PQ/EUL-related specialized technical assistance for diagnostics

David Woo
Technical Officer
Local Production & Assistance (LPA) Unit
Regulation and Prequalification Department
Access to Medicines and Health Products Division
World Health Organization

Specialized technical assistance

WHO provides Specialized Technical Assistance to help recipients achieve compliance with international regulatory norms and standards, so that they can attain WHO prequalification (PQ) for priority products or services, or emergency use listing (EUL) for unlicensed products to be used in the context of a public health emergency

- Medicines
- In Vitro Diagnostics
- Vaccines

Why would an IVD manufacturer request technical assistance from the WHO?

Two main reasons:

1. “Corrective action” to correct existing problems in a manufacturer’s product dossier or quality management system that were uncovered during a PQ, ERPD or EUL review. Problems could range from a lack of trustworthy clinical performance data to an absence of an effective ISO 13485:2016 quality management system

2. “Preventive action” to prevent the occurrence of future problems in analytical or clinical performance data, quality management system processes, or risk management measures

Who is eligible for technical assistance?

- Manufacturer who has made a pre-submission to WHO prequalification but whose product did not pass pre-submission screening of design dossier or quality management system
- Manufacturer who has made a pre-submission to the Expert Panel Review Panel for diagnostics for “risk assessment” but received an unacceptably high-risk rating
- Manufacturer of an innovative product that is still under research and development status

Some tips to overcome common deficiencies

✕ **Risk management** → ☑ **Possible solutions:**

- risk management activities are superficial and generic (e.g. lack of risk analysis on low-resource setting)
- risk management documentation is scattered and lacks linkages
- risk analysis is not applied to all aspects of the product life cycle (e.g. lack of risk analysis on business processes)

- all departments within the company are involved in risk management
- properly update the risk management documentation
- set up good traceability of risk management throughout the product life cycle
- specific training for risk management throughout the company

✕ **Panel(s) for quality assurance and quality control** → ☑ **Possible solutions:**

- the panel member is insufficiently characterized and validated
- replacement of a panel member leads to drift in device performance

- use risk assessment & experience with development to indicate which features must be verified/validated
- establish detailed SOP to control replacement of panel members, and reserve some of the working panel members validated for use when panel members are changed

Some tips to overcome common deficiencies

✗ Intended use claim lacks relevant information → ✓ **The following must be included in the intended use claim:**

- What the product is intended to detect
- The function of the product
- The clinical indication for the IVD
- The type of specimen(s) required
- The intended testing population
- The intended user

✗ Disconnect between the intended use claim and the performance claims → ✓ Intended use must be defined prior to planning and conducting performance evaluation studies.

✓ Performance claims must support the IVD intended use.

✗ The clinical studies requirements are not met. → ✓ Manufacturers must be aware that clinical studies requirements are peculiar to each device as well as the type of device.

Some tips to overcome common deficiencies

☑ Manufacturers must be aware of design and manufacturing requirements and of the fact that compliance to guidance documents and international standards help demonstrate that “Essential Principles of Safety and Performance” are met.

☑ Clear and organized evidence of compliance to guidance documents and standards must be included in the technical documentation, and justification must be provided when requirements are not met.

Thank you

For more information and updates:

https://www.who.int/teams/regulation-prequalification/lpa

localproduction@who.int

LPA_Worldwide

PQ/EUL-related specialized technical assistance overview

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Acronyms

API	Active Pharmaceutical Ingredient
CAPA	Corrective Action and Preventive Action
CRO	Contract Research Organization
EOI	Expression of Interest
ERPD	Expert Review Panel for Diagnostics
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practice
LMICs	Low- and Middle-Income Countries
LOA	Letter of Agreement
LPA	Local Production and Assistance
PQ	Prequalification
TA	Technical Assistance
WHO	World Health Organization

Outline

- Background
- Who is eligible for PQ/EUL-related specialized TA
- How to initiate the specialized TA
- How does PQ//EUL-related specialized TA work
- Some benefits for requesting specialized TA
- Additional points to note

Background

- Specialized Technical Assistance (TA) related to WHO PQ of products is provided by the **Local Production and Assistance (LPA) Unit,** WHO

- LPA Unit provides support to countries and regions in strengthening and promoting sustainable local production & technology transfer using a comprehensive approach to improve **timely access to quality-assured health products**

Who is eligible for PQ/EUL-related specialized TA

Manufacturers

- Located in LMICs
- Intend to seek **WHO PQ**
- Produce **priority health products eligible for WHO PQ**,
  - Invitations to Manufacturers and Suppliers of Medicinal Products to Submit an Expression of Interest for Product Evaluation (EOIs) for medicines
  - Vaccines Prequalification Priority List
  - List of eligible IVDS on WHO PQ IVD website

Contract Research Organizations (CROs)

- Provide services to manufacturers located in LMICs
- Conduct clinical studies (BE studies) for priority health product listed in the current EOIs and produced by the manufacturer

Some examples of types of specialized TA

Manufacturers

Facility:

- **QMS audit** and/or **mock GMP inspection** pre-WHO PQ
- Development of **CAPA** plan, including root cause analysis

Product (API, product):

- **Product-related** issues
- **Product dossier** to be submitted to WHO PQ
- Selection of appropriate products for WHO PQ

Organizing **training workshops** to build capacity on specific topics requested by manufacturers, e.g. Virtual cGMP Training Marathon

Contract Research Organizations

- **QMS audit** of facility
- Support for **GCP** compliance
- Review of a**nalytical methods** that would be used to generate data in the clinical/BE study
- **Audit of a completed study** by the CRO that is similar to the study to be done for the FPP being submitted to WHO PQ
- Assistance with required documentation for the PQ dossier

How to initiate the specialized TA

Different channels to request for PQ/EUL-related specialized TA:

- email directly to Local Production and Assistance Unit localproduction@who.int
- online request form https://extranet.who.int/pqweb/content/request-technical-assistance
- proposed by WHO PQT, international procurers (Global Fund, UNICEF, etc.), government ministries, other WHO departments

How to initiate the specialized TA

1. Request for PQ/EUL-related specialized TA
2. Completed Letter of Agreement and/or GMP pre-inspection application form to receive PQ/EUL-related specialized TA
3. Introductory meeting with the LPA Unit
    - ❖ Introduction of company, product for submission
    - ❖ Details of TA required/being requested
    - ❖ Company plan for pre-submission meeting and/or submitting to WHO PQ
4. Provision of specialized TA begins – site visits, document review, technical discussions, etc.
    - ❖ **Tailored**, **needs-based**
    - ❖ On-going communication with follow-ups and monitoring
5. WHO Prequalification / Emergency Use Listing attained

How does PQ/EUL-related specialized TA work

- From the TA request to attainment of WHO PQ/EUL
- Open communication is essential to maximize the benefits of the specialized TA
  - Declare to the LPA Unit the intention to submit to WHO PQ and when
  - Leverage on technical expertise of LPA Unit to resolve issues toward attaining WHO PQ/EUL
  - Be transparent if similar TA is being provided by other parties
  - Reach mutually-accepted technical solutions and next steps
  - Active follow-up and monitoring of progress
- Focal point in the company is a key part of this process
  - Facilitate exchange of information, data and documents when TA is provided
  - Facilitate logistics during a QMS audit/mock GMP inspection, e.g. visa, hotel selection, local transport

Some benefits for requesting specialized TA

Manufacturers

- Speed up attainment of WHO PQ/EUL
- Build capacity to:
  - understand & meet WHO quality assurance standards
  - address & strengthen quality systems
- Improve quality of other products produced in the facility
- Become eligible for international, donor-sponsored tenders
- Access procurement markets

UN agencies and other procurement agencies

- Increase the range of PQ products that can be procured
- Diversify the sources of supply of quality priority health products
- Be assured the manufacturer can produce with consistent quality

Additional points to note

- Information gathered during the TA are not shared with WHO Prequalification Unit and are kept confidential
- Care is taken to ensure any conflict of interest is avoided with WHO Prequalification Unit
- Site inspections and evaluations of product dossiers performed for WHO PQ are independent of the outcomes of TA

PQ/EUL-related specialized technical assistance information: https://www.who.int/teams/regulation-prequalification/lpa/technical-assistance-for-who-prequalification

PQ/EUL-related specialized technical assistance online request: https://extranet.who.int/pqweb/content/request-technical-assistance

Thank you

Local Production and Assistance

Jicui Dong (MSc, PhD, MBA)
Unit Head
Local Production & Assistance (LPA) Unit
Regulation and Prequalification Department
Access to Medicines and Health Products Division
World Health Organization

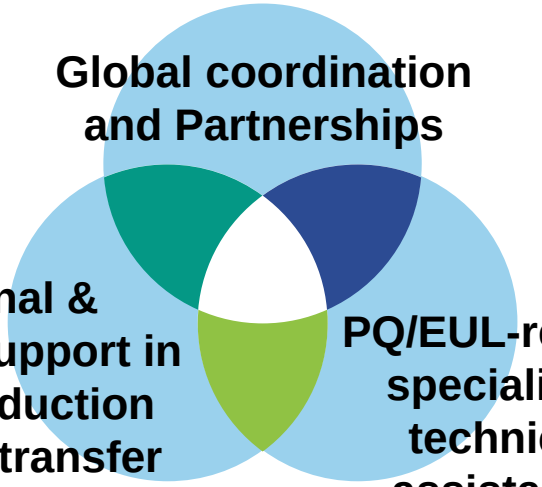
LPA Unit's mandates in strengthening quality, sustainable and eco-friendly local production & technology transfer to improve access

Further strengthened by Resolution WHA74.6:

World Local Production Forum (WLPF) Interagency statement etc.

Ecosystem assessments for quality, sustainable green manufacturing

Strategy/roadmap setting & implementation, capacity building & technical assistance



Global resources on local production and technology transfer

Facilitation of technology transfer

Capacity building and technical assistance to achieve quality, sustainable, green manufacturing and WHO PQ/EUL

EUL: Emergency use listing
PQ: Prequalification

For more information: https://www.who.int/teams/regulation-prequalification/lpa

Specialized technical assistance for vaccines

Local Production and Assistance Unit (LPA)
Regulation and Prequalification Department (RPQ)
Access to Medicines and Health Products Division (MHP)
World Health Organization (WHO)

Local Production and Assistance (LPA) Unit

What type of assistance?

- Strategy, Policy and Partnership
- Situational Analysis and Readiness
- Technology Transfer Facilitation
- Capacity Building and Technical Assistance
- Technical Assistance for WHO Prequalification
- Country Support

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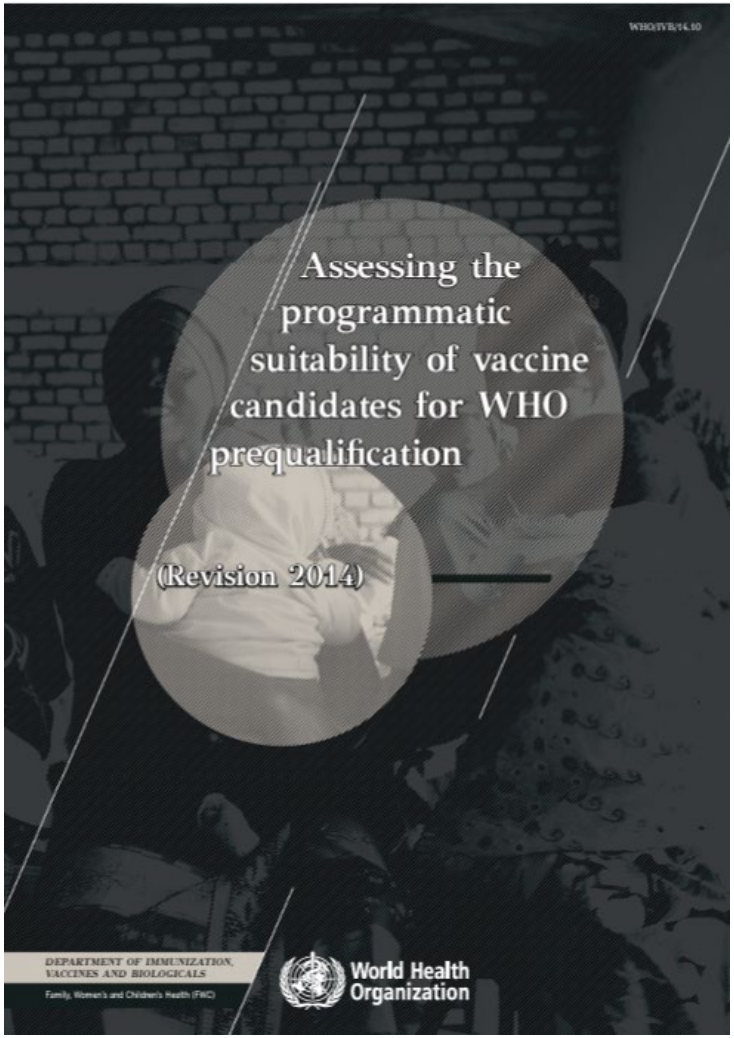
- Medicines
- In Vitro Diagnostics
- Vaccines

Where LPA can make a difference

- Assessing the programmatic suitability of vaccines candidates for WHO prequalification (PSPQ)



- WHO PSPQ

Where LPA can make a difference

- Pfizer/ BioNTech COVID-19 mRNA vaccine *Comirnaty*

- EMA: Comirnaty SmPC
- Picture from EPR

Comirnaty

1. NAME OF THE MEDICINAL PRODUCT

Comirnaty 30 micrograms/dose concentrate for dispersion for injection
COVID-19 mRNA Vaccine (nucleoside modified)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial with a purple cap and must be diluted before use.

One vial (0.45 mL) contains 6 doses of 0.3 mL after dilution, see sections 4.2 and 6.6.

One dose (0.3 mL) contains 30 micrograms of tozinameran, a COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Tozinameran is a single-stranded, 5'-capped messenger RNA (mRNA) produced using a cell-free *in vitro* transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white frozen dispersion (pH: 6.9 - 7.9).

Comirnaty

6.3 Shelf life

Unopened vial

Frozen vial

2 years when stored at -90 °C to -60 °C.
Within the 2-year shelf life unopened vials may be stored and transported at -25 °C to -15 °C for a single period of up to 2 weeks and can be returned to -90 °C to -60 °C.

When stored frozen at -90 °C to -60 °C, 195-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 3 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial

1 month at 2 °C to 8 °C within the 2-year shelf life.
Within the 1-month shelf life at 2 °C to 8 °C, up to 48 hours may be used for transportation.
Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.
Thawed vials can be handled in room light conditions.

Once thawed, the vaccine should not be re-frozen.

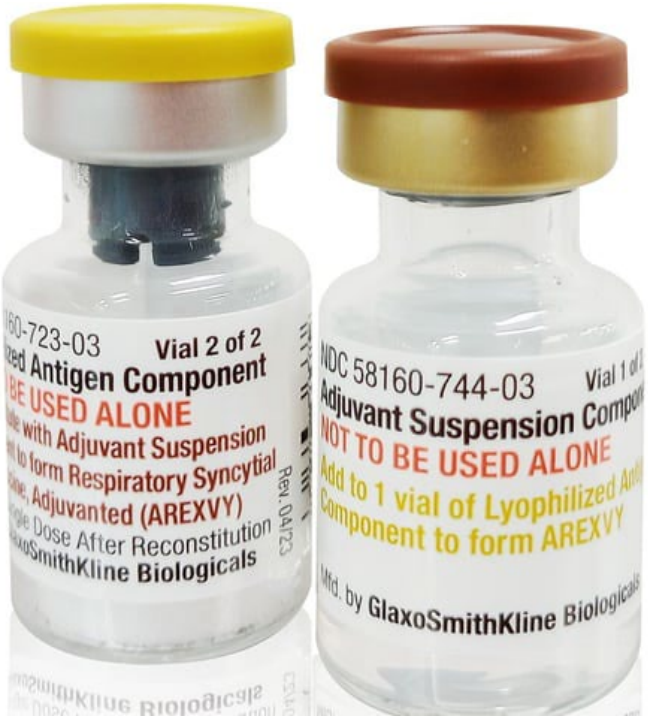
Handling of temperature excursions once removed from the freezer

Stability data indicate that the unopened vial is stable for up to:

- 24 hours when stored at temperatures from -3 °C to 2 °C
- a total of 4 hours when stored at temperatures from 8 °C to 30 °C; this includes the 2 hours at up to 30 °C detailed above

Where LPA can make a difference

- GSK Respiratory Syncytial Virus vaccine *Arexvy*



- EMA: Arexvy SmPC
- Picture from Fierce Pharma

Arexvy

1. NAME OF THE MEDICINAL PRODUCT

Arexvy powder and suspension for suspension for injection
Respiratory Syncytial Virus (RSV) vaccine (recombinant, adjuvanted)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 mL) contains:
RSVPreF3[1] antigen[2,3] 120 micrograms

[1] Respiratory Syncytial Virus recombinant glycoprotein F stabilised in the pre-fusion conformation = RSVPreF3
[2] RSVPreF3 produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology
[3] adjuvanted with $AS01_E$ containing:
plant extract *Quillaja saponaria* Molina, fraction 21 (QS-21) 25 micrograms
3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota* 25 micrograms

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and suspension for suspension for injection.

The powder is white.
The suspension is an opalescent, colourless to pale brownish liquid.

Arexvy

6.3 Shelf life

2 years

After reconstitution

Chemical and physical in-use stability has been demonstrated for 4 hours at 2 °C – 8 °C or at room temperature up to 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 4 hours.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3

Take home message

- Licensing by a regulatory authority operating at high level of performance is not guarantee that the prequalification of a vaccine will be granted.
- LPA-provided specialized technical assistance for WHO PQ can help manufacturers avoid problems that are difficult to resolve when the pharmaceutical development is completed.
- This turned out to be particularly beneficial for the specific requirements of WHO (e.g. programmatic suitability).
- For further information please:
  - ✓ visit Local Production & Assistance webpages
  - ✓ email to localproduction@who.int

Thank you for your attention.

Specialized technical assistance for medicines

Dr Kim Notenboom
Technical Officer
Local Production & Assistance (LPA) Unit
Regulation and Prequalification Department
Access to Medicines and Health products
World Health Organization

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- Medicines
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- Vaccines

Unique service by Local Production & Assistance Unit

- Across all stages of development and life cycle
- Continuous nature
- Pre-data collection / pre-production
- Knowledge construction

Across all stages of development and lifecycle

LPA Unit provides guidance and directions **at any stage** of a medicine's development, i.e. for **new generic products** but also for **locally marketed** products.

- Fermentation, semi-synthetic and chemically synthesized generics, as well as (similar) biotherapeutic products (e.g. insulin and monoclonal antibodies).
- Oral dosage forms, parenteral products, transdermal patches, vaginal ring etc.

Examples

- Priority of products within portfolio
- Presentation of API data in the dossier (use of prequalified API, CEP-procedure, APIMF)
- Assistance with a specific aspect at a late development stage, e.g. requirements for compatibility and in-use stability studies for parenteral products.

LPA Unit: Local production & Assistance Unit
EOI: Expression of Interest
API: Active Pharmaceutical Ingredient

Continuous nature

Manufacturers have the ability to provide data and pose inquiries to LPA Unit's experts **on a rolling basis**.

- Queries can be raised at **any moment** and of **any scope**.
  - ✓ GAP analysis on an API Master File (APIMF)
  - ✓ Has the polymorphism of the API been sufficiently addressed?
  - ✓ How to proceed when issues arise with the identification of impurities?
  - ✓ What are the requirements for validation of test methods for excipients?
  - ✓ Is the deviation in the composition of our product compared to that of the reference product sufficiently justified?
  - ✓ Suitability of the batch for bioequivalence and/or comparative dissolution testing (biobatch).

LPA Unit: Local production & Assistance Unit

Pre-production / pre-data collection

To help ensure that the appropriate experiments and studies are conducted, manufacturers can ask the LPA Unit for assistance beforehand.

- ✓ Characterization of the API
- ✓ How to adequately justify a control strategy for impurities or solvents
- ✓ Aspects that need to be addressed for a specific API or dosage form, e.g. stability of the polymorph, suitability of a break mark, compatibility with diluents.

Feedback on protocols before start of production or testing.

- ✓ Validation of analytical procedures
- ✓ Process validation
- ✓ Comparative dissolution testing
- ✓ Stability testing (e.g. storage conditions, parameters, test intervals)

Construction of knowledge

Experts from LPA Unit offer additional clarification to **build understanding of the rationale** behind policies and guidances.

This unique assistance aims to **help addressing queries** raised by assessors and may also **prevent their recurrence** in future applications.

Dedicated training can be provided to manufacturers on specific topics.

LPA Unit: Local production & Assistance Unit

Take home messages

✓ Specialized technical assistance by LPA Unit saves manufacturers time and efforts by diminishing the risk that new experiments and studies need to be conducted after submission and/or of a major dossier revision.

✓ Gained knowledge to be used to address deficiencies raised by assessors as well diminish their recurrence.

LPA Unit: Local production & Assistance Unit

Thank you for your attention