

NETWORK for BIOLOGICALS

Future QC approaches for efficient vaccines
quality control: global initiative

Outline

- **Vaccine quality assurance and vaccine prequalification (PQ)**
- **Challenges**
- **Developments**
- **WHO Global Network for Biologicals**

Assuring the quality of vaccines

- Ensuring consistent quality, safety and efficacy of vaccines is critical for the success of immunization programmes
- It is essential for continued public confidence in immunization
- To facilitate access to the needed vaccines of assured quality, the WHO Prequalification Team (PQT) prequalifies vaccines for procurement by UN agencies according to a defined procedure (TRS 978, Annex 6, 2010)

Prequalification of vaccines by WHO

- A prerequisite for acceptance of applications for WHO vaccine prequalification is that the National Regulatory Agency (NRA) of the producing country is proven functional with regard to regulatory oversight of vaccines according to WHO indicators
- There are three pillars for the evaluation of vaccines by WHO:
 - ✓ WHO reviews the vaccine dossier (quality & clinical data)
 - ✓ WHO inspects the manufacturing site
 - ✓ WHO tests the final product

Prequalification of vaccines – Independent testing of final product



Pre- and post prequalification (PQ) testing

Initial evaluation of a new product – Pre PQ

(WHO TRS no. 978, Annex 6, chapter 3.4)

- Three final lots are tested for consistency of final product characteristics
 - Testing by two laboratories (plus responsible NCL)
- WHO test report shared with the manufacturer

Annually performed targeted testing – Post PQ

(WHO TRS no. 978, Annex 6, chapter 10)

- Lots selected by WHO – risk based approach
 - Two to three lots close to expiry dates
 - Testing by one laboratory
- WHO testing outcome reported to donors

Testing through contracted laboratories

Based on a forecast – in total 12 contracts have been issued to cover > 350 tests for the current biennium 2016-2017

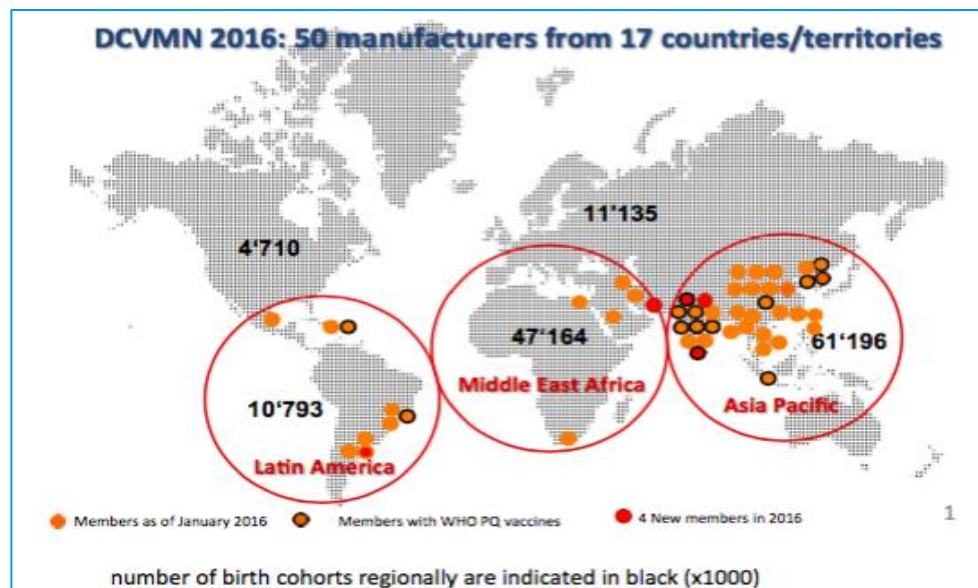
Paid service - Identical fees for each test parameter

(www.who.int/immunization_standards/vaccine_quality/Laboratories_table_08April2015.pdf?ua=1)

WHO's vaccines testing – Challenges

Prequalification started in 1987; since then much has changed in the world of vaccines:

- number of vaccine manufacturers has increased with a globalization of vaccine industry
- multiple production sites
- number of applications for vaccine PQ increased



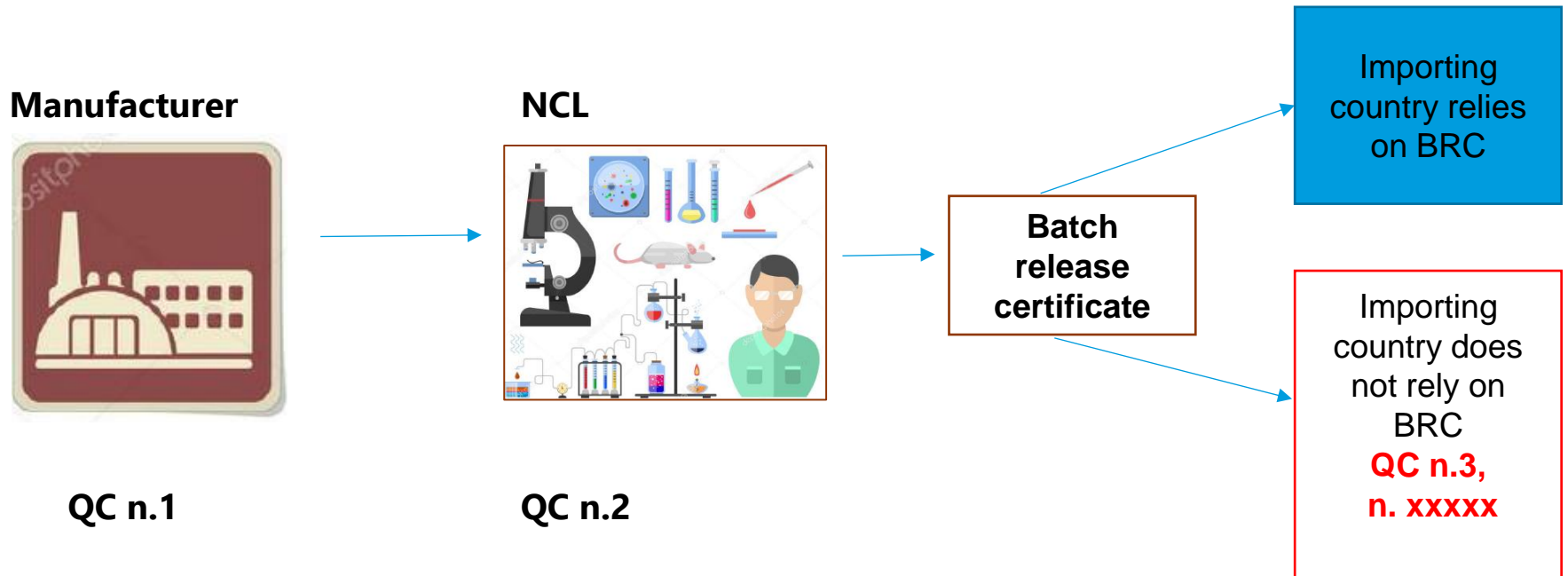
Vaccines - Global challenges

- Accessibility and supply of vaccines
- Complex situation also for Regulatory authorities' (NCL/NRA) of the vaccine producing country
- Increasing number of complex vaccines which require more sophisticated test methodologies and skills
- Pre- and post- PQ quality control testing are thus also more sophisticated and therefore costly and demanding
- Regulatory authorities' capacities are limited both in developed and in developing countries

WHO's vaccines testing – Developments

- Harmonization of test methods for PQ vaccines (Hib and Rabies vaccines)
Remark: determination of total and free Hib saccharide in DTwP-HepB-Hib vaccines by HPLC-PAD (the WHO promoted methodology) is in process for implementation in the Indian Pharmacopeia and under discussion for the Chinese Pharmacopeia
- Hands-on trainings (Hib and Meningo vaccines)
- Agreements with manufacturers of PQ vaccines enabling confidential reporting of lot release data by NCLs to WHO
- Use of NCLs of country of production for quality control testing
- Shortened lead times (vaccine shipments directly to the contracted NCL)

Vaccines - Global challenges for manufacturers

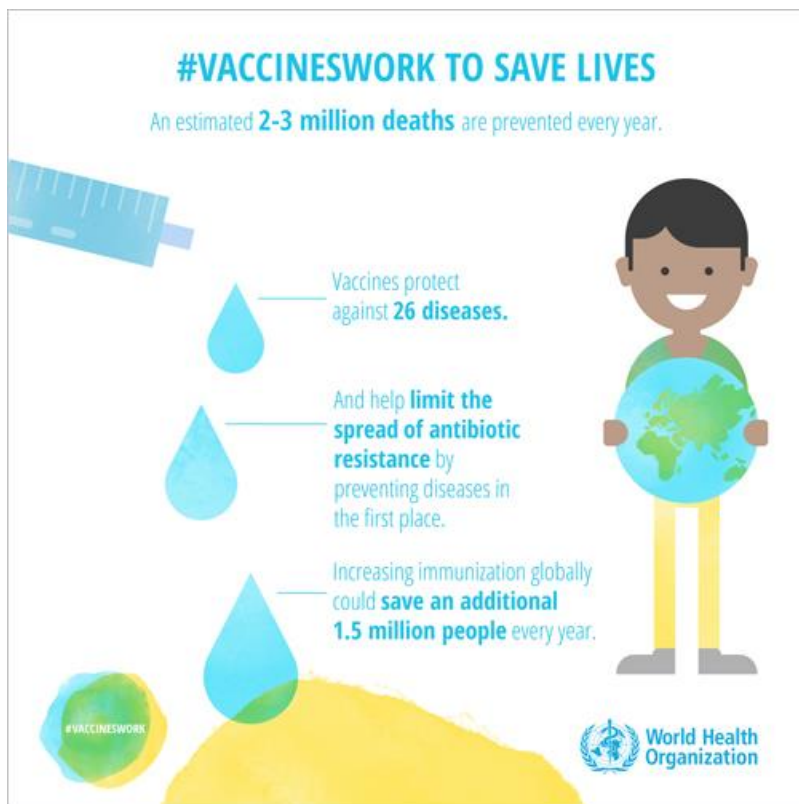


Vaccines - Global challenges for manufacturers (2)

Independent testing of vaccines by both the NCL of the producing as well as by the importing country

- ✓ Is redundant and impacts timely supply and Public Health:
- ✓ Delays availability of lots
- ✓ Loss of compliant lots
- ✓ Reduces remaining shelf life
- ✓ Generates high consumption of bio-reagents
- ✓ Unnecessary use of animals

Sustainable Development Goal 3: GOOD HEALTH & WELL-BEING - Global access



How to reach access to needed
vaccines in a timely manner?

PQ Vaccines – Directions

WHO – global mandate (194 Member States)

To enhance the PQ process and efficiency and utilization of existing resources, WHO, on the basis of the World Health Assembly resolution no. 67.20, which calls for regulatory system strengthening for medical products, proposed, in 2016, the creation of a Global Network of WHO National Control Laboratories.

Effective regulation is only possible through

Collaboration and information-sharing among NCL /NRA

Reliance and recognition of NCL/NRA activity



PQ Vaccines – Directions (2)

17th International Conference of Drug Regulatory Authorities (2016) -
Recommendation: Workshop G, Vaccine regulation

To WHO:

5. Establish a global network of national vaccine control laboratories involved in testing of WHO-prequalified vaccines.

To Member States:

2. For efficient lot release testing of vaccines, consider a risk-based approach or networking (reliance) approach.

WHO National Control Laboratory Network for Biologicals

- ✓ The WHO NCLs for Biologicals was constituted in September 2016
- ✓ 1st General Meeting of the Network : 31 October – 2 November 2017 at the National Institute of Biologicals - NOIDA, India
- ✓ Network participation of 17 full members and 3 associate members:
Australia, Bangladesh, Belgium, Bulgaria, Denmark, Cuba, France, Germany, India, Indonesia, Italy, Hungary, Senegal, South Africa, Sri Lanka, Sweden, Switzerland, Thailand, The Netherlands and United Kingdom

Network for Biologicals (cont.)

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).
- c) Observers (UN procurement agencies, manufacturer associations and other stakeholders)

Established: Terms of Reference and Participation and confidentiality agreements

Network objectives:

- Share quality and technical information related to prequalified products to 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.
- Promote the development of harmonized common standards and best practice, including the use 3R principles
- Share analytical methods

Responsible NRAs in producing countries have:

- Best oversight of PQ'd vaccines and testing methods
- Functional vaccine regulation and laboratories

Reliance on responsible NCLs release testing -

➡ Impact on recipient countries:

- ✓ reduce redundant testing (by *saving also animals!*)
- ✓ save costs
- ✓ reduce the risk of inaccurate results
- ✓ accelerated access to vaccines

Network for Biologicals – Achievements



-Publications

- Article: Global network of national vaccine control laboratories. WHO Drug Information 31(1):3-10
- ECBS Information documents:
 - WHO-NCL Network for Biologicals
 - Revised lot release certificate template
- Report 1st General meeting of the Network for Biologicals

Inventory of Lab activity

Information for the Network share point from Australia, Belgium, Bulgaria, Denmark, Cuba, France, Germany, India, Indonesia, Italy, Hungary, Senegal, South Africa, Sri Lanka, Sweden, Switzerland, Thailand, The Netherlands and United Kingdom Canada, Japan and Republic of Korea

Network for Biologicals (cont.)

Electronic platform: Share point

Welcome

Role of WHO / UN

Where we are inside WHO

Quality Surveillance

Our members

Search NCL

Search Vaccine

Meeting Documents

Sharing Best Practices

Upcoming Events and News

Useful links



Background

The NRAs/NCLs responsible for testing and release of WHO-prequalified vaccines have the best oversight of products and testing methods. Each year they test thousands of lots against approved specifications. In 2016 WHO brought together representatives of NCLs involved in testing WHO-prequalified vaccines at a [networking meeting](#). It was agreed to establish a Network providing a platform for exchange of quality and technical information on prequalified vaccines.

"Cooperation and networking can help ensure efficient testing, save costs and reduce the risk of inaccurate results. Access to vaccines can be greatly accelerated if recipient countries rely on the lot release done by the responsible NCL"

Mission

To facilitate access to and availability of prequalified vaccines (or other biological medicinal products) through reliance on the batch release of the respective Network member states, thereby reducing redundant testing, and contributing to more cost-effective testing and more effective regulatory oversight.

Objectives

- Share quality and technical information related to prequalified products.
- Facilitate recognition of lot release of the responsible NRA&NCL (as defined in WHO Technical Report Series, No. 978, Annex 2) by recipient countries.
- Promote the development of harmonized common standards and best practice, including the use of the 3R principles.
- Contribute to and support test harmonization, and to provide input to future development / revisions of WHO guidelines.
- Support strengthening of the NCLs in Network through technical assistance / training.
- Make information available to strengthen the recognition of WHO prequalification globally

Future

Directions
In the future, the Network could also serve to share information on other biological medicinal products.

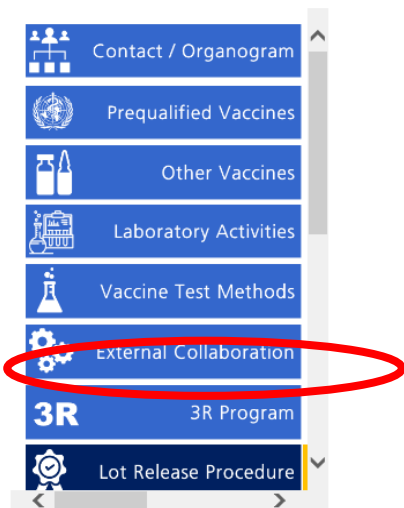
Network for Biologicals (cont.)

Share point – country page



Belgium

Scientific Institute of Public Health



Biological Standardisation Unit
(WIV-ISP)

Contracted by WHO for technical testing of vaccines
Contracted by WHO for sharing of lot release information
Lot release for Belgian and European market

Quality Assurance Standard: ISO/IEC 17025 and ISO/IEC 9001

Related national regulatory authority:
Federal Agency for Medicines and Health Products



www.wiv-isp.be

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WHO and 3R Application

Since 1980, WHO has always encouraged the respect and welfare of animals

For instance, in 1992, WHO already promoted the project on transgenic mouse for OPV



In vivo QC tests

Potency tests

Safety tests

- ✓ *Specific Toxicity* of the drug substances
- ✓ *Abnormal toxicity*
- ✓ *Pyrogen test*

Safety tests and 3R progress in human vaccine quality control

Vaccine	Safety test	Animal model	3R alternative	Kind of R
Human vaccines	Test for Innocuity /Abnormal toxicity	Mouse & guinea pig		Deletion of test
Diphtheria	Residual toxicity	Guinea pig	VERO cell test	Replacement
Whole cell pertussis	Specific toxicity (Weight gain test)	mouse	Numbers of animals	Reduction
Oral polio	Neurovirulence (NVT)	Monkey - intracerebral	Transgenic mouse (Tg) PCR method (MAD50)	Refinement Replacement
Human vaccines	Pyrogenicity	Rabbit	LAL (rFc)	Replacement

Potency testing and 3R progress in human vaccine quality control



Vaccine	Potency test	Animal model	3R alternative	Kind of R
All	Challenge test with severe clinical signs		Humane endpoints	Ref.
Tetanus	Lethal/paralytic challenge test	Mouse/ guinea pig	Serology instead of challenge or single dilution	Ref. and Red.
Diphtheria	Lethal/intradermal challenge	Guinea pig		
Tetanus, diphtheria, aP			Guinea pig serology in one set of animals	Ref. and Red.
Hep B	Serology	Mouse	Antigen quantification by ELISA	Repl.
Hep A	Serology	Mouse		
IPV	Serology	Rat		

Implementation of *in vitro* test alternative to *in vivo* tests



WHO

International regulatory requirements for vaccine safety and potency testing : a WHO perspective

Procedia in vaccinology, 2011, 5: 164-170

EMA

Guidance for individual laboratories for transfer of quality control methods validated in collaborative trials with a view to implementing 3Rs

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2018/01/WC500242193.pdf

The WHO Network for Biologicals benefits:

- NRAs
- Manufacturers
- UN procurement agencies
- Other stakeholders



... and is the instrument to facilitate access to quality vaccines and other biological medicinal products - reach SDG 3.8:

"Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all".

The WHO Network for Biologicals benefits (2):

- Cooperation and networking can help ensure efficient testing, save cost and reduce the risk of inaccurate results
- Access to vaccines can greatly accelerate if recipient countries rely on lot release done by the responsible NCL (WHO TRS 978, Annex 2)
- The use of *in vitro* assays is encouraged



Second general meeting:

25 to 27 September 2018 in Rome, Italy



... moving...
to an operational entity

Thank you



Dr Ute Roskopf

Regulatory Systems Strengthening
Regulation of Medicines and Other
Health Technologies

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Products

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