Prequalification and Post-prequalification Vaccines Testing

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Outline

• Prequalification of vaccines – Provisions
• WHO's control of vaccines – Assured quality
• Challenges faced
• Recent developments in vaccines testing
• WHO's Global Network for Biologicals
Prequalification of vaccines – Provisions

➤ Vaccine on the priority list for prequalification

➤ Functionality of the national regulatory agency (NRA): Producing country must meet WHO vaccine regulation indicators

➤ Three pillars of vaccine evaluation:
    ✓ WHO reviews the vaccine dossier (quality & clinical data)
    ✓ WHO inspects the manufacturing site
    ✓ WHO tests the final product
Prequalification of vaccines – Listing

- Issuance of acceptability letter
- Vaccine published on the WHO website: https://extranet.who.int/gavi/PQ_Web/
- Listed vaccines (more than 100) not only purchased by UN agencies, but also directly by countries & non-governmental organizations

22 producing countries
> 100 receiving countries
• Prequalified vaccines are used to immunize 65% of infants worldwide

• Immunization averts 2 to 3 million deaths per year from diphtheria, tetanus, pertussis and measles
Prequalification of vaccines – Independent testing of final product

1) **Initial evaluation of a new product** (application process)
   WHO TRS no. 978, Annex 6, chapter 3.4

2) **Annually performed targeted testing** (PQ’d vaccines)
   WHO TRS no. 978, Annex 6, chapter 10

3) **Adverse events following immunization / complaints**

**Testing is performed through** → WHO contracted labs → 12 laboratories worldwide

www.who.int/immunization_standards/vaccine_quality/Laboratories_table_08April2015.pdf?ua=1
Prequalification of vaccines – List of contract laboratories

<table>
<thead>
<tr>
<th>No.</th>
<th>Laboratory Name</th>
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<tbody>
<tr>
<td>1)</td>
<td>Biological Standardisation Unit of Scientific Institute of Public Health (IPH), Belgium</td>
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<tr>
<td>2)</td>
<td>Centre for Vaccine Evaluation of the Biologics and Genetic Therapies Directorate (BGTD), Health Canada</td>
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<td>3)</td>
<td>Institute of Biological Products (Ministry of Public Health), Thailand</td>
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<td>4)</td>
<td>National Centre for Control and Evaluation of Medicines (CNCF) of the Istituto Superiore di Sanità (ISS), Italy</td>
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<td>5)</td>
<td>National Drug and Health Products Safety Agency (ANSM), France</td>
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<tr>
<td>6)</td>
<td>National Institute for Biological Standards &amp; Control (NIBSC), Division of Bacteriology, UK</td>
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<tr>
<td>7)</td>
<td>National Institute for Biological Standards &amp; Control (NIBSC), Division of Virology, UK</td>
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<td>8)</td>
<td>National Institute for Public Health &amp; the Environment (RIVM), the Netherlands</td>
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<tr>
<td>9)</td>
<td>National Institute of Food &amp; Drug Safety Evaluation (NIFDS), Republic of Korea</td>
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<td>10)</td>
<td>Paul-Ehrlich-Institut (PEI), Germany</td>
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<tr>
<td>11)</td>
<td>South African National Control Laboratory for Biological Products; South Africa</td>
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<tr>
<td>12)</td>
<td>Swiss Agency for Therapeutic Products (Swissmedic), Switzerland</td>
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Testing – Initial evaluation of a new vaccine

- Three to five final lots are tested for consistency of final product characteristics
- Lots need to be formulated from consecutive bulk lots
- Additional information e.g. validation documents may be requested
- Usually potency is tested. On occasions other relevant tests can be performed
- Reference reagents are requested if applicable (HepB vaccine, Influenza vaccine)
- Lots are tested in parallel by two WHO laboratories
- (in case of inconsistent results: results of the national control laboratory are requested)

→ WHO test report shared with the manufacturer
Testing –
Targeted testing of prequalified vaccines

• Annually performed
• At the beginning of each year WHO approaches manufacturers to provide an overview of vaccine lots supplied to countries through UN agencies, but also direct purchases
• Lots for testing are selected by WHO
• Usually two to three lots close to their expiry dates are chosen
• Selective risk-based approach
• Testing by one laboratory

→ WHO testing outcome reported to donors
Testing –
Reported adverse events / complaints / requests

• Testing performed based on reported adverse events following immunization – if the event might be related to the product quality

• Example: Incident vaccine central store

  Exposure of vaccines to temperatures exceeding recommended storage conditions – WHO tested activity of Yellow Fever vaccine

  → WHO recommendation to the respective MoH
WHO vaccines testing (cont.)

- Service run by the WHO Technical Assistance & Laboratory Services Group (WHO/TAL)
- Control laboratories are qualified by WHO
- Audits are performed at regular intervals
- Laboratory contracts are time-limited
- Based on a forecast — in total 12 contracts have been issued to cover more than 350 tests for the current biennium 2016-2017
- Paid service - Identical fees for each test parameter
WHO's vaccines testing – Challenges

- Laboratories are testing vaccines of various manufacturers who may apply differing methods
- Occurrence of out-of-specification for Hib component in liquid formulated vaccines
- Increasing number of complex vaccines – test- and cost- intensive
- Increasing number of applications for PQ – increased number of prequalified vaccines
- Limited resources
WHO vaccines testing – Recent developments

- Introduction of direct shipments of vaccines from manufacturers to the testing laboratories
- Use of national control laboratories of producing countries for "own" products
- Harmonization of test methodologies + hands-on training
- Sharing of lot release data (reliance on WHO-contracted NCLs, expansion to all NCLs of production countries)
Quantitative determination of the saccharide content of the *Haemophilus influenzae* type B (Hib) conjugate component in liquid vaccine presentations by High-performance anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD)

- Test protocol applicable to all 8 prequalified liquid vaccine combinations containing a whole cell pertussis component
- More than 30 laboratories trained (national labs and quality control labs of manufacturers)
- Proficiency testing study under preparation (including the WHO PRP Standard)
Countries having introduced Hib vaccine in 1997 and 2014

1997
- 29 countries introduced
- 2 countries partially introduced

2014
- 190 countries introduced
- 2 countries partially introduced

WHO vaccines testing – Recent developments: Sharing of lot release data

Inclusion of quality control data gathered through the national lot release of prequalified vaccines by the WHO contract laboratory

- Consent of > 14 manufacturers
  > 16 agreements received (various NCLs in charge of vaccines from one manufacturer)

- NCLs reporting annually to WHO

- Paid service and part of the contract with WHO

- Extension to national control laboratories of all countries producing prequalified vaccines – on-going
WHO independent testing & lot release data 2016

Number of lots (in descending order of national lot release data)
WHO's vaccines testing - Developments

- Independent testing through qualified laboratories for new vaccines and monitoring of PQ’d vaccines /other incidents
- Harmonization of test methods
- Performance of collaborative studies
- Hands-on training courses facilitated by WHO contract laboratories
- Sharing of lot release data with WHO contract laboratories
- Sharing of lot release data with all responsible NCLs of producing countries
WHO's vaccines testing – Directions

Immunization has huge public health impact:
- Prevention of infectious diseases by immunizing healthy populations, including children
- Quality issues can affect public trust in vaccination

- Vaccines are complex biological products
- Quality control testing is costly and demanding
- Globalization of vaccines industry – increasing number of production sites
- Regulatory authority's capacities are limited (developed and developing countries)

Effective regulation is only possible through collaboration and information-sharing → Networking
WHO's vaccines testing – Creation of an operational network

- 2016: WHO/TAL called for a national vaccine control laboratories (NCL) networking meeting
- Meeting hosted by RIVM, 30 August – 2 September 2016, The Netherlands
- Representatives from:
  - 21 NCLs involved in testing WHO- prequalified vaccines
  - Manufacturers’ associations
  - European Directorate for the Quality of Medicines
- Meeting participants agreed on the creation of a WHO national control laboratories network
WHO National Control Laboratory Network for Biologicals
Facilitating Access to Quality Vaccines and other Biological Medicinal Products

Responsible NRAs in producing countries have:
- Best oversight of PQ’d vaccines and testing methods
- Functional vaccine regulation and laboratories

WHO – global mandate (194 Member States)
Approx. 65% of infants worldwide are immunized with PQ’d vaccines

Reliance on responsible laboratories’ release testing
⇒ Impact on recipient countries:
  ✓ reduce redundant testing
  ✓ save costs
  ✓ reduce the risk of inaccurate results
  ✓ accelerated access to vaccines
WHO National Control Laboratory Network for Biologicals – reach SDG 3.8

- Recipient countries
- WHO
- WHO-contracted labs
- Independent testing
- Share lot release data
- Reliance
- Recognition
- Proposed

Global network

- Assay harmonization: Studies, training, proficiency testing
- Share lot release data
- Other info

Recipient countries

NCLs, producing countries

Share lot release data + other info
WHO National Control Laboratory Network for Biologicals

First general meeting:
31 October to 2 November 2017 in Noida, India

Network objectives:
• Share quality and technical information related to prequalified products.
• Facilitate recognition of lot release of the responsible NRA and NCL (as defined in WHO Technical Report Series, No. 978, Annex 2) by recipient countries.
• …

Network membership:
 a) Full Members: this classification is eligible to NCLs from countries producing WHO-prequalified vaccines (or other biological medicinal products), and WHO-contracted NCLs
 b) Associate Members: this classification is eligible to NCLs or NRAs in countries that are recipients of UN-procured vaccines (or other biological products).
Acknowledgements

Bill & Melinda Gates Foundation
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The Netherlands Government
United States Agency for International Development (USAID)
#VACCINESWORK TO SAVE LIVES

An estimated 2-3 million deaths are prevented every year.

Vaccines protect against 26 diseases.

And help limit the spread of antibiotic resistance by preventing diseases in the first place.

Increasing immunization globally could save an additional 1.5 million people every year.

Thank you!