

WHO/Prequalification

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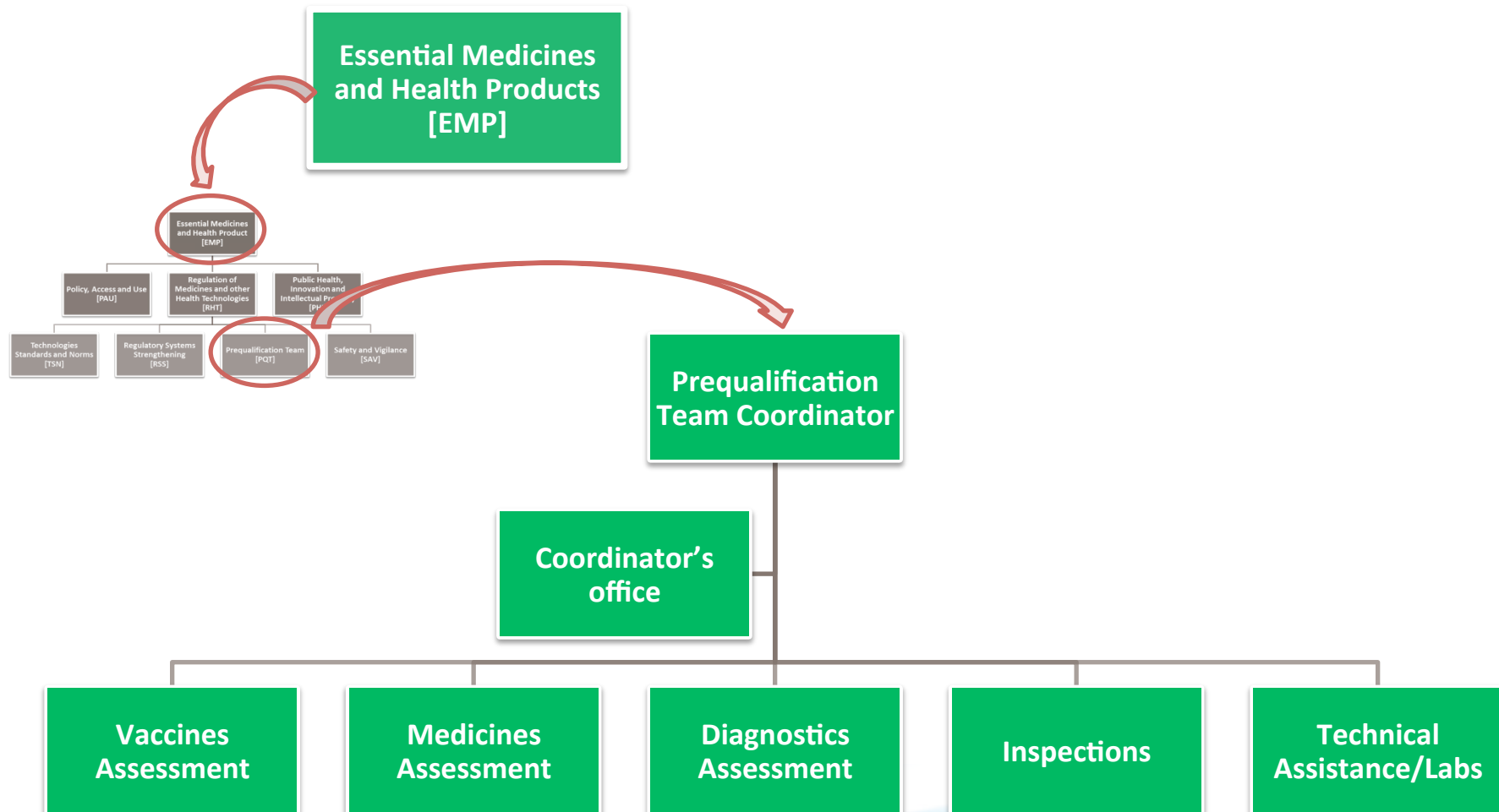


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Structure of the Prequalification Team



Role of WHO prequalification

- **Facilitate access to safe, appropriate priority IVDs, medicines & vaccines**
- **Support two of WHO's six core functions**
 - setting norms & standard/promoting their implementation
 - providing technical support, catalyzing change & building institutional capacity
- **Contribute to achieving four of WHO's impact goals**
 - reduce under-five mortality
 - reduce maternal mortality
 - reduce the number of people dying from AIDS, tuberculosis and malaria
 - eradicate polio



WHO vaccines prequalification

- **A service provided to UN purchasing agencies.**
- **Provides independent opinion/advice on the quality, safety and efficacy of vaccines for purchase**
- **Ensures that candidate vaccines are suitable for the target population and meet the needs of the programme**
- **Ensures continuing compliance with specifications and established standards of quality**



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Pre-conditions for PQT-VXA evaluation

Reliance on the National Regulatory Authority (NRA) of the exporting country

- **NRA must be assessed as functional as a result of successful evaluation using the WHO NRA assessment tool**
- **NRA's functional status needs to be sustained over time**
- **Continued regulatory oversight by NRA is required as well as communication with WHO about potential problems with the vaccine**
- **Agreements are established with the NRAs for information exchange when a vaccine is about to be prequalified**



Pre-conditions for PQT-VXA evaluation

- **Vaccine is licensed/registered by the responsible NRA (or EMA article 58 scientific opinion)**
- **There are WHO guidelines/recommendations approved by the ECBS are available for the type of vaccine (published in the WHO Technical Report Series)**
- **Listed in the vaccine priority list**



Pre-submission and Dossier Review

- Pre-submission meetings with manufacturers interested in submission are available and encouraged
- Notification of intended submission
- Dossier Submission
 - Product Summary File
 - Common Technical Document
- Screening
- Acceptance decision

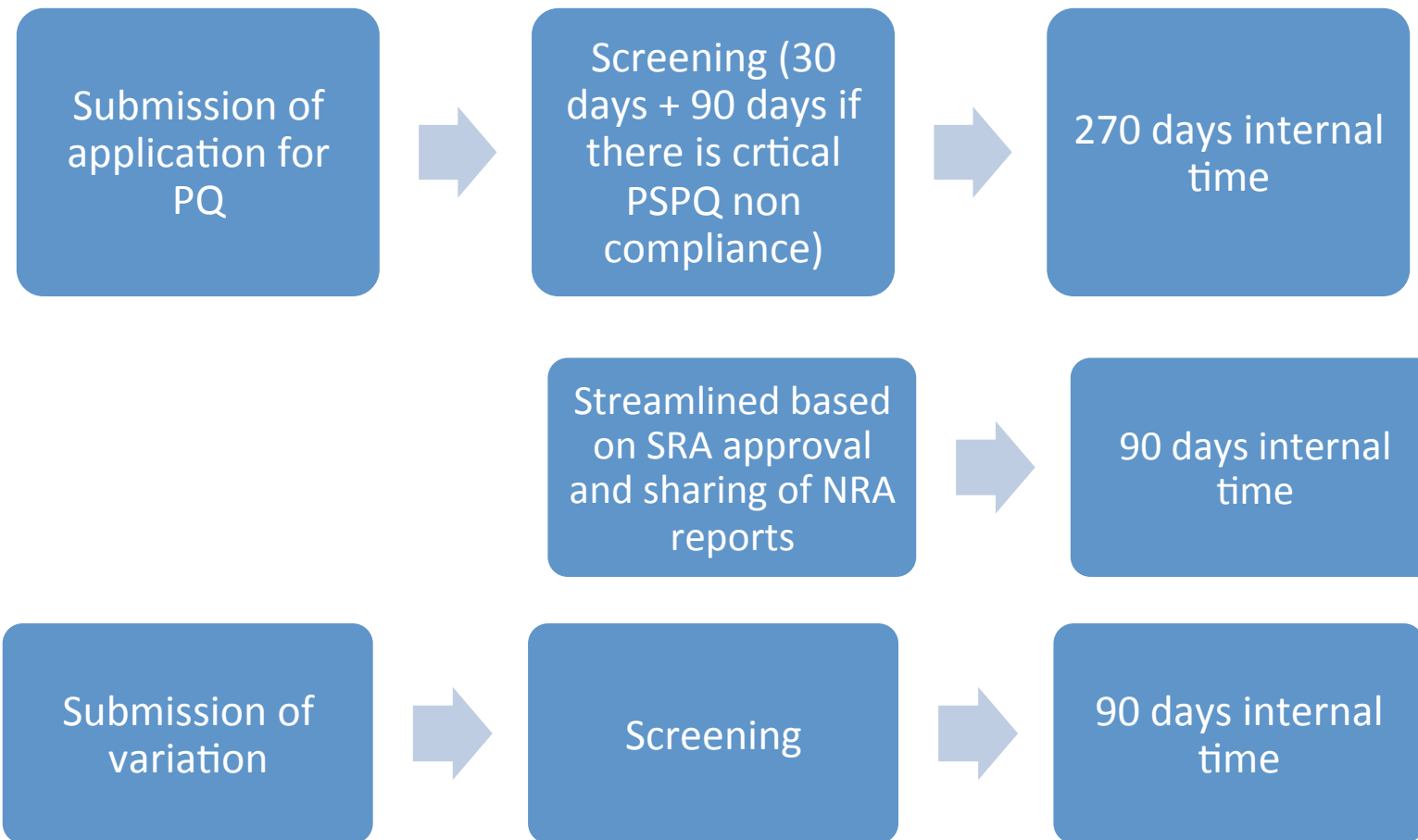


Prequalification process

- Scientific review of quality dossier
- Scientific review of clinical data
- Testing of samples
- Consultation with responsible NRA
- Site audit to manufacturing facilities



Prequalification process: timelines (excluding applicant response times)



Quality aspects considered during evaluation of vaccines for WHO Prequalification

- **Production process and quality control methods, including validation**
- **QC characterisation, including stability**
- **Production capacity and consistency at commercial scale**
- **Compliance with WHO recommendations and UN tender specifications including labels and inserts**
- **Personnel and Premises**
- **Compliance with GMP**



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Vaccine Inspection Team

- **Lead inspector from the Inspections Group in PQT**
- **Has expertise in the areas of production, quality control, quality assurance, quality system and GMP**
 - Usually includes one of the dossier (quality) reviewers
 - May include technical staff from a relevant UN procurement agency
- **The NRA of the manufacturing country, or the NRA with regulatory oversight of the product, is invited to participate in the mission**



Classification of deficiencies

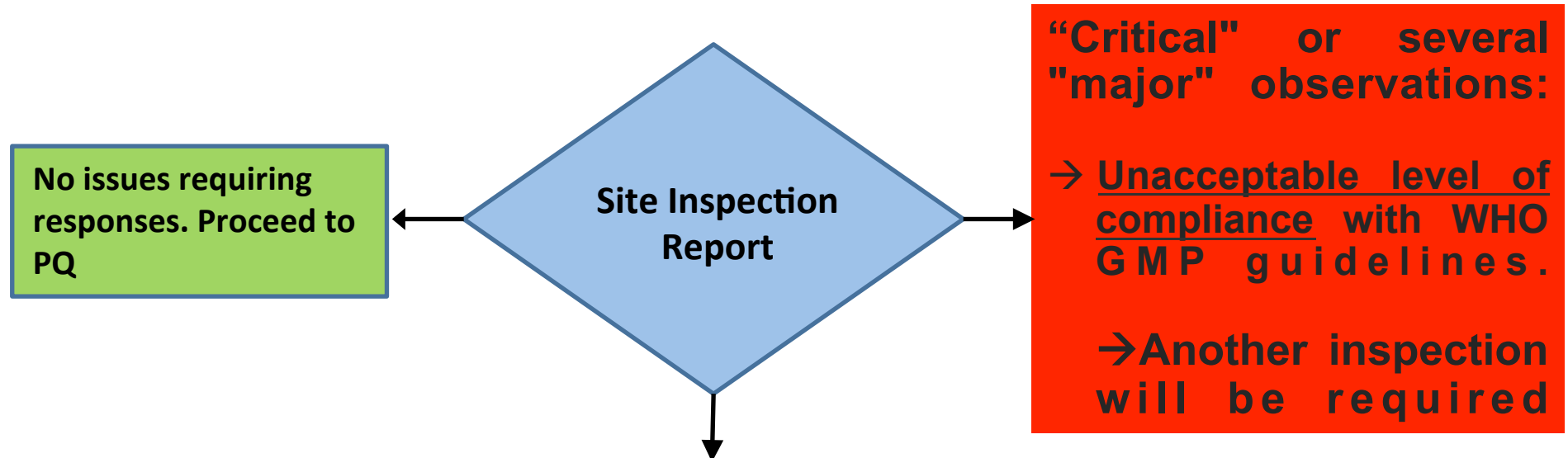
Deficiencies are descriptions of non-compliance with GMP requirements.

Deficiencies may be classified as:

- ❖ Critical Observation – potential risk harm to the user
- ❖ Major Observation – major deviation from GMP
- ❖ “Other” Observation – departure from good practice



Site Inspection Outcome



1. "other" observations only:
→ acceptable level of compliance with WHO GMP.

2. "other" and a few "major" observations:
→ compliance with WHO GMP is made after the CAPAs have been assessed.



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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



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Role of NRA during PQ process

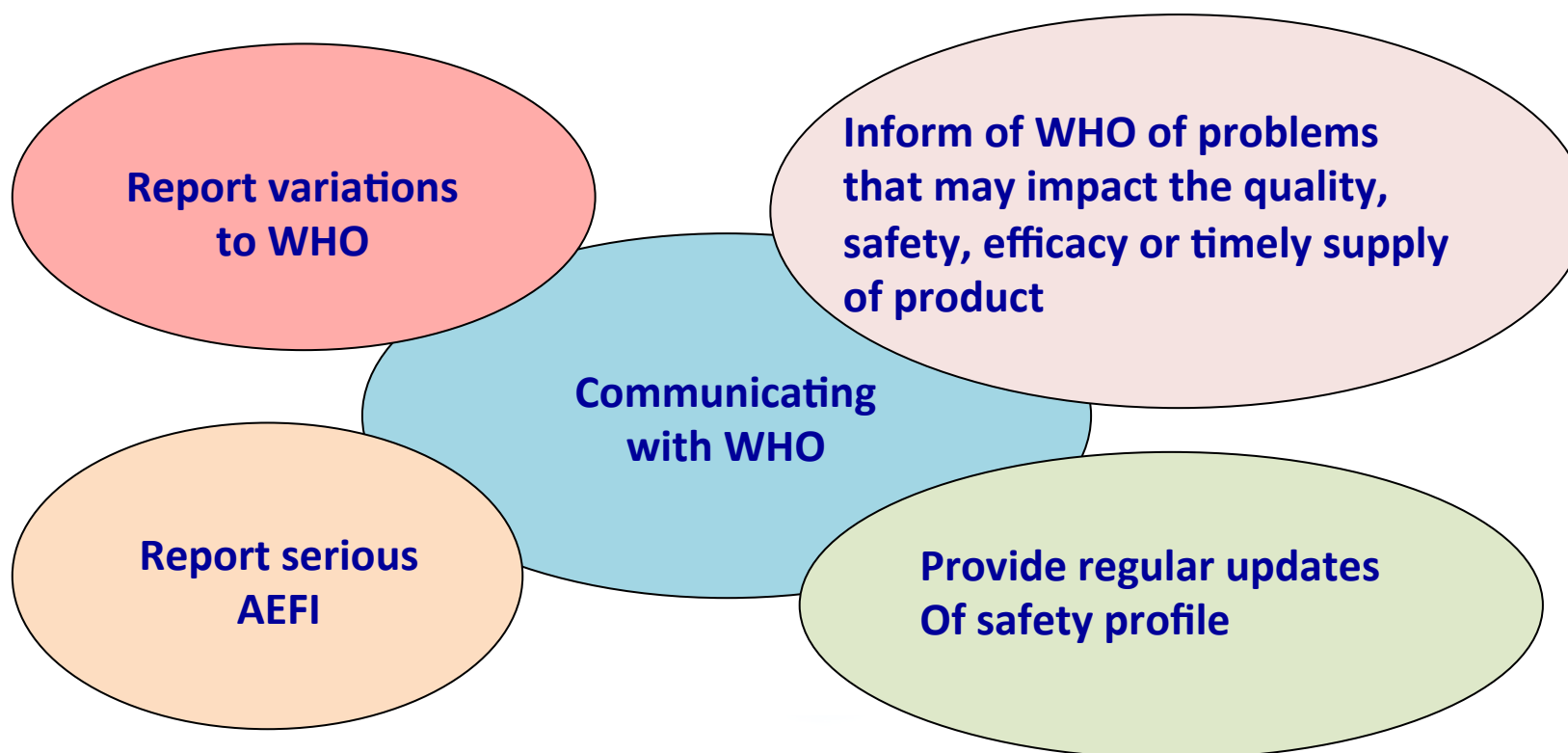
As part of the evaluation procedure, consultation with NRA discusses:

- Regulatory status of the concerned vaccine/s
- Clinical performance in country of manufacture if used
- Quality evaluation, outcome of recent GMP inspections
- Compliance with specifications (trends from lot release data)
- Regulatory actions concerning the vaccine/s



Post Prequalification

Commitments from the manufacturer



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Post Prequalification WHO Activities

- **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).**



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Targeted testing program

- Independent testing in contracted laboratories of vaccine lots supplied to UN
- Manufacturers informed in PQ approval letter of required number of samples (vaccine dependent) to be retained from each batch of vaccine supplied through UN agencies.
- Testing program established annually
- Manufacturers provide list of batches provided through UN agencies
- Three to five lots selected by WHO and samples requested from the manufacturer.



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Reassessment Process

- Updated dossier (including summary of changes from previous dossier) requested and evaluated
- Testing requirement depends on WHO experience in targeted testing programme
- Site inspection requirement depends on time since last WHO inspection and local NRA inspection and data sharing agreement with WHO



Why is Vaccines PQ important for user countries and its NRAs?

It represents a source of vaccines of "assured quality"

In addition the evaluation is focused on programmatic needs

WHO follows up on complaints and reports of AEFIs and publishes the outcome of investigations

WHO monitors the quality of prequalified vaccines on a continuing basis, through testing of samples, reassessment of the products, targeted audits, and delists vaccines if they do not meet the established specifications and/or standard

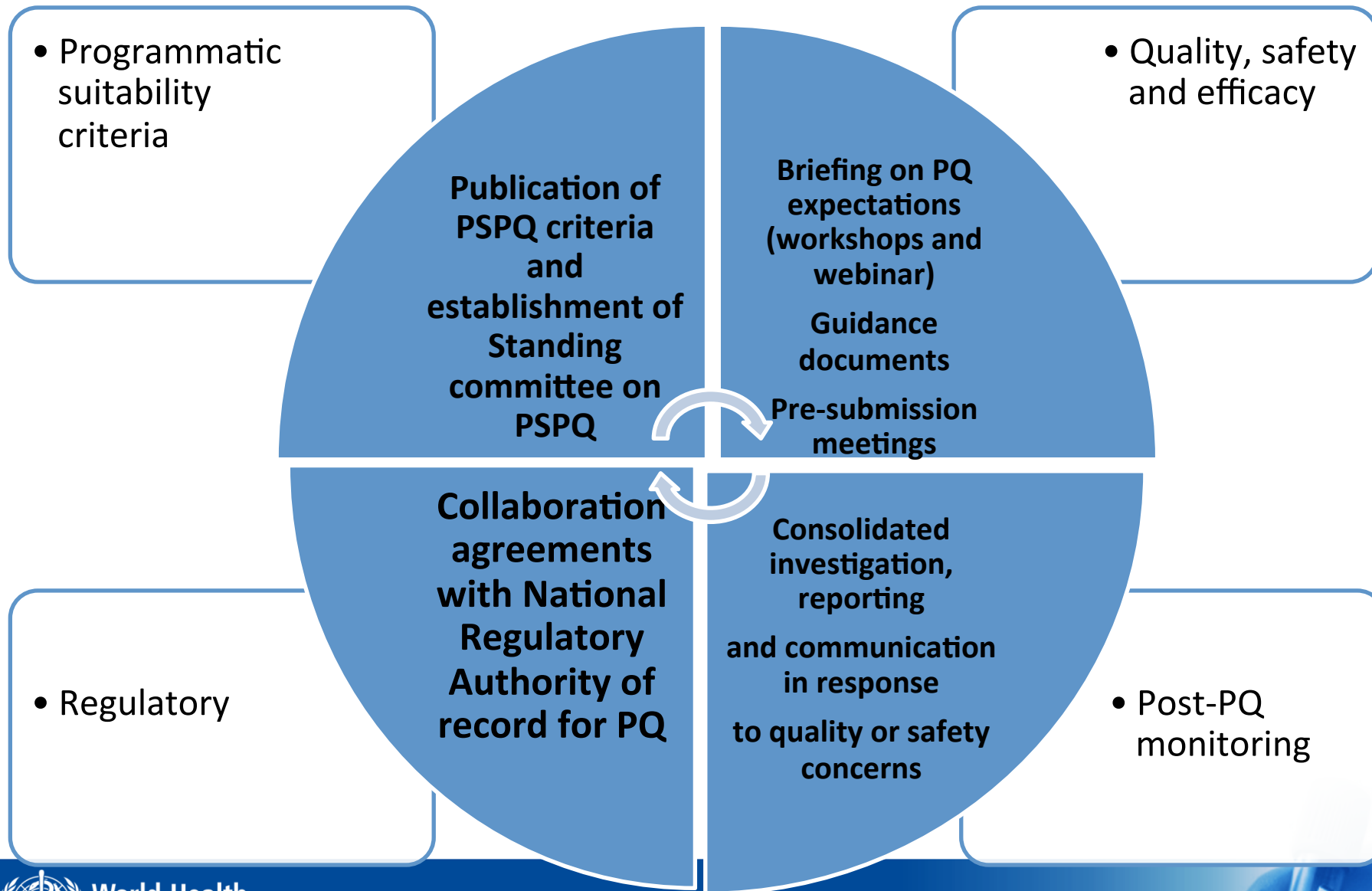
Opportunity for NRAs in user countries to save resources to focus on other priorities, since registration can be granted through a facilitated and shortened procedure



Past and current challenges

Quality	Clinical	Programmatic	GMP
<p>Incomplete dossier</p> <p>Lack of data at commercial scale</p> <p>No history of characterization</p> <p>Master and Working cell banks</p> <p>Inappropriate devices: nasal administration</p>	<p>Lack of clinical consistency data, unclear ethical oversight</p> <p>Clinical trial comparator product not acceptable</p> <p>Lack of access to data and/or old data not meeting current GCP</p> <p>Lack of registration of CTs</p>	<p>Deviation</p> <p>Programmatic suitability criteria (PSPQ):</p> <p>eg, non autodisable prefilled syringes, stability profile and VVM</p>	<p>Quality systems</p> <p>Manufacturing process</p>
Regulatory	<p>National Vs WHO requirements:</p> <p>Test methodologies and GMP</p> <p>Schedules and target population</p> <p>Monodose Vs multidose presentation (preferred)</p>		

Past/current Challenges and solutions



Technical assistance and capacity building

Meetings with manufacturers at early stages of vaccine development. Advice on product characteristics and clinical development.

PQ briefing workshops

Support to IFPMA and DCVMN

Support to regulatory networks: DCVRN, AVAREF



Thank you



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Reference documents

PQT/VXA procedure [TRS 978, Annex 6 (2013)]

http://www.who.int/entity/immunization_standards/vaccine_quality/TRS_978_61st_report_Annex_6_PQ_vaccine_procedure.pdf

PQ vaccines: Priority setting and Review

http://www.who.int/immunization_standards/vaccine_quality/pq_priorities/en/

Programmatic Suitability for Prequalification

http://www.who.int/immunization_standards/vaccine_quality/pspq2_v140512.pdf

Clinical

[http://apps.who.int/prequal/info_general/documents/TRS850/WHO TRS 850-Annex3.pdf](http://apps.who.int/prequal/info_general/documents/TRS850/WHO_TRS_850-Annex3.pdf)

http://who.int/entity/biologicals/vaccines/clinical_evaluation/en/index.htm

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

http://www.who.int/immunization_standards/vaccine_quality/pq_vaccine_evaluation/en/

Variations to prequalified vaccines

http://who.int/immunization_standards/vaccine_quality/variations_pq_vaccine/en/

HO contracted testing laboratories

http://www.who.int/immunization_standards/vaccine_quality/contracted_labs_vaccines/en/



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Reference documents

Good Manufacturing Practice

WHO GMP for biological products, Annex 2, WHO TRS 999, 2016,
[http://who.int/biologicals/areas/vaccines/
Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf](http://who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf)

WHO GMP for pharmaceutical products: main principles, Annex 2, WHO
T R S 9 8 6 , 2 0 1 4

WHO GMP for sterile pharmaceutical products, Annex 6, WHO TRS 961,
2 0 1 1



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