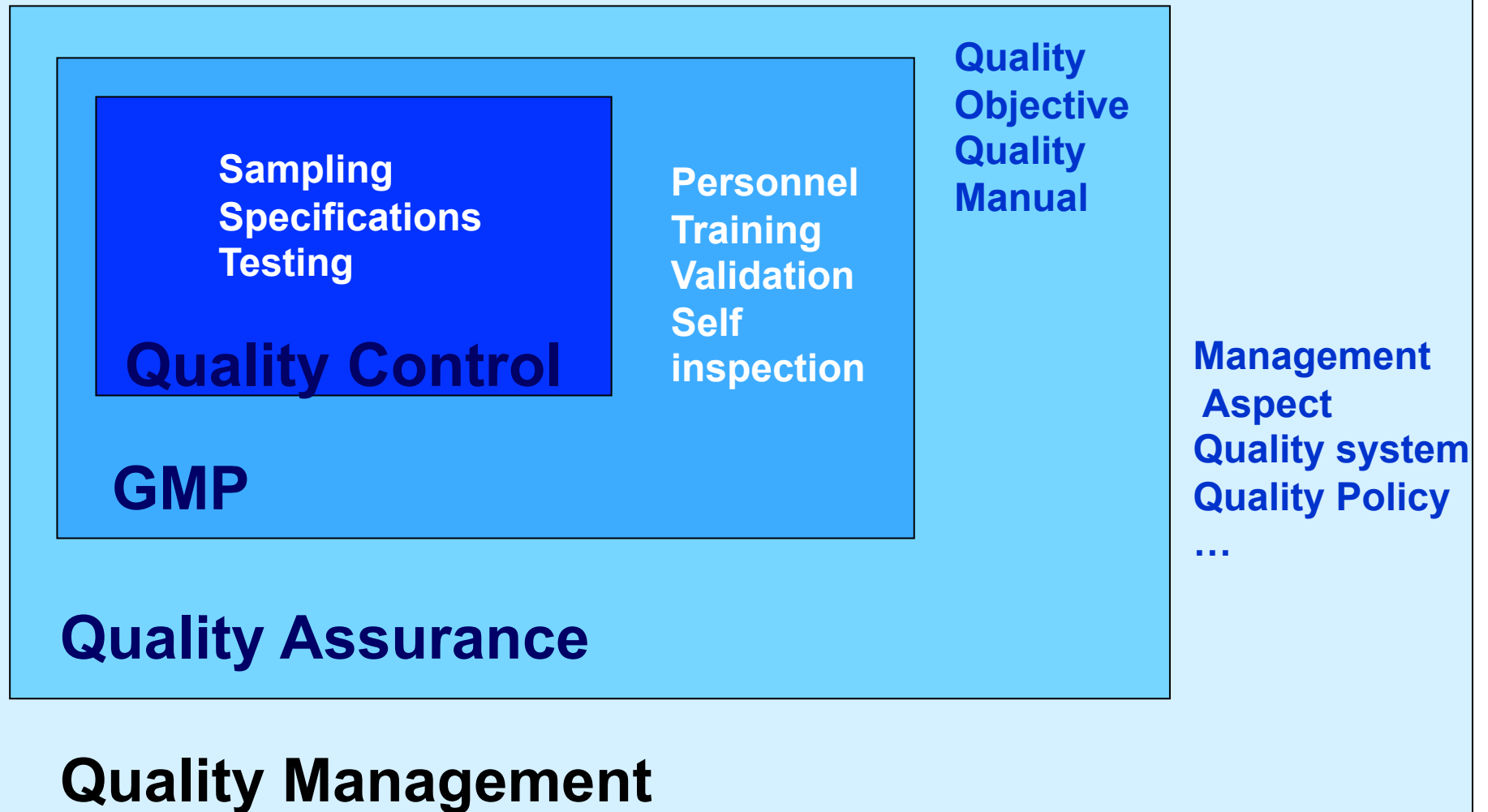


Good Manufacturing Practice (GMP)

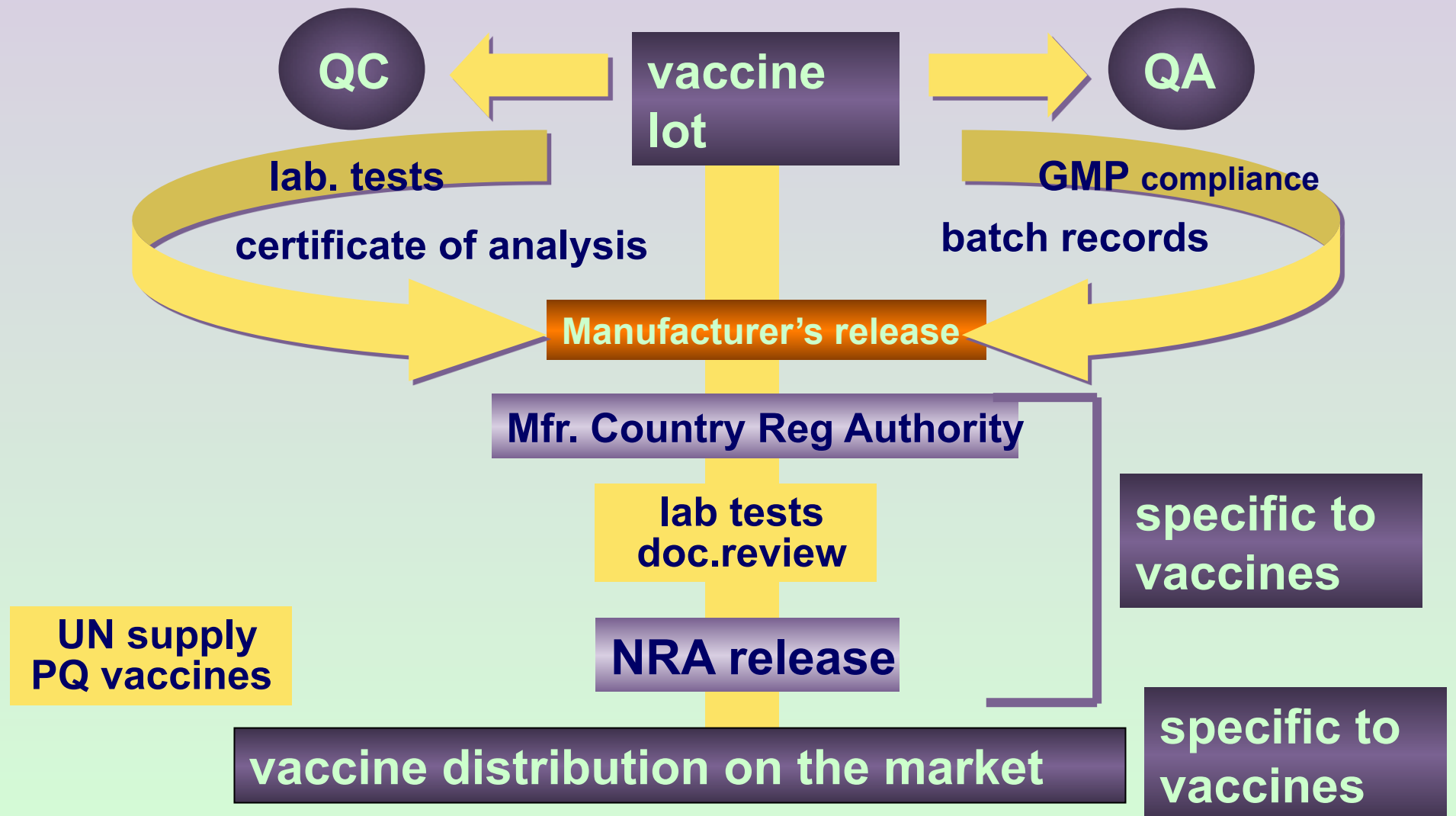
World Health Organization defines GMP as:

“that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization”

Quality Relationships



Complex release process



Quality aspects during PQ evaluation

Specific aspects considered

- General understanding of production process and quality control methods **Quality**
- Production consistency at commercial scale (assessed by testing of samples of final product) **Quality**
- Compliance with GMP **Quality**
- Compliance with WHO recommendations and UN tender specifications including labels and inserts **Quality**
- Programmatically suitable presentation **Quality**
- Clinical data relevant for the target population in the recommended schedules

Chapter 5: Production (1)

- ✓ **5.1 Manufacturing formula**
- ✓ **5.2 Description and flow chart of Manufacturing & testing**
- ✓ **5.3 General policy for process validation**

Chapter 5: Production (2)

- ✓ **5.4 Handling starting material, packaging material, bulk and finished products (Sampling, quarantine, release and storage).**
- ✓ **5.5 Handling and procedures for destruction of rejected materials and products.**

Chapter 6: Quality Control (1)

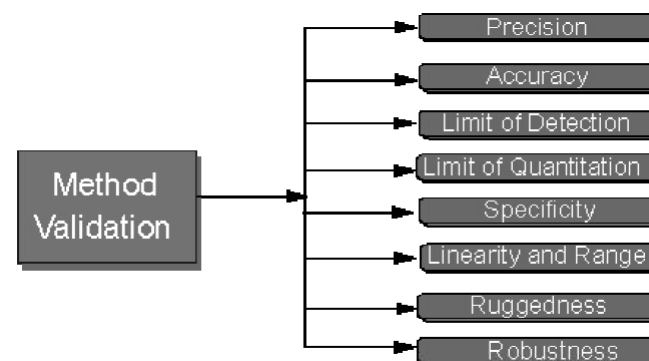
- ✓ **6.1 Starting material**
 - ✓ **6.1.1 Raw material**
 - ✓ **6.1.2 Labelling and packaging**
 - ✓ **6.1.3 Qualification of suppliers**

Chapter 6: Quality Control (2)

✓ 6.2 Intermediate products

6.2.1 Specifications and routine tests

6.2.2 Validations

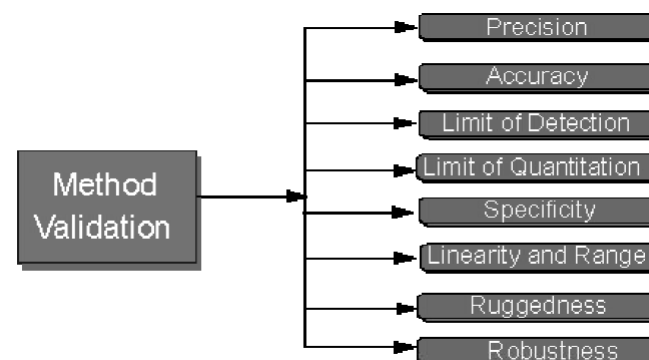


Chapter 6: Quality Control (3)

✓ 6.3 Finished product

6.3.1 Specifications and routine tests

6.3.2 Validations



6.3.3 List of Rejected Lots

Chapter 7: Stability data

- ✓ **7.1 Intermediate products**
- ✓ **7.2 Finished product : vaccine**
- ✓ **7.3 Finished product : diluent & reconstituted product**
- ✓ **7.4 Policy for assigning the date of manufacture of each component, final product and diluent**

Regulatory considerations

- **Need to ensure that adequate regulatory pathway is in place, that product is licensed, continuous regulatory oversight in place**
- **Need to assess quality**
 - Adequacy of production process
 - Adequacy of quality control methods and specifications
 - Stability data
 - Transferability of testing methods to NCL and independent labs
 - Consistency of production
 - GMP compliance, adequate Quality Management System in place

Programmatic considerations (1)

- **Vaccine used in the country of origin?**
- **Compatible with the existing EPI schedules?**
- **Stability profile: understanding of the cold chain requirements/ suitability for use under field conditions**
- **Stability profile: VVM category required**
- **Packaging: Volume of cold space required**

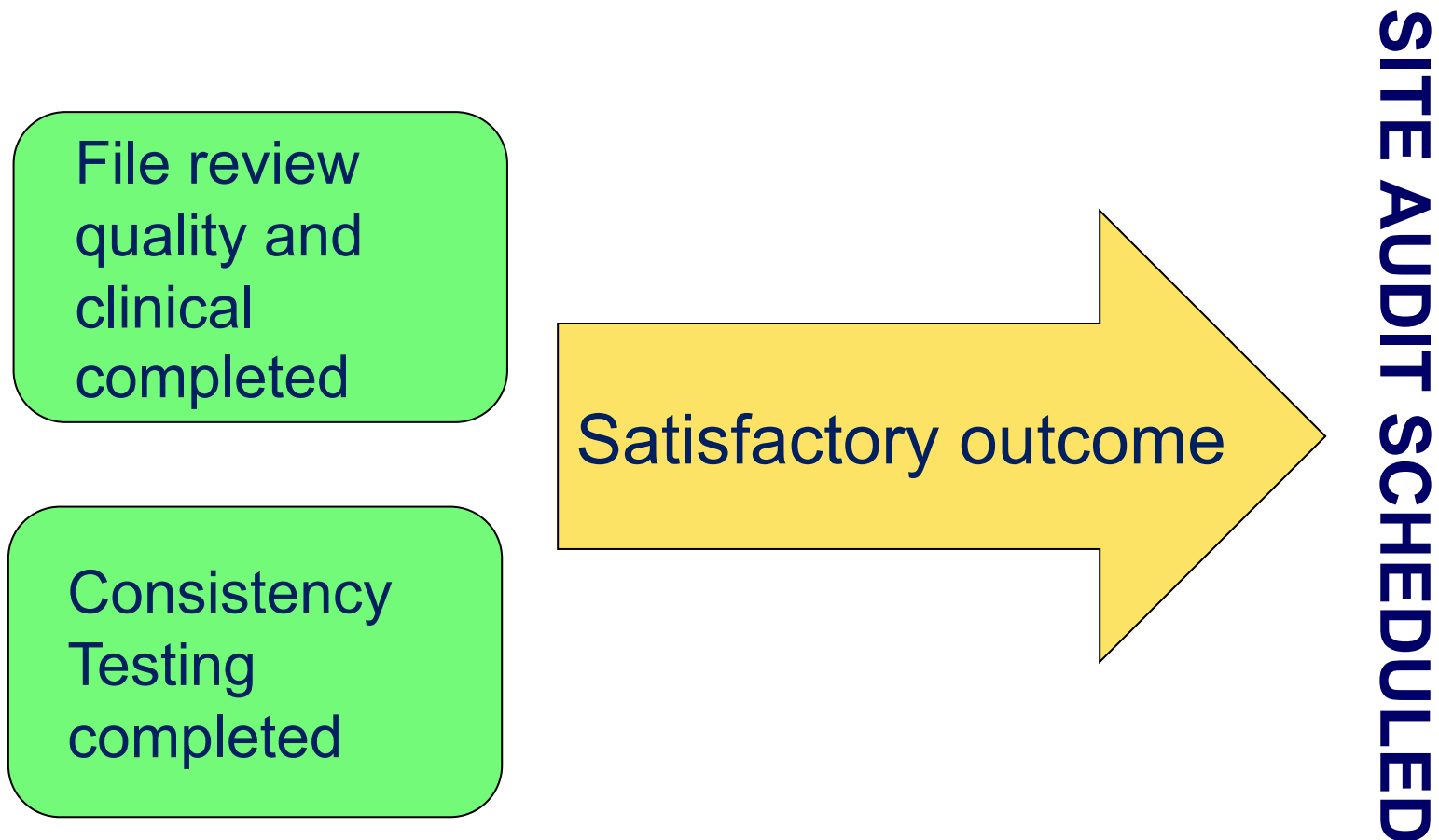
Programmatic considerations (2)

- **Presentation/primary packaging suitable?**
- **Open vial policy applicable?**
- **Information on inserts: adequate?, clear, reflects product characteristics? Available in all required languages?**
- **Transport boxes validated for international shipments?**

Outcome of the review of PSF

- **Scenario 1: PSF review does not raise any outstanding issues**
- **Scenario 2: PSF review raises outstanding issues for clarification/additional information (no major)**
- **Scenario 3: PSF review raises major technical and programmatic issues**
- **Consistency testing is scheduled**
- **Outstanding issues may be followed up at site audit &/ or request for additional information**
- **Consistency testing is scheduled**
- **Ad Hoc committee is convened**
 - Request for additional information to give final recommendation
 - Stopping the PQ

Timing for site audit



Objectives



Product is produced in accordance to WHO GMP recommended requirements



Product meets the WHO recommended requirements for quality, safety and efficacy (TRS documents)



Product meets the specifications of the UN tenders

Planning the audit: team



If more than one product will be reviewed additional experts will be proposed according to needs

Scope of Site Audit

- **Personnel- Organization**
- **Facilities and Equipment (Warehouses, production areas, QC laboratories, animal house, etc)**
- **Utilities**
- **Quality systems, Quality Assurance unit**
- **Production process and in process controls**
- **Quality control facilities, equipment and methods**

Aspects considered: Quality System

- **Quality assurance unit, roles and responsibilities**
- **Documentation system, documentation and records control**
- **Training program**
- **Post-marketing surveillance, including investigation of complaints and safety and efficacy reports**
- **Vendors qualifications**
- **Lot release system**
- **Investigation of complaints**
- **Validation master plan**



Aspects considered: Quality System

- **Handling and investigation of deviations**
- **CAPA,**
- **Recall, returns and destruction procedures**
- **Reprocess, Rework and Returned Product**
- **Internal and external audits**
- **Personnel**
- **Annual Product Review**
- **Maintenance Program, pest control, environmental control**
- **Site master plan**



HIS/EMP/ROT

Note: List is not comprehensive



**World Health
Organization**

Production System

- **Media preparation area and process**
- **Bulk production area and process**
- **Storage areas**
- **In process controls**
- **Change over procedures**
- **Environmental monitoring**
- **Gowning procedures**
- **Formulation and filling**



Production System

- **Inspection**
- **Labeling, Packaging and Shipping procedures**
- **Change over procedures**
- **Change Control**
- **Handling of Deviations**
- **Procedures, Process and systems validation**
- **Sanitation and hygiene: Cleaning validation**
- **Batch manufacturing records**
- **Note: List is not comprehensive**



Quality Control System

- **Testing methods in place and their validation**
- **Tests for intermediates and final products**
- **SOPs**
- **Sampling procedures**
- **Stability Program**
- **Documentation control**
- **Quality control facilities and equipment, including animal house**
- **Test results and trends- Handling of out of specifications**

Note: List is not comprehensive

HIS/EMP/PQT



World Health
Organization

Facilities and Equipment

- **Quality of construction, flow of: personnel, product, materials, wastage and process**
- **Utilities (HVAC, Pressure differentials, water systems, clean steam, compressed air)**
- **Clean rooms, Classification**
- **Equipment qualification: DQ, IQ, OQ and PQ**
- **Equipment calibration and verification**
- **Validation of computerized systems**

Note: List is not comprehensive
HIS/EMP/PQT



**World Health
Organization**

Key elements for success

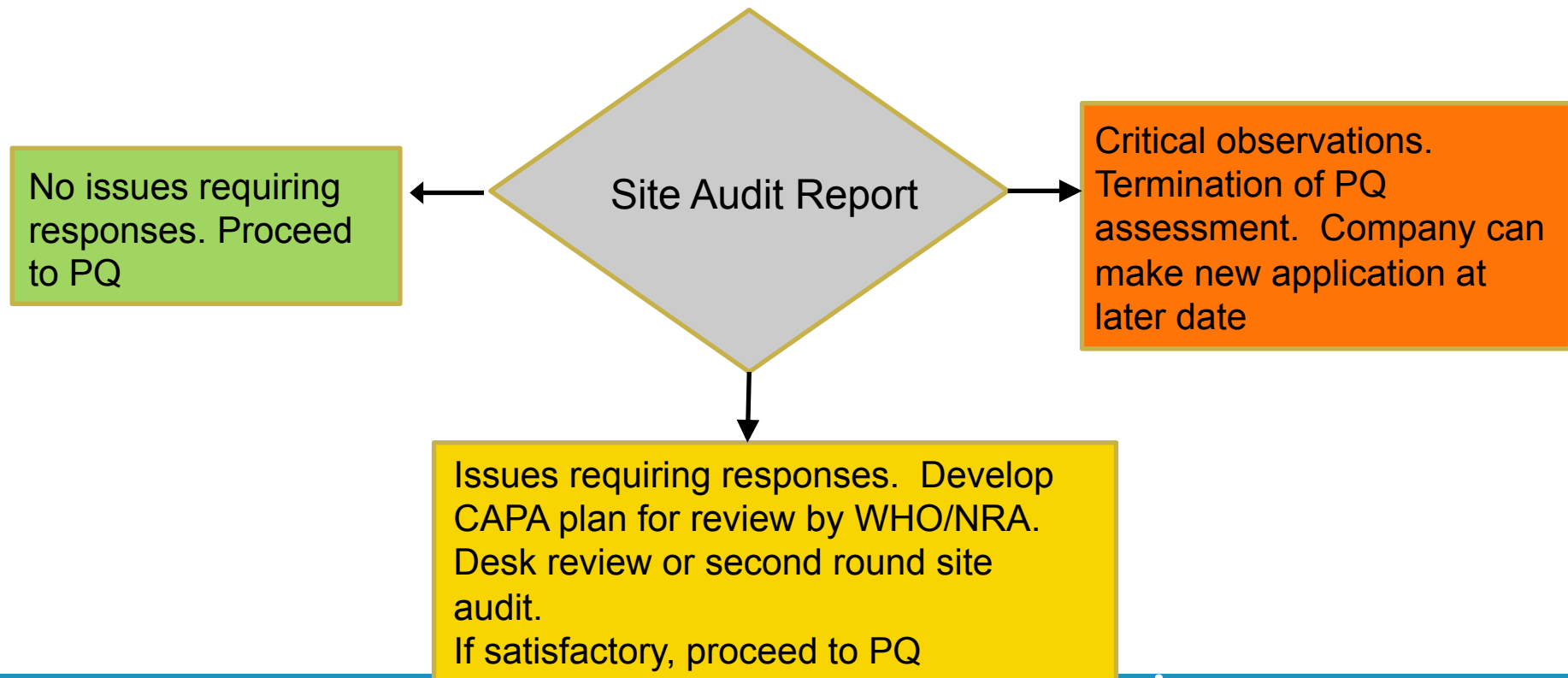
- **High commitment from management to Quality Products and to implementation of Quality Systems**
- **Full independence between production, Quality Control and Quality Assurance. Quality Assurance has last word**
- **Sound and controlled documentation system, detailed procedures (SOPs), detailed records (BPR)**
- **Well trained staff recording all data in BPR immediately, second check by supervisor. Staff trained to opening deviation reports and related investigation**
- **Presence of QA in production, major role in review of records, investigation of deviations, internal audits and CAPA system**
- **QC and QA dimensioned and equipped to match production capacity in volume and diversity of products**

Main reasons for failure

- **Lack of commitment from management to Quality**
- **Roles and responsibilities at different levels not well defined**
- **Wish to rush products into the market without enough process robustness and experience**
- **Weak QA, weak quality systems in place not matching production needs**
- **Show driven by production head or directors**
- **Lack of transparency and honesty with auditors**
- **Lack of capacity to identify, investigate and correct gaps in their systems**



Site Audit Outcome





Clinical aspects during Prequalification of vaccines

**Briefing on Vaccine Prequalification for
DCVMN manufacturers**

Webinar 23 April 2014

Chapter 8: Clinical experience

- Note 1 : Reference documents

- TRS 978, Annex 6 (2012, PQ procedure)
http://www.who.int/entity/immunization_standards/vaccine_quality/TRS_978_61st_report_Annex_6_PQ_vaccine_procedure.pdf
- TRS 850 (1995, GCP); http://apps.who.int/prequal/info_general/documents/TRS850/WHO_TRS_850-Annex3.pdf
- TRS 924 (2004; clinical evaluation of vaccines); http://who.int/entity/biologicals/vaccines/clinical_evaluation/en/index.htm
- TRS 927 (2005; non-clinical evaluation of vaccines) http://who.int/biologicals/vaccines/nonclinical_evaluation_of_vaccines/en/
- Points to consider for manufacturers of human vaccines: clinical considerations for evaluation of vaccines for prequalification
http://www.who.int/immunization_standards/vaccine_quality/pq_vaccine_evaluation/en/

Chapter 8: Clinical experience

- Note 2

- For vaccines originally licensed many years before application for prequalification, emphasis should be given to document history of safe and effective use.

- Note 3

- Provision for request of raw data

8.1 Clinical development program

- Format: tabulated summary (1 or more tables)
- Objective: identification of critical parameters that may have changed during the clinical development of the product

8.2 Clinical trial information (1)

- 8.2.1 Applicant's sponsored clinical trial overview
 - List of all clinical trials conducted (in all countries relevant to the application for WHO PQ)
 - For each study sponsored by the applicant (before and after initial licensure)
 - Approved protocol (by NRA and Ethics Committee)
 - Evidence of registration in a CT registry (WHO ICTRP)
 - Compliance with GCP

8.2 Clinical trial information (2)

- 8.2.1 Applicant's sponsored clinical trial overview (cont'd)
 - For each study, to be provided (in a table or brief summary)
 - Type of study
 - Rationale
 - Study sites
 - Dates
 - Statement of final conclusions
 - Copies of publications and abstracts to be provided
 - List of ongoing trials
 - Details of the study plan
 - Expected date of results

8.2 Clinical trial information (3)

- 8.2.2 Other studies with the applicant's product
 - Not sponsored by the applicant
 - Vaccine as intervention of main interest or used as comparator
 - Also observational studies (e.g. case-control studies)
 - Identified by literature search

Points to consider

- b) a completed clinical trial model summary protocol (according to TRS No. 924, p. 95) for pivotal (often phase III) trials;

8.2 Clinical trial information (4)

- 8.2.3 Clinical summary – (similar to CTD 2.5)
 - Detailed summary and interpretation of the safety and efficacy data of all studies (pre- and post-licensure)
 - Relevance to support worldwide use
 - WHO recommended schedules
 - Co-administration with other vaccines
 - Expected to complement (not replace) the summary written by an independent clinical expert (8.2.5)

8.2 Clinical trial information (5)

- 8.2.4 Assessment reports

- Whenever possible

- Clinical section of the national regulatory authority (NRA) assessment report from the country of origin and/or country where initially licensed
 - Assessment reports for any subsequent variations to the license for changes relevant to clinical data
 - Assessment reports from other NRAs

8.2 Clinical trial information (6)

- 8.2.5 Clinical expert report
 - Independent clinical expert report
 - Evidence of expertise and independence to be provided
 - Particularly useful for products licensed long time before
 - Limitations put in the context of the requirements at the time of licensure
 - Ethical approval / GCP
 - Study design / sample size
 - Impact on disease control after introduction in vaccine programme
 - Post-marketing safety data

8.2 Clinical trial information (7)

- 8.2.6 Preclinical studies sponsored by the applicant
 - List of all preclinical studies sponsored by the applicant
 - For preclinical studies performed after initial licensure, indicate the reasons for these studies
- TABULATED FORMAT

8.3 Documentation of safety (1)

- 8.3.1 Pharmacovigilance plan
 - Introduced in the current PQ procedure (from 2012)
 - Important to determine whether evidence to support the use of the product in different populations (geographical areas, age groups, etc...) are planned
 - Some evidence will be expected as post-prequalification commitments

8.3 Documentation of safety (2)

- 8.3.2 Initial evaluation of vaccines that have been in the market for a long time (or reassessment of already prequalified vaccines)
 - Outline of the applicant's procedures for the collection, onward notification and assessment of adverse events
 - Listing of all reported AEFIs
 - Periodic Safety Update Reports (PSURs) may provide all the information needed
 - ICH format preferable

8.3 Documentation of safety (3)

- 8.3.3 Recently licensed vaccines
 - Ongoing phase IV studies
 - Ongoing active monitoring of the safety profile

8.3 Documentation of safety (4)

- 8.3.4 Documentation of serious advent events
 - Fullest possible description of each case, including any information there may be on investigations, actions, patient treatment and outcome
 - Periodic Safety Update Reports (PSURs) may provide all the information needed

Clinical Information in Package Insert

PSF Chapter 4.4

The information in the PI must be referenced to the clinical data.

- Indications**
- dosage-regimen**
- side-effects**
- pregnancy**
- special precautions**

