Meeting Report

WHO workshop on implementation of Guidelines for procedures and data requirements for changes to approved vaccines

8-10 November 2022
Venue: Grand Millennium Muscat, Oman
Executive summary

Regulation of changes to approved vaccines is one of the most important elements in ensuring that the vaccines of consistent quality, are distributed after they receive authorization or licensure. In response to the request from National Regulatory Authorities (NRAs) of the World Health Organization (WHO) Member States on the data needed to support changes to approved vaccines to ensure the comparability with respect to quality, safety and efficacy of vaccines manufactured with the change, WHO have developed Guidelines for procedures and data requirements for changes to approved vaccines. These guidelines were adopted by Expert Committee on Biological Standardization (ECBS) in its meeting 2014 and published in the WHO Technical Report Series 993. The Guidelines provide guidance to NRAs and manufacturers on the essential data required to support the change, which does not negatively impact on the quality, safety and efficacy of the vaccines and also provide regulatory procedures to review and approve the changes submitted by manufacturers.

To facilitate the implementation of these guidelines, a three-day workshop was organized by the WHO Headquarters with great assistance from EMRO and CO in Oman, in Muscat, Oman from 8-10 November 2022 for the countries from EMR and AFR where were identified there is a need for improving the regulation of post-approval changes. The workshop was convened in the hotel of Grand Millennium Muscat. The event was organized with help of the local regulatory authority of Oman, Directorate General of Pharmaceutical Affairs & Drug Control, Ministry of Health. This workshop was participated by the representatives of national regulatory authorities from Bahrain, Egypt, Islamic Republic of Iran, Jordan, Lebanon, Oman, Pakistan, Saudi Arabia, Sudan, Syria Arabia Republic, Tunisia, and United Arab Emirates. The workshop was facilitated by experts from regulators with rich experience on regulation of post-approval changes. In the workshop the principles on categorization of quality changes and efficacy, safety and labelling information changes were presented by the facilitators. Case-studies regarding different types of changes were studied by the participants. The participants used the WHO guidelines to classify the category of each change and identify the necessary supporting data needed to demonstrate that there is no impact on the quality, safety and efficacy of the product after change. The case studies were the most welcomed sessions in the workshop and the cases studies helped the participants to understand how to use WHO guidelines on post-approval changes. It was suggested by the participants that it would be more practical and useful for the participants if more complicated cases with a set of supporting data would be reviewed and include case studies related to Covid 19 vaccines.

It was recognized that the WHO guidelines on post-approval changes is a very practical and useful document. Participants of the workshop expressed that they will implement WHO Guidelines in the regulation of changes in the future. Those countries where national guidelines are already in place, will refer to the WHO Guidelines and update or align their guidelines with the procedures and data requirement of WHO guidelines and those without guidelines will develop them based on or adopt the WHO
guidelines. It was proposed by participants that development of a database on regulatory activities such as lot release, MA, or PAC and sharing the relevant information and country’s experience with the others should be encouraged.

Introduction

Changes to the vaccine manufacturing process or product labelling information often need to be implemented after a new vaccine has been approved. Changes may be made for a variety of reasons, such as to maintain the routine production of vaccines, to improve the quality attributes of the vaccine or the efficiency of manufacture or to update product labelling information. It is recognized that: any change to a vaccine may impact upon the quality, safety and efficacy of that vaccine and any change to the information associated with the vaccine (that is, product labelling information) may impact on the safe and effective use of that vaccine. The regulation of changes to approved vaccines is one of the most important elements in ensuring that vaccines of consistent quality, safety and efficacy are distributed after they receive authorization or licensure. In response to the request from NRAs of WHO Member States on the data needed to support changes to approved vaccines to ensure the comparability with respect to quality, safety and efficacy of vaccines manufactured with the change. WHO have developed Guidelines for procedures and data requirements for changes to approved vaccines. These guidelines were adopted by ECBS in its meeting 2014 and published in WHO Technical Report Series 993. The Guidelines provide guidance to NRAs and manufacturers on the essential data required to support the change, which does not negatively impact on the quality, safety and efficacy of the vaccines and also provide regulatory procedures to review and approve the changes submitted by manufacturers.

To facilitate the implementation of the Guidelines into national regulatory practices, WHO organized the two implementation workshops in Thailand in 2015 and in Viet Nam in 2019 with participants of NRAs from regulators and vaccine manufacturers of WHO member states and the workshop was highly appreciated by the participants. Following the workshops there are requests have been received to organize more workshops to implement the Guidelines and converge the procedures and data requirements in regulation of post-approval changes for countries in WHO African and Eastern Mediterranean regions. To follow the request, a three-day workshop to facilitate the implementation of these guidelines was organized by WHO HQ with assistance of WHO EMRO and WHO country office in Oman for national regulator authority (NRA) and vaccine manufacturers who are responsible for regulation of post-approval changes in their institution at Grand Millennium Muscat in Oman, from 8-10 November 2022. This workshop was attended by the representatives of Bahrain, Egypt, Iran, Jordan, Oman, Pakistan, Saudi Arabia, Sudan, Syria, Tunisia, and UAE were present. Ms Nathalie Khawan from the WHO Country Office in Oman participated as well. Representatives of regulators from Tanzania and Kuwait and manufacturers from Iran apologized due to visa or other administrative reasons. The workshop was chaired by Dr. Heidi Meyer from PEI. Germany. Mrs. Teeranart Jivapaisarnpong from Thailand, and Dr. Lorenzo Tesolin from Sciensano Belgium were the rapporteurs. The
facilitators of the workshop were Dr Meyer, Mrs. Jivapaisarnpong, Dr. Tesolin, Dr. Dianliang Lei from WHO-HQ and Dr. Houda Langar from WHO-EMRO. Mrs Maryan Mounir Selwanis from EMRO provided administrative support to the workshop.

**Day 1**

**Session I: Opening of the meeting**

The workshop was opened by Dr. Hasshish Alaa on behalf of Dr. Jean Jabbour, WHO Representative of Oman. He welcomed facilitators and all participants from regulatory authorities. He stated the importance of ensuring the quality, safety and efficacy of health products as well as improving equitable access of health products were one of WHO mandates and to achieve these goals WHO had developed relevant guidelines and practices in order to assist national regulatory authorities of WHO member states in regulating the vaccines used in their immunization program. He informed that WHO had defined the following regulatory functions including regulatory system, registration and marketing authorization, vigilance, marketing surveillance and control, licensing establishment, regulatory inspection, laboratory testing, clinical trial oversight and NRA lot release. However, variations after granting a license or post-approval changes always happened to improve the quality of the product or to improve the efficiency of production, or update product labelling information. These changes might have a potential to impact the quality, safety and efficacy of the product. Therefore, regulation of post-approval changes is essential to assure the quality of the product and WHO had developed Guidelines on data requirements and procedures for changes to approved vaccines to assist NRAs in 2014. To promote the implementation of this guideline into national regulatory practices, WHO HQ organized this workshop with the assistance of WHO country office in Oman, to brief the participants about the main principles of the guideline and discuss on issues that the participating NRAs had been facing in routine work. He hoped all participants would get better understanding on the importance of regulation of post-approval changes and learn how the procedure could be applied in the situation of each country to reach the regulatory goal of ensuring the quality, safety and efficacy of vaccines used in their countries. Finally, he extended his sincere thanks to the experts in regulation of vaccines from Belgium, Germany and Thailand, as well as to colleagues from WHO Headquarters and Regional Office of Eastern Mediterranean who are facilitating this workshop and wished all participants enjoy this three-day workshop as well as to have a pleasant stay in Muscat.

Dr. Mohamed Al-Rubayee, Director General of Pharmaceutical Affairs and Drug Control Directorate, Ministry of Health, Oman, welcomed all participants and expressed his appreciation to WHO for organizing this workshop in Oman. He was sure that the representatives of NRAs would gain knowledges and experiences to strengthening their regulation on post approval changes to be able to ensure the quality, safety and efficacy of vaccines used in the national vaccination program in each country as well as in Oman.
Dr. Houda Langar, Regional Advisor, Vaccine Regulation and Production, WHO EMRO expressed her gratitude to Ministry of Health, Oman for coordinating this workshop as well as the facilitators for their support. She hoped all participants would learn how to monitor post approval change appropriately from this workshop.

**Update on WHO position on post-approval changes in the context of WHO biological standardization and objectives of the workshop:**

Dr. Dianliang Lei, Scientist of Technology, Standard and Norm of WHO, the organizer of the implementation workshop provided the update on WHO position on post-approval changes in the context of WHO biological standardization and objectives of the workshop. He informed the participants that WHO goal was to work together to promote health, keep the world safe and serve the vulnerable and one of the most important parts was access to safe, effective and quality medicines, vaccines and health products.

Dr Lei highlighted that changes were always made by manufacturers in production process, testing methods or labelling information and these changes might impact quality, safety and efficacy of the product. Regulation of post-approval changes (PAC) was one of the most important key elements of vaccine regulation post marketing authorization to ensure the comparability of the product made with changes to the licensed one.

In response to requests, WHO developed Guidelines on procedures and data requirements of changes to approved vaccines in 2014 through a consultation procedure with input from regulators and industry. The Guidelines were published in the WHO Technical Report Series No. 993. Implementation of these Guidelines would assist National Regulatory Authorities with the evaluation of the data and provide basic information to the authorities in the development of their own national guidelines and timely access to the vaccines needed for their immunization programs. He also emphasized that WHO recommended that each country should establish its national guidelines for procedures and criteria for the evaluation of changes to a marketing authorization to ensure that vaccines of constant quality, safety and efficacy are distributed post authorization. However, reliance and recognition of the other competent regulators’ decisions were encouraged. Dr Lei reminded the participants the objectives of the workshop were 1) to better understand the current practices of regulation of PAC in participating countries; 2) to familiarize NRAs/NCLs and vaccine manufacturers with the contents of WHO guidelines and to clarify any issues that may interfere with the implementation of the principles of WHO guidelines; and 3) To identify any potential needs for further guidance on regulation of PAC or any other relevant regulatory activity. He also expected that at the end of the workshop participants would have a better understanding of the key principles and expectations of regulation of post-approval changes and would be able to identify the current gaps in their regulation of post-approval changes and how to move forward with improvement. He also expected that the workshop would build confidence on better communication between NRAs and manufacturers in the future.
Session II: WHO Guidelines for post-approval changes

WHO Guidelines for procedures and data requirements for changes to approved vaccines: purpose and general principles:

The purpose and general principles on the WHO Guidelines on Post Approval Change (PAC) were presented by Dr. Dianliang Lei. He informed the audiences that access roadmap which ensuring quality, safety, and efficacy of health products as well as improving equitable access were included had announced in the 72nd WHA and one of major mission was strengthening regulatory systems. He stated that WHO had developed two guidelines on PAC to assist NRAs in establishing regulatory procedures for post-approval changes which one was for vaccines and the other was for biotherapeutic products. The procedures and criteria for the appropriate categorization and reporting of changes and data required to enable NRAs to evaluate the impact of the change on the quality, safety and efficacy of the vaccine were described. He emphasized that based on the potential effect of the quality change on the quality attributes of the vaccine, and the potential impact of this on the safety or efficacy of the vaccine, a change is categorized and identified as either a major quality change, a moderate quality change or a minor quality change. These major and moderate quality change required regulatory approval prior change. He mentioned that different regulatory pathways for assessing post-approval change submission could be applied by regulators which included full review of supporting data, recognition or reliance of decision of a competent NRA and review of the decision of NRA of producing countries might be considered.

The objectives of this workshop including 1) To better understand the current practices of regulation of PAC in participating countries; 2) To familiarise NRAs/NCLs and vaccine manufacturers with the contents of WHO guidelines and to clarify any issues that may interfere with the implementation of the principles of WHO guidelines; and 3) To identify any potential needs for further guidance on regulation of PAC or any other relevant regulatory activity were also presented. The outcome of this workshop that the participants would have a better understanding of the key principles and expectations of regulation of PAC as well as would be able to identify the current gaps in their regulation of PAC and how to move forward with improvement were expected. Moreover, the workshop would provide a forum for NRAs and vaccine manufacturers to build confidence on better communication in future. Finally, Dr. Lei reminded the participants that implementation of any new regulation should not affect vaccine supply and access by the public to vaccines. Therefore, NRAs were strongly encouraged to establish requirements that were commensurate with public health priorities and with their own regulatory capacity and resources to ensure the vaccine supply in their country.

How to use WHO Guidelines on post-approval change:

How to use WHO Guidelines on post-approval changes was presented by Dr. Heidi Meyer. She explained that these guidelines were providing guidance on the procedures and criteria for the appropriate categorization and reporting of changes;
and data required to enable NRAs to evaluate the impact of the change on the quality, safety and efficacy of the vaccine. She showed the outline of the guidelines including main body and appendices 1, 2, 3 and 4. She explained how to use the guidelines to categorize and report post-approval changes. She emphasized that the quality changes to approved vaccines, the marketing authorization (MA) holder was expected to perform a risk assessment to evaluate the potential effect of the intended change to the quality, safety and/or efficacy of the vaccine. Depending on the risk level identified the change needed to be categorized. In order to provide assistance to NRAs on judgement of the proper classification, comprehensive lists of major, moderate and minor quality changes were provided in Appendices 2 and 3. The conditions to be fulfilled for each change, the data sets required to support the respective changes to the manufacture or quality control of antigen, final product or its intermediates and the reporting category of the change were included in these appendices. She stated that in general the implementation of major or moderate changes required reporting to the NRA and must be reviewed and approved by the NRA prior to the implementation of the change whereas the minor quality changes might be implemented by the MA holder without prior review and approval by the NRA. Changes related to the clinical use or to the product labelling information on the safe and effective use of a vaccine, should be classified by MA holders according to the categories given in Appendix 4 of the Guidelines.

Session III: Current approaches of regulation of post-approval changes

Current practices of regulation of post approval changes to vaccines, biologicals in selected participating countries:

Representatives of NRA from each country presented their practices of regulation of post approval changes as following:

Presentation by Saudi Arabia FDA (SFDA)

SFDA regulation and the key principles of post approval changes (PAC) were presented. The SFDA was established in 2003 to regulate and control food, drugs and medical devices. SFDA was member of International Pharmaceutical Regulators Programme (IPRP), ICH and International Coalition of Medicines Regulatory Authorities (ICMRA).

The organization structure of SFDA was also presented. There were five main sectors including Operations, Food, Drug, Medical Device, and Research and lab Sectors. Drug Sector composed of Regulatory affairs, Quality evaluation of Medicines (including Biological Products evaluation), Pharmacovigilance, and Benefit-risk assessment.

The flow chart for the submission of licensing and variation application was presented. The total performance targets including timelines and classification of changes were shown. They had the first step of business validation then the assessment step followed by the evaluation of price and finally the licensing step.
Quality variations requests as well as Safety and efficacy variation requests during 2022 were shown. Some figures on the number and type of applications were presented.

National Guidelines for Variation Requirements was developed since 2019 and published on SFDA website. This guideline was adopted from the EMA Guidelines on the details of the various categories of variations, Regulation (EC).

Variations classifications as per the guidelines were shown and one example of variation was presented. They also discussed the challenges and difficulties they encountered like classification of changes, multiple changes, limited number of assessors in the team, flu cases, and also special population updates.

They made reference to their documents and proposed to visit their website where all the documents are available. Some questions were then discussed by all the group, especially special population updates. It was reminded that the pregnant population in Europe was not excluded to the use of vaccines but it was mentioned that data for those populations were not available. The decision to give the vaccine to pregnant women belonged to the physician. The immunocompromised population was dealt in separate clinical trials.

During discussion it was proposed that WHO should consider to combine different PAC guidelines which one was for biosimilar and biotherapeutics, one for vaccines and one for pharmaceuticals to be one guideline for all where possible. Moreover, It was also mentioned that there is no need to have a specific guideline for influenza vaccines.

**Presentation by Egyptian Drug Authority (EDA)**

The regulation of post approval changes in EDA was described. There were nine Central Administrations under EDA where each one has a specific role in the process of ensuring the quality, safety and efficacy of drug products distributed to Egypt. The Central administration of biological and innovative products and clinical trials was responsible for the evaluation and registration of the locally manufactured and imported products through different registration pathways to ensure its safety, efficacy and quality before introducing it into the local or international market and Variation unit was responsible for maintaining their quality through regulation of post approval changes. Definition of post approval changes as well as legal framework for Variation unit were presented. Both WHO Guidelines for PAC for Vaccines and Biotherapeutics were adopted and followed.

The following points including classification of changes, determination of the suitable procedure and then the submission of the data package, and finally the evaluation, were discussed. The handling of file variation was not only depended on the type of post-approval change but also on the type of marketing authorization. The following steps including pre-submission phase, preliminary assessment phase, submission phase, evaluation phase and then finally decision phase were elaborated.

**Presentation by Food and Drug Administration (FDA) of Iran**
It was presented that National Guidelines of Iran was developed based on WHO Guidelines on procedures and data requirements for changes to approved vaccines and Comparability of Biotechnological/biological products subject to changes in their manufacturing process as per ICH/Q5E and issued to the manufacturers since 2016. The key principles and the procedure were described. The classical classification for post-approval changes (minor moderate and major) was used. The same process was used for domestic and foreign manufacturers.

The experience on approval of new site for filling of vaccine by conducting GMP inspection, issuance of GMP certification, as well as evaluation of the number of products produced in the site and supporting data requirement for the change of approval was also presented.

Other countries

Representatives from NRAs of Bahrain, Jordan, Oman, Pakistan, Sudan, Syria, Tunisia and United Arab Emirates were invited to briefly presented their regulations and procedures on management of post-approval changes. Most of them used WHO-PQ vaccines and some of them also relied on either EMA or USFDA. For management of post approval changes, some of them follow either the WHO guidelines and/or the EMA guidelines and/or ICH. However, some of them the reference was only made to those guidelines but not fully implemented and considered on case by case basis.

Discussion and feedback on day one:

A summary of day one was made. Some questions were raised and discussed. The major topics of concern were appropriate timelines for NRA approval for post approval changes, accelerate procedure and timeline decision, addition of manufacturing site during licensing, reliance/recognition system on other NRAs' decision, what should be justified in case the NRA of country of origin had not yet approved the changes, how to manage in case of temperature excursion during shipment, criteria for selection of the external experts, how to deal with changes of virus strain in COVID19 vaccine production. The example of approval of stability studies in Europe to reduce workload was discussed. The NRAs required the stability data from the manufacturer only when there was any out of specification result or any shift in trends detected by the manufacturer (trust based).

Day 2:

Session IV: Recommendations in WHO Guidelines for post-approval changes

Reporting procedures and data requirements for quality changes – Changes to antigens and final products:
Dr. Lorenzo Tesolin and Dr. Heidi Meyer provided the key information on common principles of WHO Guidelines for procedures and data requirements for changes to approved vaccines as well as quality changes to comply with the updated compendia and/or pharmacopoeia. Specific considerations needed to be given to quality changes affecting lot release as the institution responsible for reviewing the release of vaccine lots (NCL) needed to be informed about any change that affects the lot release protocol or the official lot release process. It was highlighted that in general it was acceptable that a pre-change batch was used until depletion unless a quality change was introduced for a reason directly linked to safety or efficacy of a specific vaccine. Furthermore, observations on quality changes including the requirements for batch stability data were discussed. Specific considerations should be given to the annual strain update of influenza vaccines due to the extensive experience with such changes and in order to maximize the flexibility and brevity of the review process. It was emphasized that the need for clinical data to support a quality change should be limited to very specific cases, i.e., when comparability could not be established by quality data only. Examples of such changes included changes to the composition or to the pharmaceutical form of a vaccine or changes due to the removal or replacement of a biological component used in the manufacture and resulting in new residuals present in the final vaccine product. How to interpret the requirements for the classification of a quality change, the conditions to be fulfilled, supporting data, and reporting category as given in Appendices 2 and 3 was also elaborated.

**Working group on case studies related to the quality changes and labelling information changes:**

The participants were randomly separated into 5 groups, approximately 6 persons in each group. Five case studies which were examples of quality change and labelling information changes to vaccines were used for the working group discussion. The cases were A) change in the specification used to release the final product, B) final product manufacturing site change, C) replacement of an in vivo test by an in vitro test, D) change of a reference standard, and E) change of the labelled storage conditions for the final product.

Each group was assigned to work on two case studies and the same case was studied by two groups. Each group presented the outcome of one case in the plenary session as well as commented on outcome of the second case presented by the other group. The facilitators and all participants provided comments on the outcomes for conclusions as well as for the future improvement.

The points raised during the discussion were modification of some case studies to provide clearer descriptions, justification on selecting only potency and sterility assays for stability studies VS using the same test as for product release, and format of testing procedure as supporting data SOP VS test description.
Special considerations on multiple changes application, expedited review procedures in special or urgent circumstances, seed virus changes for seasonal influenza vaccines:

Mrs. Teeranart Jivapaisarnpong provided the information stated in WHO guidelines on special consideration on applications of multiple changes, expedited review procedures in special or urgent circumstances, and seed virus changes for seasonal influenza vaccines. General principle and examples of multiple changes and multiple change application were presented. Procedures for expedited review in special or urgent circumstances including the recognition of other NRAs’ decision or inspection were elaborated. Example of change of production site of Inactivated Influenza Vaccine and consideration of supporting data requirement in case of emergency were provided. Annual change of seed virus for seasonal influenza vaccine production and required supporting data were also presented. She also provided her opinion on the issue of COVID19 Vaccine production strain changes that this might not be able to manage in the same manner as Influenza vaccine because of inadequate experiences in the production process that impact to the quality, safety and efficacy of the vaccine. The risk-based management should be used for consideration of this change.

Discussion and feedback on day two:

Some questions were raised and discussed. The questions and answers were as following:

1) Question: What is the justification if the diluent was deleted because the product was changed from freeze-dried to liquid form?
   Answer: In many countries, this is justified as the new product.

2) Question: For scaling up, stability data 1 lot is acceptable or not?
   Answer: In general, at least 3 lots are required for stability study. In some circumstances, less than 3 lots may be accepted. Accelerated stability study can be used to compare the stability profile of the product before and after changes.

3) Question: If the minor changes found later that it related to the quality, safety, efficacy of the vaccine what to do?
   Answer: Justification should be done following WHO guidelines. In addition, for changes related to safety, the good system for causality assessment should be in place and risk benefit assessment might be used for stopping the supply of the vaccines.

   Appropriate timelines for approval were also discussed.

Day 3:

Reporting procedures and data requirements for efficacy, safety and labelling information changes:
Dr. Heidi Meyer summarized the reporting procedures and data requirements for efficacy, safety and labelling information as specified in Appendix 4 of the WHO Guidelines on post-approval changes. Due to the varying amount of safety and efficacy data needed to support a change to the safe and efficacious use of a vaccine, there is no 'one-size-fits-all' approach feasible. The examples of changes given in Appendix 4 are provided for clarification only; they are not limited, however, to those included to the guidelines. In general, there are three categories of clinical changes, i.e. safety and efficacy changes, product labelling information changes and administrative product labelling information changes. Examples of clinical changes for the different categories were provided. All clinical changes except for solely administrative changes need approval by the NRA prior to implementation of these changes.

**Working group on case studies related to safety and efficacy changes and product labelling information changes:**

Five case studies related to efficacy, safety and product labelling information were used for the working group discussion. The cases were A) change to add information on co-administration with other vaccines, B) change to add AEFI identified as consistent with a causal association with immunization, C) multiple changes of Flu vaccine including change of the vaccine formulation, change of the finished product container, and extending the use of the vaccine in another age group, D) change of vaccine composition for Human Papilloma Virus vaccine, E) change of the vaccine composition by replacing polygeline with sucrose in the final vaccine product.

Each working group composed of 6 participants and was assigned to work on two case studies and the same case was studied by two groups. Each group presented the outcome of one case in the plenary session as well as commented on outcome of the second case presented by another group. The facilitators and all participants provided comments on the outcomes for conclusions as well as for the future improvement.

**Considerations on time frame of evaluation of post-approval changes:**

Dr. Lorenzo Tesolin provided an overview on the proposed timetables for review and approval of the various change categories (e.g. major and moderate quality changes, safety and efficacy changes etc.) and the data package to be submitted to the NRA for changes to approved vaccines. Considerations should be given to implement mechanisms of reliance specifically in resource limited settings.

**Session V: Networking for participating countries**

Encouraging networking, work-sharing and reliance in the context of regulation of post-approval changes:
Dr. Dianliang Lei informed the participants how important networking and work-sharing are in the context of global vaccine supply.

During his presentation, it was agreed that reliance and mutual recognition were useful mechanisms to assist less experience NRAs and accelerate variation approval.

It was needed to build capacity to be able to assess a dossier when there was an urgent need of vaccine supply and an assessment had not been received by the country of origin/NRA of reliance.

It was proposed that development of database on regulatory activities such as lot release, MA, or PAC and sharing the relevant information and country’s experience with the others should be encouraged. Besides vaccine, the other biological products especially biosimilars were proposed for information sharing.

It was also agreed that ICH Q5E and EMA guidelines can be a source of information for PAC.

Round table discussion on the regulation of post-approval changes:

All participants were requested to provide their opinions on identification of area for improvements, needs from the countries, and implementation plan for the regulation of vaccine post-approval changes as well as feedback on the workshop.

All participants agreed that this workshop was very useful and WHO guidelines provided clear guidance for the users. However, the categories of changes and approval timelines in some countries were different from WHO guidelines. Some countries had only two categories, major and minor. Some countries had already amended their regulations following WHO Guidelines.

Regional networking with MOU to recognize was encouraged. In the African region, AVAREF Networking had been established but there was no recognition between members because there were different competencies. Capacity and trust needed to be built in order to be comfortable to recognize the decision of other NRAs in the network. The question on how to approve the changes which had not yet been approved by the NRA of country of origin was also raised.

The establishment of electronic data base of post approval changes was also proposed as it would be useful for information sharing among the members of the network.

The participants encouraged WHO to harmonize this WHO guidelines for procedures and data requirements for changes to approved vaccines with the one developed by the prequalification team.

Some areas for improvement of the workshop were also raised including clearer background information in some case studies should be provided such as the quality of supporting data submitted as well as examples of supporting data and how to assess them should be added in the case studies. Capacity building in good review practice for the supporting data was also requested.
Authors:

Mrs Teeranart Jivapaisarnpong, Thailand, Dr Lorenzo Tesolin, Sciensano, Belgium, Dr Heidi Meyer, PEI, Germany and Dr Dianliang Lei, WHO, Geneva, Switzerland on behalf of the WHO Workshop to implement WHO Guidelines for procedures and data requirements for changes to approved vaccines.
Appendix 1: Meeting participants

Dr Khadija Radhi Alzaimoor, Pharmacist, National Health Regulatory Authority, Manama, Bahrain; Dr Hebatalla Abdelsalam Ibrahim, Head of Biologicals Registration Department

Egyptian Drug Authority, Cairo, Egypt; Dr Reem Mahmoud Eltanahy, Head of Biologicals Variation Unit, Egyptian Drug Authority, Cairo, Egypt; Dr Talat Ghane, Technical experts at Biologic Department, Iran Food and Drug Administration, Tehran, Islamic Republic of Iran; Dr Maryam Ahmadzadeh, Technical experts at Biologic Department, Iran Food and Drug Administration, Tehran, Islamic Republic of Iran; Dr Suna Mohammad Habahbeh, Senior Regulatory Affairs Specialist, Jordan Food and Drug Administration, Amman, Jordan; Dr Ameena Mohd Haj Hussein, Regulatory Affairs Officer, Jordan Food and Drug Administration, Amman, Jordan; Ms Roula Fawaz (apology), Ministry of Health, Beirut, Lebanon; Dr Hussain Al Ramimmy, Director of Pharmacovigilance and Drug Information, Ministry of Health, Muscat, Oman; Dr Nabila Al Lawati, Director of Central Quality Control Laboratory, Ministry of Health, Muscat, Oman; Ms Mariam Al Shaibi, National Supervisor of Immunization, Vaccine Preventable Disease Section, Ministry of Health, Muscat, Oman; Ms Noura Al Farsi, National Supervisor of Immunization, Vaccine Preventable Disease Section, Ministry of Health Muscat, Oman; Dr Shaikha Sulaiman Al-Wahibi, Rapporteur of Stability Committee, Ministry of Health, Muscat, Oman; Ms Shaimaa Hamed Naser Al Salmi, Senior Lab Analyst, Ministry of Health, Muscat, Oman; Ms Rim Ali Al Kharusi, Pharmacist, Stability Studies and Analytical Requirements Evaluation Committee, Ministry of Health, Muscat, Oman; Ms Shaimaa Hamed Al-Burtamani, Quality Control Laboratory Technician (Biotechnologist), Ministry of Health, Muscat, Oman; Dr Wafa Salim Al Shukaili, Pharmacist, Drug Registration Department, Ministry of Health, Muscat, Oman; Dr Abdulaziz Sulaiyim Al Shukaili, Pharmacist, Drug Registration Department, Ministry of Health, Muscat, Oman; Mrs Aisha Irfan, Additional Director, Biological Evaluation and Research Division, Drug Regulatory Authority of Pakistan, Islamabad, Pakistan; Ms Haleema Sharif, Assistant Director, Biological Evaluation and Research Division, Drug Regulatory Authority of Pakistan, Islamabad, Pakistan; Dr Masheal Saad Al Nufeay, Scientific Evaluation Specialist, Efficacy and Safety Department, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Dr Naser Obed Aldosri, Scientific Evaluation Expert, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Dr Hind Ali Mohamed Ali, Pharmacist, Assessor Dossier, Human Medicines Section, Directorate General for Registration, National Medicines and Poisons Board, Khartoum, Sudan; Dr Isra Abdelmuneim Elamin Dawelbait, Pharmacist, Variation Section, Directorate General for Registration, National Medicines and Poisons Board, Khartoum, Sudan; Dr Razan Saluta, Deputy of Minister of Health, Pharmaceutical Affairs, Ministry of Health, Damascus, Syria; Dr Manar Kamel, National Immunization Programme, Primary Health Care, Ministry of Health, Damascus, Syrian Arab Republic; Dr Imen Mersni, Directorate of Pharmacy and Medicines, Ministry of Health, Tunisia; Dr Sonia Ben Amor, National Laboratory for Medicines Control, Ministry of Health, Tunisia; Dr Sultana Essa Omer Ali Binhaider, Pharmacist, Ministry of Health and Prevention, Abu Dhabi, United Arab Emirates; Dr Muna Ali Hamdan Ali Alhammadi (did not
come), Pharmacist, Ministry of Health and Prevention, Abu Dhabi, United Arab Emirates; **Dr Reshma Ashoky Dharamus (did not come)**, Assessor, Tanzania Medicines and Medical Devices Authority, Dar Es Salam, Tanzania; **Dr Tryphone Octavian Gujema (did not come)**, Desk Officer, Variation in Approved Vaccines, Tanzania Medicines and Medical Devices Authority, Dar Es Salam, Tanzania.

**MANUFACTURERS**
Dr Talie Sabouni (did not come), Technical Responsible for Vaccines, Pasteur Institute, Tehran, Islamic Republic of Iran; **Dr Majid Teymoori (did not come)**, Project Manager for Vaccines, Biosun Pharmed Company, Tehran, Islamic Republic of Iran.

**FACILITATORS**
The workshop was facilitated by: Dr Heidi Meyer, Section Viral Vaccines, Paul-Ehrlich-Institut, Langen, Germany; Dr Lorenzo Tesolin, Batch release of vaccines, In vivo & Immunology Unit, Sciensano, Belgium, Mrs Teeranart Jivapaisarnpong, National Pharmaceutical Facility, King Mongkut’s University of Technology Thonburi, Bangkok, Thailand; Dr Houda Langar, Regional Advisor, Regional Adviser and Unit Lead, Access to Medicines and Health Technologies, World Health Organization, Regional Office for the Eastern Mediterranean, Cairo, Egypt and Dr Dianliang Lei, Norms Technical Standards and Specifications Unit (TSS), Health Products Policy and Standards Department, Access to Medicines and Health Products, World Health Organization, Geneva, Switzerland.

**WHO**
Dr Jean Jabbour, WHO Representative, Oman; **Dr Houda Langar**, Regional Advisor, Regional Adviser and Unit Lead, Access to Medicines and Health Technologies, World Health Organization, Regional Office for the Eastern Mediterranean, Cairo, Egypt; **Mrs Maryan Mounir Selwanis**, Programme Assistant, Access to Medicines and Technologies, WHO/EMRO, Cairo Egypt; Ms Nathalie Khawam, UN Volunteer, WHO, Oman; **Dr Dianliang Lei**, Scientist, Technical Standards and Specifications Unit (TSS), Health Products Policy and Standards Department, Access to Medicines and Health Products, World Health Organization, Geneva, Switzerland.
Appendix 2. Agenda

WHO Workshop on Implementation of Guidelines for procedures and data requirements for changes to approved vaccines

8-10 November 2022

Venue: Muscat Oman

Day 0 (7 November)

Pre-meeting with Facilitators to review agenda, presentations and case studies.

Chairperson: Heidi Meyer

Rapporteur: Lorenzo Tesolin and Teeranart Jivapaisarnpong

Day 1

Session I Opening of the meeting
8.30-9.00 Registration
9.00-9.30 Opening Remarks & Welcome Speech

CO WHO/MoH Oman

Self-introduction All participants

Housekeeping announcement Houda Langar

Group Photo

9.30-9.50 Update on WHO position on post-approval changes in the context of WHO biological standardization and objectives of the workshop

D Lei, WHO

9.50-10.00 Discussion

10.00-10.30 Coffee break

Session II WHO Guidelines for post-approval changes
10.30-11.00 WHO Guidelines for procedures and data requirements for changes to approved vaccines: purpose and general principles

D Lei

11.00-11.30 How to use WHO Guidelines on post-approval changes

H Meyer
<table>
<thead>
<tr>
<th>Time</th>
<th>Session/Activity</th>
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<tr>
<td>11.30-12.00</td>
<td>Discussion</td>
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<tr>
<td>12.00-13.00</td>
<td>Lunch Break</td>
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<tr>
<td><strong>Session III:</strong></td>
<td>Current approaches of regulation of post-approval changes</td>
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<td>13.00-15.00</td>
<td>Current practices of regulation of post approval changes to vaccines, biologicals in selected participating countries Egypt, Iran, Saudi and UAE (apology)</td>
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<td>15.00-15.30</td>
<td>Coffee Break</td>
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<td>15.30-16.10</td>
<td>Industry’s experiences and perspectives</td>
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<td>Pasteur Institute and Biosun Pharmed Company (apology)</td>
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<td>16.10-17.00</td>
<td>A round table discussion and feedback on day one</td>
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<td>all participants</td>
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<td>facilitators</td>
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<td><strong>Day 2:</strong></td>
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<td><strong>Session IV:</strong></td>
<td>Recommendations in WHO Guidelines for post-approval changes</td>
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<td>9.00-10.30</td>
<td>Reporting procedures and data requirements for quality changes – Changes to antigens and final products</td>
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<td>L Tesolin, H Meyer</td>
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<td>10.30-11.00</td>
<td>Coffee break</td>
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<tr>
<td>11.00-11.10</td>
<td>Presentation on case studies</td>
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<td>L Tesolin, H Meyer</td>
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<td>T Jivapaisarnpong</td>
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<td>11.10-12.30</td>
<td>Case study 1-5 – examples of quality change and labelling information changes to vaccines</td>
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<td>Participants</td>
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<td>facilitators</td>
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<td>12.30-13.30</td>
<td>Lunch break</td>
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<tr>
<td>13.30-14.00</td>
<td>Preparation of the outcomes of the group discussion</td>
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<td>Group work</td>
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14.00-15.30 Reporting of the outcomes of group and discussion

15.30-16.00 Coffee break

16.00-16.30 Special considerations on:
  - multiple changes application
  - expedited review procedures in special or urgent circumstances
  - seed virus changes for seasonal influenza vaccines

  *T Jivapaisarnpong*

16.30-17.00 discussion and feedback on day two

  *Participants*  
  *facilitators*

17.00 Closure of the day

**Day 3,**

9.00-9.30 Reporting procedures and data requirements for efficacy, safety and labelling information changes

  *H. Meyer*

9.00-10.30 Group on Case studies

  5 Case studies (efficacy, labelling info focused

  Preparation of the outcomes of the group discussion

  *Group work*

10.30-11.00 Coffee break

11.00-12.30 Preparation and Reporting of the outcomes of group and discussion

  *Group 1-5*

12.30-13.30 Lunch break

13.30-13.45 Considerations on time frame of evaluation of post-approval changes

  *L Tesolin*

**Session V  Networking for participating countries**

15.15-15.45 Encouraging networking, work-sharing and reliance in the context of regulation of post-approval changes

  *D Lei*
Round table discussion on the regulation of post-approval changes:
  identification of area for improvements
  needs from the countries
  Implementation plan
  Feedback on the workshop

Participants and Facilitators

15.45-16.00  Closing of the meeting