Distribution: General

English only

Meeting Report

WHO informal consultation on revision of the WHO guidelines on regulatory preparedness for provision of marketing authorization (MA) of human pandemic influenza vaccines in non-vaccine producing countries (TRS NO. 1004, ANNEX 7) Revision to Annex 7 of Technical Report Series, No 1004

April 17-19, 2023

Istanbul, Turkey

Executive Summary

During the two and a half-day meeting (April 17-19th, 2023), representatives from various WHO member states, philanthropic organizations, and WHO teams/affiliations met in Istanbul, Turkey, to revise the draft guidance in consideration of the feedback received from the first public consultation. In addition to addressing the feedback, meeting participants heard from representatives of various member state National Regulatory Authorities (NRAs) with experiences related to the importation of vaccines during the recent SARS-CoV2 pandemic. Representatives were requested to comment on the regulatory status of the country prior to and during the pandemic with respect to their regulatory preparedness for the importation and authorization of vaccines, challenges encountered or lessons learned, and their future expectations of the WHO related to pandemic preparedness. Representatives' input and experiences were discussed and considered throughout the meeting and incorporated into the revision of the draft guidance.

By the end of the meeting, all sections of the draft guidance had been thoroughly discussed by meeting participants. Consensus was achieved on the content that was to be revised/incorporated into each of the sections and how the guidance should be restructured to improve clarity and readability. Next steps for the draft guidance were communicated and dates tentatively set for the preparation of the revised draft (May 19th, 2023), receipt of comments on the revised draft from meeting participants (June 2nd, 2023), finalized guidance by the drafting group (June 16th, 2023), and submission of the guidance to the Expert Committee on Biological Standardization (July 1st, 2023).

Throughout the meeting, participants shared their experiences during the pandemic, commenting on their best practices, lessons learned, and noting the barriers/difficulties they encountered. Many participants highlighted the important role of WHO in terms of being the "connection hub" to facilitate access to the relevant quality, safety and efficacy data and assessment reports to allow in-country decision. However, concerns were raised about the timely access to these reports used for authorization or post-approval changes, and the fact that there were limitations in accessing the unredacted assessment reports (including WHO PQ and EUL reports) from reference NRAs. It was understood that various NRAs have legal restrictions in providing these reports, however, it was acknowledged that improved transparency would significantly reduce the resource burden for all stakeholders and would facilitate faster authorizations in the future.

Introduction

Pandemics and large-scale disease outbreaks caused by newly emerging or known pathogens affecting many people may result in severe disease burden and can claim millions of lives globally. Pandemic influenza and coronaviruses are significantly different from seasonally circulating viruses for which some immunity against the viruses is observed in the population.

They may evolve from subtypes that previously only circulated in animals or from subtypes currently circulating in humans (examples are the SARS-CoV-2 and 2009 H1N1 influenza (swine flu) pandemics). In addition, large-scale outbreaks such as the Ebola, Zika and the cholera outbreaks revealed an urgent need for medical countermeasures, including vaccines, to limit the spread of these diseases.

One of the highest priorities in global health security and public health is to identify strategies that shorten the time between the emergence of a human pandemic virus, or occurrence of severe disease outbreaks, and the availability of safe and effective vaccines.

History of the development of the regulatory preparedness guidelines

The WHO Guidelines on regulatory preparedness for human pandemic influenza vaccines (*1*) were first adopted by the WHO Expert Committee on Biological Standardization in 2007. Consultations with stakeholders following the 2009 H1N1 influenza pandemic identified the lack of regulatory preparedness as one of the factors that delayed or prevented the deployment of pandemic influenza vaccine in importing countries. This was especially the case for vaccines destined for donation or deployed by United Nations agencies in response to the pandemic emergency (*2–4*). Therefore, guidelines were developed for non-vaccine producing countries on the identification of appropriate regulatory approaches to the marketing authorization of pandemic influenza vaccines, and on the arrangements for the lot release of these vaccines in public health emergency conditions. These Guidelines were developed in the context of the Pandemic Influenza Preparedness (PIP) Framework's Partnership Contribution Implementation Plan 2013–2016 for regulatory capacity-building and strengthening of pandemic preparedness and response (*5*). Consultations with stakeholders following the Ebola epidemic and COVID-19 pandemic identified the need for the review of the guidelines to expand the scope to cover all vaccines used in pandemics and public health emergencies and draw from the lessons learned during these recent emergencies. In addition, several guidance documents such as the WHO guidelines on *'Good regulatory practices in the regulation of medical products'* (6), '*Good reliance practices in the regulation of medical products: high-level principles and considerations'* (7), *'Import procedures for medical products'* (8) *and Guidance on Development and Implementation of a National Deployment and Vaccination Plan (9)* have since been published or updated and the principles have been incorporated into this revision of the guideline.

<u>Day 1, April 17, 2023</u>

Session I: Opening of the meeting

The meeting was opened by Dr. Alireza Khadem (WHO, Team Lead, MHP/RPQ/REG/RSS) who gave a brief history on how the guidance document has evolved from an influenza pandemic preparedness guidance to a more general pandemic preparedness guidance. Following the

introduction, it was confirmed that none of the meeting participants had any declared conflicts of interest, and a brief roundtable introduction of all participants was performed.

Session II: Objectives and expected outcomes of the meeting

Following introductions, Dr. Dianliang Lei (WHO, Scientist, Health Products Policy and Standards Department) detailed the meeting objectives and expected outcomes. The stated objectives included 1) hearing about the experiences from countries that imported COVID-19 vaccines during the recent pandemic, 2) reviewing of the guidance and discussion of comments received from the first public consultation, and 3) discussing any pending issues raised by participants during the consultation meeting.

Session III: Introduction to the draft WHO guideline V3

Subsequently, Dr. Razieh Ostad Ali Dehaghi (WHO, Scientist, MHP/RPQ/REG/RSS) introduced the draft WHO guidance (Version 3) by highlighting some of the key differences between the current guidance and the guidance published in 2017. Most notably, the guidance from 2017 focused on non-producing countries and specifically for market authorization of pandemic influenza vaccines. In contrast, the current document aims to provide guidance to importing countries and the lifecycle management of vaccines authorized during a pandemic or public health emergency. It was highlighted that key post-authorization processes are critical, such as post-authorization change management, vaccine traceability and import authorization, and pharmacovigilance. In addition, the scope of the current guidance was discussed. During the public consultation process, feedback was received about the scope of the guidance only referring to vaccines and that other medicines and products should be included. After much consideration, it was agreed that the scope of the document should remain specific to vaccines, but that the general principles and processes described in the current guidance could be applied across pandemic medicines and products.

Session IV: Presentations on practices in the countries on the regulation of pandemic vaccines

Participating representatives of various countries were asked to share their experiences with respect to the importation of vaccines during the SARS-CoV2 pandemic. Representatives were asked to prepare brief presentations that provided details on the following topics/questions;

1) Is there a guideline in place in your country to approve pandemic vaccines during or prior to a pandemic?
2) If yes, what are the key principles and procedures?
3) If not, how did you regulate Covid 19 vaccines?
4) Any difficulties you encountered and any experiences you would like to share with the participants on regulation of pandemic vaccines during the SARS-CoV2 pandemic?
5) What do you expect from WHO?

Representatives from Nepal, Jordan, Egypt, Cuba, South Africa, and Thailand presented on Day 1, and the representative from Indonesia presented on Day 3 due to earlier travel disruptions. While each representative detailed specifics that were unique to their country, there were several aspects that were common across presenting NRAs. In general, the following points were common amongst countries that presented:

- Most countries had a legal framework that was in-place or amended to accommodate regulatory flexibility during the pandemic
- Various Reliance mechanisms (including Recognition) were used to authorize vaccines during the pandemic, however delays in authorization were still experienced
- Most emergency use authorizations were specific only for the period of the pandemic
- Challenges were experienced in the monitoring of post-authorization changes/updates to authorized vaccines (i.e. updated stability data, new clinical indications, changes to CMC)
- Timely access to unredacted assessment reports was considered a barrier to Reliance/Recognition pathways
- Continued capacity building and collaboration through WHO or other reference NRAs will improve information sharing and the speed of responsiveness during pandemics

Session V: Discussion of technical comments received during Public Consultation (Jan-Mar, 2023)

During the final session of Day I, Dr. Tariro Sithole (Co-rapporteur) provided a summary of comments received during the public consultation. The comments were categorized into major (potential to impact the outcome of the guidance), minor (to be considered by drafting group) or editorial. Only a few of the received comments were considered major, and of these comments, all concerned the requirement for unredacted assessment reports from reference NRAs. It was highlighted that various countries/NRAs are legally prohibited from providing unredacted assessment reports. This barrier was commonly identified by meeting participants as a significant barrier to timely approval of vaccines during the pandemic. There was consensus that the provision of unredacted assessment reports, either from the NRA or the vaccine manufacturer, would facilitate improved responsiveness during the time of a pandemic, and would reduce the burden on both sponsors and NRAs as there would be a significant reduction in the amount of communication/information requests required for approval in the importing countries. However, it was noted that in certain situations or depending on the level of reliance, an unredacted assessment report may not be required. Nevertheless, there were noted concerns about the accessibility of assessment reports on the WHO database. More specifically, full assessment reports were not always available or were delayed in being uploaded to the database platform (EUL/PQ), or only summary assessment reports were uploaded. While it was noted that the immense volume of information/documentation managed through the WHO data platform (e.g. assessment reports and updates) likely contributed to the delayed access, relying countries experienced difficulties managing/tracking

changes and updates to dossiers through this access point. These experiences raised the concern that although the guidance promotes Reliance pathways, strengthened wording should be used to emphasise the value of Recognition during a pandemic. It was conveyed that expedited approval of life-saving vaccines should be the objective of a pandemic response, highlighting once again the benefit of providing unredacted assessment reports to relying/importing countries.

Additional discussion focused on the strengthening of key principles that were integral to the guidance. More specifically, meeting participants discussed the need for the guidance to highlight the importance of a risk-based approach to pandemic preparedness. It was agreed that national pandemic preparedness plans should be flexible and agile in nature and allow the NRA to apply a risk-based approach in order to quickly respond to any future pandemic or public health emergency. As a consequence of the increased flexibility, participants expounded on the importance of pharmacovigilance and emphasised that the guidance should strengthen the need for post-authorization pharmacovigilance plans for importing countries. In addition, the issue of product labelling and the feasibility of a universal label was considered by meeting participants. It was noted that a universal label would be difficult to apply across all NRAs as labelling requirements were enshrined in legislation for some NRAs, therefore discussion focused on what minimal information should be available on the final container of a vaccine. Much of the discussion focused on whether expiry dates or dates of manufacture should be included on the labels. It was acknowledged by participants that inclusion of expiry dates on labels presented difficulties as often novel or previously unauthorized vaccines do not have extensive stability data at the time of a pandemic or public health emergency authorization. Instead, expiry dates are updated as real-time stability data are contemporaneously generated. As an alternative to expiry dates, a date of manufacture was proposed as an alternative, but legal requirements for labelling of expiry dates was noted by some countries. Subsequently, strategies for accessing updated stability information was discussed. Considerations regarding the utility of QR codes was discussed following feedback from some countries that they were not equipped to easily implement QR code technologies. Alternative approaches, such as company managed websites, were discussed as a source of updated product stability/expiry dates. In the end, it was concluded that the guidance should aim to produce recommendations to importing countries that emphasize the need for speed, flexibility, and risk-based principles during a pandemic or public health emergency, yet the individual countries should apply the recommendations within the framework of their legislation.

<u>Day 2, April 18, 2023</u>

Session I. Discussion of technical comments received during Public Consultation (Jan-Mar, 2023) continued

During the second day of discussion, each section of the draft guidance was discussed in sequential order by meeting participants. This format provided meeting participants the opportunity to provide additional comments on the draft guidance that had not been made during the public consultation process.

For the purposes of this meeting report, only key points relevant to each section will be mentioned, however the draft guidance will be updated to reflect all discussion points for which meeting participants agreed were important revisions.

Introduction

- Need to update the guidance to reflect 'urgency' as a key component in a pandemic/public health emergency preparedness plan, and that any plan should remain flexible and agile, and should emphasize the importance of Reliance and Recognition pathways to authorize vaccines.

Purpose and scope

- Scope should remain specific to vaccines, but state that principles can be applied to other medicines and health products.

Terminology

- Need to update terminology to avoid using definitions (e.g. Emergency Use Authorization or Conditional Marketing Authorization) that are specific to certain jurisdictions. Define a more general term, such as Emergency Authorization, that encompasses terminology used by a wider range of jurisdictions.
- Update and define new terms considered relevant to guidance (e.g. reference NRA, pandemic, public health emergency).

General considerations for regulatory preparedness for vaccines used in pandemics and public health emergencies

- Removal of the section 'Link to WHO Global Benchmarking Tool' and alternatively include recommendations that importing NRAs identify gaps in their own regulatory processes/systems which require strengthening.

- Removal of guidance redundancies in Section 4 and Section 5 (Regulatory evaluation and authorization processes) and rearrange the order and content of these two sections to improve document flow and readability.
    - Rearrangement of content should place priority on Reliance and Recognition pathways in pandemic preparedness plans.

Day 3, April 19, 2023

Discussion of technical comments received during Public Consultation (Jan-Mar, 2023) continued

Discussion continued for the remaining sections of the draft guidance.

Regulatory evaluation and authorization processes

- Clear delineation of recommended minimal documentation expected for various authorization pathways.
- Refinement of pandemic phase definitions in accordance with current WHO guidance.
- Removal of 'Final Evaluation' subsection to reduce redundancies.

Post-authorization activities

- Recommend flexibility in importation documentation to facilitate distribution of vaccines, particularly in countries with limited to no regulatory capacity.
- Recommend flexibility in lot release documentation and emphasis placed on lot traceability and expedited release of imported vaccine lots.
- Strong recommendation against testing of imported vaccine lots during a pandemic or public health emergency.
- Update 'Vigilance' section to 'Pharmacovigilance' and highlight the importance of strengthening procedures to identify post-authorization safety and effectiveness signals to better inform public health policy and recommendations.

Appendices

- Removal of Appendix 2 as guidance principles and recommendations can be applied to strain or variant change considerations.

Session III. Wrap up and Summary

In the final wrap up, Dr. Meyer provided a high-level summary of discussion points to be incorporated in the revised draft. Drs. Sithole and Siggers also provided updates about key highlights to be detailed in the meeting report and captured in the Executive Summary.

Session IV. Next steps

Dr. Lei provided a brief summary of proposed timelines and expectations for the drafting group and meeting participants in order to submit the proposed guidance to the ECBS by 1 July, 2023. Following the meeting, Dr. Lei provided the following timeline:

1. Updated version of the guideline will be prepared by the drafting group by 19 May;
2. The updated version to be reviewed and commented by the meeting participants by 2 June;
3. The guideline to be finalized by the drafting group by 16 June;
4. Final layout and reading by 30 June;
5. Submission to ECBS on 1 July;
6. Second round public consultation on WHO website (https://www.who.int/groups/expert-committee-on-biological-standardization) from 7 July to 22 September;
7. ECBS review in October 2023.

Session V. Closing

Dr Khadem closed the meeting by thanking all participants for a very engaged and productive meeting and thanked all staff and team members for contributing to the success of the meeting.

A special thanks was given to the funding support of Pandemic Influenza Preparedness.

Appendix 1. Meeting Participants

Participants

Ms Sangay Choden, Bhutan Food and Drug Authority (BFDA), Thimphu, Bhutan; Dr Danay Mora Pascual, Centre de Control Estatal de Medicamentos Equipos y Dispositivos Médicos (CECMED) Cuba; Dr Hoda ElSaeed Mohamed Metwally Attiam, Egyptian Drug Authority (EDA), Cairo, Egypt; Dr Diah Puspitasari, Food and Drug Administration, Jakarta. Indinesia; Dr Suna Habahbeh, Jordan Food and Drug Administration, Amman, Jordan; Dr Nyshanbaev Mirbek, Department of Medicines and Medical Devicesm Bishkek, Kyrgyzstan; Ms Vongsy Phanthavong, Department of Food and Drug, Ministry of Health, Lao, Lao People's Democratic Republic; Ms Usha Tandukarm Ministry of Health and Population, Kathmandu, Nepal; Ms Royce Ann M. Vicentino, Food and Drug Administration (FDA), Manila, Philippines; Dr Portia Nkambule, South African Health Products Regulatory Authority (SAHPRA), Pretoria, South Africa; Dr Adam Hacker, Coalition for Epidemic Preparedness Innovations, London, United Kingdom; Mrs Le Thi Tuyet Lan, Drug Administration of Viet Nam (DAV), Hanoi, Viet Nam.

Drafting group members

Dr Tariro Sithole, Medicines Control Authority of Zimbabwe, Harare, Zimbabwe; Dr Edwin Nkansah, Ghana Food and Drugs Authority, Accra, Ghana; Dr Heidi Meyer, WHO Cooperation Center for the Standardization and Evaluation of Vaccines, Paul-Ehrlich-Institut, Germany; Mr Pramote Akarapanon, Food and Drug Administration, Ministry of Public Health, Thailand; Dr Malik Obaidullah, Drug Regulatory Authority of Pakistan, Islamabad, Pakistan; Dr Othmar Engelhardt, Medicines and Healthcare Products Regulatory Agency, Potters Bar, United Kingdom; Dr Richard Siggers, Vaccines Quality Division 1, Centre for Vaccines, Clinical Trials and Biostatistics (CVCTB), Health Canada, Ottawa, Canada.

WHO Regional Offices

Dr Mohamed Ismail, Team Lead, Medicines Supply Health Infrastructure, AFRO; Ms Alexandra Mata, Specialist, Quality Management System, AMRO/PAHO; Ms Begona Segastuy, AMRO/PAHO; Dr Adi Fawzi Mohammad Al-Nuseirat, Regional Adviser, EMRO; Ms Dorina Pirgari, Technical Officer, Access to Medicines and Health Products, EURO; Dr Adrien Inoubli, Regional Adviser, Medical Products Quality & Regulation, SEARO; Dr Geraldine Hill, Coordinator, Essential Medicines and Health Technologies, WPRO.

WHO Headquarters

Dr Alireza Khadem Broojerdi, Team Lead, Regulatory Systems Strengthening; Dr Razieh Ostad Ali Dehaghi, Scientist, Regulatory Systems Strengthening; Dr Dianliang Lei, Scientist, Norms and Standards for Biological Products; Ms Jennifer Barragan, Project Manager, Pandemic Influenza Preparedness; Mrs Marie Valentin, Technical Officer, Regulatory Convergence and Networks; Ms Eun Mi Kim, Technical Officer, Pharmacovigilance.

WORLD HEALTH ORGANIZATION

WHO informal consultation on revision of the WHO guidelines on regulatory preparedness for provision of marketing authorization (MA) of human pandemic influenza vaccines in non-vaccine producing countries (TRS NO. 1004, ANNEX 7)

17 to 19 April 2023

Agenda

Chairperson: Heidi Meyer

Rapporteur: Tariro Sithole, Richard Siggers

Day 1, 17 April 2023 (Monday)

9.00-10.00 Session 1. Opening of the meeting

Opening remarks and introduce of chair and rapporteurs	A Khadem
Statement on DoI assessment	A Khadem
Self-introduction	All participants

10.00-10.30 Session 2.

Objectives and expected outcomes of the meeting	D Lei

10.00-12.30 Session 3.

Introduction to the draft WHO guideline V3	R Ostad

13.45-15.15 Session 4.

Presentations on practices in the countries on the regulation of pandemic vaccines

13.30-13.45 Warm up A Khadem

15.30-17.00 Session 5.

Review the comments received during Public Consultation (Jan-Mar 2023) T Sithole

Discussion of technical comments received during Public Consultation (Jan-Mar 2023)"

- General comments

17.00-17.30 Session 6.

Summary and evaluation of the day D Lei

Day 2, 18 April 2023 (Tuesday)

8.30-09.00 Warm up

09:00-12:30 Discussion of technical comments received during Public Consultation (Jan-Mar 2023)" **(cont.)**

1. Introduction
2. Purpose and scope
3. Terminology
4. General considerations for regulatory preparedness for vaccines used in pandemics and public 6 health emergencies
   - 4.1. Acknowledgement of the role of the NRA in the national pandemic and emergency 9 preparedness plan
   - 4.2. Considerations for national regulatory preparedness
   - 4.3. Reliance for the timely and effective introduction of vaccines
5. Regulatory evaluation and authorization processes
   - 5.1. Expected basic documentation according to the source of the pandemic or emergency use vaccine
   - 5.2. Possible regulatory review pathways in a pandemic or public health emergency (Pre-market procedures)
   - 5.3. Final evaluation
   - 5.4. Emergency approval by an authority other than the NRA

6. Post–authorization activities
7. Post approval changes
8. Market Surveillance and Control
9. Vigilance
10. Lot Release

APPENDIX 1

APPENDIX 2

Day 3, 19 April 2023 (Wednesday)

8.30-09.00 Warm up

09:00-10:30 Summary of the discussion of comments received during Public Consultation (Jan Mar 2023)

Heidi Meyer

10:45-12:30 Session 2.

- Summary of inputs — Richard Siggers
- Wrap-up and next steps — D Lei
- Evaluation of the day/ closing — A Khadem