Meeting Report

Informal consultation on WHO biosafety risk assessment and guidelines for the production and quality control of novel human influenza candidate vaccine viruses and pandemic vaccines

Domaine de Penthes, Geneva, Switzerland
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Executive Summary

At the beginning of an influenza pandemic it is necessary to produce Candidate Vaccine Viruses (CVVs) quickly and safely so that vaccine manufacture can begin expeditiously. CVVs are produced by only a few laboratories such as those associated with the World Health Organization’s (WHO) Global Influenza Surveillance and Response System (GISRS), manufacturers, national regulatory authorities and other specialist laboratories. Safety is a priority to protect operators and the environment. The facilities must be secure to ensure that CVVs and influenza viruses with pandemic potential (IVPP) do not escape from laboratories and affect animals and possibly reassort to threaten humans. The WHO Technical Report Series (TRS) No.941, Annex 5 (1) document published in 2007 gives expert guidance to specialist laboratories on the safe handling and production of CVVs and IVPP. In light of knowledge and experience gained over the past decade and in response to the request from stakeholders, WHO initiated the revision of the TRS No.941, Annex 5 in 2017. WHO organized a working group meeting, held in Geneva from 9 to 10 May 2017, to review up-to-date practice and knowledge on the safe production of influenza vaccines, identify gaps in the current TRS and discuss key issues that need to be addressed (2). A draft revised guideline was produced and made available subsequently for public consultation and reviewed by a broad group of experts including those from academia, industry and regulatory authorities, resulting in a further revised draft with a new structure and updated sections. WHO then organised this informal consultation meeting on 23-24 April, 2018, held in Geneva to discuss the new draft, the public comments received, and propose further improvements to the document. The outcomes of this meeting would help further development of the guidelines which will then be subject to a second round of public consultation and the final draft guidelines will be considered by the Expert Committee on Biological Standardization (ECBS) in October 2018.

I. Introduction

The World Health Organization (WHO) published the “biosafety risk assessment and guidelines for the production and quality control of human influenza pandemic vaccines” in 2007 in the Technical Report Series (TRS) No. 941, Annex 5 (1). This guideline provides guidance to regulators, public health authorities, research laboratories and vaccine manufacturers on safe handling and testing of human influenza pandemic viruses during vaccine development, production and evaluation. In light of knowledge and experience
gained over the past decade and in response to the request from stakeholders, WHO initiated
the revision of this document in 2017. A working group meeting was convened to review up-
to-date experience, discuss the gaps, reach consensus on the scope, outline and key issues of
the revision (2). Subsequently, a draft revised document with a new structure and updated
sections was prepared and posted on the WHO website for a first round of public consultation
during late November 2017- mid February 2018. Comments were received from experts
including academic, industry, public health and regulatory experts. WHO then organized this
informal consultation meeting on 23-24 April 2018, in Geneva to discuss the public
comments, review a proposed new draft, and to seek consensus on the content and proposals
for further improvements to the document before expected submission to the Expert
Committee on Biological Standardization (ECBS) in October this year.

The meeting was attended by experts and representatives of WHO Collaborating Centres
(CC) and Essential Regulatory Laboratories (ERL) for influenza, national regulatory
authorities for vaccine regulation and for biosafety/biocontainment, World Organisation for
Animal Health (OIE), industry - the International Federation of Pharmaceutical
Manufacturers and Associations (IFPMA) and the Developing Country Vaccine Manufacturers Network (DCVMN), and WHO staff from relevant programmes.

The meeting was chaired by Dr Jerry Weir. Dr Gary Grohmann was the Rapporteur.

II. Background, objectives and presentations on relevant issues

Dr Ivana Knezevic welcomed all participants to the working group meeting and provided an
update on WHO biological standardization activities. Her presentation on global standards
and norms covered global written standards (which involved tools for appropriate regulation
of quality, safety and efficacy) and global measurement standards (which involved tools for
product development, licensing and lot release). The promotion, monitoring and update of
these documents and activities are a WHO core function with the support of long standing
expert groups. Moreover, WHO has a unique role to support regulatory authorities
throughout the world - WHO Guidelines are meant to complement guidance issued by other
bodies, not to create conflicts or ambiguity between guidelines.
Dr Knezevic presented information on new WHO written standards established by the ECBS in October 2017 (published in WHO TRS No.1011), which included: Guidelines on the quality, safety and efficacy of Ebola vaccines; Procedures and data requirements for changes to approved biotherapeutic products; Rapid diagnostic tests for HIV infection for professional use and/or self-testing and establishing the stability of in vitro diagnostic medical devices. A number of international measurement standards were established by ECBS in Oct 2017 – these included: the first international standard (IS) for potency assays of Oral Polio Vaccines (monovalent and bivalent); the first IS for anti-Typhoid capsular Vi polysaccharide IgG (human); the first IS for Vi polysaccharide; the third IS for Pertussis toxin; the first IS for Ebola virus antibodies, and the first IS for antiserum to Respiratory Syncytial Virus. She reminded the participants that the next meeting of the ECBS is scheduled from 29 October – 2 November 2018 and the following proposed written standards would be considered by ECBS: recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines; biosafety risk assessment and guidelines for the production and quality control of novel human influenza candidate vaccine viruses and pandemic vaccines (the subject of this consultation) and guidelines for the safe production of polio vaccines. In addition, the following projects were in preparation for ECBS in 2019: Guidelines for RSV vaccines; and new projects involving “Nucleic acid based vaccines of importance for priority pathogens for public health emergency” including the revision of guidelines for DNA based vaccines and points to consider on RNA based vaccines.

Dr Tiequn Zhou introduced the process of developing and revising WHO written standards, which is based on wide scientific consultation and international consensus. These are living documents that may be revised in response to scientific advances. Dr Zhou explained why a revision of TRS 941, Annex 5 was underway as the Guidelines are more than 10 years old (developed in 2005, published in 2007) and since 2007, technologies have evolved in influenza virus testing and vaccine production and knowledge and experience have increased. There had also been calls for a review and revision of the Guidelines from various stakeholders to accommodate the evolving situation in a pandemic.

Dr Zhou focused on a number of key challenges regarding the handling of influenza CVVs including: the potential for a new or novel influenza pandemic virus to emerge and pose a threat to human health; the unpredictable nature of influenza pandemics; the need for sufficient and appropriate characterization and safe handling/containment of CVVs and
associated hazardous biological materials which are essential for the production of influenza vaccines for a pandemic, and the need for international guidance and harmonized criteria. Dr Zhou highlighted that CVVs need to be made available to manufacturers as quickly as possible to enable the earliest possible start of vaccine production and deployment during a pandemic and that a risk-based approach was necessary during any emergency response. Thus, there is a need for WHO guidance documents to be flexible so as to accommodate the evolving situation in a pandemic.

Dr Zhou reminded the participants that the purpose of this meeting was to bring together experts representing interested parties (including WHO CCs, ERLs, vaccine and biosafety regulators, manufacturers and other partners), to discuss the key issues raised from the public consultation, propose further improvements and achieve consensus on the guideline towards its finalization and submission to ECBS in 2018. She encouraged the strong participation of all participants in the discussions. There is a stringent timeline as follows: following this consultation meeting a further draft will be prepared and circulated among participants for review during May; a final draft will be prepared during June and then submitted to ECBS in early July; during July-September the draft will be subject to a second public consultation via the WHO website. The comments from public consultation will then be analysed and addressed at the 69th ECBS meeting, along with the review of the proposed guidelines, during 29 October-2 November 2018 where the Committee will decide whether or not to approve the document. If approved, the document will be published on WHO website.

Dr Gary Grohmann gave a presentation focusing on the key issues raised during the public consultations on the draft revised guideline. He reiterated that there was a strict timeline to reach the ECBS and that the input from all participants was critical. He reminded participants that the TRS 941, Annex 5 document was critical guidance to CVV and GISRS laboratories, national regulators and all manufacturers, as well as other international organizations such as the OIE and national competent authorities. Also, he noted that during a pandemic threat speed was necessary to make a CVV available safely and quickly; this is the first step in a GMP process that is needed to protect operators and manufacturing processes as well as the environment and the CVV/reagents. Further, wider safety issues need to be considered as vaccines are destined for healthy individuals of all age groups. Dr Grohmann reminded participants of the recommendations from the working group meeting in May 2017 as
reported previously (2) and then presented a summary of the issues already addressed since then in the current draft, which included the following updates:

- The guideline was expanded to cover influenza viruses of all subtypes.
- The guideline was given a new title to reflect the above change.
- It was proposed that the new revision would replace the WHO TRS 941 (Annex 5) and also specific WHO documents and updates on H1N1 and H7N9.
- The structure of the document was changed and streamlined to include three main sections: hazard identification, safety testing of CVVs, and risk assessment and management.
- All sections were updated and streamlined to account for new knowledge. References were also updated.
- The hazard identification section now included: vaccine viruses (also covering future options, such as vectored vaccines using other viruses; virulence factors associated with donor and wild type (wt) viruses, receptor specificity, transmissibility, cleavability, stability, drug resistance; manufacture in different substrates (eggs, cells); hazards from the vaccine; and genetic stability. The new guideline also includes the use of other potential backbones, backbones with altered genes and synthetic viruses.
- A clear distinction between hazards and mitigating factors/measures was implemented in the revised guideline.
- Receptor specificity information was deleted.
- The number of categories of vaccine viruses was reduced from 8 to 6.
- Genetic stability and sequence identification for all categories of CVVs was included.
- The plaque assay (+/- trypsin) requirements for CVVs derived from LPAI viruses of subtype H5 and H7 were reduced.
- The requirement to conduct IVPI for CVVs derived from LPAI viruses of subtype H5 and H7 was removed. The test will only be conducted for CVVs derived from HPAI viruses of subtype H5 and H7.
- The testing schedule i.e. Table 1 for safety testing of CVVs was updated as follows:
  - CVVs derived from zoonotic or pandemic influenza viruses are required to be safety tested.
CVVs may be shipped before the completion of the ferret pathogenicity test and can be handled in BSL-2 laboratories with BSL-3 precautions and an expert WHO working group will define safety testing requirements;

- The revised testing requirements are now documented in the revised Table 1 of the guideline.
- The testing of CVVs in mice was removed and ferret pathogenicity and the chicken pathogenicity tests are now limited to certain CVVs
- Similar CVVs will not require animal testing.

- A CVV with a new backbone (i.e. one that is not PR8 or one of the two approved LAIV backbones) will require animal testing
- Biocontainment levels are to be determined on the basis of risk assessment
- The IFPMA White Paper was largely taken into account into the revision (section 6)
- Manufacturers will be allowed to proceed with pandemic vaccine production prior to completing safety testing during a pandemic alert period, provided agreed-upon BSL safety conditions can be met.
- Regarding mitigation of possible exposure, vaccination and antivirals are recommended, as well as medical surveillance of staff. The use of experimental vaccines was deleted in the text.

Dr Grohmann then presented a summary of the key comments from the 1st public consultation that needed to be discussed in this meeting, these included: definitions and consistent use of terms was required e.g. ‘donor virus’ ‘parent virus’, BSL, the need for an IVPI threshold for HPAI viruses, the use of terms such as hazard, risk and likelihood of harm, and the issue of repetition between Sections 4 & 6 which still needed consolidation.

Pathogenicity testing of CVVs in ferret model needed further discussion, agreement and conclusion by the participants. There was a question on whether or not full sequencing of the CVV was required and if trypsin for virus growth would be a requirement for live virus vaccines. There were requests to elaborate on the reasons why safety tests in chickens and ferrets were no longer required for HPAI H5 and H7 viruses. Overall, the table and appendix needed discussion, review and consensus at this meeting. For section 6, the 14-day quarantine recommendation for staff exposed to IVPP or a pandemic CVV needs to be finalized. He proposed that the group live edit each section to bring each issue to a conclusion.
Dr Kazunobu Kojima presented an update on the revision of the WHO Laboratory Biosafety Manual (LBM), which was last revised in 2004 (3). It was argued, using examples, that very few people had been exposed to pathogens from current containment measures and that some of these stringent conditions could be relaxed on the basis of risk assessment with more effort being put on updated Standard Operating Procedures and training. Moreover, that high containment facilities brought further added challenges of ongoing costs, sustainability, staff training and various technical challenges. Dr Kojima argued that there should be an emphasis on risk assessment and training rather than having the best designed and engineered facilities. The revised LBM would propose a practical, risk-and evidence-based approach to biosafety while maintaining flexibility, upholding Good Laboratory Practice and encourage the building of cheaper but sustainable facilities. Dr Kojima proposed that a designated risk group (hazard group) did not equal biosafety level and described a number of situations where risk factors affected possible consequence, e.g. pathogens with high severity/mortality, procedures with a high likelihood of exposure, and procedures with a low likelihood of exposure. Dr Kojima stated that this was the basis of risk assessment which led to a new proposed risk assessment model involving new classifications or work areas in the laboratory i.e. Core requirements (BSL2 equivalent); Heightened control measures (BSL2-3 equivalent); and Maximum containment (BSL4 equivalent). WHO’s plan of action involved the creation of a central core document with additional monographs that go into detail on several key aspects including: Risk assessment, Biosafety programme management, Laboratory design and maintenance, Biological safety cabinets and isolators, PPE, Decontamination and waste management, and emergency/outbreak response. Further, a position paper would be published prior to release of the LBM to outline the rationale for the changes.

Dr Wenqing Zhang gave a presentation on ‘Biosafety Activities by the Global Influenza Programme (GIP)’. Various approaches and current guidance documents were outlined such as the general recommendations covered by the WHO laboratory biosafety manual, and the transport and vaccine related issues covered by WHO GISRS and TRS guidance. General biosafety principles were then discussed which involved the protection of the individual, use of PPE, protection of the environment, appropriate conditions for specimen transport and receipt as well as appropriate waste disposal. Regarding biosafety level (BSL), every biosafety level must have appropriate equipment, appropriate practices and appropriate procedures for the safe conduct of work; the four levels of containment laboratory are: biosafety levels 1 and 2 - basic laboratories; biosafety level 3 - containment laboratories, and
biosafety level 4 - high containment laboratories. BSL2-3 levels may also have extra enhancements. Diagnostic and health-care laboratories must all be at BSL2 at a minimum. Regarding GISRS laboratories: the National Influenza Centres adhere to their national and/or international biosafety standards for work with influenza viruses and also adhere to national and international regulations on the transport of dangerous goods when shipping clinical specimens and/or virus isolates; while WHO Collaborating Centres and H5 Reference Laboratories must have full and unrestricted access to BSL3 laboratory facilities that meet recognized international and national standards. These laboratories must also be able to assess the bio-risk associated with the handling and storage a pandemic influenza virus. Containment for IVPP and CVVs is based on a case-by-case risk assessment as recommended by a WHO expert group defining safety testing and BSL requirements. Dr Zhang noted the final responsibility for the identification and implementation of appropriate containment measures for handling and storage of a pandemic influenza virus lies with individual countries and the national competent authorities.

Dr Othmar Engelhardt gave a presentation on ‘The development of influenza virus pathogenicity standards for safety testing’. He reiterated that CVVs were crucial for the production of influenza vaccines and that CVVs and IVPP required safety testing, including pathogenicity testing in ferrets. The laboratories currently generating CVVs for IVPP are the US CDC, CBER (US FDA), St Jude Children’s Research Hospital, NIBSC, the China CDC and NIID as well as contracted specialist laboratories such as the NYMC and Seqirus in Melbourne, but there are also new laboratories interested in these activities and they will also require ferret pathogenicity testing. While there were no major issues expected in developing standards for such tests, there were a few factors to consider, including: the likely variability of the ferret test which may lead to complex data; possible difficulties in setting cut-offs and ranges; and, the supply of suitable animals may be a factor. In October 2107, ECBS gave partial endorsement to the proposal of developing virus standards for ferret pathogenicity test and ECBS will review the progress and consider the proposal again in the future. It was clear that agreement needs to be reached on the use of wt viruses and CVVs as standards between participating laboratories and that a preliminary collaborative study will be required prior to submitting this proposal to ECBS (planned submission in 2019).

III. Review of the draft guidelines
The review of Sections 1-4 and then 6 was led by Dr Gary Grohmann and Dr Jerry Weir. These sections were reviewed and live edited by the participants. The comments received from the 1st public consultation were generally accepted however, comments which were rejected or partially accepted were done so with justifications and the document updated accordingly. There was agreement that the areas of repetition in sections 4 and 6 needed to be rationalized and paragraphs dealing with manufacturing risks were consolidated into section 6 and those dealing with hazards and virulence were consolidated into section 4. Regarding the definition of BSL it was agreed that the current terminology of BSL1-4 would remain in the document as per the current WHO Laboratory Biosafety Manual (2004) (LBM) (3) and future changes to the WHO LBM would be taken into consideration when the next edition is published. Furthermore, it was not yet clear if the proposed changes to the LBM would be accepted or require further comment and that until there was clarity around this issue, the TRS document should continue to use the BSL1-4 classifications.

It was agreed in the previous working group meeting that safety testing of CVVs should stand as a separate section (Section 5) linked to a table listing the required safety testing of different CVVs and proposed containment levels for vaccine production, and that an appendix describing testing for the attenuation of influenza CVVs in ferrets should be added. Dr Engelhardt led the discussion on the review of Section 5, the Table 1 and the Appendix 1. It was agreed to accept the changes suggested from the public consultation and to remove the specific reference to so-called synthetic H5 and H7 CVVs in Table 1. The term “BSL3 large scale manufacturing” was also removed but detailed specifications would be provided in the guidelines for production scale activities e.g. BSL3 (production facilities). Further clarity was given to the use of the terms BSL2 enhanced and BSL3. It was agreed that genetic stability testing should be performed on all CVVs, including on wt viruses, if the latter are proposed for use in manufacturing; moreover, genetic stability testing should consist of 6-10 passages in a relevant substrate (eggs or cell culture). It was further agreed that while genetic stability testing was important to be performed it should not delay the distribution and use of the CVVs by manufacturers, as genetic stability testing could be performed subsequently. It was agreed to remove the test on ability to cause chicken embryo death from the safety testing schedule because this test does not provide additional useful information: for CVVs derived from HPAI, only the intravenous chicken pathogenicity index (IVPI) test is internationally accepted.
The need for the ferret test in all cases was discussed; the group agreed that, to achieve the highest level of confidence in the safety of a CVV, the ferret test should be kept in most cases (see Table 1 of the draft guideline). The WHO CCs/ERLs present at the consultation (CDC, NIBSC, St Jude’s) are still reviewing historical data on ferret testing in their labs in order to propose a revision of the protocol including attenuation criteria. It was agreed that comparison with wt virus in the ferret test should be abandoned and that the chicken pathogenicity test (IVPI) should only be conducted for CVVs derived from HPAI viruses of subtype H5 and H7. Unfortunately, not all invited participants could attend the meeting and it was decided to add their input post meeting.

Finally, after extensive discussion it was agreed to modify the title of the proposed guidelines to ‘Guidelines for the safe development and production of vaccines to human influenza pandemic viruses and viruses with pandemic potential’, to better reflect the contents of the document. It was agreed that the document should be open to future developments in the field of CVVs, e.g. the option of having more vaccine virus segments (i.e. more gene segments than HA and NA from wt vaccine virus), or having more than one backbone donor virus in one CVV, resulting in a variety of gene constellations.

There were a number of other issues raised during the discussion, including: the guideline should give clear guidance on the requirements for safety testing before and after distribution of CVVs - this is particularly important in response to a pandemic; there should be cross reference in this document with the WHO TRS guidance for inactivated and live attenuated influenza vaccines; some countries may need help to conduct risk assessment.

**IV. Conclusion and next steps**

During the 2-day meeting, participants reviewed the proposed draft document focusing especially on the safety testing and biocontainment aspects of CVVs/IVPP and pandemic influenza vaccine production, reached consensus on certain issues and proposed improvements towards finalizing the document for submission to ECB in due course. These are summarized as below:

1. The title of the guideline has been revised.
2. The scope of the guideline has been further clarified and expanded to cover all subtypes.
3. The structure of the guideline has been further streamlined and areas of similarity consolidated. Further revisions were made for better clarity where needed.

4. WHO CCs/ERLs (CVV-testing labs) will review historical data on ferret test and propose criteria to be included in the revised ferret test protocol.

5. Regarding defining BSL it was agreed that the current terminology of BSL1-4 would remain in the document as per the current WHO Laboratory Biosafety Manual (2004) (LBM) (3) and future changes to the WHO LBM would be taken into consideration when the next edition is published. Furthermore, as it was not yet clear if the proposed changes to the LBM would be accepted or would require further comment and until there was clarity around this issue, the current draft guidelines will continue to use the BSL1-4 classifications.

6. All the terminology in the document was reviewed and will be harmonized/standardized post meeting e.g. the use of the terms backbone donor virus, CVV and IVPP; the use of the BSL was also streamlined as described above in point 5.

7. Some participants agreed to provide up-to-date references post meeting which will be added to the next draft.

8. A further draft document will be prepared and shared with the participants of this meeting in May for final comment. Subsequently a final draft will be prepared and submitted to ECBS in early July followed by a 2nd round of public consultation. All comments will then be analysed and addressed, along with the review of the draft guidelines, at the 69th ECBS meeting during 29 October-2 November 2018 where the Committee will decide whether or not to approve the document. If approved, the document will be published on WHO website.

9. Participants also recommended that the process of WHO expert review of safety testing data for CVVs/IVPP should be formalized to provide recommendations to stakeholders.

References


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