Report of the fifth general meeting of the WHO national control laboratory network for biologicals

Bangkok Sukhumvit, Thailand
13-15 December 2023
Report of the fifth general meeting of the WHO national control laboratory network for biologicals
The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

This publication contains the report of the fifth general meeting of the WHO National Control Laboratory Network for Biologicals and does not necessarily represent the decisions or policies of WHO.
Contents

Executive summary ...................................................................................................................................... v
Abbreviations and acronyms ..................................................................................................................... vi
Opening and welcome ................................................................................................................................1
Updates from WHO on laboratory networks and services ....................................................................... 2
New members (and observer) of the WHO-NNB ...................................................................................... 3
  Comoros ................................................................................................................................................... 3
  Finland ...................................................................................................................................................... 3
  Guinea........................................................................................................................................................ 4
  Iran (Islamic Republic of) ........................................................................................................................ 5
  Pakistan ................................................................................................................................................... 6
  Philippines .............................................................................................................................................. 6
  Uganda .................................................................................................................................................... 7
  China ........................................................................................................................................................ 8
  Discussion ............................................................................................................................................... 9
Updates from WHO-NNB members ........................................................................................................... 9
  Thailand ................................................................................................................................................... 9
  Indonesia ................................................................................................................................................ 10
  South Africa .......................................................................................................................................... 10
  United Kingdom of Great Britain and Northern Ireland ..................................................................... 11
  Discussion ............................................................................................................................................... 12
Updates from WHO .................................................................................................................................... 12
  WHO Technologies, Standards and Norms .......................................................................................... 12
  WHO Good Regulatory Practices, Reliance And Networks ................................................................. 13
  WHO South-East Asia Region ................................................................................................................ 13
  WHO Western Pacific Region ................................................................................................................ 14
  WHO African Region .............................................................................................................................. 14
  Discussion ............................................................................................................................................... 14
Sharing practices: perspectives on risk-based lot release ...................................................................... 15
  Thailand ................................................................................................................................................... 15
  Canada .................................................................................................................................................... 16
  Senegal .................................................................................................................................................... 16
  Republic of Korea .................................................................................................................................. 17
  Discussion ............................................................................................................................................... 17
Sharing best practices: 3R ......................................................................................................................... 17
  Belgium: Sciensano ................................................................................................................................. 18
  India: Central Drugs Laboratory, Kasauli .............................................................................................. 18
Executive summary

The fifth general meeting of the World Health Organization – National Control Laboratory Network for Biologicals (WHO-NNB) was held in Bangkok Sukhumvit, Thailand from 13 to 15 December 2023 with support from the Institute of Biological Products, Thailand.

The meeting was attended by 120 participants from 58 Member States across all six WHO regions, including representatives from regional and international organizations, industry associations and partners.

The meeting offered a forum to share practical experiences on the theme of reliance and recognition – the “2Rs” of lot release of vaccines operationalized through the WHO-NNB to facilitate access to quality-assured vaccines in low- and middle-income countries. It also provided WHO-NNB members and partners with an important opportunity for exchange of knowledge and best practices in strengthening regulatory capacity and quality monitoring to ensure the highest standards in the production and release of vaccines.

The WHO-NNB provides a unique platform for sharing best practices and promoting regulatory reliance on lot release to avoid redundant testing of quality-assured vaccines. The network has witnessed significant growth in membership from 15 in 2017 to 52 in 2023, clearly demonstrating the need for work and information-sharing in laboratory testing and lot release for timely access to safe, effective and quality-assured vaccines.

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

Meeting highlights included:

- updates from national control laboratories, national regulatory authorities and WHO offices (WHO headquarters and the WHO regional offices for Africa, South-East Asia and the Western Pacific);
- perspectives on risk-based lot release approaches and best practices on 3Rs from both regulators, industry and partners;
- project updates and technical discussions on quality monitoring;
- presentations from the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA, presented by Vaccines Europe) and the Developing Countries Vaccine Manufacturers’ Network (DCVMN) on the importance of reliance and access to vaccines;
- quality monitoring updates;
- practical approaches to dealing with OOS testing results;
- demonstration and better use of the SharePoint platform and presentation and discussion on the use of the WHO-NNB SharePoint;
- break-out sessions on how to better use reliance between members and what is needed for the sustainability of the network/ impact of the WHO-NNB;
- added value of the network, as expected by the participants, for sharing of best practices and promoting reliance and best practices through access to information on national control laboratories, lot release practices, quality assurance policies, annual quality reports and detailed lot release data.
### Abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3Rs</td>
<td>Replacement, reduction and refinement</td>
</tr>
<tr>
<td>AMRH</td>
<td>African Medicines Regulatory Harmonization</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine triphosphate</td>
</tr>
<tr>
<td>AUDA-NEPAD</td>
<td>African Union Development Agency – New Partnership for Africa’s Development</td>
</tr>
<tr>
<td>AVAREF</td>
<td>African Vaccine Regulatory Forum</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacillus Calmette Guérin vaccine</td>
</tr>
<tr>
<td>BRDD</td>
<td>Biologic and Radiopharmaceutical Drugs Directorate (Canada)</td>
</tr>
<tr>
<td>BSP</td>
<td>Biological Standardization Programme</td>
</tr>
<tr>
<td>CBÉR</td>
<td>Center for Biologics Evaluation and Research</td>
</tr>
<tr>
<td>CFU</td>
<td>Colony-forming unit</td>
</tr>
<tr>
<td>CSL</td>
<td>Common Services Laboratory</td>
</tr>
<tr>
<td>DCVMN</td>
<td>Developing Countries Vaccine Manufacturers’ Network</td>
</tr>
<tr>
<td>DTP</td>
<td>Diphtheria, tetanus and pertussis vaccine</td>
</tr>
<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines &amp; HealthCare</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (Philippines)</td>
</tr>
<tr>
<td>GAVI</td>
<td>The Vaccine Alliance (originally the Global Alliance for Vaccines and Immunization)</td>
</tr>
<tr>
<td>IEC</td>
<td>International Electrotechnical Commission</td>
</tr>
<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency (United Kingdom)</td>
</tr>
<tr>
<td>NC3Rs</td>
<td>National Centre for the Replacement, Refinement &amp; Reduction of Animals in Research (United Kingdom)</td>
</tr>
<tr>
<td>NCL</td>
<td>National Control Laboratory</td>
</tr>
<tr>
<td>NIFDC</td>
<td>National Institutes for Food and Drug Control (China)</td>
</tr>
<tr>
<td>NIFDS</td>
<td>National Institute of Food &amp; Drug Safety (Republic of Korea)</td>
</tr>
<tr>
<td>NRA</td>
<td>National Regulatory Authority</td>
</tr>
<tr>
<td>OCABR</td>
<td>Official Control Authority Batch Release</td>
</tr>
<tr>
<td>OMCL</td>
<td>Official Medicines Control Laboratory</td>
</tr>
<tr>
<td>OOS</td>
<td>Out-of-specification</td>
</tr>
<tr>
<td>PQM+</td>
<td>Promoting the Quality of Medicines Plus</td>
</tr>
<tr>
<td>SAHPRA</td>
<td>South African Health Products Regulatory Authority</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>USFDA</td>
<td>United States Food and Drug Administration</td>
</tr>
</tbody>
</table>
Opening and welcome

Dr Pichet Banyati, Deputy Director General of Department of Medical Sciences, Ministry of Public Health (MOPH), Thailand, opened the meeting and welcomed the participants from national vaccine control laboratories, partners and stakeholders representing almost 60 Member States (MS) of the World Health Organization (WHO). He also extended a welcome on behalf of the Department of Medical Sciences of the MOPH. Dr Banyati emphasized that the operational activities of the network were made possible under the auspices of WHO’s Laboratory Networks and Services (LNS) team. The operational network has a pivotal role in facilitating access to, and ensuring the quality of, vaccines by providing a platform for information-sharing, transparency and the cultivation of trust and confidence among its members. As a full member of the World Health Organization-National Control Laboratory Network for Biologicals (WHO-NNB), Thailand’s National Control Laboratory (NCL) consistently encourages fellow members to share high-quality and technical information related to prequalified vaccines in order to foster reliance on the batch release of vaccines.

Mr Hiiti Sillo, Head of the Regulation and Safety (REG) Unit at WHO’s headquarters in Geneva, extended a warm welcome to participants and provided an update on the WHO-NNB, acknowledging the inclusion of eight new associate members namely Comoros, Finland, Guinea, Iran (Islamic Republic of), Pakistan, Philippines, Rwanda and Uganda. The primary objectives of the network include: 1) sharing quality and technical information related to prequalified vaccines (or other biological medicinal products); 2) facilitating reliance of lot release of the responsible National Regulatory Authority (NRA) and/or the national control laboratory (NCL) by recipient countries; and 3) promoting reliance through the development of harmonized standards and best practices.

Mr Sillo also highlighted the enhanced sharing of manufacturer-specific lot release information through the WHO-NNB SharePoint. This initiative has significantly expedited access to Emergency Use Listed (EUL) COVID-19 vaccines, showcasing the role of information-sharing in reducing the time it takes for vaccines to reach populations.

In conclusion, Mr Sillo encouraged all Member States to collaborate in overcoming barriers, promoting reliance, facilitating recognition and ensuring the delivery of safe and effective vaccines of assured quality to all those in need.

Dr Supaporn Phumiamorn, Director of the Institute of Biological Products (IBP) in the Department of Medical Sciences, Ministry of Public Health, Thailand, conveyed her appreciation to WHO and extended a warm welcome to all participants at the meeting, which was the first to be held in four years since the previous gathering in South Africa. Dr Phumiamorn highlighted the advantages of participation, emphasizing the value of confidentiality agreements that facilitated access to vaccines, expertise, novel method development and harmonization. She acknowledged the achievements so far and emphasized the need to consider carefully the continuity and sustainability of the network in the future.

To address the reliance and mutual recognition of the network, Dr Phumiamorn emphasized that establishing “Trust and Confidence” is paramount in achieving its goals. Despite the diversity of laws and regulations in different countries, she highlighted the need for robust collaboration and communication between NRAs and NCLs, coupled with a high level of transparency. She expressed confidence that these factors would contribute significantly to the successful realization of the network’s objectives.
Updates from WHO on laboratory networks and services

Mr Mustapha Chafai, the acting Team Lead for LNS within the REG Unit, provided an overview of the activities in this area of work and gave updates on laboratory strengthening and promotion of networks.

WHO’s work on laboratory networks and services plays a pivotal role in safeguarding and ensuring vaccine quality and facilitating and accelerating access through coordination of several activities, including: management of the WHO National Control Laboratory Network for Biologicals (WHO-NNB), including the WHO-NNB SharePoint and the annual meetings; overseeing WHO independent testing during the prequalification and post-prequalification of vaccines; and managing WHO-contracted laboratories in charge of the testing of vaccines on behalf of WHO. In addition, WHO collects and analyses data from the official batch release results of prequalified vaccines; conducts training, workshops, collaborative studies and proficiency testing; and identifies the bottlenecks and needs in vaccine quality control in order to facilitate timely prequalification and access to vaccines.

The vaccine prequalification programme, which was created in 1987 as a service to United Nations (UN) agencies wishing to purchase and procure vaccines, provides independent advice on the quality, safety and efficacy of vaccines. The prequalification procedure was briefly presented, as described in Annex 6 of WHO Technical Report Series No. 978. The evaluation process comprises review of vaccine dossiers, inspection of manufacturing sites, and the conduct of final product testing. The LNS team plays a crucial role in the prequalification process by organizing the testing of the final products and thereby directly contributing to the prequalification process.

The LNS team manages WHO-contracted laboratories, maintaining the list of these laboratories and providing technical assistance to ensure adherence to WHO’s standards through WHO laboratory audits. In 2023, audited laboratories included SwissMedic, Thailand’s Institute of Biological Products (IBP) and Indonesia’s National Quality Control Laboratory of Drug and Food (NQCLDF), while an audit of India’s Central Drugs Laboratory (CDL) in Kasauli is still in the planning stage. WHO has contracts with 15 NCLs globally that perform physical testing of prequalified vaccines on behalf of WHO.

The establishment of the WHO-NNB is an initiative of the LNS team which aims to facilitate access to and availability of prequalified vaccines. The WHO-NNB SharePoint is a confidential and secure platform for information-sharing on testing and lot release of vaccines, use of common standards and best practices, and the promotion of the 3Rs (Replacement – Reduction – Refinement) principles. It serves as a meeting point for stakeholders in fostering relationship-building and promoting the recognition of batch release by responsible NRAs and NCLs in order to reduce redundant testing and to facilitate access.

The WHO LNS team supports the strengthening and promotion of networks. This involves organizing independent testing for prequalified vaccines and biologicals, expanding the list of WHO-contracted laboratories, advocating for WHO-NNB adoption globally, increasing manufacturers’ agreements to share lot release data, improving technical information-sharing via SharePoint, organizing workshops for best practices, developing a Laboratory Information Management System, and exploring a link to WHO-NNB SharePoint for relevant data-sharing. Overall, the LNS team is dedicated to enhancing global vaccine quality, safety and availability through collaborative efforts and efficient regulatory processes.
New members (and observer) of the WHO-NNB

Seven new members namely Comoros, Finland, Guinea, Iran (Islamic Republic of), Pakistan, Philippines and Uganda attended the WHO-NNB meeting for the first time. Each country provided an overview of its regulatory organization and structure, with a particular focus on the vaccine-related aspects, along with information on vaccine coverage and lot releases. China, as an observer to the WHO-NNB, provided a presentation on the organization of its National Institutes for Food and Drug Control and described related responsibilities with regard to vaccine batch release.

Comoros

Dr Ahamada Said Fazul, Director General, Agence National des Medicaments et des Evacuations Sanitaires (ANAMEV)

As Comoros was a new member of WHO-NNB, Dr Fazul described the work of the country’s medicines agency and its organizational structure. The administrative framework includes general management, while the technical division encompasses specialized units such as communication, medical evaluation, informatics, regulation, quality control, pharmacovigilance and inspection. In terms of vaccine access and coverage, Comoros has procured vaccines through United Nations sources such as COVAX, UNICEF and GAVI, along with direct purchases from manufacturers. The country’s strategy aims to ensure flexibility and comprehensiveness in securing vaccines.

Procedures for vaccine release onto the market involve market surveillance testing and sampling, with a detailed protocol for post-marketing surveillance. To address the problem of falsified vaccines, designated focal points oversee all products in this category. Additionally, a lot release procedure is outlined and managed by the importation service. Comoros does not currently produce any vaccine but remains open to exploring possibilities for future local manufacture.

Externally, Comoros has extended collaborative efforts through partnerships with various organizations and countries, taking pride in membership of networks such as the Southern African Development Community, WHO, the African Vaccine Regulatory Forum, as well as others within the Ministry of Health and international collaborations such as ZaZiBoNa and African Medicines Regulatory Harmonization (AMRH). This collaborative approach is integral to staying informed, sharing best practices, and contributing to a global perspective on public health initiatives. The inclusion of Comoros as an Associate Network Member in WHO-NNB underscores its commitment to global health and collaborative efforts within the network.

In this session, WHO provided updates on technologies, standards and norms related to WHO good regulatory practices, reliance and networks, along with the latest information from WHO regional offices.

Finland

Dr Jaana Vesterinen, Head of section, Finnish Medicines Agency

Finland, an associate network member, presented its regulatory structure with various departments falling under the Director General’s responsibilities. These include marketing authorizations, safety and effectiveness, supervision and availability, along with additional services such as communications, information and development, and a joint service unit.
Finland emphasizes strong access to vaccines, all of which are licensed and produced by authorized manufacturers. The country adopts two primary routes for incoming vaccines. The Ministry of Social Affairs and Health Care manages the procurement for population vaccination programmes, which may involve vaccines from various sources, including those procured by the European Commission. For other vaccines, most are directly purchased from manufacturers.

Market surveillance testing and sampling are possible but are usually not performed due to the application of official batch release of vaccines. In dealing with suspected falsified vaccines, Finland would consider testing and would contact the marketing authorization holder.

For vaccine release onto the market, Finland employs a passive lot release system, approving Official Control Authority Batch Release (OCABR) certificates from authorized NCLs, either those from the European Commission or those with a mutual recognition agreement with the European Commission. Before being released onto the Finnish market, each vaccine batch undergoes scrutiny to ensure that it has a valid OCABR certificate and related marketing information.

In terms of local vaccine production, Finland does not have any vaccine manufacturers.

Externally, Finland collaborates with other countries and organizations such as the European Medicines Agency and the European Directorate for the Quality of Medicines and HealthCare (EDQM) and is a member of the Official Medicines Control Laboratory (OMCL) network and WHO-NNB.

There is special expertise within the Finnish Medicines Agency laboratory which performs a range of analyses, including microbiological analyses, cell-based assays for potency assessment, and activities related to the European Pharmacopoeia – such as biological monographs, methodological chapters and monoclonal antibody products.

**Guinea**

**Dr Keita Djoran, Laboratoire National de Contrôle de Qualité des Médicaments (LNCQM)/National Drug Quality Control Laboratory**

The National Drug Quality Control Laboratory of Guinea operates with legal status as an attached service under the authority of the Minister of Health. The laboratory plays an important role in implementing the department’s policy on the quality control of medicines and other health products. The laboratory is entrusted with special missions, encompassing the establishment of a quality control policy for both modern and traditional medicines, oversight of the quality of imported and locally-produced medicines, scientific judgements for marketing authorization, epidemiological studies on water surveillance, involvement in student training at the Faculty of Pharmacy, and active contributions to the improvement, promotion and enhancement of the Guinean pharmacopoeia.

The laboratory comprises various technical teams including: the physico-chemistry team, which manages sample reception, recording and analysis according to standards; the microbiology team, conducting drug sterility controls and germ counting in medicines and water; the research and development team which focuses on identifying counterfeit medicines and developing analytical methods; the medical devices unit, ensuring the quality control of medical devices, preservatives and additives; and the quality assurance unit which establishes and maintains a collection of specifications and documents for laboratory use.
Future plans for the laboratory include obtaining ISO 17025:2017 accreditation, operationalizing the microbiology and medical devices units, establishing regional representation on the national territory, and constructing a new laboratory building that is compliant with ISO 17025 standards. These strategic developments reflect the laboratory’s commitment to ensuring the quality and safety of medicines in Guinea.

Iran (Islamic Republic of)

Dr Saeed-Reza Pakzad, Head of the Biologicals Laboratory

In the Islamic Republic of Iran, the NRA operates under the Islamic Republic of Iran Food and Drug Administration and adheres to the quality system standard of ISO 17025:2017 and WHO guidelines. However, ISO accreditation has not yet been attained. The Islamic Republic of Iran’s NRA was considered “functional” in 2010 after a WHO assessment.

With regard to vaccine access and coverage, the Islamic Republic of Iran primarily engages in direct purchases from manufacturers, predominantly opting for WHO-prequalified vaccines. Market surveillance sampling and testing are routine procedures, with samples collected from various provinces on the basis of a risk-based plan formulated by another office within the NRA and sent to the NCL for testing. Although incidents of falsified vaccines were not reported before the COVID-19 pandemic, limited cases of falsified Astra-Zeneca COVID-19 vaccine emerged in 2021–2022 (involving the refilling of used vials with saline solutions). These instances were promptly identified and addressed through collection and destruction.

Vaccine lot release, a responsibility of the NRA, involves sending batches of all products to the NCL for testing based on risk assessment and approved study plans. All imported vaccines are WHO-prequalified, and testing is conducted as far as possible. Currently, there is no formal reliance on other regulatory authorities but batches from renowned manufacturers with release certificates are sometimes released on the basis of document review.

The Islamic Republic of Iran has a diverse range of registered vaccines, including 61 vaccines covering a range of 21 vaccine types that are tested independently by the NCL. The NCL maintains a quality system and will be WHO-audited next year for Global benchmarking tool status. A network of laboratories collaborates with the NCL for various analyses. The performance of these laboratories is monitored by initial and periodic inspections and testing of unknown samples (proficiency testing). Quality agreements define the responsibilities of these laboratories.

The Islamic Republic of Iran’s local vaccine production involves several manufacturers, including Razi Vaccine and Serum Research Institute, Pasteur Institute of the Islamic Republic of Iran, Cinnagen, Masoun Darou, Shafa Pharmed, Nivad, Biosun Pharmed and Padraserum Alborz. These manufacturers produce a variety of vaccines, antisera and biotherapeutics, contributing to both human and veterinary (Razi Institute) health care needs.
Pakistan

Dr Mahvash Ansari, Additional Director, Division of Quality Assurance and Drug Regulatory Authority of Pakistan

As an institution under the Government of Pakistan, the drug regulatory authority operates as an autonomous body under the administrative control of the Ministry of National Health Services, Regulation and Coordination. Pakistan’s immunization programme, established in 1978, currently includes vaccine coverage for 12 diseases in the childhood vaccination schedule. Procurement is managed by the Federal Directorate of Immunization, through either competitive bidding or cofinancing through UNICEF.

For post-marketing surveillance, the National Control Laboratory for Biologicals – part of the Drug Regulatory Authority of Pakistan – conducts testing and analysis of vaccine samples sent by federal and provincial inspectors of drugs. The National Control Laboratory for Biologicals issues lot release certificates for human vaccines, plasma-derived products and anti-sera products on the basis of the review of summary protocols and/or testing, following relevant WHO technical guidelines using the reliance approach.

In terms of market surveillance, Field Force inspectors obtain samples from biopharmaceutical manufacturing units and imported biological products from the market or institutions during routine surveys or when triggered by complaints. Pakistan has consistently updated data from the National Control Laboratory for Biologicals, capturing new issues or lot releases since 2000 up to today. Although Pakistan fulfils its need for vaccines and other biological products mainly through import, a few establishments that manufacture anti-snake venom and veterinary vaccines, while several others produce vaccines from ready-to-fill bulk import.

Philippines

Ms Caren R. Mangorangca, RPh Food-Drug Regulation Officer IV, Head - Vaccine and Biological Unit/ Drug Section

The Common Service Laboratory (CSL) of the Philippines Food and Drug Administration (FDA) comprises three accredited laboratories: 1) FDA-CSL Alabang Testing and Quality Assurance Laboratory; 2) FDA-CSL Davao Testing and Quality Assurance Laboratory; and 3) FDA-CSL Cebu Testing and Quality Assurance Laboratory. All these laboratories adhere to ISO 17025:2017 accreditation.

The scope of activities mandated for the CSL involves conducting laboratory tests on health products – encompassing foods, drugs, cosmetics and medical devices – to ensure their safety, efficacy, quality and purity. The FDA-CSL, as an ISO 17025:2017-accredited laboratory, is authorized to issue laboratory certifications, including lot release certificates for vaccines and biological products, batch notifications for antibiotic products, and certificates of evaluation for food contact materials.

The national lot release system is grounded in legal frameworks, including Administrative Order No. 47-A which stipulates the rules and regulations on the registration, approval and conduct of clinical trials and lot or batch release certification of vaccines and biological products.

General considerations for lot release certificates involve the review of summary protocols, independent testing, and the recognition or acceptance of lot release certificates from the responsible NRA or NCL. The evaluation of imported vaccine samples is an integral aspect of the CSL’s activities.
Lot release evaluation encompasses multiple criteria, including the review of summary lot protocols, product specifications approved by the FDA, laboratory test results, the actual condition of samples, and information from international bodies. The CSL also actively engages in market surveillance activities under the responsibility of the Center for Drug Regulation and Research, following established protocols for post-marketing surveillance.

Market surveillance activities include collection, sampling and testing conducted through annual post-marketing surveillance plans and routine monitoring. Surveillance also includes product verification, monitoring of advertisements and promotion, and responding to recalls or withdrawals of substandard and falsified health products from the market. Regulatory actions, communication and dissemination efforts are undertaken to address violations and ensure public awareness.

The CSL is closely networked with various international and local organizations, including WHO, CODEX, the United States Pharmacopeia, the Association of Southeast Asian Nations and others. For the future, the CSL envisions the establishment of an NCL for vaccines and biologicals in 2024, capacity-building for staff involved in quality control testing, attainment of Global benchmarking tool maturity level 3, and WHO-prequalified NCL status.

Uganda

Dr Amoreen Naluyima, Director of Laboratory Services, National Drug Authority

The National Drug Authority (NDA) of Uganda maintains high quality standards, adhering to international norms such as ISO 9001:2015 and ISO 17025:2017, as well as WHO’s Good practices for pharmaceutical quality control laboratories. The NDA is accredited by both the Kenya Accreditation Service and the American National Standards Institute National Accreditation Board.

The marketing authorization process is managed by the Directorate of Product Assessment and Registration. Grounded in the National Drug Policy and Authority Act and the Drug Registration Regulations (2014), this process is supported by various guidelines and is currently being updated to match the evolving regulatory environment.

Uganda employs a multifaceted approach to vaccine procurement. Public-sector vaccines are obtained through United Nations agencies, while the private sector relies on independent sourcing. To combat counterfeit vaccines, Uganda enforces stringent testing protocols, legal actions leading to prosecution, and collaboration with international regulatory bodies for information exchange.

The distribution of vaccines in Uganda is stringently controlled. Vaccines included in the national immunization programme are WHO-prequalified. The approval process for COVID-19 vaccines involves a comprehensive documentation review and reliance on established standards. Importantly, the NDA is committed to developing a strong lot release system for vaccines, reflecting the country’s increasing investment in the local biopharmaceutical sector.

For the release of vaccine lots, a detailed risk assessment and categorization system is applied to all vaccines and biologicals. This system classifies products into high, medium and low risk categories. Criteria for assessment at the stages of import or manufacture include dossier review, physical inspection and laboratory testing. The release of products is based on the outcomes of these assessments, with WHO being promptly notified of any findings of concern.

In terms of market surveillance, an annual post-marketing surveillance plan that includes vaccines is maintained and is informed by a risk-based approach. Currently, the NDA is enhancing its capabilities
to monitor biological products on the Ugandan market. This includes expanding the Directorate of Laboratory Services for testing and the Directorate of Inspectorate and Enforcement for sampling. Construction of the vaccines and biopharmaceutical laboratories in the Authority’s state-of-the-art laboratory tower is in progress.

**China**

**Dr Jianhui Nie**, Researcher at the National Institutes for Food and Drug Control

The National Institutes for Food and Drug Control (NIFDC), which serves as a national regulatory resource, is owned and managed by China’s National Medical Products Administration. The NIFDC plays a crucial role in providing scientific support for health product regulation through fostering collaboration between agencies, academia and industry.

The NIFDC’s responsibilities encompass testing pharmaceutical and biological products, medical devices, excipients, packaging materials, food and cosmetics, for both pre- and post-market. Additionally, it establishes national reference standards, develops and validates analytical methods, conducts drug safety evaluations, and offers technical assistance and guidance to local drug control institutes. The quality management system of the NIFDC aligns with international standards such as ISO/IEC 17025 and WHO’s *Good practices for pharmaceutical quality control laboratories*.

The Institute of Biological Products Control (IBPC) operates within the NIFDC and oversees biologicals, including vaccines. Comprising 12 divisions, IBPC handles the registration of biological products, lot release, post-marketing surveillance, development of national biological reference materials, research and development of testing methods, and international collaboration. IBPC operates the only biosafety level three (3) laboratory in the NRA of China.

The NIFDC’s primary testing products include vaccines, blood products, antibody drugs, recombinant drugs, cell therapy products, microbiological products and toxins. The institute is actively involved in various collaborations, including being a WHO Collaborating Centre and a WHO Vaccine Contract Laboratory.

NIFDC plays a crucial role in developing and distributing national biological standards, complying with ISO 17034. The institute is responsible for some 140 national biological standards, with collaborative projects underway with the National Institute for Biological Standards and Control.

In the context of lot release in China, the NIFDC faces challenges of a large population to inoculate, a diverse range of vaccine products, multiple manufacturers to be regulated, and a heavy lot release workload, processing around 4000–5000 lots per year.

The institute has played a pivotal role in the development and marketing of COVID-19 vaccines. The NIFDC established an emergency response mechanism, ensuring quality and supply through a unified command approach. In response to the global pandemic, the NIFDC facilitated the conditional marketing or emergency use of 15 vaccines in China, with three vaccines included in the WHO Emergency Use listing.

Furthermore, on 23 August 2022, WHO announced that China, through the National Medical Products Administration (NMPA), had successfully passed the National Regulatory System assessment for vaccines, reflecting the commitment to international quality and regulatory standards.
Discussion

There were notable discussions on vaccine categorization, lot release procedures and encounters with falsified or substandard vaccines. The emphasis was on risk-based categorization, with high-risk vaccines undergoing testing. Instances of past complaints influencing categorization were also highlighted, including a 2019 case that led to a hepatitis B vaccine recall and prosecution. Participants shared their experiences by engaging in discussions on detecting and tracking falsified vaccines, addressing challenges in testing processes, and highlighting the critical role of collaboration and information-sharing between NCLs.

Updates from WHO-NNB members

Members of WHO-NNB presented updates on the activities of their NRAs/NCLs. The updates covered a range of topics, including testing and lot release procedures for vaccines, participation in collaborative studies, and development of new external collaboration and 3R initiatives. The presentations aimed to provide insights into the ongoing efforts and advancements within each regulatory authority, fostering a shared understanding of the diverse activities undertaken by WHO-NNB members.

Thailand

**Dr Wipawee Wongchana**, Institute of Biological products (IBP)

Dr Wipawee Wongchana provided an overview of the roles and responsibilities of the Institute of Biological Products. The first responsibility is independent lot release, which primarily involves reviewing the lot summary protocol as the minimum requirement. The second responsibility is laboratory testing, entailing a visual inspection of imported products and full tests for local products. The final responsibility is the quality control technical support which involves the review of quality and the execution of tests. The number of products released from 2021 to 2023 was presented, revealing the trends of each activity across the three years and indicating that vaccine products accounted for the main proportion of biological products, followed by plasma-derived products and therapeutic biotechnological products.

Thailand has actively engaged in international collaboration with organizations, such as WHO, EDQM and the Developing Countries Vaccine Manufacturers’ Network (DCVMN). In the 2021 WHO benchmarking assessment, the IBP achieved maturity level 4 for laboratory access and testing and maturity level 3 for independent lot release. The updated method developments supporting laboratory testing were presented. The methods align with the 3Rs principle to minimize animal use. Three ongoing projects exemplifying this approach include: 1) replacement of the rabbit pyrogen test and endotoxin test by the limulus amebocyte lysate (LAL) test; 2) replacement of the potency test of tetanus antitoxin and snake antivenom; and 3) the reduction/refinement project related to the pertussis vaccine, which is under validation.
**Indonesia**

*Dr Dio Ramondrana, National Quality Control Laboratory of Drug and Food*

Dr Dio Ramondrana provided a comprehensive review of the organization, focusing on technical units and the legal framework. The organization uses lot release and laboratory testing systems to ensure the quality, safety and efficacy of vaccines. Lot release is executed for domestic vaccines, monovalent bulks of vaccines, and imported vaccines. Laboratory testing covers quality control for lot release, post-marketing surveillance, and the second reading of slides for non-vaccine trials involving monovalent bulks of poliomyelitis.

Dr Ramondrana presented the number of vaccine lot releases from 2021 to 2023, comparing batches from domestic and imported sources. The data revealed that during the COVID-19 pandemic (2021) there was an increase in imported vaccine. In addition to transitioning from in vivo to in vitro methods, Indonesia implemented a reduction strategy by switching from the multi-dilution assay to the single dilution assay. This change resulted in a notable reduction in the number of mice used, decreasing from over 150 animals per run to 40 animals per run. Furthermore, Indonesia has also made strides on the implementation of 3R by deleting the abnormal toxicity test on vaccine and immunosera in monographs since 2022 and through efforts to enhance animal welfare in alignment with the refinement principle, thus aiming to minimize severity in animal experimentation.

**South Africa**

*Dr Quinton Meyer, Director of the South African National Control Laboratory for Biological Products*

The South African human vaccine market is characterized by imports from 14 international manufacturers spanning 11 countries (Belgium, Canada, China, Cuba, Denmark, France, India, Indonesia, Netherlands, Republic of Korea and the United States of America). Additionally, there are two local contract manufacturing organizations, with 49% of the products exclusively utilized in the private market.

Historically, the South African NCL has processed an average of 219 batches per year. This robust processing volume highlights the laboratory’s important role in ensuring the quality, safety and efficacy of vaccines in the South African market.

Anticipating an upswing in local vaccine production, projections have been done by using baseline data on the historical Expanded Program on Immunization (EPI)/private market volume. Two contract manufacturing organizations are involved in this projection, covering a range of vaccines – including hexavalent vaccines, PCV10, meningococcal, rotavirus and COVID-19 vaccines. The testing policy involves a meticulous selection process of batches, considering a risk-based approach for imported vaccines and assessing the consistency of production. All batches of locally manufactured vaccines undergo testing, and the testing policy is approved by the South African Health Products Regulatory Authority (SAHPRA). The laboratory conducts testing by using four ISO 17025 accredited methods, along with 14 non-accredited methods, controlling a total of 61 human vaccines. The termination of in vivo testing is rationalized on the basis of various factors, including challenges in animal supply, suboptimal husbandry conditions, high assay variability, requirement for specialized skills, and logistical complexities and high costs. The laboratory participated in several collaborative studies, such as the standardization of an ELISA for human rabies vaccine potency testing (BSP148), which demonstrated the laboratory’s commitment to advancing testing methodologies.
The South African NCL is engaged in new external collaborations, including supporting SAHPRA in its role as a Regional Centre of Regulatory Excellence for vaccine regulation, designated by the African Union Development Agency (AUDA-NEPAD). The establishment of SAHPRA as a reliance NRA was done through the Partnerships for African Vaccine Manufacturing project and the African National Control Laboratory Reliance Network which involves Egypt, Ghana, Nigeria, South Africa and the United Republic of Tanzania, which is to be operationalized in 2024 and which highlights the collaborative efforts in the region. SAHPRA has also entered into memoranda of understanding with other African NRAs, such as the Egyptian Drug Authority and Nigeria’s National Agency for Food and Drug Administration and Control.

**United Kingdom of Great Britain and Northern Ireland**

**Dr Silke Schepelmann**, Deputy Director Control, Medicines and Healthcare products Regulatory Agency (MHRA)

The MHRA South Mimms laboratories (formerly known as NIBSC) function as the United Kingdom’s designated NCL to conduct independent examinations of all vaccine and blood product batches before use. This ensures consistent adherence to safety and efficacy specifications outlined in the marketing authorization. Governed by Regulations 60A and 60B of the Human Medicines Regulations 2020, certification of compliant batches is a statutory requirement for release on the United Kingdom market.

Since 2021, the United Kingdom has observed significant developments. There has been a 100% increase in the number of products for United Kingdom certification, covering a broader range of different products that represent the entire United Kingdom market. Notably, there is no mutual recognition of European Union and United Kingdom batch release certificates. Instead, the MHRA unilaterally accepts OCABR certificates from other NCLs as evidence of independent laboratory assessment. The United Kingdom follows a risk–proportionate approach in deciding when to apply its own laboratory testing, with typical assays for vaccines encompassing potency, identity, purity/integrity tests and a thorough review of the manufacturer’s data.

The MHRA’s laboratory has evolved to accommodate new products and methods, ensuring compliance with ISO17025 standards (United Kingdom Accreditation Service, EDQM Quality Management Programme). This involves implementing new types of laboratory assays, such as those required for COVID-19 mRNA vaccines, including in vitro expression assays. The laboratory builds on established assays such as ELISA, and embraces “platform” methodologies while phasing out in vivo assays. A risk-proportionate approach guides the prioritization of full MHRA laboratory assessments for “higher risk” products, taking account of United Kingdom-specific factors, new manufacturers, novel vaccine technologies and 3Rs consideration. The MHRA decides whether to perform its own laboratory testing or rely on batch testing certificates from other NCLs, such as OCABR OMCLs.

The United Kingdom is an official observer to the European Union’s OCABR network through a memorandum of understanding. The United Kingdom’s reliance on laboratory testing by another NCL, especially OCABR OMCLs, involves shared batches for products used in the United Kingdom. This includes information exchange, attendance in OCABR network meetings, membership in the General European OMCL network, and adherence to confidentiality standards. Such reliance requires real-time data exchange and access to databases, taking into account the broader public health impact of developing and maintaining in-house laboratory testing capacity.
Discussion

The discussion covered diverse aspects of vaccine testing and standardization methods. Key topics included the development of an in vitro assay for mRNA-based vaccines and the implementation of animal alternative tests in Thailand, with a central focus on ensuring consistent testing across all batches. The risk assessments to testing and lot release in Indonesia and Thailand were explored, emphasizing strategies to handle unforeseen situations and prevent market delays during vaccine distribution. The control of new adjuvants in vaccines and the management of new chemical reagents in tests emerged as significant challenges. In parallel, participants discussed information-sharing on the NRA platform, with insights into the types of shared data. Specific inquiries about an in vitro assay for a mRNA-based vaccine were addressed, emphasizing its development through research and focusing on identity testing. Insights were also shared regarding managing shortages of COVID-19 vaccines, highlighting the crucial role of NCLs in ensuring efficient and high-quality processes during times of scarcity. The broader discussions centered around the complexities of testing methods, particularly in vitro techniques and challenges associated with adjuvants in vaccines.

Updates from WHO

In this session, WHO provided updates on technologies, standards and norms related to WHO Good regulatory practices, reliance and networks, along with the latest information from WHO regional offices.

WHO Technologies, Standards and Norms

Dr Dianliang Lei

Dr Lei presented the main outcomes of the 77th and 78th meetings of the WHO Expert Committee on Biological Standardization in 2023 and showcased the recently adopted and revised WHO standards for biologicals. He also noted ongoing consideration of new standards and revisions planned for development, and new measurement standards planned for implementation from 2024 onwards. The key concepts of the WHO guidelines include:

• providing fundamental principles for evaluating biologicals as a foundation for setting national requirements;
• allowing flexibility for NRAs to formulate specific requirements based on WHO standards;
• maintaining a living document that aligns with advancements in scientific knowledge and experience;
• assisting in the implementation of WHO guidelines in regulatory and manufacturing practices; and
• considering guidance issued by other standard-setting bodies.

With regard to implementation of the 3Rs principles, WHO – through recommendations published in the WHO Technical Report Series – has encouraged regulatory authorities and manufacturers to use alternatives to animal models for lot release of vaccines in testing of potency, toxicity, pyrogen etc. Dr Lei further illustrated four examples of the WHO approach for application of the 3R principles, namely:

• removal of innocuity testing;
• polio neurovirulence testing;
• reduction and refinement of use of animals in diphtheria, tetanus and pertussis (DTP) vaccines; and
• rabies vaccines potency testing.

The next step in the process involves developing a guidance document on the application of the 3R principles in WHO recommendations and guidelines through a consultation process.
Dr Azatyan emphasized that access to essential medicines is integral to the right to health, as stated in the WHO Constitution, stressing the universal entitlement to the highest achievable standard of health. Currently, nearly half of the global population faces challenges in accessing vital medications— a predicament attributed to financial barriers, intellectual property rights, infrastructure issues, limited health-care workforce, supply chain challenges and regulatory shortcomings.

WHO recognizes the significance of strong regulatory capacity within health-care systems, yet over 70% of countries globally possess weak regulatory systems. The Organization’s programme for strengthening regulatory systems aims to address these deficiencies through benchmarking, capacity-building and promotion of smart regulation practices. The initiative advocates reliance on regulatory decisions made by trusted authorities, fostering cooperation, convergence and harmonization.

Good regulatory and reliance practices are pivotal in achieving public health objectives efficiently. WHO promotes these practices to enhance national regulatory decisions, emphasizing transparency, good governance and workforce development. The scope of reliance activities spans the entire life cycle of medical products, covering medicines, vaccines, blood products and medical devices.

Collaborative efforts, such as the WHO prequalification collaborative registration procedure and mutual recognition agreements, facilitate reliance mechanisms, reducing redundancy in testing and accelerating approval processes. Harmonization of standards, capacity-building and information-sharing further contribute to the efficiency and consistency of regulatory processes.

The call to action is to build a harmonized regulatory framework through international collaboration, emphasizing the critical role of WHO, NRAs, industry and procurers. By embracing collaboration, networking and reliance, timely access to medical products can be accelerated, regulatory convergence enhanced and global health resilience strengthened, ultimately improving the well-being of people worldwide.

Dr Anil Chawla

Dr Chawla presented insights into the global vaccine supply, revealing that 46% of vaccines are sourced from countries in the South-East Asia Region. These countries—particularly Bangladesh, India, Indonesia and Thailand—possess significant local production manufacturing capacity. WHO’s South-East Asia Regional Office has actively supported the regulatory systems of NCLs by convening virtual workshops on COVID-19 vaccines and developing standard operating procedures. The South-East Asia Regional Office further established the Regional Centre for Excellence in Bhutan, focusing on vaccine testing, method development and personnel training with comprehensive access to equipment. The Regional Office functions as the regional coordination centre for vaccine proficiency studies and information-sharing on vaccine lot release. Proposed actions by NCLs in the region include data collation for lot release analysis and sharing with WHO, identification of in-country training needs, collaboration with WHO and the World Customs Organization, collection of data on individual country strengths for WHO, and online tests for Global benchmarking tool qualification as expert assessors. Additionally, the South-East Asia Region has proposed a range of training courses and workshops for NCLs, covering hands-on training and proficiency studies, support for surrogacy and adoptions, consultations with vaccine developers and manufacturers, development of regional reference preparations, and a regional workshop for vaccine evaluators and regulatory inspectors.
WHO Western Pacific Region

Dr Jinho Shin

Dr Shin provided an overview of WHO’s Western Pacific Region, outlining mandates set by the 2017 Regional Committee. Regulatory cooperation through the Western Pacific Regional Alliance of National Regulatory Authorities for Medical Products commenced in 2011, initially focusing on vaccine regulators and later expanding to include medicine regulators. The scope is now further extending to incorporate medical devices. Dr Shin emphasized the need to give comprehensive support to regulatory systems, especially in the context of vaccine coverage (import, production and export), in order to achieve universal health coverage and the sustainable development goal for health. He presented the NRA maturity levels and WHO-listed Authority (WLA) status, shedding light on the challenges faced by regulatory systems during the COVID-19 pandemic.

Discussion among NCLs revolved around quality control methods for new technologies, including mRNA vaccines, and the significance of post-marketing release surveillance testing for vaccine quality. The value of random sampling based on quality surveys was questioned due to widely variable test results. Additionally, compliance with Good Storage and Distribution Practice was emphasized, focusing on collaborative efforts with regulatory inspectorates, vaccine-induced sero-surveillance, and pharmacovigilance for vaccine effectiveness and safety. Points raised by NCLs in developing lot release functions included involvement during marketing authorization/registration, participation in method validation/method transfer from sponsors/manufacturers for lot release testing, and collaborative studies on reference standards and proficiency testing.

WHO African Region

Mr Babatunde Jayeola

Mr Jayeola presented an overview of immunization and the current and upcoming vaccine manufacturing arrangements in Africa. He illustrated the trends in immunization coverage for priority vaccine-preventable diseases in Africa from 2012 to 2021. As the demand for vaccines increased due to population growth, the achievement of quality and sustainable local vaccine production in Africa became crucial. Consequently, there has been growth in the global vaccine market and planned manufacturing capacity in Africa. This reflects the readiness of WHO’s Regional Committee for Africa to enhance local vaccine production. However, despite initiation of the regulatory system, several challenges still exist. There is a need for closer collaboration between, and support for, regulatory harmonization efforts across the African continent to facilitate far-reaching strengthening of the regulatory capacities of Member States in order to have a direct impact on public health.

Discussion

The discussion included questions and comments concerning laboratory networks in Asia, specifically within the South-East Asia regulatory network. Participants were actively exploring the establishment of a laboratory network within this regulatory framework and fostering collaboration between NCLs in the WHO regions. The focus was on information-sharing, collaborative studies and the international dimension of these initiatives. Harmonizing methods of analysis, particularly for biologicals and vaccines, was a central concern. The conversation touched on ongoing efforts to minimize or eliminate animal testing for biologicals, highlighting disparities between the European Pharmacopoeia and the United States Pharmacopeia, where the latter still included animal testing requirements. The call for harmonization in this area was emphasized. Furthermore, participants stressed that the decision to eliminate animal testing should be grounded on scientific justification, with a need for individual evaluation for the replacement of each test. The challenges and nuances of substituting specific tests, such as the rabbit pyrogen test and endotoxin test, were thoroughly examined.
Sharing practices: perspectives on risk-based lot release

Various countries have demonstrated encouraging advances by incorporating alternative animal test methods into their testing protocols. The overarching goal for these countries is to reduce and replace the use of animals in routine testing procedures. Nevertheless, challenges persist in terms of the need for improvement in certain areas. A crucial requirement involves the establishment of guidelines to attain a common standard for risk-based lot release. Such guidelines play a pivotal role in ensuring consistency across countries and minimizing redundancy. More importantly, the development of these guidelines should consider the variations resulting from the capacity of human resources, equipment and novel technology in different countries. This approach ensures that the transition towards animal-free testing is not only comprehensive but is also tailored to the specific capabilities of each country.

The adenosine triphosphate (ATP) assay was presented as a quicker approach than the viable counts assay, therefore shortening the timeline for testing of Bacillus Calmette Guérin (BCG) vaccines during lot release.

Thailand

Mrs Sukanlayanee Chaimee, Institute of Biological Products

Establishing potency and stability release specifications: alternative ATP assay of Tokyo 172-1 BCG vaccine

The establishment of potency and stability release specifications for the Tokyo 172-1 BCG vaccines in Thailand has involved the adoption of an alternative ATP assay, in accordance with the requirements outlined in the WHO Technical Report Series No. 979 (2013). It is noteworthy that there is an international reference standard for the intracellular ATP assay. The timeline of the intracellular ATP assay implementation showed that the ATP method was in development in 2016, followed by method validation in 2017, including a comparative analysis of test results with the standard method. In 2018, the ATP assay was presented at the second NCL network conference in Italy, marking a significant step towards broader recognition. Subsequently, in 2019, the ATP assay was successfully incorporated into the quality control processes of the BCG vaccine for lot release, demonstrating its practical application and integration into routine testing procedures. Further advancements in 2020 involved WHO training in the establishment of an ATP assay, followed by the development of proficiency testing services in 2021. By 2023, the ATP assay achieved certification under ISO/IEC 17025 standards. The focus of the effort was on establishing specifications, particularly with regard to the relationship between dose and response from both ATP and colony-forming unit (CFU) methods, aiding in the determination of potency and stability release.

The study found that the potency for the minimum limit release specification at $2 \times 10^6$ CFU/mL was equivalent to an ATP content of 25 ng ATP/mL. Stability release specifications hinged on the consistency testing of the ATP assay, with an expected survival rate of 40%. Long-term monitoring of 43 batches revealed a significantly positive correlation, indicating that the intracellular ATP assay served as a viable alternative to the traditional method. In summary, the long-term assessment has confirmed the efficacy of the ATP assay, positioning it as a suitable alternative to traditional methods since the beginning of 2017 for which the results are now published, demonstrating consistency and correlation with the traditional method.
Canada

Dr Chad Irwin, Senior Scientific Evaluator, Vaccine Quality Division 2, Centre for Vaccines, Clinical Trials and Biostatistics, Biologic and Radiopharmaceutical Drugs Directorate (BRDD), Health Products and Food Branch, Health Canada

Health Canada’s lot release programme, administered by the BRDD, plays a pivotal role in ensuring the quality and safety of vaccines. As both the NRA and the NCL for biologicals, including vaccines, the BRDD follows a risk-based approach that is aligned with WHO guidelines. The programme spans the product lifecycle, encompassing pre-approval clinical trials and post-approval phases with distinct evaluation groups. Deriving its authority from Section C.04.015 of the Canadian Food and Drug Regulations, the current system, adopted in 2005, aligns with the WHO Technical Report Series No. 978 for independent lot release of vaccines by NRAs. The BRDD utilizes a risk-based approach for lot release evaluation, considering factors such as the nature of the product, the targeted population, the lot release history, and the manufacturer’s production and testing history. Periodic reassessment allows for adjustments in the level of product oversight in response to manufacturing changes or safety profile alterations.

Health Canada employs a risk-based approach not only in its lot release evaluation but also in its testing procedures that are performed by the BRDD. The ISO 17025: 2017-accredited laboratories conduct value-added tests, evaluating key attributes (e.g. potency, impurities) for products that are considered riskier. Strategies to optimize testing include periodic testing, standardized assays for similar products, and reliance on foreign NCL testing data. Health Canada’s commitment to the 3R principles is evident in its history of adopting alternative testing methods, such as ELISAs for DTP and inactivated polio vaccines, leading to the cessation of animal testing during routine lot release testing as of 2022. Recent updates from 2022 highlighted the implementation of new methods, collaborative studies and WHO testing for various vaccines. These initiatives have demonstrated Health Canada’s ongoing commitment to staying at the forefront of vaccine quality assurance and embracing advancements in testing methodologies. However, the BRDD is in a trial period for evaluating less oversight of clinical material depending on the experience of the manufacturer and nature of the product.

Senegal

Dr Djibril Fall, Director of Quality Control, Agence sénégalaise de Réglementation pharmaceutique/ Senegalese Pharmaceutical Regulatory Agency, Ministry of Health and Social Action, Dakar

The Senegalese Pharmaceutical Regulatory Agency adheres to the WHO lot release approach to ensure the quality and safety of pharmaceutical products, particularly vaccines, prior to distribution or administration. The lot release guidelines encompass a summary protocol review, a combination of summary protocol review and laboratory testing, and reliance on the batch release certificates of imported vaccines from countries with NRAs at maturity level three (ML 3) or equivalent. Additionally, vaccines produced in Senegal undergo a summary protocol review and laboratory testing, with a maximum regulatory process timeline of four months for locally produced vaccines and a swift 10 working days for imported ones.

The outcomes of this approach include the release of all vaccines, a reduction in the timeline for lot release requests, strengthened communication with stakeholders, publication of released lots on the agency’s website, staff training initiatives, and laboratory renovation projects. However, the agency faces several constraints, such as equipment shortages, troubleshooting issues, reagent shortages, and a lack of training in some new technologies. The challenges ahead include the lot release of other biological products, reaching ML 3, participating in interlaboratory proficiency studies and obtaining
ISO 17025 accreditation. In conclusion, the importance of competent and qualified human resources within the agency was emphasized, highlighting the need for collaboration with other NRAs to address challenges effectively.

Republic of Korea

Dr In Yeong Hwang, Senior Scientific Officer, National Institute of Food & Drug Safety (NIFDS), Ministry of Food and Drug Safety, Republic of Korea

The national lot release system of the Republic of Korea was presented, providing details on the interaction process and organizational framework. The ministry utilizes an electronic system by which manufacturers and importers apply for the national release of drugs, and then a government officer’s visit for sampling, testing and reviewing. The data highlight the scope of the national release list, featuring various vaccines and items, with a notable emphasis on domestic vaccines which constitute 63.9% of the market share. The regulatory process entails rigorous testing, review, and the issuance of certificates based on predetermined criteria. The risk assessment score determines the annual guides for decision-making and incorporating factors such as product history, safety issues and manufacturing sophistication. The international reliance of Korea’s national lot release system is also emphasized, focusing on collaboration and recognition through global assessments. Overall, the lot release system of the Republic of Korea strives for efficiency, quality management and international alignment to ensure the safety and efficacy of pharmaceutical products in the market.

Discussion

The discussion encompassed widespread concerns regarding redundancy in lot release procedures, prompting a collective call for a unified approach to mitigate duplication. The imperative need for risk-based strategies in regulatory processes and acknowledgment of challenges arising from limited resources emphasized the need for support to review and update guidelines. A prevailing aspiration for a standardized and consensus-driven regulatory framework was also evident, reflecting ongoing efforts to streamline evaluation procedures by focusing on risk factors. The forthcoming actions that were outlined included the revision of guidelines, particularly for reliance and lot release processes, ongoing development of ELISA for DTP and specific antigen-detecting antibodies, the publication of ongoing work on the ATP assay for BCG vaccine in Thailand, and consultations coupled with revision to scoring tables in the Republic of Korea to refine risk evaluation methodologies.

Sharing best practices: 3R

During the session, members of WHO-NNB and partners offered insights into alternatives for animal testing in vaccine development while sharing best practices centred on the principles of 3Rs.

The discussion highlighted concerted global efforts in implementing 3R principles, featuring noteworthy practices from countries such as Belgium, India, Thailand and the United States of America. Presentations delved into various aspects, including the challenges and successes of changing animal species and incorporating 3Rs in vaccine lot release procedures. The overarching theme emphasized collaboration between nations and the pursuit of global regulatory alignment to enhance the ethical and efficient development of vaccines.
Belgium: Sciensano

Dr Geneviève Waeterloos

EDQM is a pioneering force in championing the principles of 3Rs within its Biological Standardization Programme (BSP). At the forefront of innovation, this programme places a robust emphasis on validating progressive pharmacopoeial methods and establishing reference preparations to elevate the standards of quality control. Committed to exploring alternative 3R methods, EDQM has initiated 125 BSP projects, with 21 projects dedicated explicitly to finding alternatives to animal testing, especially in the realm of human vaccines. One notable achievement is Belgium’s transition from a multi-dilution assay to a one-dilution assay, resulting in an 80% reduction in animal use. The proactive implementation of this approach has already yielded significant success in reducing the number of animals in testing, exemplifying the tangible outcomes of EDQM’s commitment to advancing alternative methodologies within the field of biological standardization.

Simultaneously, the adoption of alternative methods is exemplified by Sciensano’s incorporation of the single dilution assay and diphtheria, tetanus and acellular pertussis vaccine serology, along with the utilization of recombinant factor C assay (rFC). The Vac2Vac European project aligns with these efforts, emphasizing advancements in vaccine testing methods. However, the OMCL faces specific challenges in validating multiplex operations to achieve the 3R concept. Future perspectives include improvements in diphtheria and tetanus serology through single dilution assays, reduction schemes and a transition towards diphtheria, tetanus and acellular pertussis vaccine serology. The validation of in vitro multiplex assays is highlighted for being animal-free, time-efficient and cost-effective, enabling the comprehensive assessment of multiple antigens in a single run with lower variability compared to in vivo methods.

India: Central Drugs Laboratory, Kasauli

Mr Sumir Rai Bhalla

Implementation of 3Rs in lot release of vaccines

Because they are of biological origin, vaccines undergo rigorous batch-to-batch testing that often involves animals in quality control procedures before market release. Animal testing has raised ethical concerns due to its impact on a large number of animals. However, the implementation of the 3R principles has provided a pathway for the reduction and replacement of animals, along with the refinement of testing procedures for vaccines. In India, the Central Drugs Laboratory has successfully embraced the 3R approach, collaborating with regulatory authorities and the Indian Pharmacopoeia Commission to grant permissions for non-animal-based assays in vaccine manufacturing. This positive outlook is reflected in the Central Drugs Laboratory’s active participation in global initiatives, such as the DCVMN’s pertussis serological potency test study, WHO’s NC3R project, and collaboration with Human Society International, demonstrating a commitment to refining testing methods and gradually replacing animal testing in the development of human vaccines.

Within the Central Drugs Laboratory, specific actions have been taken to implement the 3Rs approach in vaccine testing. For instance, the replacement of guinea pigs with mice in lethal challenge methods for DTP vaccines showcases a reduction in animal use. Furthermore, the Central Drugs Laboratory’s approval for manufacturers to replace in vivo assays with in vitro assays in hepatitis B and inactivated polio vaccines demonstrates the commitment to refining testing procedures. The Central Drugs Laboratory’s involvement in studies and projects, such as the DCVMN’s pertussis serological potency test study and the WHO-NC3R project, further underscores its dedication to implementation of the 3Rs in vaccine testing.
The Center for Biologics Evaluation and Research (CBER) of the United States Food and Drug Administration (USFDA) does not perform animal testing for lot release. Around 1998, CBER discontinued the use of animals for routine confirmatory lot release as it was determined to be no longer necessary to ensure the safety, purity and potency of licensed biological products. This decision was reinforced in 2015, when the USFDA removed the general safety test requirements for biological products, stating that this regulation was duplicative of requirements that are also specified in biologics licences and are no longer necessary to ensure the safety, purity and potency of the licensed product. Removal of the general safety test regulations from the United States Code of Federal Regulations did not remove the general safety test requirements specified in a manufacturer’s approved biologics licence applications. Manufacturers are required to submit a supplement to their licence application for the USFDA to consider the removal of the general safety test from their licensed manufacturing process. The USFDA reviews such requests on a product-by-product basis and has approved exemptions for several products. Assurance provided by historical test results, post-marketing surveillance and improvements in controlled Good Manufacturing Practice are some of the factors assessed to support the removal of a general safety test from a prior approved licensed application.

CBER maintains animal safety protocols that can be activated if concerns arise regarding a released product or to support a licence application. These protocols are approved by the Institutional Animal Care and Use Committee and must comply with United States federal guidelines for animal use, including documentation on efforts to adhere to the principles of 3Rs. CBER last performed certain animal tests, including the general safety test, in 2007, the rabies animal safety test in 2006, and the rabbit pyrogen test in 2001 — all requested by USFDA product offices for licensing support. Some animal safety protocols remain active and are utilized for calibrating CBER biological standards (e.g. for tetanus antitoxin) that are essential for quantifying product potency during manufacturing and regulatory release.

In the pursuit of implementing the 3Rs, in 2010 a transition from guinea pigs to mice was made for the United States standard tetanus antitoxin, demonstrating a commitment to refining testing methodologies. Despite this shift, the animal safety protocol of the guinea pig is still maintained, following the policy of using the same test method for product confirmatory testing as used during licensed approval, thus ensuring consistency for potential future needs. Additionally, driven by considerations of workload, safety and changes in standard preparation requirements, CBER has inactivated animal test protocols, including the rabies animal safety protocol and the tuberculin skin test. However, challenges persist in implementing alternative methods, encompassing time-consuming validation processes, the need for in vivo assay comparisons, differences in biological processes between in vivo and in vitro methods, the potential high costs associated with alternative assays, and the sophistication of read-outs that necessitate expensive commercial kits and specialized equipment.
Substitution of animal testing in vaccines batch release testing; ongoing projects and future opportunities

The Research and toxicology programme of Humane Society International represents a multidisciplinary team of experts in regulatory science, biomedicine, government and corporate relations, advocacy and science communications. Through the Animal Free Safety Assessment Collaboration, Humane Society International collaborates with various stakeholders – including industry, regulators, lawmakers, researchers and funding bodies – aiming to bring about enduring change. The challenge at hand involves the extensive reliance on animal testing for legacy vaccines, with an estimated 14 million animals per year globally used for quality control. The Research and toxicology team is actively engaged in shifting from traditional animal testing to novel methodologies, especially for batch release testing of human vaccines. The goal is to accelerate the implementation and regulatory acceptance of non-animal approaches such as in vitro potency tests for diphtheria, tetanus, pertussis, rabies, and hepatitis A and B, and to remove or replace obsolete safety tests, with a specific focus on developing countries. The approach includes creating stakeholders and country-specific implementation plans involving Brazil, China, India, Indonesia and the Republic of Korea. The International Steering Committee plays a crucial role in strategizing both locally and globally, and fostering multi-stakeholder workshops, joint position statements, webinars and the development of implementation plans. The ultimate aim is to present these plans collaboratively in a dedicated international event by the end of 2025, emphasizing a unified voice through joint position statements and widespread awareness of novel methods through webinars in 2024. The webinars will be dedicated to introducing the theoretical principles for the substitution of in vivo methods with in vitro methods, the status of the implementation of alternative methods for DTP and the implementation of the monocyte activation test and rFC. The comprehensive strategy of Humane Society International encompasses scientific and technical expertise, a commitment to understanding local, regional and global complexities in replacing animal testing in human vaccine and finding solutions via dialogue and collaboration with multiple stakeholders.

Review of animal testing requirements in WHO Guidelines and recommendations for biologicals: implementing 3R principles

This project, led by the NC3Rs in the United Kingdom and co-funded by the Bill & Melinda Gates Foundation, undertook a thorough examination of animal testing requirements outlined in the WHO guidance documents for biologicals and vaccines, with a primary focus on integrating the 3Rs principles. Objectives encompassed assessment of the extent of animal testing, identification of alternative methods, evaluation of the potential utility of a WHO guideline for incorporating the 3Rs in vaccine quality control and lot release and understanding the barriers to 3Rs adoption. The review process involved scrutinizing 81 guidelines, with 63 falling within the project’s scope. An expert working group consisting of global regulators and manufacturers was established to support the review. Rigorous evaluation by at least three working group members identified 352 animal tests linked to batch/lot release testing. Each of these was documented in a comprehensive Excel database that not only offers a systematic overview but also serves as a platform for the biologicals community to contribute insights, informing recommendations and implementation by WHO. Focus groups were established to develop scientifically evidenced alternative text that incorporated the latest technologies and 3Rs opportunities to replace each current instance where animal testing is described. The database, including the recommended alternative text, has been recreated as a fully searchable online resource that can be freely accessed.
The initiative’s forward-looking approach includes regional workshops and surveys to engage the biologicals community, fostering collaboration and feedback that would help inform the final recommendations to WHO. This collaborative effort aims to surmount barriers to 3Rs adoption, contributing to the harmonization of non-animal methods and the promotion of ethical practices in vaccine quality control and lot release. The project culminated in a final report presented to the WHO Expert Committee on Biological Standardization in October 2023, providing a narrative report justifying the recommended alternative text, a table of current animal tests and proposed alternative language incorporating the 3Rs, a proposal for standalone guidance on pyrogenicity/endotoxin testing, a proposal for WHO to develop a general 3Rs statement/guidance, and recommendations for the Expert Committee on Biological Standardization. Ongoing efforts include further reviews of the database, continued support for recommendations, engagement with WHO on implementation, and collaboration with the NC3Rs in the anticipated second phase. Overall, this project marks a commendable stride towards aligning global guidelines with contemporary principles in animal welfare and scientific advancement.

Discussion

The discussion underscored the significant reduction in animal usage achieved through alternative test methods and a single dilution assay, while also acknowledging the necessity of periodic multiple assays to ensure consistency in compliance with specifications. To expedite the adoption of innovative methods during the review process, a general guideline which focused on fostering a collaborative community approach was developed. Participants explored the relevance of potency testing for stability and emphasized the need to have precise assays and alternative methods in order to achieve more accurate results. The information exchange highlighted a collective commitment to refining testing methodologies, reducing reliance on animal testing, and exploring alternatives for a more efficient and standardized evaluation of pharmaceutical products.

Partner forum

The partners of WHO-NNB from vaccine manufacturers’ associations and the United States Pharmacopeia provided updates on lot release and reliance from the perspectives of industry and regulatory capacity-strengthening.

Developing Countries Vaccine Manufacturers’ Network

Dr Sunil Goel

The implementation of a risk-based approach in lot release and reliance practices is crucial for the efficient evaluation of, and access to, vaccines as well as biological medical products. The NCLs play a pivotal role in employing risk analysis with three modes of lot release: 1) review of the summary lot protocol only; 2) partial testing of samples; and 3) full testing of samples. Considerations for the evaluation group include product nature, Good Manufacturing Practice inspection history, testing history and safety information. For consistently high-quality products, reliance on reviewing summary lot protocols leads to reduced time and costs. Expedited lot release is granted under exceptional circumstances, such as product shortages or public health emergencies. Regulatory harmonization and standardization would further strengthen risk-based lot release. DCVMN International plays a crucial role in supporting and implementing reliance mechanisms, emphasizing factors validating the reliance process. Good reliance practices contribute to timeline reduction and effective resource utilization. There is a necessity to promote regional/global networking based on the commonality of regulatory policies and strategies which can be used for other regulatory functions such as inspection, lot release or import-testing. Challenges include the globalization of the vaccine industry, limited regulatory resources, redundant testing and non-compliance. It was also proposed to consider entering into
mutual recognition agreements that aim to facilitate market access and encourage greater international harmonization of compliance standards while protecting consumer safety. These agreements can benefit regulatory authorities by reducing duplication of inspections on each other’s territory, allowing for greater focus on sites that could have a higher risk and broadening the inspection coverage of the global supply chain. The conclusion underscores the network’s role in accelerating access to quality vaccines and positioning regulatory reliance as the 21st-century best practice applicable to both well-resourced and less-resourced regulatory agencies. It promotes smarter regulation through collaboration, convergence and adherence to common international standards.

International Federation of Pharmaceutical Manufacturers & Associations

Dr Philippe Juvin, on behalf of the batch release expert group of the IFPMA

The evolution of testing for batch release of imported products reflects a historical need to address quality issues that were not initially identified during release, to reconfirm release testing, to identify transportation issues and to counteract counterfeit or substandard products. Over time, additional regulations and procedures – including Good Manufacturing Practice requirements, ICH Q9 and Q10, and adherence to Good Distribution Practice during shipping – have been enforced. Technological advancements and market surveillance tools contribute to manufacturing robustness and product characterization. Despite these improvements, challenges persist in analytical transfer and maintenance, high-volume reagent requirements and redundant testing, leading to difficulties in predicting batch release timelines. In response, reliance solutions have emerged, such as the unilateral recognition of reference NCL testing certificates, the reliance on the WHO Network, and the European Union’s batch release system. These approaches aim to streamline processes, avoid redundant testing and ensure the safety, quality and efficacy of imported vaccines. The strengthened regulatory environment and application of reliance principles not only guarantee product quality, but also avoid wastage of resources and delays in patients’ access. In conclusion, the reliance approach applied to batch release emphasizes risk-based decision-making, reduces redundant testing and prioritizes timely access of patients to quality vaccines.

Paul Ehrlich Institute

Dr Heidi Meyer

Regulatory capacity-building in the field of vaccines: training and scientific advice on official lot release

The Global Health Protection Programme, initiated by the Federal Ministry of Health in Germany, focuses on international cooperation to support the prevention and management of health crises worldwide. In Phase II, around 40 projects are funded, including those at the Paul Ehrlich Institute aimed at establishing and strengthening regulatory and research processes and structures for vaccines, medicinal products and blood products. The programme, from 2016 to 2022, involved workshops and collaboration with sub-Saharan African countries. The emphasis was on mutual reliance and trust, with activities such as country visits, assessments and various training sessions, including virtual and on-site training at the Institute and collaboration with other development agencies. The Global Health Protection Programme VaccRelease also supports the development of official lot release processes in vaccine-producing countries, including by WHO benchmarking, drafting of institutional development plans, and training on vaccine-specific summary lot protocols and test procedures. The programme emphasizes country ownership, while ensuring compliance with international standards and providing tailored support based on individual country needs. Ongoing activities include virtual and hands-on training, study tours and collaboration with partner countries and institutions to strengthen regulatory capacity in the field of vaccines.
United States Pharmacopeia

Dr Zlatka Kostova Lenard, United States Pharmacopeia (USP), Chemistry, Manufacturing, and Controls (CMC) and Vaccine Director, Promoting the Quality of Medicines Plus (PQM+) Program

Overview of laboratory systems strengthening in Africa and Asia

The United States Pharmacopeia is an international scientific non-profit organization that is committed to improving global health by establishing public standards and related programmes that ensure the quality, safety and efficacy of medical products, including vaccines and foods. The vision of the United States Pharmacopeia is to create a world in which everyone can have equitable access to high-quality medical products and that is free from substandard and falsified medicines. With a global team of approximately 1300 staff, the organization allocates more than half of its workforce to developing physical and documentary standards and associated activities to deliver its mission. About 10% of the workforce of the United States Pharmacopeia is in the Global Health and Manufacturing Services division which is dedicated to improving the health and well-being of populations around the world. Within the Global Health and Manufacturing Services division, the flagship programme on Promoting the Quality of Medicines Plus (PQM+) – a six-year (2019–2025) technical assistance programme funded by the United States Agency for International Development – reflects the shared vision of that agency and the United States Pharmacopeia to strengthen sustainably medical product quality assurance systems in low- and middle-income countries, thus contributing to the global goal of enhancing access to and ensuring the quality of medical products in resource-constrained settings.

With a total history of 31 years with its predecessor programmes, the objectives of PQM+ are to enhance governance for medical product quality assurance systems, improve regulatory systems at both country and regional levels, optimize financial resources, increase the supply of quality-assured essential medical products, and advance global learning and operational agendas in medical product quality assurance.

Over the past 23 years, PQM+ and its predecessor programmes have provided technical assistance to laboratories that support public health systems in 36 countries, focusing on applying international standards and best practices to enhance the capacity of laboratories involved in testing medicines, vaccines, medical devices and clinical specimens at national and regional levels, as well as private and university laboratories with public health objectives. The programme’s laboratory systems strengthening activities have historically focused on the testing of medicines; however, with the COVID-19 pandemic, the scope has expanded to include vaccines and/or biological products. PQM+ has provided technical assistance to national control laboratories in Bangladesh, Burkina Faso, Ethiopia, Ghana, Kazakhstan, Kenya, Nigeria, Senegal, Pakistan and South Africa particularly to strengthen vaccine testing capacity to facilitate lot release and/or the respective regulatory agencies’ pursuit of WHO Global benchmarking tool maturity level 3. PQM+ tailors its technical assistance to each country’s legislative framework, aiming to improve or establish quality systems both to capacitate laboratories and align them with international standards, including those set by WHO. Emphasizing sustainability and institutional strengthening, PQM+ approaches capacity-building through the lens of local ownership and engagement, prioritizing knowledge-sharing and collaboration, conducting joint training sessions and activities across laboratories and countries to foster relationships and promote sustainable practices. Long-term funding support for the laboratories is guided by strategic plans and interventions are designed to allow for flexibility to adapt to changing needs.
Actively participating in regional and continental efforts, PQM+ developed a framework in support of the creation of the African National Control Laboratory Reliance Network. Aligned with the African Union’s vision for 60% local vaccine production by 2040, this initiative is in partnership with the AU-NEPAD AMRH initiative. PQM+ collaborates closely with the African CDC, AMRH technical committees and WHO, with a commitment to complementarity and effective resource utilization. PQM+ remains open to collaboration with countries and partners, and acknowledges the importance of leveraging limited resources for maximum impact.

Discussion

The discussion touched on several crucial points in the context of vaccine testing and regulatory processes. The participants emphasized the need for transparency in testing regimens, and particularly the friction surrounding reliance on laboratories. The willingness of manufacturers to share data with non-WHO entities, especially for forecasting, raised considerations about confidentiality in government contracts. The importance of engaging with WHO and establishing connections was highlighted for navigating issues such as animal testing. The “Global Vax” programme of the United States Pharmacopeia, which focuses on supporting vaccine production in six African countries, was noted as an initiative for aligning with regulatory bodies and manufacturers for sustainable progress. However, the challenges of building reliance systems in Africa were acknowledged, emphasizing the importance of trust and citing the European model of mutual reliance. Moreover, the consensus leaned towards encouraging reliance mechanisms until countries can develop sufficient internal capacity. The important role of the WHO prequalification programme and WHO-NNB on promoting reliance and capacity-building initiatives was emphasized. The importance of a global network, trust-building and considerations for redundant testing in the case of multiple vaccine shipments were also discussed, highlighting the complexities and collaborative efforts necessary for a robust and efficient global vaccine regulatory framework.

Quality monitoring updates

This last session on quality monitoring updates of EDQM and the United States Pharmacopeia provided information about biological standardization programme studies and quality standards used to support vaccine manufacturing.

European Directorate for the Quality of Medicines & Healthcare

Dr. Catherine Milne, EDQM Head of Section, Biological Standardization, ISA and OCABR

Update on EDQM biological standardization programme studies: current and foreseen projects

The European Directorate for the Quality of Medicines & HealthCare (EDQM) is a Directorate of the Council of Europe. The Council of Europe (COE) was founded in 1949 and represents 46 Member States with a commitment to promote human rights, democracy and the rule of law. The EDQM was founded in 1964 and works within the framework of a Partial Agreement for the European Pharmacopoeia Convention which comprises 39 members and the European Union (EU) and contributes to public health and access to good-quality medicines and health care. The Biological Standardization Programme (BSP) was initiated by the EDQM in 1991 and has been jointly funded by the Council of Europe and the European Commission since 1994. The main objectives of the programme are to establish reference standards and methods for biologicals for human and veterinary use in the context of the European Pharmacopoeia. A key objective is the implementation of 3R methods, as is the interaction with
partners around the world to ensure a global perspective and maintain interconnectedness within the global community.

The presentation highlighted ongoing projects and looked to the future. A significant ongoing project within the BSP is the collaborative study for the standardization of an ELISA for human rabies vaccine potency testing. This project, BSP148, is aimed at replacing the vaccination challenge assay for rabies potency (National Institutes of Health test), which is animal-intensive, harsh and highly variable. The proposed alternative is an ELISA based on two well-characterized neutralizing monoclonal antibodies. These antibodies recognize the trimeric glycoprotein that induces protection, discriminate subpotent vaccine lots and also recognize most virus strains used for human rabies vaccines. Both monoclonal antibodies are available globally from two different providers. The method format and key antibodies were selected in a project run previously by the European Partnership for Alternative Approaches to Animal Testing. The collaborative study of BSP148 (Phase 2) involved 30 participants from around the world with 25 reporting results in time for evaluation. Results confirmed the applicability of the ELISA to the different vaccine strains. The study evaluated two different statistical models and showed good agreement of potency estimates between participants with satisfactory precision, repeatability and reproducibility. The results support the conclusion that this could be a viable replacement for standardized potency testing. A reporting phase (phase 3) was to be launched at the end of 2023 and will run for 1 year. The goal is to test different product batches to gather data on routine quality control testing. This phase aims both to support discussions about specifications and validity criteria and to support the ELISA’s inclusion in the European Pharmacopoeia. Also highlighted was the project BSP136, a collaborative study for the standardization of an in vitro test for absence of tetanus toxin in tetanus vaccines (human and veterinary). The assay, developed at the Paul Ehrlich Institute is referred to as BINACLE (for BinDing And Cleavage). It is a fully in vitro assay which mimics the two most important steps of the mechanism of action of the toxin. The final stage of the study has been completed with promising results with respect to detection limits and precision. At the time of the meeting the report was under review by the BSP Steering Committee for adoption. The final study report will be published in 2024 and a webinar to promote implementation is foreseen in the latter half of 2024.

The ongoing progress in standardizing in vitro tests highlights the BSP’s commitment to advancing efficient and humane testing methodologies for human vaccines. 3R projects anticipated in the future will look at possibilities for full in vitro tests for diphtheria, tetanus and acellular pertussis vaccines, following on from the successful conclusion of the VAC2VAC project. Once all the data from VAC2VAC are publicly available through publications, plans for the studies will begin – including consultation with stakeholders and with a focus on added value in terms of collaboration to complement the product-specific validation efforts required by the manufacturers for the different vaccines.

The BSP plays a crucial role in contributing to standards through the validation of methods, particularly those related to the 3Rs. The establishment of various reference preparations – including biological reference preparations, chemical reference substances and biological reference reagents – is a significant element of the programme’s contribution. Upcoming studies, such as for replacement of the biological reference preparations for diphtheria toxin, replacement of the biological reference preparations for diphtheria vaccines (adsorbed) and a study to develop non-endotoxin pyrogen biological reference reagents for use in the monocyte activation test were noted. BSP studies include participation of NCLs/OMCLs and manufacturers from Europe and beyond. The programme is presented on the EDQM website and qualified laboratories interested in participating can contact EDQM. The reference substances each have a defined purpose which may be for calibration, system suitability or as reagents depending on the context. The broad scope of application underscores the programme’s impact in supporting method validation and, on a broader scale, contributing to the standardization of biological medicines (which consequently contributes to public health). This reiterates the importance
of the BSP in advancing and maintaining high standards in the field of biological standardization. In addition to the work in the BSP, other contributions of EDQM to biological standardization were briefly highlighted, such as the work of the European Pharmacopoeia in development of texts for mRNA vaccines, development of a general chapter on high-throughput sequencing/next-generation sequencing and viral-vector-based vaccines, as well as the longstanding activity of the European Union Official Control Authority Batch Release network for which EDQM acts as the secretariat.

United States Pharmacopeia

Dr Dipankar Das

United States Pharmacopeia quality standards to support vaccine manufacturing

Facilitating the worldwide distribution of high-quality vaccines is part of the United States Pharmacopeia’s () mission and legacy of setting public standards for over two centuries. As a scientific nonprofit body, the USP focuses on instilling confidence in the supply of safe, quality medicines, with the goal of creating a world that trusts and has access to medicines that can save lives. Through global collaboration with partners, the USP develops standards and tools that enable proper vaccine storage, transportation and administration. To support the development, manufacturing and global distribution of vaccines, the USP consistently expands and provides standards and tools to support quality vaccines. This involves creating standards, publications and guidance for potential vaccines and treatments, establishing partnerships for global vaccine access, and enhancing partners’ analytical and regulatory capabilities. Collaboration with stakeholders is a crucial element, utilizing innovative approaches to gather feedback and leveraging global outreach to maximize impacts. In response to the challenges posed by the COVID-19 pandemic, the USP played a pivotal role in ensuring the availability of quality vaccines through initiatives such as the COVID-19 vaccine handling toolkits, COVID-19 quality attribute toolkits, and draft guidelines on analytical procedures for mRNA and viral vectored vaccine quality. The draft guidelines help to build consensus on quality attributes for new vaccine platforms such as mRNA and viral vectors and provide detailed test methods that can be used as starting points for vaccine testing and quality control.

Looking forward, the USP continues to update the draft guidelines and test methods based on public comments. The organization plans to evaluate analytical procedures in the vaccine guidelines, identify and develop the standards and controls required to support these methods, and develop or expand training tools to support global access to quality vaccines. These proactive measures underscore the commitment of the United States Pharmacopeia to continuous collaboration, evaluation and education, reinforcing its role in upholding the highest standards in vaccine manufacturing for the betterment of global public health.

Discussion

The discussion covered inquiries about mRNA vaccine procedures, particularly regarding preparations for future pandemics in low- and middle-income countries. Focus was placed on the use of bioburden instead of specific tests in the context of mRNA vaccines, with ongoing discussions and developments in endotoxin testing. The experts from the European Pharmacopoeia mentioned the monographing of viral vector vaccines developed during the COVID-19 pandemic and ongoing work on next-generation vaccines. Additionally, there was a question about planning for a worldwide collaborative study for BSP136 (BINACLE), to which the response indicated that the results would be published at the end of the study period and that potential future workshops or webinars will be provided rather than having another collaborative study phase. The content of the discussion reflected a comprehensive overview of current developments and inquiries in vaccine testing and development.
Practical approach to dealing with out-of-specification (OOS) testing results

The session began by noting the unavoidable nature of out-of-specification (OOS) testing results and the importance of dealing with them, highlighting that laboratories should be prepared to deal with this issue.

Belgium: Sciensano

Dr Geneviève Waeterloos

The regulatory context is outlined in the lot release guideline in Annex 2 of *WHO Technical Report Series, No. 978* (2013) regarding the evaluation of NCL results, and Annex 6 of *WHO Technical Report Series, No. 978* (2013) on prequalification procedures for vaccines. NCL test results should comply with the defined acceptance criteria and approved specifications, as detailed in the marketing authorization dossier. Additionally, standard operating procedures (SOPs) should clearly define the retest policy, the evaluation process for the results, and procedures for addressing noncompliant results. Key indicators under the WHO Global benchmarking tool (GBT) for laboratory testing related to OOS testing were presented. In cases of invalid assay results, the “5M” investigation rule, which involves the assessment of manpower, method, machine, material and environmental factors is employed before drawing any conclusions. Assessing biological products and biological assays has posed some challenges. Belgian retest policy specifies a maximum of one repeat of valid assay for in vivo assays and a maximum of two repeats for in vitro assays. Upon obtaining valid assay results, the average is compared against the specifications before initiating 5M investigations. If the average remains OOS, an additional test may precede the 5M investigation. Thorough documentation of the investigation process is essential. Batches with OOS results can be either released under scientifically justifiable deviation, subject to approval by the head of service, or labelled noncompliant after completion of the nonconformity form. The decision-making process determining compliance of the tested batch involves the detection of trends, internal and manufacturer investigations, communication and exchange of data between the NCL and manufacturer and visit on site or test by a second NCL depending on the case.

One example of OOS results occurred during the mumps potency assay of the mumps combined vaccine. The batch underwent three assays for which the average failed to meet specifications. No root cause for the OOS was identified upon internal investigations, analysis of quality control and production data, and testing by another NCL. The batch was ultimately released on the basis of the results of the other NCL results.

Another example involved the percentage of adsorption of HBsAg in a combined vaccine, where six final batches showed OOS results. The 5M investigation and communication with the manufacturer were done to assess the potential root cause. The NCL test revealed positive correlation between the manufacturer and the NCL release results, showing two bulks to be out of trend. Manufacturer investigations confirmed the NCL results and the atypical adsorption profile of HBsAg affecting batch stability. Although no common root cause was formally identified, the manufacturer decided to discard the lots concerned, withdrew the batch release request, and started monitoring the adsorption level of the final lots to ensure stabilization.

The final example pertained to the diphtheria potency assay in a combined vaccine. Both the single dilution and multi-dilution assays confirmed OOS results, leading to subsequent 5M investigations. While the validity criteria were met in both assays, the results were atypical when compared to other batches. A different laboratory conducted a retest and declared the batch to be compliant with the specifications. In view of this, the batch was released under deviation of the procedure.
In summary, biological products are complex and biological assays should be validated despite the challenges involved. The quality assurance system requires internal investigation, routine testing, historical data, production consistency data and trend analysis. From the manufacturer’s perspective, effective communication, information exchange, real consistency data, batch record review and ongoing investigation are of paramount importance. Comprehensive consideration of all elements should be done before reaching a decision on compliance in order to ensure that only vaccines of assured quality are released. Moreover, fostering technical collaboration between NCLs proves to be useful during the investigation and retesting processes.

Brazil: National Institute for Quality Control in Health/FIOCRUZ

Dr Antonio Eugenio de Almeida, Director of the National Institute for Quality Control in Health

The Brazilian standard operating procedures (SOPs) that were presented for retesting and managing nonconforming biological product samples included definitions of a valid assay, unsatisfactory results and nonconforming samples. Valid assays encompass any control test(s), confirming compliance with the established criteria. Unsatisfactory results are valid quantitative and qualitative test results which do not meet the criteria for acceptance of the product. Nonconforming samples are samples that presents unsatisfactory results in a valid test.

The responsibilities of various entities in the laboratory involved with handling OOS products were outlined. Laboratory professionals are responsible for conducting tests in adherence to specific procedures to ensure the reliability of results. If a procedure is not specified in the Brazilian Pharmacopoeia, international compendiums serve as the guideline. Heads of sectors, laboratories and departments hold accountable roles in managing analysis, execution and issuing partial reports. The coordinator of the Technical Center for Biological Products is tasked with issuing final reports and certificates. The coordinator collaborates with the Board of Directors to convene critical analysis meetings on OOS cases of biological products. Moreover, apart from convening these critical analysis meetings, the directors are responsible for institutionally enabling the actions outlined during these sessions, as appropriate.

At the National Institute for Quality Control in Health (INCQS), the retest policy for invalid assays mandates a repeated test after assessing potential causes of deviations, with a requirement for confirming result validity. Valid assays yielding unsatisfactory results for biological product samples undergo retesting by the responsible sector, adhering to the retest policy of each specific procedure. The process involves a critical analysis of the results, evaluation by the INCQS, and potential referrals to manufacturers or other institutions. Critical analysis serves to identify the causes and establish corrective measures in order to prevent future cases of nonconformities. The analysis is recorded as part of the sample process, detailing the actions, proposals and other alignments. The Technical Centre for Biological Products maintains an annual record of nonconforming samples.

The main categories of vaccines analysed during 2021–2023 were COVID-19 vaccines, yellow fever vaccine, trivalent influenza vaccine, attenuated G1P(8) human rotavirus vaccine and other vaccines.
France: National Agency for Medicines and Health Products Safety
Dr Cano François

The dedicated standard operating procedures within the quality management system are necessary for effective management of OOS test results. France’s National Agency for Medicines and Health Products Safety (ANSM) currently relies on EDQM documents as the basis for its OOS processes, referring to specific guidelines tailored to different types of tests (e.g. quantitative, qualitative, in vivo).

In France, the initial approach to address an OOS result does not involve an immediate retest. Instead, it entails conducting the crucial “5M” investigation (Ishikawa diagram), in which the machine (equipment), medium (environment), method (process), material (raw materials) and manpower are assessed. Having a special form or checklist in the quality management system is also helpful. If the investigation uncovers an issue during the test, it will lead to test invalidation. Conversely, if no issues are identified, a retest plan will be initiated.

For quantitative in vitro assays, if an issue is detected from the 5M investigation, the result would be deemed invalid. However, if no issues are identified, a second test will be conducted by a different technician. The combination of results from the first and second tests then determines whether the final result is compliant or noncompliant. If the outcome is noncompliant, a third test will be conducted to establish the OOS status conclusively, potentially leading to the rejection of the batch.

In the case of a retest for an in vivo assay, following the initial OOS result, an adapted retest plan could be applied. With regard to this, an emphasis has been placed on how tests involving animals should be designed in a way that can minimize the use and the suffering of the tested animals. Further tolerances are subsequently applied to the specification limit for potency and specifics of the retest programme which will vary according to the type of product and assay.

If the retest yields a noncompliant outcome, the NCL will proceed to inform top management, seek confirmation of the results from another NCL, and arrange a meeting with the manufacturer to exchange data in order to ensure the accuracy of OOS findings. Subsequently, a noncompliance certificate will be issued.

In cases where vaccines have two approved sets of specifications – i.e. release specifications and shelf-life (stability) specifications – there is a question about which set the NCL should adhere to. In Europe, the release specification is often used due to the common practice of releasing vaccines through the parallel test system (where the batch testing date is very close to the manufacturing date). However, there have been instances where this method resulted in noncompliant outcomes. Alternatively, the shelf-life specification can be applied under specific circumstances – as when parallel testing is not in place, the batch is tested some time after the release testing by the manufacturer, and the batch is still within the end of shelf-life specification and still complies with the marketing authorization. Nonetheless, if there are unexpected observations or values out of trend, it is crucial to conduct further assessment of supporting data. This information can be obtained from the marketing authorization – thus underlining the importance of having access to the marketing authorization.

To conclude, the complexity of managing cases of OOS is significant. Robust, dedicated standard operating procedures, a good knowledge of the product and interaction with manufacturers are crucial elements in approaching OOS cases. Additionally, the significance of WHO-NNB as a valuable resource in managing OOS situations has been underscored. The speaker concluded by stating that when network members face problems they can reach out to a colleague.
The National Institute of Food and Drug Safety (NIFDS) has established “Regulations on decision of testing and inspection results” which differ in application for biological products, food and medical devices, yet share similar processes for qualitative and quantitative tests. Retesting conditions for biological products fall under two categories. The first category includes cases when abnormal symptoms or deaths occur in the tested animals, when sudden environmental or ecological factors potentially affect the animal, and when abnormalities in reagents, equipment or operations suggest abnormal test results. For this category, a satisfactory first retest would deem the batch valid.

If the first retest is unsatisfactory, up to three retests are conducted with at least two satisfactory results required for the product or device to be deemed compliant. The second category applies to situations in which the test results are unsatisfactory, or the reliability of the test results is insufficient, making final judgement difficult so that reconfirmation is necessary. In such cases, three tests are conducted with at least two satisfactory results required to be deemed compliant. Data from the last three years have shown abnormalities in reagents, equipment and operations to be the leading causes of retesting.

The NIFDS internal guideline generally follows the WHO Technical Report Series guidelines, mandating an investigation to determine the root cause before retesting. The procedure lists four investigations: 1) the accuracy of adhering to testing protocols outlined in the standard operating procedures; 2) the usage of reagents and reference standards; 3) the use and calibration of the equipment; and 4) the system suitability of testing.

An example of a case of OOS, in which the product did not meet either the potency assay or the identification test, was presented. The issue was reported to the company, necessitating an extension of the processing deadline. Subsequent investigation pinpointed an anomaly in the CO2 incubator that was the root cause of the issue. Following the equipment repair, a retest was performed and the results were considered acceptable.

In cases where the retests ultimately lead to a noncompliance result with fewer than two tests having satisfactory results, the notice for rejection as well as the fail report will be issued to the relevant division and the company.

In summary, NIFDS implements proactive measures to prevent OOS results. The measures include regular equipment qualification, meticulous management and upkeep of Biological Safety Level 3 and sterility rooms, thorough inspection of animal conditions prior to testing, and an annual trend analysis of national lot release testing for all products. These measures are crucial for improving reliability and reducing the likelihood of errors during testing.

Discussion

With regard to the differences in testing methods employed by institutes and manufacturers in the case of OOS, method validation was emphasized. The institution’s utilization of a validated method was found to be important as it provided a strong basis for defending results during discussions with manufacturers. Recognizing that the laboratory’s method might differ from the manufacturer’s method, assay variability would be considered first when addressing minor OOS cases. It was added that the laboratory’s test method could be used as a screening process, while still using the manufacturer’s method for the actual test for OOS.
Earlier in the meeting, a query arose regarding whether two different lot releases or assays were necessary if one batch was dispatched in two separate shipments. It was suggested that this scenario mirrored the standard situation applicable to each distribution and wholesaler. Another viewpoint expressed was that a separate test should be mandated only if there were reasonable doubts about the shipping conditions.

In terms of the policy for sterility tests, it was highlighted that such tests were generally not conducted by many national control laboratories. Ensuring of sterility relies primarily on the production process. The immediate compromise of a sample’s sterility upon opening for testing was also emphasized, making it challenging to determine whether contamination originated from the product or the testing process. In this regard, an endotoxin test was discussed as a helpful indirect test for sterility.

**Network SharePoint**

**Update on SharePoint**

*Ms Alaa Magdy*

The on-site poll indicated that most respondents had not used the SharePoint site in the past month. This finding aligned with website statistics, revealing that only 23% of users engaged with the site during this period, amounting to over 900 visits averaging approximately 7 minutes per visit. In terms of the most visited page, most participants reported having visited the full and associate members’ websites. Analysis of the recent month’s data highlighted that 66% of overall site visits originated from full members, with Austria exhibiting the highest percentage. Meanwhile, associate members accounted for 34% of visits, with Comoros emerging as the top country in this category. It is worth noting that the traffic may have been driven by specific members updating their own information.

The new SharePoint design, which would be launched after the meeting, was shown to be more aligned with the needs of members and providing better ease of access than the older version.

Regarding security and permission levels, participants were assured that permission levels were different for each site. All members were granted access to the main site to view new announcements and download documents from it. Conversely, exclusive editing rights for respective country sites were granted solely to the country focal points, while other countries retain only viewing privileges.

It was indicated that members can keep themselves updated with all new changes and can obtain a notification from the site by setting alerts on items of interest.

Further clarifications indicated that multiple members from the same institute can gain access to the site upon completion of a confidentiality agreement and submission of the required information. A record of persons with site access is being maintained. In the event of a staff change within an institute, it is essential to report this change promptly to ensure the deactivation of access for the departing staff member.

**Discussion about results of survey on SharePoint**

*Ms Alexandrine Maes*

It was reported that 35% of members participated in the survey on the WHO-NBB SharePoint with a balanced participation between full members and associate members. Participants were reminded about how information-sharing was crucial for gaining trust, which would lead to reliance. The survey
indicated that 61% of the respondents were able to find relevant information easily, underscoring the platform’s effectiveness in accessibility.

Members expressed their interest in seeing a diverse range of information and features on the main site. One suggestion was to incorporate details about the reagents utilized in specific analytical methods. Notably, some of the suggested information – such as the Annual Quality Reports, quality control test data for biological products, and information on 3Rs implementation for alternative methods – had already been accessible on either the main site or the country-specific pages. Additionally, there were recommendations emphasizing the importance of timely updates and notifications.

The survey showed that most respondents found the purpose of the SharePoint understandable and clear, and the features on the site were helpful, informative, useful, well-structured and easy to navigate. However, only 50% found “Full member” country site to be useful and up to date, raising a significant point for further discussion. Respondents expressed interest in having certain information – such as the roster of newly approved vaccines and lot releases, necessary specifications for biological tests, updates on the laboratory’s accreditation/attestation status, and advancements in new vaccine methodologies if any are under development – featured on the “Full member” sites. In response, it was underscored that a critical issue for improvement was regular updating by members. It was also crucial to acknowledge that sharing specifications and lot release data might be restricted in many cases where permission to share was required from the manufacturer.

Similarly, only 50% of respondents found “Associate member” country sites to be useful and informative. Respondents expressed interest in seeing more information on “Associate member” sites such as the list of newly approved vaccines and lot releases, results of quality control tests, updates on accreditation/attestation status of the laboratory, and new vaccine methods being developed. There was a highlighted emphasis on the importance of the lot release procedure and how it was developed. Additionally, it was suggested that updating information regarding in-house tests and each country’s expertise could prove beneficial for neighbouring countries.

For the COVID-19 main site, there was interest in seeing more information on dossier review results from the NRA of each country, as well as molecular tests and regulatory updates. The majority of respondents found information on the Janssen manufacturer site to be useful – particularly the COVID-19 page of the site that included information on lot summary protocols and batch release certificates. This was considered a good example of information-sharing between the NRA and manufacturers. Other information that respondents wished to see from the manufacturer included amendment information, methodologies for analysis and information from further manufacturers.

The survey results also showed a balanced response between those in favour of and those against having a publicly accessible SharePoint. Notably, the majority of those advocating for restricted access were identified as full members. Respondents supported increased accessibility but highlighted some specific information that should be kept confidential. This confidential information encompassed details such as the grounds for vaccine registration rejection, lot release rationale, specific lot release data, editable documents, outcomes of quality control tests, the testing activity of the NCL, and manufacturers’ quality report test results pertaining to vaccines.

With regard to the type of information that could prompt visits to the SharePoint, WHO was urged to consider supplementing the platform with published research in the field. Additionally, the inclusion of maturity level reported on each country’s website was suggested. However, it was pointed out that such information could be obtained from members’ publicly available information and thus might not be prioritized. Another suggestion was that it would be worthwhile for potential members to know about the network’s current members and to have an idea of what kind of information is being shared.
In general, most of the suggestions on making the SharePoint more effective addressed the need for more information to be shared, as well as routine updates. Consequently, members were reminded of their responsibility to upload and update their information and were encouraged to share their information.

**Break-out session**

In this session, participants were divided into five groups for discussion of two questions, namely:

1) How can we better use reliance between members?
2) What is needed for the sustainability of the network/impact of the WHO-NNB?

**How to better use reliance between members**

Each group reported the results of its discussion separately to the full meeting. It was evident that several common themes had emerged during the discussions. In essence, the suggestions put forward during the discussions revolved around key concepts such as transparency, information-sharing, collaboration, capacity enhancement and the establishment of standardized guidelines.

The meeting highlighted the fundamental role of “trust-building” as a basis for reliance within the network. To foster trust, transparency within the network was emphasized, and it was noted that this would be achievable through the sharing of data and experiences. Collaborative activities through various means such as meetings, memoranda of understanding and joint studies were proposed as effective strategies to cultivate mutual understanding and trust, while simultaneously enhancing members’ capacities. Exchange visits for training and technology transfer were also suggested. Furthermore, comprehending the strategies of other countries could facilitate collaboration and provide guidance for seeking assistance when needed. Lastly, the development of standardized guidelines was deemed to be crucial for aligning members’ efforts and promoting more efficient collaboration.

**What is needed for the sustainability of the network/impact of the WHO-NNB?**

As with the previous query, there were shared consensus points in all discussion groups concerning the requisites for the network’s sustainability. Broadly, communication and member commitment emerged as the pivotal factors. Notably, there was a unanimous call across all groups for regular meetings, held either virtually or in person. Additionally, recommendations were made for network focal points or steering committees dedicated to various subjects, alongside the establishment of regional networks.

Effective communication among members was also highlighted as being instrumental in facilitating information-sharing, enabling mutual support through the exchange of best practices and fostering peer reviews.

**Conclusions and Recommendations**

The outcomes as specified in the meeting terms of reference were as follows: participated to the fifth general meeting of the Network; established contacts among meeting participants and became acquainted with new Network members; shared insight on regulation, vaccine access, release and control applied by newly participating members; gave overview of applied strategies of vaccine quality control by newly participating NCLs; provided update on progress and activities of the Network and insight to participating donors; provided a forum for topics raised by manufacturer associations; agreed to content and features of the Network SharePoint; discussed measures for promoting and enhancing
reliance among the members of the Network and sustainable Network performance; shared best practices; drafted meeting report (i.e., a record of discussions and agreed upon decisions).

Recommendations from the 5th General Meeting of the WHO NCL Network on Biologicals related to:

Structure and organization of annual meeting:

- Maintain annual face to face meeting to advance work on promoting reliance and recognition, strengthen relations and facilitate enhanced collaboration and harmonization
- Provide for remote participation
- Network members should assist in the organization and chairing of annual meetings

Agenda of the annual meeting:

- Agenda to be based on topics of greatest interest to members and the objectives of the Network
- Keep NCL updates of new members
- Limit NCL updates of established members to issues related to the objectives of the Network (e.g., discuss 3R, risk-based approach, standardization and harmonization of test methods, testing related issues)
- Discuss the practical approaches to dealing with OOS testing results
- Provide project updates and technical discussions on quality monitoring
- Discuss the added value of the network, as expected by the participants, for sharing of best practices and promoting reliance and best practices through access to information on national control laboratories, lot release practices, quality assurance policies, annual quality reports and detailed lot release data

Other recommendations that were raised:

- Plan and organize technical training and side meetings
- NCLs in developing lot release functions to be involved in marketing authorization and registration, participation in method validation and method transfer from sponsors and/or manufacturers for lot release testing, and collaborative studies on reference standards and proficiency testing
- Consider suggestions from break-out sessions as recommendations for updates of the technical information on the share point and sustainability of the Network, engage with memoranda of understanding and joint studies among the members of the Network
- The importance of attracting more members to the Network
- Encouraging more manufacturers of prequalified vaccines to share data
- Discuss and propose amendments to the existing WHO guideline on lot release with more emphasis on the risk-based approach

The meeting closed with thanks expressed to the Network’s Thailand hosts, to the donors who made the meeting possible and to the participants for their constructive contributions to the sustainability of the Network and to their colleagues around the world.
<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adekunle-Segun, Olawale</td>
<td>Laboratory Services Directorate, National Agency for Food and Drug Administration and Control (NAFDAC)</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Affonso Boller, Maria Aparecida</td>
<td>National Institute of Quality Control in Health, Oswaldo Cruz Foundation (FIOCRUZ)</td>
<td>Brazil</td>
</tr>
<tr>
<td>Ahamada, Said Fazul</td>
<td>Agence Nationale des Médicaments et des Evacuations sanitaires (ANAMEV)</td>
<td>Comoros</td>
</tr>
<tr>
<td>Al Abudahash, Mubark</td>
<td>Saudi Food and Drug Authority (SFDA)</td>
<td>Saudi Arabia</td>
</tr>
<tr>
<td>Al Lawati, Nabila</td>
<td>Central Quality Control Laboratory Directorate General of Pharmaceutical Affairs and Drug Control (DGPA&amp;DC)</td>
<td>Oman</td>
</tr>
<tr>
<td>AlMusharraf, Abrar</td>
<td>Saudi Food and Drug Authority (SFDA)</td>
<td>Saudi Arabia</td>
</tr>
<tr>
<td>Amen, Assajun</td>
<td>Institute of Biological Products (IBP)</td>
<td>Thailand</td>
</tr>
<tr>
<td>Ansari, Mahvash</td>
<td>Drug Regulatory Authority of Pakistan (DRAP)</td>
<td>Pakistan</td>
</tr>
<tr>
<td>Arpan, Susan</td>
<td>National Quality Control Laboratory of Drug and Food (NQCLDF)</td>
<td>Indonesia</td>
</tr>
<tr>
<td>Balderrama, Jocelyn E.</td>
<td>Food and Drug Administration (FDA)</td>
<td>Philippines</td>
</tr>
<tr>
<td>Bhalla, Sumir Rai</td>
<td>Central Drugs Laboratory (CDL), Kasauli</td>
<td>India</td>
</tr>
<tr>
<td>Bruysters, Martijn</td>
<td>Centre for Health Protection, Department for Biologicals, Screening and Innovation Dutch National Institute for Public Health and the Environment (RIVM)</td>
<td>Netherlands (Kingdom of the)</td>
</tr>
<tr>
<td>Caforio, Maria Pia</td>
<td>Istituto Superiore di Sanità (ISS)</td>
<td>Italy</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
<td>Country</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Campitelli, Laura</td>
<td>Istituto Superiore di Sanità (ISS)</td>
<td>Italy</td>
</tr>
<tr>
<td>Cano, François</td>
<td>L'Agence nationale de sécurité du médicament et des produits de santé (ANSM)</td>
<td>France</td>
</tr>
<tr>
<td>Chaimee, Sukanlayane</td>
<td>Institute of Biological Products (IBP)</td>
<td>Thailand</td>
</tr>
<tr>
<td>Chilinde, Bonaventure</td>
<td>Zambia Medicines Regulatory Authority (ZMRA)</td>
<td>Zambia</td>
</tr>
<tr>
<td>Choi, Hyeonhye</td>
<td>National Institute of Food and Drug Safety Evaluation (NIFDS)</td>
<td>Korea, Republic of</td>
</tr>
<tr>
<td>Chow, Ai Lee</td>
<td>Health Sciences Authority (HSA)</td>
<td>Singapore</td>
</tr>
<tr>
<td>Das, Dipankar</td>
<td>United States Pharmacopeia (USP) India (P) Limited</td>
<td>India</td>
</tr>
<tr>
<td>de Almeida, Antonio Eugenio</td>
<td>National Institute of Quality Control in Health, Oswaldo Cruz Foundation (FIOCRUZ)</td>
<td>Brazil</td>
</tr>
<tr>
<td>Di Carlo, Beatrice</td>
<td>Istituto Superiore di Sanità (ISS)</td>
<td>Italy</td>
</tr>
<tr>
<td>Didukh, Iryna</td>
<td>Central Laboratory for Quality Control of Medicines and Medical Products</td>
<td>Ukraine</td>
</tr>
<tr>
<td>Dybwad, Anne</td>
<td>Norwegian Medicines Agency (NOMA)</td>
<td>Norway</td>
</tr>
<tr>
<td>Essam, Tamer</td>
<td>Egyptian Drug Authority (EDA)</td>
<td>Egypt</td>
</tr>
<tr>
<td>Fall, Djibril</td>
<td>Agence sénégalaise de Réglementation pharmaceutique (ARP)</td>
<td>Senegal</td>
</tr>
<tr>
<td>Figueras Ferradas, Liana</td>
<td>Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos (CECMED)</td>
<td>Cuba</td>
</tr>
<tr>
<td>Gebrehiwot, Awot</td>
<td>Ethiopian Food and Drug Authority (EFDA)</td>
<td>Ethiopia</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
<td>Country</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Gilgen, Michael</td>
<td>Swiss Agency for Therapeutic Products (Swissmedic)</td>
<td>Switzerland</td>
</tr>
<tr>
<td>Goel, Sunil</td>
<td>Serum Institute of India Pvt Ltd</td>
<td>India</td>
</tr>
<tr>
<td>Guzmán, Imelda</td>
<td>National Control Laboratory of Mexico Commission for Analytical Control and Expansion of Coverage</td>
<td>Mexico</td>
</tr>
<tr>
<td>Hamza, Reham</td>
<td>Egyptian Drug Authority (EDA)</td>
<td>Egypt</td>
</tr>
<tr>
<td>Herian, Monir</td>
<td>Food and Drug Control Reference Laboratories (FDCRL)</td>
<td>Iran (Islamic Republic of)</td>
</tr>
<tr>
<td>Holmes, Anthony</td>
<td>National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs)</td>
<td>United Kingdom of Great Britain and Northern Ireland</td>
</tr>
<tr>
<td>Hwang, InYeong</td>
<td>National Institute of Food and Drug Safety Evaluation (NIFDS)</td>
<td>Korea, Republic of</td>
</tr>
<tr>
<td>Irwin, Chad</td>
<td>Centre for Vaccines, Clinical Trials and Biostatistics (CVCTB), Health Canada</td>
<td>Canada</td>
</tr>
<tr>
<td>Ishii, Koji</td>
<td>National Institute of Infectious Diseases (NIID)</td>
<td>Japan</td>
</tr>
<tr>
<td>Iwaki, Masaaki</td>
<td>National Institute of Infectious Diseases (NIID)</td>
<td>Japan</td>
</tr>
<tr>
<td>Jarstadmarken, Hilde</td>
<td>Norwegian Medicines Agency (NOMA)</td>
<td>Norway</td>
</tr>
<tr>
<td>Juvin, Philippe</td>
<td>International Federation of Pharmaceutical Manufacturers &amp; Associations (IFPMA)</td>
<td>France</td>
</tr>
<tr>
<td>Kanyenvu, Diketso</td>
<td>Botswana Medicines Regulatory Authority (BOMRA)</td>
<td>Botswana</td>
</tr>
<tr>
<td>Keita, Djoran</td>
<td>Laboratoire National de Contrôle de Qualité des Médicaments (LNCQM)</td>
<td>Guinea</td>
</tr>
<tr>
<td>Kenney, James</td>
<td>United States Food and Drug Administration (USFDA)</td>
<td>United States of America</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
<td>Country</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Kostova Lenard, Zlatka</td>
<td>United States Pharmacopeia (USP)-Promoting the Quality of Medicines Plus (PQM+)</td>
<td>United States of America</td>
</tr>
<tr>
<td>Kullabutr, Kornnika</td>
<td>Institute of Biological Products (IBP)</td>
<td>Thailand</td>
</tr>
<tr>
<td>Kunarak, Jidaporn</td>
<td>Institute of Biological Products (IBP)</td>
<td>Thailand</td>
</tr>
<tr>
<td>Low, Min Yong</td>
<td>Health Sciences Authority (HSA)</td>
<td>Singapore</td>
</tr>
<tr>
<td>Luu, Dung</td>
<td>National Institute for Control of Vaccine and Biologicals (NICVB)</td>
<td>Viet Nam</td>
</tr>
<tr>
<td>Manatunga Arachchige Don, Vidyani</td>
<td>Therapeutics Goods Administration (TGA)</td>
<td>Australia</td>
</tr>
<tr>
<td>Mangorangca, Caren</td>
<td>Food and Drug Administration (FDA)</td>
<td>Philippines</td>
</tr>
<tr>
<td>Mbongo, Lavinia</td>
<td>Namibia Medicines Regulatory Council (NMRC)</td>
<td>Namibia</td>
</tr>
<tr>
<td>Meier, Silvio</td>
<td>Swiss Agency for Therapeutic Products (Swissmedic)</td>
<td>Switzerland</td>
</tr>
<tr>
<td>Meyer, Heidi</td>
<td>Paul-Ehrlich-Institut (PEI)</td>
<td>Germany</td>
</tr>
<tr>
<td>Meyer, Quinton</td>
<td>South African National Control Laboratory for Biological Products (SANCLBP)</td>
<td>South Africa</td>
</tr>
<tr>
<td>Milne, Catherine</td>
<td>European Directorate for the Quality of Medicines &amp; Healthcare (EDQM)</td>
<td>France</td>
</tr>
<tr>
<td>Mlynarczyk, Peter</td>
<td>VE/ International Federation of Pharmaceutical Manufacturers &amp; Associations (IFPMA) - MSD</td>
<td>United States of America</td>
</tr>
<tr>
<td>Mohd Suror, Azua</td>
<td>Quality Division National Public Health Laboratory</td>
<td>Malaysia</td>
</tr>
<tr>
<td>Moreno Exebio, Luis Enrique</td>
<td>Centro Nacional de Control de Calidad Instituto Nacional de Salud (CNCC)</td>
<td>Peru</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
<td>Country</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Mtenga, Adelard</td>
<td>Tanzania Medicine and Medical Devices Authority (TMDA)</td>
<td>Tanzania, United Republic of</td>
</tr>
<tr>
<td>Muganga, Raymond</td>
<td>Rwanda Food and Drug Authority (FDA)</td>
<td>Rwanda</td>
</tr>
<tr>
<td>Naluyima, Amoreen</td>
<td>National Drug Authority (NDA)</td>
<td>Uganda</td>
</tr>
<tr>
<td>Ng, Kok Peng</td>
<td>Health Sciences Authority (HSA)</td>
<td>Singapore</td>
</tr>
<tr>
<td>Nguyen Thi, Kieu</td>
<td>National Institute for Control of Vaccine and Biologicals (NICVB)</td>
<td>Viet Nam</td>
</tr>
<tr>
<td>Nhukarume, Linda</td>
<td>Medicines Control Authority of Zimbabwe (MCAZ)</td>
<td>Zimbabwe</td>
</tr>
<tr>
<td>Nie, Jianhui</td>
<td>National Institutes for Food and Drug Control (NIFDC)</td>
<td>China</td>
</tr>
<tr>
<td>Òppling, Volker Alfons</td>
<td>Paul-Ehrlich-Institut (PEI)</td>
<td>Germany</td>
</tr>
<tr>
<td>Quedraogo, Soutongo Sita Sandrine</td>
<td>Agence Nationale de Régulation Pharmaceutique (ANRP)</td>
<td>Burkina Faso</td>
</tr>
<tr>
<td>Owusu-Danso, Patrick</td>
<td>Food and Drugs Authority (FDA)</td>
<td>Ghana</td>
</tr>
<tr>
<td>Pakzad, Saeed-Reza</td>
<td>Food and Drug Control Reference Laboratory (FDCRL)</td>
<td>Iran (Islamic Republic of)</td>
</tr>
<tr>
<td>Pezzella, Cristina</td>
<td>Istituto Superiore di Sanità (ISS)</td>
<td>Italy</td>
</tr>
<tr>
<td>Phumaimorn, Supaporn</td>
<td>Institute of Biological Products (IBP)</td>
<td>Thailand</td>
</tr>
<tr>
<td>Phuwanartnarunubarn, Kanitta</td>
<td>Institute of Biological Products (IBP)</td>
<td>Thailand</td>
</tr>
<tr>
<td>Pomsuwan, Saowalak</td>
<td>Institute of Biological Products (IBP)</td>
<td>Thailand</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
<td>Country</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Ramondrana, Dio</td>
<td>National Quality Control Laboratory of Drug and Food (NQCLDF)</td>
<td>Indonesia</td>
</tr>
<tr>
<td>Safoora, Fathimath</td>
<td>Maldives Food and Drug Authority (MFDA)</td>
<td>Maldives</td>
</tr>
<tr>
<td>Salvati, Valentina</td>
<td>Istituto Superiore di Sanità (ISS)</td>
<td>Italy</td>
</tr>
<tr>
<td>Sanarico, Nunzia</td>
<td>Istituto Superiore di Sanità (ISS)</td>
<td>Italy</td>
</tr>
<tr>
<td>Sanou, Gisèle</td>
<td>Agence Nationale Régulation Pharmaceutique (ANRP)</td>
<td>Burkina Faso</td>
</tr>
<tr>
<td>Sasaki, Yuko</td>
<td>National Institute of Infectious Diseases (NIID)</td>
<td>Japan</td>
</tr>
<tr>
<td>Sawadogo, Ruth</td>
<td>Agence Nationale de Régulation Pharmaceutique (ANRP)</td>
<td>Burkina Faso</td>
</tr>
<tr>
<td>Schepelmann, Silke</td>
<td>Medicines and Healthcare Products Regulatory Agency (MHPPRA)</td>
<td>United Kingdom of Great Britain and Northern Ireland</td>
</tr>
<tr>
<td>Schindl, Heidemarie</td>
<td>Austrian Medicines and Medical Devices Agency, Official Medicines Control Laboratory (OMCL)</td>
<td>Austria</td>
</tr>
<tr>
<td>Shamimuzzaman, MD</td>
<td>National Drug Control Laboratory, Directorate General of Drug Administration (DGDA)</td>
<td>Bangladesh</td>
</tr>
<tr>
<td>Shukurov, Chingiz</td>
<td>Analytical Expertise Center, Ministry of Health</td>
<td>Azerbaijan</td>
</tr>
<tr>
<td>Smirnov, Gennadiy</td>
<td>Russian Federation</td>
<td>Russian Federation</td>
</tr>
<tr>
<td>Sondach, Nongyao</td>
<td>Institute of Biological Products (IBP)</td>
<td>Thailand</td>
</tr>
<tr>
<td>Somov, Dmitry</td>
<td>FSBI IMCEOASMP of Federal Service for Supervision in the field of Healthcare</td>
<td>Russian Federation</td>
</tr>
<tr>
<td>Ssenyange, Comfort</td>
<td>National Drug Authority (NDA)</td>
<td>Uganda</td>
</tr>
<tr>
<td>Name</td>
<td>Institution</td>
<td>Country</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Stoyanova, Pavlinka</td>
<td>Bulgarian Drug Agency (BDA)</td>
<td>Bulgaria</td>
</tr>
<tr>
<td>Tan, Shiau Yi</td>
<td>National Pharmaceutical Regulatory Division (NPRA)</td>
<td>Malaysia</td>
</tr>
<tr>
<td>Tebib, Imen</td>
<td>Laboratoire National de Contrôle des Médicaments (LNCM)</td>
<td>Tunisia</td>
</tr>
<tr>
<td>Tenzin, Jigme</td>
<td>Bhutan Food and Drug Authority (BFDA)</td>
<td>Bhutan</td>
</tr>
<tr>
<td>Tettey, Rebecca</td>
<td>Food and Drugs Authority (FDA)</td>
<td>Ghana</td>
</tr>
<tr>
<td>Tibbatuge, Madushika</td>
<td>Medical Research Institute</td>
<td>Sri Lanka</td>
</tr>
<tr>
<td>Tran, Tram</td>
<td>National Institute for Control of Vaccine and Biological (NICVB)</td>
<td>Viet Nam</td>
</tr>
<tr>
<td>Trisiriwanich, Sakalin</td>
<td>Institute of Biological Products (IBP)</td>
<td>Thailand</td>
</tr>
<tr>
<td>Ul Abidin, Zain</td>
<td>Drug Regulatory Authority of Pakistan (DRAP)</td>
<td>Pakistan</td>
</tr>
<tr>
<td>Van Ooij, Mark</td>
<td>Vaccine Europe/ International Federation of Pharmaceutical Manufacturers &amp; Associations (IFPMA) working for Janssen vaccine</td>
<td>Netherlands (Kingdom of the)</td>
</tr>
<tr>
<td>Vesterinen, Jaana</td>
<td>Finnish Medicines Agency (FIMEA)</td>
<td>Finland</td>
</tr>
<tr>
<td>Virtuoso, Sara</td>
<td>Istituto Superiore di Sanità (ISS)</td>
<td>Italy</td>
</tr>
<tr>
<td>Viviani, Laura</td>
<td>SciEthiQ</td>
<td>Switzerland</td>
</tr>
<tr>
<td>Vumbunu, Ruvimbo</td>
<td>Medicines Control Authority of Zimbabwe (MCAZ)</td>
<td>Zimbabwe</td>
</tr>
</tbody>
</table>
The WHO Declaration of Interest (DOI) and the Agreement of Confidentiality (CA) forms were signed by all relevant participants, and no conflict of interest was detected.