ACCESS TO MEDICINES, VACCINES AND PHARMACEUTICALS

MEETING REPORT

Second General Meeting
WHO-National Control Laboratory Network for Biologicals
(WHO-NNB)

25 - 27 September 2018
Rome, Italy
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Executive summary

The Second General Meeting of the WHO-National Control Laboratory Network for Biologicals (WHO-NNB - “the Network”) was held 25 - 27 September 2018 in Rome, Italy. The meeting was organized by the World Health Organization (WHO) Department of Essential Medicines and Health Products (EMP), Regulatory Systems Strengthening (RSS) team and hosted by the Centro Nazionale per il Controllo e la Valutazione dei Farmaci / Istituto Superiore di Sanità (CNCF/ISS). A total of 23 national control laboratories (NCLs) were represented at the meeting, including 20 of the 24 NCLs currently responsible for lot release and/or contracted for testing of WHO-prequalified vaccines. Representatives from six national regulatory agencies (NRAs) also joined the meeting as well as representatives from the Developing Countries Vaccine Manufacturers Network (DCVMN), the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the Pasteur Institute, Serbia. Appendix 1 presents a complete list of participants.

The Network’s activities and annual meeting were made possible thanks to funding from the Bill & Melinda Gates Foundation, the United Nations Children’s Fund and the Government of the Netherlands.

The Second General Meeting marked the completion of the first year of the operational phase of the Network. The Network’s growth, progress and activities during this period were highlighted. Participants established new contacts; learned about the applied vaccine quality control strategies of newly participating NCLs; and gained insight on regulation, access, release and control applied by vaccine importing countries. In addition, participants received information on NCL activities in three WHO regions: Eastern Mediterranean Region (EMR), South-East Asia Region (SEAR) and Western Pacific Region (WPR).

The WHO secretariat gave an update on the Network’s electronic information-sharing platform (SharePoint) and conducted a live demonstration. A validation protocol is being implemented to evaluate the site against user and security requirements. Participants provided feedback on the SharePoint’s contents, features and usability.

A proposal submitted by manufacturer associations aimed at collaboration for testing and data sharing with NRAs in importing countries, was discussed during a plenary session.

The final day of the meeting was dedicated to sharing of best practices in quality control methods with a focus on new developments and projects centred on harmonization.

The following action points were agreed:
- WHO will continue to increase user-friendliness of the Network SharePoint, conduct validations and follow up on changes proposed during the meeting.
- WHO will prepare and circulate a meeting report of the discussions and agreed decisions.
- WHO will announce the date and location of the Third WHO-NNB General Meeting (2019) as soon as it is confirmed. Participants are encouraged to submit topics for the meeting.
- Participants are encouraged to stay engaged and support Network activities, especially in areas where volunteers with specific expertise and resources are needed.

1 In follow up to the meeting, the South Africa National Control Laboratory for Biological Products graciously agreed to host the Third General Meeting in Bloemfontein, South Africa, in 2019.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CNCF/ISS</td>
<td>Centro Nazionale per il Controllo e la Valutazione dei farmaci / Istituto Superiore di Sanità</td>
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<tr>
<td>DCVMN</td>
<td>Developing Countries Vaccine Manufacturers Network</td>
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<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines &amp; Health Care</td>
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<tr>
<td>EMP</td>
<td>WHO Department of Essential Medicines and Health Products</td>
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<tr>
<td>IFPMA</td>
<td>International Federation of Pharmaceutical Manufacturers &amp; Associations</td>
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<td>NCL</td>
<td>National Control Laboratory</td>
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<td>NRA</td>
<td>National Regulatory Authority</td>
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<td>OCABR</td>
<td>Official Control Authority Batch Release</td>
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<td>RSS</td>
<td>WHO Regulatory Systems Strengthening Team</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WHO-NNB</td>
<td>WHO-National Control Laboratory Network for Biologicals</td>
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1. **Background**

The WHO-National Control Laboratory Network for Biologicals (WHO-NNB – “the Network”) was established in 2016 at the WHO networking meeting in the Netherlands by representatives from 21 national vaccine control laboratories responsible for testing of WHO-prequalified vaccines. This operational network is a platform for collaboration and technical exchange on quality control and quality assurance of vaccines or other biological medicinal products. WHO-NNB’s main objectives are to share quality and technical information related to prequalified products; facilitate access to and availability of prequalified vaccines (or other biological medicinal products) through reliance on the batch release of the respective, responsible Network members by recipient countries, thereby reducing redundant testing; promote development of harmonized common standards; and share best practices.

2. **Meeting objectives**

The objectives of the Second General Meeting of the WHO-NNB were to:
- Meet face-to-face with representatives of Network members and other stakeholders
- Exchange information on applied control strategies of newly participating NCLs (Network full membership)
- Learn about vaccine access and release onto the market by newly participating vaccine importing countries (Network associate membership)
- Provide information about progress and activities of the Network
- Provide an update on electronic information-sharing platform (SharePoint)
- Discuss current content and features of the Network SharePoint
- Discuss a proposal submitted by manufacturer associations
- Debate Network operations – resources
- Listen to needs and expectations expressed by WHO regions and recipient countries
- Share best practices (quality control methods – new developments and harmonization)
- Agree on the date and venue of the Third General Meeting (2019)

3. **Meeting opening**

Dr Christina von Hunolstein opened the meeting on behalf of Professor Walter Ricciardi, President of the Istituto Superiore di Sanità (ISS). The Professor delivered welcoming remarks by video. He emphasized the importance of the WHO-NNB and the critical nature of the work carried out by its member NCLs, especially in light of the global problem of vaccine hesitancy. Professor Ricciardi noted that the Network can help to optimize not only the scientific aspects of quality assurance of vaccines, but also the managerial and communications aspects.

Mr Mike Ward, Coordinator of WHO’s Regulatory Systems Strengthening Team welcomed the audience on behalf of WHO and thanked ISS for hosting the WHO-NNB Second General Meeting. Mr Ward stressed the vital importance of the work carried out by NCLs, which is becoming more challenging given the growing number and complexity of vaccines. He noted that the increase in members throughout the past year attests to the Network’s growing importance. The Network serves an essential role in access to and quality assurance of vaccines by providing a platform for information sharing, transparency, and the building of trust and confidence by the members who do this work.

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Dr Carlo Pini, Director National Centre for the Control and Evaluation of Medicines (CNCF), ISS and Dr Giulio Pisani, Director Biologicals and Biotechnological Unit, ISS, added their words of welcome and presented an overview of the Institute’s organisational structure and activities.

4. Progress update
Dr Ute Rosskopf, Network Lead, welcomed the audience and gave an update on WHO-NNB’s progress and achievements since the First General Meeting in 2017.

4.1 Wrap-up of action points from the First General Meeting
Dr Rosskopf confirmed that all agreed action points from the First General Meeting had been addressed. The Network successfully pursued membership agreements and gained new members, laboratory inventories were distributed among contributing laboratories, the WHO data management team further developed the electronic sharing platform and completed the first round of validation, WHO approached manufacturers to extend existing information-sharing agreements to include Network members and the Second General Meeting of the Network, hosted by ISS, was organized in Rome, Italy.

4.2 Advocacy
Information about the Network was widely disseminated in published reports and through oral presentations at international meetings. The report of the First General Meeting, as agreed by the participants, was circulated among stakeholders and posted on the WHO website; an article about the WHO-NNB was published in WHO Drug Information; information about the Network was presented to the WHO Expert Committee on Biological Standardization (ECBS) at its 68th Meeting, October 2017, Geneva, Switzerland; and a presentation about the Network was given remotely for the Vaccine Industry Consultation convened by UNICEF, October 2017, Copenhagen, Denmark. Further presentations were delivered at the Second Annual Meeting of the South-East Asia Regulatory Network (SEARN), March 2018, Colombo, Sri Lanka; the Developing Countries Vaccine Manufacturers Network (DCVMN) workshop on "Optimization of vaccines’ manufacturing, containers and testing for global supply," May 2018, Hyderabad, India; and the meeting on "International Standards for Oral Whole Cell Killed Cholera Vaccines, May 2018, Seoul, Republic of Korea.

4.3 Network membership
Network membership has increased throughout the past year. Thus far, 75% (18 of 24) countries eligible for full membership have joined the Network. The following countries have formalized their participation in the Network by signing participation and confidentiality agreements.

- Full memberships (18): Australia, Belgium, Bulgaria, Canada, Cuba, Denmark, France, Germany, India, Indonesia, Italy, Republic of Korea, Senegal, South Africa, Switzerland, Thailand, The Netherlands and United Kingdom.


In follow up to the meeting, Austria and the Russian Federation formalized their participation and became associate and full members, respectively.
- Memberships in progress or under consideration (7): Austria, Bhutan, China, Japan, Russian Federation, Sweden and Tanzania.

4.4 Information-sharing
WHO has 19 formal agreements with manufacturers, allowing 10 NCLs to share their lot release data and related information for prequalified vaccines with WHO. This data-sharing is part of the contract between WHO and the respective NCLs. 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. An agreement letter, developed with input from the WHO legal department, specifies that information will be shared with WHO and with all NRAs and NCLs that are full or associate members of the WHO-NNB. The letter covers information-sharing with countries that join the Network after the agreement is signed so that a new letter will not be needed. WHO has sent 12 requests for extended agreements and thus far, four have been signed: BDA for BB-NCIPD Ltd. (Bulgaria), LG Chem Ltd. (Republic of Korea), Pfizer Inc. (United States) and Valneva Sweden AB (Sweden).5

4.5 Electronic platform - Network SharePoint
The WHO data team updated and enhanced the SharePoint, uploaded the completed laboratory profiles and completed the initial round of validation by test users from NCLs.

4.6 Supporting activities
The Network Secretariat engaged in fundraising activities throughout the year, including submission of proposals to The Bill & Melinda Gates Foundation and UNICEF. In addition, the Secretariat submitted a proposal for the WHO Junior Professional Officer programme.

The Network’s revised lot release certificate, which was discussed extensively in the First General Meeting in 2017, was submitted in the context of the public consultation of the “Proposal for the revision of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce” [2]. The aim is to uncouple the batch certificate issued and submitted by manufacturers from the certificate issued by regulatory authorities for the release of biological products onto the market and include separate appendices for both documents. The submitted certificate, as agreed by the WHO-NNB, has been amended to comply with section 4.1: “This certificate conforms to the format recommended by the World Health Organization (WHO)” and to comply with section 4.10, including a field that indicates the country where the batch is intended to be marketed and space for a stamp. A copy of the revised certificate is available in Appendix 2.

4.7 Second General Meeting
The Second General Meeting of the Network, hosted by ISS, was organized in Rome, Italy.

5. Stakeholder presentations

5.1 Network members
Brief updates were presented from 18 Network members that participated in the 2017 meeting:

5 A fifth manufacturer, Merck (United States), signed the extended agreement subsequent to the meeting.
Australia, Belgium, Bulgaria, Canada, Cuba, France, Germany, Hungary, Indonesia, Italy, Japan, the Netherlands, Republic of Korea, Russian Federation, South Africa, Switzerland, Thailand and United Kingdom. No major changes were reported in terms of the strategies and procedures applied for testing. Some laboratories reported having achieved ISO accreditation for additional vaccines or additional methods. Restructuring was planned, ongoing or completed at several laboratories, but this did not have a major impact on vaccine lot release. Of special note, the United Kingdom is in discussions with the EU OCABR network and manufacturers about the United Kingdom’s impending withdrawal from the European Union (Brexit). Also noteworthy: the Russian Federation is building a new state control laboratory for medicines and immunobiologics which is scheduled to open in 2019.

5.2 Newly participating NCLs and NRAs
Six NRAs (Bhutan, Ghana, Sri Lanka, Tanzania, Zambia and Zimbabwe) and three NCLs (Austria, Bangladesh and United States of America (US)) were represented in the Network meeting for the first time. These participants provided overviews of their organisational structures, their work and their strategies for quality control of vaccines.

The country representatives reported a wide range of approaches to lot release of vaccines. Several follow WHO guidelines for vaccines procured by UN programmes, with lot release performed by the designated responsible NRA. Some countries review the lot summary protocol (LSP) only, and others review the LSP and conduct independent testing (full or selected testing). In some cases, different approaches are used for different vaccines in the same country.

The Austrian NCL representative gave an overview of their laboratory activities which include contribution to the elaboration of the European Pharmacopoeia and participation in the IMI2 project VAC2VAC –Vaccine Batch to vaccine batch consistency testing. With respect to lot release, Austria follows EU Official Control Authority Batch Release (OCABR) guidelines.

The US NCL representative provided comprehensive insight into their lot release process, which is risk-based. The types of tests performed, and the frequency of testing are determined during the Biologics License Application (BLA) approval process and documented in the product testing plan. Tests performed are to ensure product safety and efficacy. Frequency of testing is based on manufacturing history, inspectional observations, adverse event reports and other factors. Audits of test plans are carried out annually and consider the data collected during protocol review/testing and information with potential to impact product safety or efficacy. Tests and/or frequency may be reduced or increased.

Due to the significant number of questions and discussion elicited by the US’ presentation, it was suggested to present case studies at the next Network meeting to: focus on what risk-based approaches countries are taking; discuss how to achieve a level of confidence without conducting all of the testing; and determine how and where to focus resources.

5.3 WHO regional networks
Dr Houda Langar gave an overview of the regulatory landscape of the Eastern Mediterranean Region (EMR) and indicated that an initiative to establish regional collaboration for testing, using existing in-country capacities, has been envisaged since 2010 but has not been launched due to turnover in Ministries of Health, NRAs and NCLs, as well as the geo-political situation in the region affecting collaboration and networking. The Eastern Mediterranean Drug Regulatory
Authority Conference (EMDRAC), held most recently in 2014 and 2018, is a means of facilitating communication between NRAs and NCLs in the region and responding to their needs. A suggestion from the 2018 EMDRAC was to establish five groups of countries to communicate and collaborate on regulatory matters, particularly registration, lot release, quality control and pharmacovigilance. Groups would be selected based on similarities in terms of interests and country situation (political, humanitarian emergency, security etc....) Future work on the part of WHO includes supporting the organization of joint review meetings to facilitate registration of biosimilars; facilitating access to technical assistance from functional NCL’s to strengthen quality control activities of NCL’s in the region; and disseminating information about the WHO-NNB to encourage participation of regulatory authorities in the region.

Dr Jinho Shin provided information on the Western Pacific Region (WPR). There are currently five vaccine-producing countries with laboratory testing capacity in the region, and an additional two countries conduct lot release of imported vaccines. Two countries recently began conducting risk-based lot release of vaccines and plasma-derived products: Korea in 2016 and China in 2017. There are several networks of NCLs for vaccines and biologicals in the region, including Vaccine Research and Regulatory Science, Western Pacific NCL Net for Vaccines and Biologicals and Regional Forum of WHO Collaborating Centres. NCLs in the WPR also participate in relevant global and regional networks such as the WHO-NNB, WHO Collaborating Centre Network for Vaccine Standardization and the South-East NCL Network. Dr Shin cited the lack of details on how to conduct risk-based analysis as a significant gap in the regional regulatory framework and suggested that setting indicators will help NCLs to apply an unbiased transparent strategy.

Dr Ute Rosskopf gave a summary of the outcomes of the Second Annual Meeting of the South-East Asia Regulatory Network (SEARN) which was held in March 2018 in Colombo, Sri Lanka. One outcome, of special relevance to the Network, stated that SEAR countries should rely on the regulatory oversight of the responsible NRA/NCL, and that all SEAR countries should become members of the Network. India, Indonesia and Thailand had already joined the Network as full members, and Bangladesh and Sri Lanka joined as associate members following the Colombo meeting.

6. Network SharePoint

6.1 Update, validation and live demonstration
Ms Alaa Magdy provided an overview of the current status of the Network SharePoint and described several new features. Throughout the past year, the WHO data team updated and enhanced the Network SharePoint. The main site now contains more information, including news, events, meeting documents and templates. Country sites can be accessed from the main site in several user-friendly ways.

The number of country sites with complete information increased from 21 in 2017 to 28 in 2018. Laboratory inventories submitted by NCLs were restructured to make the information clearer and easier to understand. All the information included on previously uploaded documents has been transferred directly onto the SharePoint site and can now be more easily accessed and maintained by the country. In addition, members are now able to download lists from the SharePoint and follow trends. Country pages have been updated to include location and contact information for each NCL/NRA. Some aspects of the SharePoint are still under development and will continue to evolve.
Both full and associate members have the same access and permission levels: access to the main site and their own country site. They have editing rights for their own country site and can view other country sites. The WHO secretariat will grant access for exchange of specific confidential information among concerned countries upon request.

Dr Alexandrine Maes gave an update on the validation protocol that is being implemented to evaluate the site against user and security requirements. The first phase of the protocol tested members’ ability to access the main site, their own country site, and verified that members did not have access to other country sites. This phase also tested the validity of the information uploaded to the country’s site. The second phase, currently underway, tests members’ editing rights for their own country site. The third phase, which will begin once countries complete phases one and two, validates security and will unlock members’ ability to view other country sites. All Network members need to complete the three phases of the validation prior to gaining access to other country sites.

Ms Magdy and Dr Maes conducted a live demonstration of the SharePoint during the meeting. Participants were encouraged to make suggestions for improvement of the SharePoint. Key points raised included concerns about disclosure of information and requests for hands-on training and/or a manual illustrating how to enter and update information on the SharePoint. These issues will be addressed with Network members in follow-up to the meeting and during the next WHO-NNB General Meeting.

**6.2 Information-sharing**

6.2.1 WHO annual vaccine quality report

Dr Martijn Bruysters provided an overview of the WHO annual vaccine quality report, which is a summary of testing performed by WHO-contracted laboratories during initial evaluation of new products submitted for prequalification, and after prequalification under a targeted testing plan for products supplied to UN-funded programs. The report also includes national lot release data and related information for prequalified vaccines. The outcomes of the WHO targeted testing and the lot release data are tabulated in an annex to WHO’s annual vaccine quality report.

The WHO Secretariat is proposing to share this report with WHO-NNB members within the secure confines of the Network SharePoint. The report would be shared under the extended information sharing agreements that WHO is currently pursuing with manufacturers which specify that lot release and related information will be shared with WHO and with all full or associate members of the WHO-NNB. Advantages of sharing the information within WHO-NNB include: supporting WHO-NNB’s mission to create reliance and mutual recognition, enabling recipient countries to acquire information on product quality without conducting their own testing, facilitating interaction between the recipient country and the NCL and increasing trust in prequalified vaccines.

WHO will continue to seek agreements with manufacturers for information-sharing, promote membership in the Network and disseminate information. The roles and responsibilities of NRAs/NCLs and manufacturers associations in this context are to continue to engage in open and constructive dialogues within appropriate fora such as the WHO-NNB, to continue to identify and respond to the needs of recipient countries and to promote membership in the WHO-NNB.
6.2.2 Discussion of DCVMN and IFPMA proposal

Dr Nora Dellepiane, on behalf of DCVMN, presented a proposal aimed at collaboration for testing and data sharing between WHO and NRAs in importing countries. Manufacturers proposed that reliance on data available from WHO-NNB member NCLs could be a mechanism for NRAs of importing countries to obtain independent results on vaccine quality. Although this data would be available within the Network for WHO-prequalified vaccines, the number of lots tested may be limited and therefore may not satisfy the requirements of some countries. Moreover, for vaccines that are not prequalified, such data may not be available. In view of these factors, manufacturers raised the question of whether WHO laboratories would consider performing additional testing on request by manufacturers and for a fee.

During the subsequent discussion, Dr Ute Rosskopf emphasized that the mechanism to share information and data, as outlined in the proposal, is one of the objectives of the WHO-NNB and is already in place. She stated that WHO’s goal is for the same process to be applied to all vaccines regardless of whether they are intended for export or for the domestic market. Therefore, according to WHO standards, the target market should have no bearing on physical testing of vaccines by the responsible releasing NCL. Dr Roskopf reminded participants that responsible Network members share information on vaccines that are not prequalified on their SharePoint sites. Additional information and data can be requested by interested recipient countries.

In order to enhance information-sharing, WHO-NNB needs support from manufacturers associations in the following areas: encouraging manufacturers to sign the extended information-sharing agreement; encouraging all importing countries to join the network; and disseminating information about the network.

7. Reliance and mutual recognition

On the second day of the meeting, participants divided into groups to address four questions related to reliance on shared information. Each group answered the same set of questions. The outcomes of the working groups were discussed in a plenary session later the same day.

Question 1: The first question focused on the Network SharePoint and asked what information recipient countries (associate members) expect to see on the country sites of full members.

Discussion 1: Participants indicated that, in addition to the information already available on the site, it would be helpful to know the date the country site was last updated; information on reduction schemes employed by that country; what certificates are issued for prequalified vaccines, and the testing strategy used. A mechanism enabling members to direct questions to one another from within the SharePoint was also proposed as a helpful addition.

Question 2: The second question focused on what additional information an associate member or national regulatory authority should include on its SharePoint country site.

Discussion 2: Participants responded that it would be helpful to know about the country’s pharmacovigilance system and its interface with the NRA/NCL.

Question 3: Considering inconsistencies in completing the laboratory inventory/SharePoint country sites, participants were asked whether a manual or hands-on seminar would be helpful.

Discussion 3: Participants agreed that a detailed guide on how to input information into the
SharePoint, including examples, would be very helpful. Guidance on when and how often to update the SharePoint would also be useful. Participants suggested additional enhancements to the SharePoint including: tooltips, a glossary, a frequently asked question (FAQ) section and video clips demonstrating how to input and update information.

Question 4: The WHO model test certificate is intended to facilitate recognition in recipient countries. Participants were asked whether they anticipated any problems in issuing the WHO model certificate in addition to their official batch release document if requested by the manufacturer.

Discussion 4: Most participants indicated that they did not expect any difficulty as the official certificate would remain in force for the country, while some indicated that they were undecided or unsure.

Issues raised during the discussions will be addressed with Network members in follow-up to the meeting and during the next WHO-NNB General Meeting.

At the end of the plenary session, participants requested that questions of this nature be circulated well in advance of future meetings to allow participants enough time to consult with colleagues in their respective agencies.

8. Project updates
8.1 WHO proficiency testing study
Dr Ute Rosskopf described a study conducted by the WHO Secretariat aimed at establishing a methodology with a single test protocol for the quantitative determination of the total saccharide and free saccharide content of the Haemophilus influenzae type b (Hib) conjugate component of liquid vaccine presentations (suspension). The project was successful in finding a methodology and test protocol for high performance anion exchange chromatography with pulsed amperometric detection (HPAEC-PAD) applicable to all (eight) liquid formulated prequalified pentavalent vaccines containing a whole-cell pertussis component. The reproducibility and robustness of the test protocol was further assessed in a collaborative study [3].

The objective of the current project is to assess the proficiency of participating laboratories, that have been trained in the HPAEC-PAD test method, in quantifying the total and free polyribosyl-ribitol-phosphate (PRP) content of the Hib in liquid combined vaccines. The project also seeks to test the WHO 2nd PRP International Standard, using the same protocol applied to the test samples, against a ribitol calibration curve.

Twenty NCLs and manufacturers’ quality control laboratories that use the WHO protocol expressed interest in participating in the study which is scheduled to start in Q4 2018.

8.2 Oral whole-cell killed cholera vaccines (OCVs)
Dr. Rosskopf summarized the key outcomes from the "Meeting on International Standards for Oral Whole Cell Killed Cholera Vaccines" organized by the International Vaccine Institute (IVI) in Seoul, South Korea, from 17 to 18 May 2018. With regard to potency determination, an agreement was reached to apply the lipopolysaccharide (LPS) inhibition ELISA for release of drug substance and drug product. Consensus was reached on reference materials for LPS
inhibition ELISA. A collaborative study will be conducted using the different ELISA formats with the aim of making the reference reagents available as WHO International Standards. LPS inhibition ELISA is used in stability testing, but further discussion is needed regarding which assay is most appropriate. The utility of in vivo analyses was discussed, and it was determined that it is possible to use these analyses for preclinical studies, but not for batch release or potency determination.

8.3 WHO vaccine profiling pilot project
Dr Michael Gilgen gave an overview of a WHO vaccine profiling pilot project that aims to characterize the proteins in WHO-prequalified vaccines to differentiate them based on their protein profile and to be able to identify counterfeit vaccines.

The study, which looked at two influenza vaccines, one produced in cell cultures and one produced in embryonated chicken eggs, applied liquid chromatography with tandem mass spectrometry (LC-MS-MS) as a non-targeted screening approach to list all proteins found in the two vaccines, including API proteins and background proteins. Multiple reaction monitoring initiated detection and sequencing (MIDAS) technique was used as a targeted approach to confirm certain background proteins detected in the previous screening or suspected to be present.

The study found an obvious difference between the protein profiles of the cell-based and egg-based vaccines: the two vaccines can easily be distinguished from each other based on their screening protein profiles. Good lot-to-lot consistency was demonstrated among the same vaccine. An additional targeted approach would be needed to differentiate between different influenza vaccines produced in embryonated chicken eggs.

The vaccine profiling project also includes investigation of cholera, meningococcal, DTwPHepB-Hib and rotavirus vaccines.

9. Sharing of best practices
Day 3 of the meeting was dedicated to sharing best practices with presentations on new developments in quality control methods and on projects promoting harmonization.

9.1 Introductory speech: 3Rs achievements and perspectives
Dr Coenraad Hendriksen opened the session by providing an overview of 3Rs achievements and perspectives. He described ethical and scientific drivers to moving away from laboratory animal use and gave examples of 3Rs progress and ongoing projects in the European Union. Dr Hendriksen explained that one of the biggest barriers to 3Rs progress is the paradoxical situation faced by manufacturers and regulatory bodies: manufacturers are reluctant to invest in an alternative test without assurance of regulatory acceptance, and regulators are reluctant to assure acceptance in the absence of data. He emphasized that a coordinated approach involving good communication and commitment on the part of both industry and regulatory authorities is essential to overcoming barriers to 3Rs progress.

9.2 Suitability of alternative ATP potency assay for lot release of BCG vaccine in Thailand
Mrs Wereyarmarst Jaroenkunatham reported on the verification of the suitability of an adenosine triphosphate (ATP) potency assay as an alternative to culturable particle count for
lot release of Tokyo-172 BCG vaccine in Thailand. The ATP assay showed good accuracy, precision and robustness; had high correlation between intracellular ATP concentrations and the number of viable bacilli in vaccine samples; was comparable with culturable particle test method; and could be done rapidly, taking only two days to produce the estimate of the viable cell content compared to four weeks for the conventional method. Based on the results of the study, Thai Institute of Biological Products is implementing this method for lot release of BCG vaccine.

9.3 Pyrogen testing of human vaccines by MAT
Dr Marilena Etna delivered a presentation on pyrogen testing of human vaccines using the monocyte activation test (MAT). MAT, which is intended as a replacement for the rabbit pyrogen test, uses human whole blood or monocytes and is based on the human fever reaction. The method is described in the general chapter of the European Pharmacopoeia and therefore does not require re-validation (in Europe); however, product (vaccine)-specific optimization is needed. ISS adapted the conditions for the test to analyse tick-borne encephalitis virus (TBEV) vaccine and designed a final protocol to validate the optimized MAT conditions. They found that the choice of cell source (whole blood, isolated PBMCs or monocytic cell lines) is critical to define the sensitivity of the optimized MAT assay; the choice of method is dependent on the vaccine composition; an in the absence of cytokine production, cell viability should be checked. Dr Etna concluded by stating that MAT is effective in ruling out the presence of endotoxin and non-endotoxin pyrogens in vaccines and could be applied during development of the production process, during the manufacturing process or for batch release.

9.4 VAC2VAC project
Dr Christina von Hunolstein provided an overview of the vaccine batch to vaccine batch – comparison by consistency testing (VAC2VAC) project, an initiative that aims to provide data to support the consistency approach for quality control of established vaccines. Consistency testing aims to use non-animal assays, instead of animal tests, to ensure that each vaccine batch produced is consistent with a clinical/historical batch already proven to be safe and efficacious in registration studies or clinical use. VAC2VAC project partners develop, optimise and evaluate non-animal methods that cover key parameters for demonstrating batch consistency, safety and efficacy. They (pre-)validate methods and, together with regulators, define guidance for regulatory acceptance and routine use. Dr Hunolstein introduced VAC2VAC’s seven ‘work packages’ and provided a summary of progress for each. Detailed information is available on the VAC2VAC website: http://www.vac2vac.eu

9.5 Inclusion of WHO protocol in the Indian Pharmacopoeia
Dr Christina von Hunolstein delivered a presentation on behalf of Dr Surinder Singh (National Institute of Biologicals (NIB), India) on the inclusion of the WHO protocol for Hib vaccine testing by HPAEC (please see section 8.1) in the Indian Pharmacopoeia. Final validation studies run by individual manufacturers are in progress, and manufacturers are expected to submit their validation data to NIB by end of March 2019. NIB will verify the data and submit it to the Indian Pharmacopoeia by May 2019 for incorporation into the Pharmacopoeia Addendum 2020.

9.6 WHO rabies vaccine potency determination by serology
Dr Ralf Wagner gave an overview of the NIH potency assay and emphasized the need, based on 3R principles, to identify an appropriate alternative to this test. Dr Wagner provided a summary of the main findings of a feasibility study [4] initiated by WHO to determine whether a
multi-dose serological assay, based on vaccination of mice and subsequent determination of neutralizing antibodies \textit{in vitro}, may be a suitable alternative for use by vaccine control laboratories globally. The findings suggest that the assay is feasible, but the current design is too cumbersome due to the high number of microtiter plates needed.

Meeting participants voiced their support for WHO’s plan to invest in an immunogenicity assay to prospectively replace the NIH test.

\textbf{9.7 DCVMN workshop Hyderabad 2018 – Updates}

\textbf{9.7.1 International collaborative study for replacement of NIH test}
Dr Bhaveshkumar Shah expressed interest, on behalf of a manufacturer, in participating in Phase II of the EDQM collaborative study for which the company, Zydus Cadila Healthcare; India, would like to include an in-house in vitro potency assay based on the G-Protein ELISA method.

In the discussion following the presentation it was clarified that participants in the collaborative study will be asked to use two specific monoclonal antibodies that have been well characterized and are known to recognize the trimeric form of the glycoprotein. These antibodies are available to everyone and have been pre-assessed against vaccines available globally in a project supported by the European Partnership for Alternative Approaches to Animal Testing (EPAA). One of the reagents used by the company are in-house characterized antibodies; however, participation in the upcoming study does not prevent testing alternative reagents in parallel.

Later, the company stated that they also have participated in a study conducted by NCL (CDL; Kasauli, India) and wish to support global endeavor of 3R and harmonize use of in vitro ELISA for rabies potency test and has confirmed that they will share the antibodies with public at mutually agreeable terms.

\textbf{9.7.2 Replacement of Kendrick test for whole cell pertussis vaccine}
Dr Christina von Hunolstein commented on a collaborative study carried out with the support of EDQM. The collaborative study, run by EUROL-ECVAM, followed up on a 2008 study that evaluated two serological methods for potency testing of whole-cell pertussis vaccines and identified pertussis serological potency test whole-cell ELISA (PSPT-wC-ELISA) as a promising approach for batch release potency testing of whole-cell pertussis vaccines for which consistency in production has already been demonstrated by a mouse protection test based on the Kendrick assay [5]. The method was developed in guinea pigs and mice and works well in both models. Data analysis is not yet finalized but results look promising.

\textbf{9.7.3 Acceptance of paralysis endpoint (T3 stage) for tetanus challenge tests}
Dr Gopal Singh gave a brief presentation, on behalf of DCVMN, on the application of 3R principles to the challenge procedure carried out in mice and guinea pigs for batch release of tetanus vaccines. To reduce the pain and suffering of the animals, DCVMN promotes regulatory acceptance of application of at least grade T3 as the endpoint for tetanus toxemia (paralysis of the toxin-injected hind leg, which does not function for walking) instead of death, which is currently consistently accepted by regulators. Furthermore, based on the extensive experience of the applicant, grade T2 (paresis of the toxin-injected hind leg, which can still function for walking) could be used as the endpoint.
9.8 Use of humane endpoints for animal-based challenge tests
Dr Ute Rosskopf provided a summary of WHO guidance on the use of humane endpoints for diphtheria, tetanus, whole cell pertussis and rabies potency assays. She noted that information on this topic is not consistently found in one specific section or chapter of WHO guidelines and that chapters containing information on animal health status often provide little practical guidance. Dr Rosskopf proposed focusing the Network’s efforts on collecting and compiling existing information, including scoring, for each type of vaccine and species (this would include internal written guidance, training videos and other resources) as well as monitoring sheets and templates. Dr Rosskopf asked for volunteers to compile and prepare templates for best practices. These ready-to-use templates will ultimately be posted on the SharePoint to serve as a shared resource.

10. Closed sessions for WHO-NNB full members
Closed sessions at the end of the first and second days of the meeting provided an opportunity for the WHO Secretariat and full members of the Network to discuss issues and concerns in a private setting. These sessions proved helpful and will continue to be included in future meetings.

11. Conclusions and next steps
The outcomes as specified in the meeting terms of reference were as follows: established contacts among meeting participants; overview of applied strategies of vaccine quality control by newly participating NCLs; insight on regulation, vaccine access, release and control applied by recipient countries; agreed content and features of the Network SharePoint; discussed measures for sustainable Network performance; volunteers to support Network activities; proposed venue and date of the next general meeting; shared best practices; proposals of themes for best practices at next meeting; meeting report (record of discussions and agreed decisions).

The participants considered that the above outcomes were achieved or will be achieved in follow-up to the meeting.

The following action points were agreed:
- WHO will continue to work on the WHO-NNB SharePoint, including starting the third round of validation and assessing the feasibility of the changes proposed during the meeting.
- WHO will prepare a meeting report of the discussions and agreed decisions and circulate it among meeting participants for comment.
- WHO will announce the date and location of the Third WHO NNB General Meeting (2019) as soon as it is confirmed. Participants are encouraged to suggest themes for the meeting. Thus far, the following proposals have been put forth:
  - Case studies on risk-based testing and discussion on how to reflect information regarding reduction schemes on the SharePoint. Volunteers are needed for the case studies.
  - Update on VAC2VAC project and other ongoing projects.

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6 In follow up to the meeting, South Africa National Control Laboratory for Biological Products graciously volunteered to host the Third General Meeting in Bloemfontein, South Africa, in 2019.
Dr Ute Rosskopf encouraged participants to stay engaged, especially in areas where volunteers with specific expertise and resources are needed, including:

- **Humane end-points for animal-based testing**
  Volunteers are needed to compile and prepare the templates (analytical worksheets and validation protocol) for best practices in the application of humane end-points for animal-based testing. These templates will ultimately be posted on the SharePoint to serve as a shared resource.

- **Proficiency testing schemes for vaccines**
  Volunteer NCLs are needed to work together with WHO to organize proficiency testing for vaccines. During the workshop, diphtheria vaccine was discussed as the next candidate for a proficiency testing scheme.

- **Training on establishment of single dilution potency assays**
  WHO is seeking assistance from NCLs that can host an on-site hands-on training focused on advising and assisting trainees in establishment of single dilution potency assays. Applicants for training should express their interest as well.

In closing, Dr Rosskopf thanked the ISS team for hosting the meeting and the participants for their active engagement and contributions.

Participants were informed that the meeting documents and presentations (from Day 3) would be made available on the Network SharePoint.
12. References
## Appendix 1. List of participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization</th>
<th>Institution</th>
<th>Country</th>
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<tr>
<td><strong>ANDERSON, Marie</strong></td>
<td>NCL</td>
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Appendix 2. Model certificate for the release of vaccines by NRAs

Model certificate for the release of vaccines by NRAs

Lot-release certificate

Certificate no._____________________

The following lot(s) of ___________________________ vaccine produced by ____________

______________________

1 whose numbers appear on the labels of the final evaluated containers, complies with the relevant marketing authorization, the national specifications and provisions for the release of biological products\(^2\) and Part A\(^3\) of the WHO Recommendations to assure the quality, safety and efficacy of the concerned vaccines (yyyy)\(^4\), and with corresponding WHO recommendations for each of the vaccine's individual components, as well as with WHO good manufacturing practices for pharmaceutical products\(^;\(^5\) Good manufacturing practices for biological products\(^6\), and Guidelines for independent lot release of vaccines by regulatory authorities\(^7\).

<table>
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<tr>
<td>International non-proprietary Name / Common name:</td>
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<tr>
<td>Batch numbers appearing on package and other identification numbers associated with this batch(^7):</td>
</tr>
<tr>
<td>Type of container used:</td>
</tr>
<tr>
<td>Total number of containers or lot size:</td>
</tr>
<tr>
<td>Number of doses per container:</td>
</tr>
<tr>
<td>Date of start of period of validity (e.g. manufacturing date):</td>
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<tr>
<td>Date of expiry (DD/MM/YYYY):</td>
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<td>Storage conditions(^8)</td>
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<td>Name and address of manufacturer:</td>
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<tr>
<td>Site(s) of manufacturing:</td>
</tr>
<tr>
<td>Name and address of marketing authorisation holder if different:</td>
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</table>

\(^7\)Such as batch number of final bulk.

\(^8\) Some products may also have approved extended controlled temperature conditions at the end of use.
Certificate no. ______

This batch has been examined using documented procedures which form part of a quality system which is in accordance with the ISO/IEC 17025 standard.

The release decision is based on the elements described in paragraph 7.3 of the Lot Release guideline:

This batch has been found compliant with the above by the institute below, member of the WHO National Control Laboratory Network for Biologicals.

Name (typed) ____________________________
Institute ________________________________
Position ________________________________
Signature ________________________________
Date ________________________________

[ stamp ]

Importing / requesting authority:

This certificate conforms to the format recommended by the World Health Organization (WHO).

1 Name of manufacturer.
2 If any national requirements have not been met, specify which one(s) and indicate why the release of the lot(s) has nevertheless been authorized by the NRA.
3 With the exception of provisions on distribution and shipping, which the NRA may not be in a position to assess.
4 The relevant WHO Technical Report Series, No. XXX, Annex Y.