Regulatory networks

Update on the WHO-National Control Laboratory Network for Biologicals

WHO prequalifies vaccines for use in Member States. In 2016 WHO initiated the establishment of a Network of national control laboratories (NCLs) that test prequalified vaccines. The Network aims to reduce redundant lot release testing and contribute to more cost-effective testing, thereby improving overall regulatory oversight and reducing regulatory burden. An article about the Network was included in Issue 1 (2017) of this journal.

At the end of 2017 the Network held its First General meeting, which marked the move to the operational stage. This paper provides an update on achievements and next steps.

Background
WHO prequalifies vaccines for procurement by UNICEF, the PAHO Revolving Fund and GAVI among others. Prequalified vaccines are used to immunize approximately two thirds of the global birth cohort each year. A condition for acceptance of prequalification applications for a vaccine is that the national regulatory authority (NRA) responsible for its oversight has passed a WHO assessment of defined vaccine-related functions, including the evaluation of vaccine batches before they are released onto the market. Testing of vaccines is complex and expensive. The NCLs responsible for lot release of prequalified vaccines have in-depth experience with regulatory

1 List of prequalified vaccines available at: https://extranet.who.int/gavi/PQ_Web/


This update is based on the report of the First General Meeting of the WHO-NNB Network, held in Noida, India, on 31 October –2 November 2017. We thank Mr Mike Ward, Coordinator, WHO Regulatory Systems Strengthening (RSS) Team, for helpful comments on the manuscript. Contact Dr Ute Rosskopf (rosskopfu@who.int) for further information.
Globally however, as the number and capacity of NCLs have increased, the same vaccine batches are often re-tested in multiple recipient countries. This is causing unnecessary delays in supply and sometimes leads to rejection of lots that do actually meet specifications, due to differences in testing methods.

To reduce redundant testing and facilitate access to prequalified vaccines, WHO therefore initiated the establishment of the WHO National Control Laboratory Network for Biologicals in 2016.3 An update on progress is provided below.

**Progress update**

*Advocacy*

The Network was discussed at the 17th International Conference of Drug Regulatory Authorities (ICDRA), leading to two formal recommendations:

- *(To WHO):* Establish a global network of national vaccine control laboratories involved in testing of WHO-prequalified vaccines.
- *(To Member States):* For efficient lot release testing of vaccines, consider a risk-based approach or networking (reliance) approach.(4)

Information about the Network was also presented to the WHO Expert Committee on Biological Standardization (ECBS), which sets the global standards that underpin WHO prequalification of vaccines.

*Network membership*

The Network’s terms of reference and the participation and confidentiality agreement, were finalized with input from the WHO legal department. The NCLs of the following countries have formalized their participation:

- Full members (responsible for testing of one or several prequalified vaccines): Australia, Belgium, Bulgaria, Cuba, Denmark, France, Germany, India, Indonesia, Italy, Senegal, South Africa, Switzerland, Thailand, the Netherlands and the United Kingdom. Agreements with the NCLs of Brazil, Canada, China, the Republic of Korea, Russia and Sweden were pending signature at the time of writing.
- Associate members (importing prequalified vaccines): Bangladesh, Hungary and Sri Lanka. The authority of Bhutan is expected to join in the near future, and the authority of Ghana is considering to become a Network member.

Going forward it is envisaged that regulatory authorities of all WHO Member States will participate in this Network, which offers a pathway for mutual recognition and reliance at the global level.

*General Network meetings*

One of the two main routes of Network operations is through regular face-to-face meetings. In 2017 the Network held its First General Meeting in Noida, India. The meeting was hosted by the National Laboratory of Biologicals (NIB) of India and organized by WHO. Representatives from 20 of the 24 NCLs currently testing WHO-prequalified vaccines, manufacturers and other stakeholders participated. The meeting marked the move to the Network’s operational stage. Funding from the Bill & Melinda Gates Foundation for the meeting is gratefully acknowledged.

One day of each general meeting is devoted to technical sessions on sharing best practice. The topics at the First General Meeting were the design and interpretation

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of control charts, and handling out-of-specification results.

Preparations are ongoing for the Second General Meeting of the Network, to be held in Rome, Italy, on 25–27 September 2018. The meeting will be hosted by the Centro Nazionale per il Controllo e la Valutazione dei Farmaci / Istituto Superiore di Sanità (CNCF/ISS).

**Information-sharing**

The other main route of Network operations is information-sharing through a password-protected platform hosted on a WHO server. An early pilot version was demonstrated at the First General Meeting. Development is ongoing. Once the platform is operational, WHO and NCLs will upload and maintain relevant information on an ongoing basis.

The platform will host the following main types of information:

- **Laboratory profiles**: As agreed in 2016, the participating NCLs have completed a systematic mapping of their set-up and lot release systems and activities. Twenty such laboratory profiles were sent to WHO ahead of the First General Meeting and were subsequently shared among all contributing NCLs. The laboratory profiles are currently being uploaded to the subsites of the member NCLs on the information-sharing platform (Box 1), for an initial round of validation by test users from NCLs.

- **Outcomes of WHO lot testing**: WHO tests vaccines as part of the prequalification process and implements a targeted testing plan of prequalified vaccines supplied to UN-funded

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**Box 1:**

**Example of a NCL subsite on the pilot version of the WHO-NNB electronic platform**

[Image of a subsite example]
programs. The testing is performed by WHO-contracted laboratories\(^4\) that are audited every 3-4 years. Currently the outcomes are reported to procurers—notably UNICEF—and manufacturers. The electronic platform will enable WHO to share this information with the Network members.

- **Regulatory lot release outcomes:** Over the past few years WHO has established 19 agreements with manufacturers, allowing a total of 10 NCLs to share their lot release data for prequalified vaccines (whether or not supplied to UN-funded programmes) with WHO. This data-sharing is part of the contract between WHO and the respective NCLs (Box 2). WHO is now approaching manufacturers to allow information exchange on lot release outcomes among Network members. The extent of what will be shared will depend on each individual agreement. Some regulatory lot release information is already publicly available. For example, Swissmedic provides monthly updates on lots released either based on its own review, or in recognition of the OCABR process.\(^5\) Sharing of the responsible NCLs’ lot release outcomes through the Network will support reliance initiatives in countries importing prequalified vaccines in a more systematic way.

**Benefits**

The WHO Network offers some unique benefits in the global context.

**Common standards**

WHO is well placed to convene a global Network of partners aiming at reliance in vaccine lot release. The NRAs and NCLs found capable to oversee the quality of prequalified vaccines have all passed a comprehensive, stringent WHO assessment. In fact, the WHO indicator tool used for benchmarking regulatory systems is being refined and now also incorporates a classification system that characterizes

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\(^5\) [https://www.swissmedic.ch/swissmedic/en/home/services/laboratories--omcl-/approved-batches.html](https://www.swissmedic.ch/swissmedic/en/home/services/laboratories--omcl-/approved-batches.html). A specific batch number can be found through a site-specific search in the browser, e.g.: “AHBV630A site:swissmedic.ch”

**Box 2: National lot release data reported to WHO (2016)**

In 2016 ten NCLs responsible for releasing prequalified vaccines shared lot release data for a total of 2543 batches of prequalified vaccines with WHO, based on agreements with manufacturers. For comparison, 115 lots were tested on behalf of WHO.
mature regulatory authorities on whose findings WHO and others may choose to rely.6

Common methods and best practice
Standardized vaccine testing methods would be a great help for manufacturers and regulators. WHO has been collaborating with Network partners to develop and implement such methods. A recent example is an assay for the Hib-component in liquid vaccine combinations,(5) which has been widely implemented. A proficiency study is under way, and the pharmacopoeial authorities of both China and India intend to incorporate the method in the next editions of their pharmacopoeias. The Network will provide a platform to encourage the adoption of harmonized methods and best practices.

In addition, some of the partners in the Network have valuable specialized expertise to offer. For example, a pilot project is under way to collaborate with Swissmedic in the framework of the authority’s proteomics project that would enable “profiling” of vaccines to monitor the products circulating on the market.

Facilitating reliance
While the online information-sharing platform is still under construction, the Network has already stimulated information exchange on an as-needed basis. The NCL of Bulgaria has started to share its lot release data with WHO based on a collaboration agreement.

There is considerable scope for reduction of redundant lot testing both in countries that are full and associate Network members. However, decisions are needed at national level to change the current lot testing policies. The example of Senegal shows that this is achievable: As a result of its Network participation, the NCL is no longer re-testing batches of imported WHO-prequalified vaccines.

Conclusion
Vaccines and other biological products are essential for public health. In the era of globalization, “big data” and increased challenges faced by regulators, an in-depth understanding of processes is becoming ever more crucial to make good use of data on vaccine quality. By providing an independent global forum for information exchange, the WHO-NNB Network meets an important need.

References


