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Meeting Report

WHO Informal consultation for the guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related biological products intended for the prevention or treatment of human infectious diseases

Royal Society of Medicine (in-person and virtual), London, United Kingdom
28-30 November 2022[1]

[1]Disclaimer: This report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned.

Day 1

Introduction

An Informal Consultation on the draft WHO *Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related biological products intended for the prevention or treatment of human infectious diseases* was held at the Royal Society of Medicine, London, 28th-30th November 2022. Nineteen invited participants included members of the drafting group as well as representatives from academia, industry and regulatory authorities. In addition, six WHO staff participated either in person or virtually. The meeting was opened by **Dr Richard Isbrucker** (WHO, Norms & Standards for Biological Products (NSB) Team, Switzerland) who briefly outlined its objectives. These were to review the comments received on the first draft of the guidelines which had been posted for public consultation in August 2022, to discuss the key issues identified, as well as to exchange scientific and regulatory experiences and perspectives pertinent to the guidelines and to propose revisions to the text. It was also expected that the Consultation would provide WHO with some feedback on the strengths / weaknesses of the guidelines, the future of these products and an awareness of potential further needs regarding monoclonal antibodies (mAbs) against infectious diseases.

Dr Clive Ondari, Director, Health Products, Policy and Standards (WHO, Switzerland), welcomed participants on behalf of WHO drawing attention to the importance of standardization of the quality, safety and efficacy of the growing number of mAbs coming into clinical use as technical advances enable increased yields, product sophistication and a wide range of uses including prevention or treatment of infectious diseases such as malaria, RSV, rabies and HIV. Dr Ondari noted that the use of mAbs against infectious diseases was particularly important in situations where immunization of the target population was not possible, such as in the immunocompromised or in situations of public health emergencies. He noted the WHO prequalification of the first mAb against an infectious disease, which was to treat COVID-19, and which would now allow access to UN procurement programmes. Nevertheless, access to these sophisticated biological medicines was still an issue especially in low- and middle-income countries (LMICs) where mAbs against infectious diseases would be particularly important. Dr Ondari reminded the Consultation that the WHO Expert Committee on Biological Standardization (ECBS) at its meeting in April 2022 had already adopted technologically up to date guidelines for the production and quality control of mAbs and related products for medicinal use in general, which was a major step forward. It was clear that specifications and expectations would now be needed for the nonclinical and clinical evaluation of mAbs for preventing or treating infectious diseases. It was expected that clarifying issues unique to the evaluation of mAbs against infectious diseases would help harmonize regulatory expectations during their development and licensing and, in due course, facilitate their global access. He thanked Dr D McManus for Chairing the current consultation, Dr E Griffiths for acting as Rapporteur and Dr R Isbrucker and the NSB team for organizing the event. He added that the NSB team had considerable experience in vaccines and biotherapeutics for many years and thanked them for their work.

Following self-introductions by all participants, Dr Isbrucker reviewed the declaration of interests of participants according to WHO procedure. These were judged as not being an impediment to all those present from participating in the meeting. He then announced that that the Consultation would be Chaired by **Dr Dan McManus** (Health Canada) and that **Dr Elwyn Griffiths** (Consultant, UK) would act as Rapporteur.

Update on WHO activities in Biological Standardization

Dr Ivana Knezevic (WHO/NSB, Switzerland) then provided an update (virtual) on the biological standardization activities of the WHO including the outcomes of recent meetings of the WHO ECBS. She described the WHO measurement and written standards programme for vaccines and other biologicals, explaining that the intention of the written standards was to provide key principles for the evaluation of biologicals as a basis for setting national requirements and for WHO Prequalification, leaving space for national regulatory authorities (NRAs) to formulate additional or more specific requirements if so desired. It was emphasized that these were science-based living documents that are developed further in line with progress in scientific knowledge and experience. The implementation of WHO Guidelines and Requirements into regulatory and manufacturing practice was facilitated through global, regional and national workshops involving regulators, manufacturers and relevant experts. It was also noted that WHO guidelines consider guidance issued by other bodies with the intention of complementing them and not to create a conflict.

WHO measurement standards were considered to be essential elements for the development, licensing and lot release of vaccines and biotherapeutics. They are used in the standardization of biological assays, in the further development and refinement of quality control tests and often provide the scientific basis for setting product specifications. The adoption of written standards and establishment of measurement standards are functions of the WHO ECBS, the report of which is published in the WHO Technical Report Series (TRS). Mention was also made of the eight WHO Collaborating Centres for the Standardization and Regulatory Evaluation of Vaccines, which provide input to many WHO standardization projects.

Two virtual meetings of the WHO ECBS had been held in 2022: the 75th and 76th meetings of the Committee. The Executive Summary of the 75th meeting as well as the full meeting report, were already publicly available. It was at this meeting that the WHO Guidelines for the production and quality control of monoclonal antibodies and related products for medicinal use were adopted. The main outcome of the 76th meeting, held in October 2022, was the adoption of two written standards (Recommendations to assure the quality safety and efficacy of poliomyelitis vaccine (oral, live attenuated) and WHO global model regulatory framework for medical devices including in vitro diagnostic medical devices). Additional issues related to written and measurement standards discussed included WHO Guidance on the development of regulatory frameworks for cell and gene therapy products intended to facilitate both the establishment of such frameworks and associated regulatory

convergence, current practice for assigning IU to antibody standards and the evaluation of the potential applicability of emerging and novel assay technologies and analytical methods. In particular, the utility of High Throughput Sequencing (HTS) technologies (deep sequencing) in the quality control of vaccines was extensively discussed. Twenty new and four replacement WHO International reference preparations were also established at this meeting and eight proposals for new standards endorsed. The Executive Summaries of all ECBS meetings are available on the WHO biological standardization website.

Dr Knezevic also provided a list of recently adopted written standards for biologicals, as well as new or revised versions which were under consideration. The revised and updated WHO Guidelines on the evaluation of biosimilars had been adopted by the ECBS at its 75th meeting and it was planned to hold an informal consultation in Q2 2023 to share the experience of using the revised guidelines and to discuss how to increase the efficiency of the regulatory evaluation of biosimilar mAbs. This list also included plans for the development of the general guidelines for the nonclinical and clinical evaluation of mAbs and related products for the prevention and treatment of infectious diseases and noted the future development of disease-specific supplements for COVID-19, RSV, Rabies, Malaria and HIV.

Dr Knezevic concluded by thanking the WHO Norms and Standards for Biological Products team, members of WHO drafting and working groups and colleagues from the Collaborating Centres and Custodian Laboratories as well as many individual experts for their contribution to international biological standardization efforts.

Dr McManus thanked Dr Knezevic for her overview of current standardization activities at WHO and invited comments and questions. A number of points for clarification were raised in the following discussion including the expected timing of the proposed separate infection-specific guidance, for example for rabies, malaria, HIV and COVID-19, which would help industry with time lines and to make sure they are in-line in their development programs, how many of the 194 Member States use the WHO Guidelines and Recommendations as their main regulatory documents, as well as the role of these documents in the WHO Prequalification process.

Dr Knezevic explained that guidelines published by the WHO are intended to be scientific and advisory in nature but that some countries incorporate these documents into their national requirements, whereas others modify sections sometimes into more stringent or more definitive requirements and WHO has no issue with that approach. It would be concerned, however, with a lowering of the guiding principles or making them too flexible. Ideally, the aim of the documents is to promote regulatory convergence. Dr Knezevic also explained the role of WHO Guidelines and Recommendations in the WHO prequalification programme (PQ), for which there was long experience with vaccines. Manufacturers submitting their products for PQ need to follow the appropriate WHO Recommendations and Guidelines, where they exist, thus their importance for the purpose of providing guidance to interested UN agencies and WHO Member States in their procurement

decisions for such products. WHO Guidelines thus form a basis for setting national regulatory requirements and are also the basis for WHO PQ.

As for the timing of the infection-specific supplements were concerned, Dr Knezevic said that the plan is to have an RSV and COVID-19 document ready for consideration by the ECBC in 2023 and those for malaria, rabies, and HIV, ready in 2024, but that this may be a too ambitious a programme of work.

Another issue raised in discussion was that of the clinical use of mAbs against infectious diseases in real life situations. **Dr Erin Sparrow** (WHO, Immunization Vaccines and Biologicals (IVB) Department, Switzerland) explained that IVB is interested in the application of mAbs for the prevention of infectious diseases and has an active monitoring and research programme in this evolving area, following, for example, RSV, HIV, rabies and malaria mAbs. It is developing preferred product characteristics for some of these products. As mAb products in development move closer towards marketing authorization, the issue of their use comes to the fore. The IVB Department will likely be convening meetings around the definition of clinical endpoints and size of trials in the evaluation of specific products in the future, and it is expected that such meetings might identify the need for further work. In response to a question about rabies mAbs, Dr Sparrow mentioned an issue that had arisen, but not yet resolved, which involved the PQ of mAbs against rabies, where such products might be considered as treatment or therapeutic and not preventative and could fall under the PQ procedure for medicines rather than for vaccines. This evaluation pathway is significantly different from that for vaccines. Some mAbs against infectious diseases might be considered vaccine-like but this seemed to be a grey area at present. Participants agreed that it was important that appropriate and clear language be written into the infection-specific supplements so that the PQ process, which follows the drafting and adoption of WHO Guidelines, is less ambiguous in interpretation and outcomes. The possibility of considering therapeutic mAbs separately from those for use in pre-exposure or post-exposure prophylaxis might also be investigated. Discussions between the WHO NSB Team and the PQ team should be undertaken so that any language difficulties or ambiguities can be quickly ironed out (see also presentation by Dr J Ritchey, below).

Background to the monoclonal antibody project

Dr Isbrucker then proceeded to outline the background to the mAb guidelines project and its timelines. He mentioned that mAbs were the leading class of biological therapeutics in clinical use, although mostly in oncology and for inflammatory disorders. To date, very few had been licensed for the treatment or prevention of infectious diseases although in 2020 very many were in development for SARS-CoV-2 and a few had already been licensed for other infectious diseases (RSV, anthrax toxin, *Clostridium difficile* and HIV-1). Nevertheless, it was clear that many others were in development with some having already entered the clinical studies stage of development, such as Ebola, HBV, Zika, dengue, rabies, malaria, influenza, Chagas disease and several toxins. There were many regulatory questions relating to specifications and QC testing of these products and especially

to nonclinical and clinical evaluation of mAbs against infectious diseases. In addition, a report on access to monoclonal antibodies[1] published in 2020 by the Wellcome Trust and IAVI highlighted the fact that access to these products is severely limited in LMICs. This was due to multiple factors including low production yields leading to high costs; however, poor harmonization of licensing/registration processes, lack of harmonization in specifications, regulations and regulatory expectations, as well as limited knowledge, experience and capacity in the evaluation of mAbs were also contributing factors hindering accessibility to these products in LMICs. A review of WHO guidance documents relevant to mAbs had revealed that these were primarily focused on non-communicable diseases and provided little direction on nonclinical and clinical evaluation of mAbs for pre-exposure or therapeutic indications to infectious against diseases. Based on the outcomes of the review, a proposal was made to the ECBS in December 2020 to draft two separate guidelines: one on the production and quality control of mAbs regardless of therapeutic intent and which would include newer production technologies, and a separate guideline on the nonclinical and clinical evaluation of mAbs intended for the prevention or treatment of infectious diseases. As already mentioned, this would be a general document applicable to all infecting organisms and their bioactive products (e.g., bacterial toxins) but with disease-specific supplements to provide additional regulatory considerations as appropriate.

Dr Isbrucker described the intended scope of the guideline on the nonclinical and clinical evaluation of mAbs to human infectious diseases which should include mAb fragments, conjugates, bi-specific and co-formulated products, as well as mAb mimetic proteins. Also, they would apply to mAbs directed against any pathogen-derived products such as bacterial toxins. However, the guideline would not apply to nucleic acid-encoded mAbs, nor to those which targeted endogenous human antigens such as cytokines which may be expressed in response to an infection, nor to veterinary products. Also, they would not contain pathogen-specific guidance except when provided as examples. Such guidance would be provided subsequently in short companion type documents specific to a particular disease and would include background on the infecting agent, pathology, epidemiology, modes of transmission, known key antigens, epitopes and variants, as well as nonclinical study information such as animal models and *in vitro* assays. In addition, these documents would contain relevant information on the clinical evaluation of vaccines and clinical endpoints used in their evaluation including human challenge studies, where relevant. Planned disease-specific supplements include those for COVID-19, RSV, rabies, malaria and HIV.

It was also reported that the drafting group for the Guidelines had been assembled and that the first draft had been completed in August 2022, and was posted for the first round of public consultation and comment. The present Informal Consultation would review the comments received during the first public consultation and propose revisions as appropriate. It was expected that a second draft would be

[1] Wellcome and IAVI (2020). Expanding access to monoclonal antibody-based products. A global call to action. Available at: https://wellcome.org/sites/default/files/expanding-access-to-monoclonal-antibody-based-products.pdf

prepared and as before posted for global public comment in January – February 2023. Revisions based on public comments received would take place in February-March 2023 and a final draft presented for adoption to the WHO ECBS in March 2023.

Dr McManus thanked Dr Isbrucker for the overview of the current state of the proposed guidelines and noted that, in view of the issues noted earlier regarding the interpretation of therapeutic and prophylactic use of mAbs and its impact on WHO prequalification procedures, there was a need to pay special attention to language used in the general document as well as supplements, especially language about prevention of infectious diseases. Participants agreed that special attention should be paid to the clarity of sections such as the document scope and terminology, in particular in relation to pre-exposure protection, disease prevention, and terms such as “vaccine-like”.

Review of comments received and proposals for revision of the First Draft Guidance Document

General comments received:

Dr Isbrucker led the detailed discussion of the comments received on the first draft document of which there were over 290. Altogether, comments had been received from 16 organizations and manufacturers. These ranged from substantive to more editorial or language preferences and had been collated and numbered by Dr Isbrucker for ease of reference and review, as well as for recording recommendations from the present Consultation for text amendment as appropriate. The Drafting Group had over several teleconferences already made a preliminary review of the comments received and, in many cases, had proposed text amendments. Some were straightforward and needed little further discussion. However, there were some comments which needed wider discussion in the present Consultation.

Overall, the general comments received were favorable and supportive, and welcomed the document as timely, well written, concise and clear guidance in the monoclonal antibody field. There were, however, a number of important aspects where it was considered that clarity could be improved and which would benefit from amendment of the text. One major comment concerned the status of the WHO guideline in the ongoing regulatory harmonization activities of various organizations and regulatory authorities in this field. It was agreed that this misunderstanding was likely due to the fact that the usual general statement concerning the nature of WHO guidelines had been inadvertently omitted from the first draft of the document but would be included in the next version.

Along similar lines, was encouragement to include references to other national and regional regulatory guidelines where appropriate so as to promote consistency and to make the document more practical for sponsors to implement. It was agreed that amendments would be made to clarify the role of the guidelines and references, including other international guidelines added where appropriate (e.g.,

International Council for Harmonization (ICH) guidelines). Statements concerning the need for sponsors to justify a particular action and to discuss them with the relevant NRA would also be added where relevant.

Other comments highlighted the importance of considering the 3Rs (Reduce, Replace, Remove) in recommending animal testing, the need to explicitly state in the guideline when discussing antigens of infectious agents that this also included related toxins (e.g. tetanus, diphtheria, botulinum, enterotoxin etc.), the need to discuss further novel mAbs and mAb mimetics and related proteins, more on the "animal rule", although it was recognized that this term is specifically one from the US FDA, further attention to the list of abbreviations, the terminology and possibly further strengthening coverage of the application of the guidelines in low resource settings. The meeting agreed that most of these points should be clarified in revision to the relevant sections of the text but considered that further discussion of the relevance of the guidelines to LMIC regulators was more to do with health policy and less with specific technical guidance presented here and was, therefore, out of context of the document. It was noted also that reference should be made in the revised guidelines to the International Nonproprietary Names (INN) nomenclature scheme for monoclonal antibodies[2] which was updated in 2021 and that the former, now well-known, INN suffix "-mab" is no longer used as new mAb products are developed.

Introduction, Scope, Terminology and General Considerations

Review of the comments received on these sections identified several points worthy of consideration as well as several edits. Others were considered not relevant to the current text and not included.

Points raised included:

- the need to emphasize, in revised or rearranged text, the role of mAbs not only in the treatment of infectious diseases but also in their prevention and management;
- the need to include modified mAbs, such as by sequence substitutions and/or glycosylation, for the purpose of extending shelf-life or reducing or enhancing its effector function;
- rewording the mAb mimetics sections but retain notes on possible differences in bioavailability and importance of formulation issues in relation to these products as well as those administered by different routes;
- to add new terminology and delete the term "humanized IgG" as there is now less clarity as to what is and what is not "humanized";
- retain the biosimilars term and add latest reference; and also revise or update some of the definitions.

[2] World Health Organization. New INN monoclonal antibody (mAb) nomenclature scheme. November, 2021. https://cdn.who.int/media/docs/default-source/international-nonproprietary-names-(inn)/new_mab_-nomenclature-_2021.pdf

Important text indicating that mAbs offer the possibility of real-time response to emerging infectious diseases should be revised and better aligned with that in the WHO Guidelines for the development and production of mAbs in general but to indicate clearly why mAbs could have an advantage over vaccines in dealing with emerging infections and for immunocompromised populations.

Other points identified and needing attention included the need to clarify the impact of resistance of infecting pathogens to mAb products due to the emergence of variant strains, the use of antibody cocktails and future modified mAbs and more discussion of the importance of potential antibody-dependent (disease) enhancement (ADE). The meeting participants agreed that ADE was an important issue and that it should be mentioned in the General sections as well as in nonclinical and clinical sections, even though it is a difficult area to evaluate in early studies.

Prior to starting discussion of the many comments received on the Nonclinical Section, it was agreed that the few comments received on the Appendix should be taken at this stage.

The Appendix was the first supplement to be developed to deal with a special topic, in this case **Considerations towards an abbreviated submission for mAbs against an infectious disease during a public health emergency**

Dr Isbrucker noted that essentially all the comments received dealt with improving clarity by amending or rearranging text. It was agreed that the General Introduction to the whole document should refer to the Appendix indicating the importance of abbreviated pathways under conditions of health emergencies. It was important to explain that this is a conditional authorization based sometimes on real world evidence, when clinical trials may not be feasible for one reason or another for full approval. Good communications between the sponsor and the regulator were essential to clarify expectations when submitting for marketing authorization through an abbreviated pathway. The package should include toxicity evaluation in the form of good quality tissue cross reactivity data sets, pharmacodynamic proof of concept studies and pivotal toxicity studies conducted under GLP. Commentators had noted that NRAs with limited experience in reviewing mAb product applications and/or with limited resources were encouraged to practice evidence-based reliance with trusted NRA partners which are able to provide assessment reports; this should also include regional regulatory bodies. A revised text would now be developed incorporating these amendments.

To help focus further discussion, several presentations were then made in the area of novel mAbs, mAb mimetics and other technologies used in mAb development, as well as relating to the use of preventive mAbs.

The first was titled **“Rapid preclinical optimization strategies for single chain antibodies”** and presented by **Dr Scott Dessain**, Lankenau Institute for Medical Research (LIMR), USA.

Dr Dessain reported that on-cell mAb screening technologies, which had been developed, in part, at the LIMR, had subsequently been licensed to OCSM Bio for

commercialization. The latter is a monoclonal antibody discovery company involved in speeding up the discovery process by using, primarily, on-cell fluorescent imaging methodologies. Several clinical examples from different manufacturers of known single chain antibodies were described as well as the challenges of single chain antibody development. These include the fact that some IgGs may not be easily converted to single chain molecules, some require humanization, others removal of glycosylation sites or cysteines, in yet other cases there may be mammalian cell expression issues leading to low yields or aggregation problems. Dr Dessain explained that molecular modelling and artificial intelligence (AI) could help overcome some uncertainties but that every mAb needed to be expressed and tested individually and that discovery was limited by screening capacity, especially by wet-lab bottlenecks. OCMS Bio had developed quick-screening procedures involving cell-specific antibody capture and subsequent antibody screening based on fluorescent antigen to enable the identification of the most appropriate of millions of mAbs. In this way the effects of single mutations in mAb molecules could be evaluated and libraries developed. Dr Dessain considered the on-cell mAb screening (OCMS) platform hugely helpful in reducing uncertainty and time involved in selecting mAb targets for further evaluation and screening. In conclusion, he believed that there is enormous potential for the therapeutic impact of single chain antibodies and that sophisticated bioengineering technologies will continue to reduce development times and to fill the discovery pipeline.

Discussion raised a few points of clarification covering the effects of single amino acid substitutions, mistranslations during antibody expression and the evolving nature of antibody mimetic technologies, as well as whether the current draft guidelines adequately covered these developments. General agreement was that they did so.

The next presentation was by **Dr Veysel Kayser**, The University of Sydney, Australia, who discussed **Blue-sky thinking on mAb-based products, approaches, formulations and delivery.**

Dr Kayser first discussed new developments such as mAb-nanoparticle conjugates, Ab mimetics and other engineered proteins such as Fc-fusions, DARPins, monobodies and nanobodies, as well as new formulations which were more stable at room temperature and could be delivered by microneedle, orally or by inhalation. He then highlighted new biophysical methodologies, many of which were already available, such as computational, spectroscopy, new separation technologies and microscopy, emphasizing that the new methods were not only more sensitive than previously but now included high throughput capabilities. However, he also raised a number of questions relating to new products, such as how to test for safety and efficacy, whether the approval processes for a product that is stable at room temperature, or a mAb product for inhalation or for oral delivery, differ from current products. In addition, how much toxicity testing might be required during emergency situations for new components, such as an ionic liquid used in injectables, components of nanoparticle-based formulations. He asked whether new

guidelines were needed for such products or whether the currently adopted guidelines for the production and QC of mAbs, and the current draft of their nonclinical and clinical evaluation, adequately covered such issues. Dr Kayser also reviewed novel mAbs and mAb-based formats including issues related to delivery strategies. In his view, new formats, ADCs, bispecific mAbs, mAb complexes, monobodies and nanobodies have a great potential and it was important to ensure that the current draft guidelines do cover these types of products. In the case of antibody engineering, especially where incorporation of engineered glycosylation sites and PEGylation have been introduced to improve thermodynamic stability, solubility, half-life and prevent protein aggregation, it would be important to consider whether the current draft guidelines were sufficiently comprehensive or whether further analytical evaluations were needed for such products.

In discussion it was agreed that issues such as safety testing of conjugates should not be ignored. In his presentation, Dr Kayser had also mentioned that studies were underway to explore the effect of replacing H2O with D2O (heavy water) in order to improve stability of these molecules. It was mentioned during discussion that such an approach had been explored many years ago with the view of improving the stability of OPV vaccine with respect to its reversion. Although D2O did improve reversion stability, the idea was dropped due to public perception that D2O was associated with nuclear energy and radioactivity and possibly might have caused problems for vaccine acceptance.

The final presentation in this session of the meeting was by **Dr Julian Ritchey**, Sanofi Vaccines and nominated representative for BIO, entitled **Preventative Monoclonal Antibodies- Implementation Considerations: starting with the end in mind.**

Dr Ritchey made the case for WHO to navigate the field of mAbs and vaccines early in product development so as to influence their equitable global access. He reviewed the experience of BIO in this area which began in 2019 when BIO members began discussing emerging issues that could affect preventive mAbs from being considered for use for public health purposes or in routine immunization programmes. BIO had identified a number of issues in the USA which might influence outcomes unless properly addressed. These included:

- Legislative (Statutory definition of “vaccine” vs “immunization”);
- Regulatory (FDA review of mAbs vs biotherapeutics and vaccines – CDER vs CBER);
- NITAG (Advisory Committee on Immunization Practices (ACIP) evaluation and recommendations – Similar to vaccines?);
- Public and private sector coverage and procurement (Vaccines For Children (VFC) program eligibility);
- Indemnity coverage (Inclusion in the Vaccine Injury Compensation Program (VICP));

- Coding, tracking and surveillance (Use in Electronic Health Records (EHR) & Immunization Information Systems (IIS));
- Safety tracking (Tracking adverse events in vaccine safety systems such as VAERS);
- Education and training (Information and codes (CPT) different from traditional vaccines):
- Precedent (Multiple mAbs in market and in development, but only few are “vaccine-like”);
- Financial perception (The high price point associated with therapeutic mAbs)

Similar issues might affect other countries and international use of preventive, vaccine-like mAbs could be an issue as had already been highlighted earlier in the meeting with respect to the WHO Prequalification process.

BIO had established a Task Force to evaluate policy approaches to ensure broad, equitable access to novel mAb products for routine immunization and working to identify companies developing mAbs for preventive indications. It had engaged with the ACIP Executive Secretariat in relation to the evaluation process for mAbs and the ACIP Charter had been updated to allow the Committee to evaluate preventive mAb products intended for routine immunization. Dr Ritchey also reported that the Task Force had shared a potential categorization of mAbs for consideration by US CDC and ACIP:

- Preventative mAbs that could be used like a routine vaccine in a large population;
- Preventative mAbs that could be used for prophylactic immunization of a select population;
- Therapeutic mAbs not for review by ACIP in order to help address volume and scope concerns.

Dr Ritchey considered there were opportunities here for early global consideration of the situation, especially at WHO and country NITAG level, as well as engagement with global immunization stakeholders to ensure issue awareness and opportunities with respect to impact on decision making. He considered that early WHO attention could benefit implementation issue detection and policy / process improvement.

Whilst participants recognized the importance of the issues reported by Dr Ritchey, it was unclear how widespread the problem might be globally, that is in countries other than the USA, although a not too dissimilar issue of terminology had been identified earlier in the meeting relating to the WHO PQ procedures. In discussion, it was pointed out that this seemed to be a problem of legislation terminology rather than regulatory. In Canada, and some other jurisdictions, for instance, legislation is kept to overarching principles, leaving the detailed regulatory elements to regulations based on evolving science, generally a much less prescriptive system. It was agreed that technical guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related biological products intended

for the treatment or prevention of human infectious diseases were not the right place to include such issues. However, the issues raised by Dr Ritchey should be noted by the WHO ECBS and WHO's IVB Department, as well as the WHO Prequalification programme for further action as appropriate.

Following these presentations, Dr Isbrucker continued his review of comments received on the first draft of the guidelines and initiated discussion of the general comments received on the Nonclinical Evaluation section.

Nonclinical Evaluation

Several comments had been received concerning the text on compliance of nonclinical toxicity studies with Good Laboratory Practices (GLP) and the use of internal SOPs. The current text was considered too restrictive and not in line with current practices. It was agreed to amend the current text to clarify the role of GLP in pivotal nonclinical toxicity studies as well as the role of internal SOPs and add an appropriate reference. After considerable discussion, it was also agreed that the text should be amended to clarify that, where available, consideration should be given to the use of validated alternative *in vitro* methods for toxicology evaluation studies and that *in vivo* animal studies should be terminated as early as possible to minimize animal suffering. Responding to comments received regarding text relating to the nature of the lots used for nonclinical testing, it was agreed that this should be clarified to indicate that such lots should be adequately representative of the quality and formulation of lots intended for use in subsequent clinical investigations.

Dr MacManus thanked all the speakers for their contributions and the participants for their excellent and open discussion during the first Day and indicated that review of the Nonclinical Section would continue on Day 2.

Day 2

The Chair, Dr McManus, opened the meeting and invited Dr Isbrucker to resume reviewing the comments received on the first draft of the Guidelines

Review of comments received and proposals for revision of the First Draft Guidance Document

Nonclinical Evaluation (Continued)

Several comments had been received regarding the assessment of unwanted and unexpected cross reactivity of mAbs, nonclinical study design issues and the type of information being sought. In response, and following considerable discussion, new text was agreed emphasizing that nonclinical study designs should be guided by and tailored to the type of data needed, including the use of *in vitro* studies as appropriate, and where justified. Similar amendments would be made in relevant subsections to the document. Proposed revisions were also made to clarify the relevance to humans and interpretation of data on anti-mAb antibodies detected in animal studies. In addition, proposed new text was agreed to deal with comments

concerning Fc dependent effector functions of the mAbs under study. The new text would cover toxicity and pharmacological properties, species specific issues and similarity of the animal model to human infection.

As agreed earlier in the meeting, antibody dependent enhancement of disease (ADE) was again mentioned and slight amendment to the Nonclinical section made to clarify that a dedicated animal study for ADE may not be warranted and that potential ADE could be assessed during PD / proof of concept studies (POC) in an animal model of disease, if available. The intent of text relating to evaluating the proof of concept or providing evidence of potential efficacy and in identifying a potential therapeutic window was extensively discussed and it was agreed that sections needed clarification, as was clear from the comments made. Similarly, apparent misunderstanding of the original text on safety pharmacology was also discussed, including the issue of product nature and potential differences in distribution, and suggested clarifications proposed.

There was also extensive discussion of several points raised relating to the evaluation of PK and TK. It was clear that some of the text needed clarification, for example relating to the limitations of interpreting PK and TK due to the possible lack of a relevant animal model when the mAb is directed against an infectious agent. There had also been comments on sections relating to assay methods and it was agreed that this was better referred to as assay formats and that evaluation should broadly cover all functions. Revised text would be developed, and care taken to minimize redundancies. Absorption studies were another issue which had raised comments and it was agreed that clarified text should mention that evaluation of absorption should be conducted before human phase I studies. Comments had also been received on text relating to the distribution and metabolism of mAbs which were best considered together and related to bioavailability of the mAb. Following considerable discussion, amended wording was agreed which would clarify issues of clearance / elimination in relevant animal models noting especially issues related to immunoconjugates.

There had been considerable comments on the toxicology section indicating a need for better clarity of intent. This was a difficult section in a document covering a wide range of different types of mAbs and related biologicals, as well as infections, and it was expected to be easier in the infection-specific supplements. The choice of animal model and safety testing that could be usefully carried out should essentially be decided on a case-by-case basis, justified and take note of the half-life of the mAb. Where this was not feasible, mitigation studies would need to be developed and discussed with the NRA. Amended text, emphasizing justification, and covering the half-life and recovery period issues was agreed.

To aid discussion of tissue cross reactivity studies, **Dr Alvin Chia** (Health Sciences Authority, Singapore) gave a presentation entitled **“Alternative Approaches to Tissue Cross reactivity Studies”.**

Dr Chia explained that tissue cross-reactivity (TCR) studies relied on well-known screening assays used to identify mAbs with off-target and targeted binding capacity. They involve the use of immunohistochemical (IHC) techniques to stain panels of tissues (human or animal) with labelled antibodies. Such techniques provide information on expected as well as unexpected potential binding sites of the mAbs and cover endogenous (Human) or exogenous (e.g., viral) targets. There are two major guidelines on the use of TCR: the USA FDA guidance document "Points to consider in the Manufacture and Testing of mAb products for Human use"[3] and the ICH guideline on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals[4]. The FDA guidance notes that TCR studies with human tissues should be conducted prior to phase I study and employ IHC techniques or appropriate newer technologies as they become available and validated. The ICH guidance recommends TCR studies with a panel of tissues as a component of the safety assessment package supporting initial clinical dosing studies. However, it also notes that TCR studies may not always be technically feasible if the mAb product is not a good IHC reagent. In such cases, other technologies could be employed as alternatives. In fact, Dr Chia noted instances where mAb candidates did not bind to tissues known to express target antigen (positive control), such as infected tissue expressing viral antigens or transfected cell line with viral antigen. This raised the issue of false negatives and false positive results. In such cases, possible alternatives to TCR include bioinformatic tools (databases) (BLAST, 3D BLAST Protein Structures, PDBe PISA), protein microarrays (protein-protein interaction) and cell-based microarrays.

A number of questions were raised in discussion. If TCR is not feasible, what alternative methods are deemed acceptable from a regulatory perspective? In the case of a mAb directed at an exogenous target, such as a viral or bacterial antigen, what other safety assessment approaches could be considered if TCR is not feasible and there are no acceptable alternatives? Should the use of alternative methods be addressed in the WHO Guidelines being drafted? Is there sufficient information to draw attention to this issue and what about TCR with soluble antigens (i.e., non tissue bound antigens)? General opinion among the participants was that this is an issue for exploration rather than for regulatory guidance at this stage and that further public consultation might lead to a way forward. Other issues raised included the need for TCR studies with tissue from juveniles when considering mAbs for pediatric use. There were also questions relating to the influence of human genetics and population differences on TCR. Although there were many questions, there were no clear answers and certainly nothing new for inclusion into the present general guidance document, although it was important that it was aligned with other guidance and that the text should recognize the limitations. It was pointed out,

[3] US FDA (1997) Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human use. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/points-consider-manufacture-and-testing-monoclonal-antibody-products-human-use

[4] ICH (2011). Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals S6(R1). Available at: https://database.ich.org/sites/default/files/S6_R1_Guideline_0.pdf

however, that mAbs currently being developed were usually designed with less cross reactivity than before.

Dr McManus thanked Dr Chia for his presentation and asked Dr Isbrucker to continue his review of the comments received on the first draft of the Nonclinical section of the Guidance document.

Nonclinical Evaluation (Continued)

Comments had been received about the limited value of undertaking toxicity testing in healthy animals in the case of mAbs against a pathogenic agent, a view with which the drafting group disagreed. The Consultation concurred that this recommendation should be retained but that the text could be clarified, and the need for discussion with the NRA indicated. It was agreed that toxicity testing in healthy animals was important and allowed for a clearer interpretation of toxicity (in the absence of disease) and represented healthy subjects to be evaluated in the case of prophylactic products. A comment on the use of the term “age” in relation to the animals used for studies was noted and discussed, leading to the recognition of the need for better clarity in language. The issue of two or more mAbs being developed to be used in combination, co-formulated or otherwise, had also led to comments and new text to clarify the intent was proposed.

Several comments had been received about the issue of repeat dose studies, the importance of the recovery period and the effects of anti-mAb antibodies (ADAs). It was agreed that clearer guidance was needed involving the potential development of ADAs and their implications for interpreting animal model results, an issue which might be discussed with the NRA. Likewise, comments had been received concerning the nonclinical developmental and reproductive toxicity sections and it was agreed that the text should be revised to make it less prescriptive and indicate that early discussions with the NRA would be important as requirements, including the issue of pregnant women, may vary between countries. Furthermore, most clinical experience with mAbs to date has been with IgG but many different molecules were now under development, and this should be borne in mind.

Dr MacManus thanked the speakers and participants for their valuable contributions and indicated that Day 3 would deal with the review of the Clinical Evaluation Section. There would also be two presentations.

Day 3

Dr McManus opened the meeting by inviting Dr Isbrucker to initiate discussion on the comments received on the first draft of the Clinical Evaluation section of the Guidelines.

Review of comments received and proposals for revision of the First Draft Guidance Document

Clinical Evaluation

Dr Isbrucker explained that there had been several general comments relating to the Clinical Evaluation section and these would be dealt with first, before moving to the more specific comments.

There was some concern that the guideline was set up for a standard clinical development programme and, although covering accelerated approaches in the event of a public health emergency in the Appendix, it did not take sufficient account of issues related to neglected or emerging diseases. These differed from those covered under accelerated pathways in, for example, the small numbers of patients available with which to demonstrate efficacy and safety as well as the possible need to use animal or human challenge studies for regulatory purposes. Following considerable discussion, including the threshold for a disease to fall into such categories, it was agreed that the need for different development pathways should be highlighted and new text under general considerations would be developed to address this issue. The new text should draw attention to the fact that it would be important to discuss any alternative nonclinical and/or clinical plans with the NRA early in development. Other general points discussed were the issues of patient reported outcomes or engagement and the need for further guidance on clinical design for co-formulated products. It was considered that the first issue was out of context in this guideline, and it was agreed that the text on co-formulated products would be amended where appropriate to mention issues, such as safety, related to the clinical evaluation of co-formulated vs co-administered products.

More specific comments regarding the Clinical Evaluation section were considered next. Several minor points had been accepted by the drafting group and the appropriate text would be amended accordingly. Others needing further discussion included provision of adequate educational resources on mAbs for trial participants, additional guidance for trial participants and investigators in low resource settings on issues relating to the epidemiology of the infectious disease in question, and a suggestion to include discussion of adaptive platform trials. It was considered that all these were out of context of this particular guideline and more suitable for investigators' brochures. They were already covered in the cited WHO Guidelines on Good Clinical Practice. Adaptive Trials were complex and were mentioned in the Appendix in relation to public health emergency settings.

A recommendation to diversify the geography of investigators and participants, including robust Phase IV studies, was noted and following considerable discussion it was agreed this was an opportunity to amend the text to obtain more information about safety and effectiveness of a mAb product, especially about the influence of previous exposure to the infection. There was also a need to clarify real world data and evidence, as well as to mention the need for discussion with the NRA as appropriate.

A suggestion to clarify the basis for deciding the dose for the first in human studies in situations where animal models of infection were judged impossible, or of no relevance, led to considerable discussion. It was agreed that PD studies can inform on the starting dose, but this should start low if no appropriate animal model was available. The text would be revised to reflect this point and also to include a

comment that safety/ toxicity studies may still be needed. It was recognised that each NRA may have different requirements on this subject, and it would again be important to discuss the issue with the relevant NRA. At present, short-term toxicity studies were required by some but not all NRAs. Mention was also made of biosimilars in the sense that decisions would be based on the overall package of data available as well as the level of confidence in the manufactures' data.

Discussion of comments concerning the relationship between PD and concentration of the product under evaluation, as well as on the samples and data necessary for PD studies, led to agreement for revising the text, although more detailed guidance might be appropriate in disease-specific supplements. The nature of bioanalytical samples necessary for PD studies had also been raised and this could, for example, be viral load or colony forming units, as appropriate. It was considered beneficial if samples were collected and studied throughout the clinical development programme, including phase III studies. There were also comments on endpoint selection including requests for improved clarity regarding the need for subgroup analysis by serostatus at baseline which led to considerable discussion. It was agreed that endpoints should be able to distinguish between efficacy and the control groups and that it should be possible to distinguish efficacy from immunological confounders related to the host's immune response. However, it was pointed out that serostatus was essentially an indicator of previous exposure, and not necessarily an indication of any protective response. The text would be amended to indicate that a mAb product should show promise of efficacy in terms of a clinically relevant endpoint. Text dealing with biomarkers also needed revision to better reflect their role as useful secondary and complementary information to be considered and analysed along with the primary clinical outcome. Their usefulness as early readouts should also be considered. ~~It~~ In addition, it was agreed that minor modification of the text regarding placebo controls and single arm studies would be beneficial. Comments on clinical trial design again raised the issue of the so called "animal rule" for mAb development. It was pointed out that this term is a US FDA specific regulation although similar principles, but not terminology, applied in other jurisdictions in certain situations. The guidelines would be revised to indicate, in general terms, that such mechanisms exist and should be used in situations where it would be unethical to undertake human clinical trials such as in the case of a bioterrorism agent like anthrax.

The public consultation had commented on the need to improve text dealing with the issue of circulating variant strains of the infecting pathogen which might impact efficacy outcomes if binding affinities differ between variants. Although perhaps more appropriate for the disease-specific supplements, it was agreed that this could be clarified, and reference made to local epidemiology of circulating strains of pathogen. However, caution was expressed regarding the notion that mAb therapy itself was the major force driving strain changes. In the case of SARS-CoV-2, variants emerged from places where mAbs were not used and before vaccine and mAb therapy had been developed.

Other clinical evaluation issues raised and debated during the public consultation included safety evaluation and the need to cover a reasonable length of

time following product administration, differences between immunogenicity and reactogenicity and the need to screen for both. Different population groups also needed to be highlighted in clinical development, the need for juvenile toxicity studies, including the timing of pediatric studies, studies in the elderly, and in pregnant women. The latter topic generated considerable discussion, recognizing the ethical differences between countries regarding undertaking clinical testing in this population. It was agreed that text should be appropriately amended to accommodate the testing of mAbs in pregnant and breast-feeding women as well as the inclusion of a pregnancy registry. Nonclinical data could also help support such studies. A request for clarification of text relating to formulation and manufacturing changes was requested to clarify what was meant by text within the draft guidance which stated, “if this is not feasible”. A comment that the text on pharmacovigilance and risk management should be strengthened to include a critical point about the importance of appropriate stewardship for biologicals was accepted and the second draft will reflect this change.

Amended texts to address these various issues were agreed and they would be incorporated into the updated version of the guidelines for the second public consultation

Appendix on Considerations towards an abbreviated submission for mAbs against an infectious disease during a public health emergency

Two presentations dealing with regulatory measures developed to deal with urgent public health emergencies, such a pandemic, were taken during Day 3 as a background to any further consideration of the Appendix which deals with considerations towards an abbreviated submission for mAbs against infectious disease during a public health emergency.

The first presentation was by **Dr Thomas Kirchlechner** (Sandoz Biopharmaceuticals, Austria, and representative of the International Generic and Biosimilar medicines Association) and was entitled “**Emergency use Authorization (EUA) applications in a pandemic”**.

The presentation essentially dealt with lessons learnt from the COVID-19 pandemic. Dr Kirchlechner noted that the US FDA was the first agency to publish specific guidelines on what was expected in EUA submissions. Full process validation was not expected to be completed in such applications, but sufficient process characterization was expected and should be consistent with the overfall benefit-risk assessment of the product. The EUA for SARS-CoV-2 related products followed this guidance as well as similar but not identical guidance from the EMA. Both processes include commitments to provide updated reports at specified timepoints. Manufacturers used FDA guidelines and EMA experiences to guide strategy. Terminology was, however, slightly different in that the FDA issues an authorization and EMA issued a conditional approval. This process took slightly longer than the FDA review as it involved the appointment of a rapporteur and co-rapporteur NRAs to undertake the reviews. Dr Kirchlechner reported the interesting

observation that review times by the FDA for 4 mAbs / combination mAbs products increased compared to the previous approved product, from 34 days for the approval of the first mAb to 85 days for the fourth, even though all were under the same public health emergency situation. It appeared that a regulator's willingness to accept an EUA depended on the severity status of the pandemic, as also seemed the "entry barrier" for review, which was, perhaps, not surprising. Following an EUA authorization, the expectation was that a full license (e.g., a US FDA Biologics License Application) would be sought after one year or the authorization would expire. The difficulty here was that patient recruitment required to generate necessary clinical data depended on pandemic virus epidemiology, which was itself a changing scenario.

Discussion recognized the issues noted but there were few answers to questions raised. A serious problem with SARSCoV-2 was the rapid evolution of new variants more resistant to the emergency authorized mAb, further complicating the issue since it was unlikely that the authorized product would be used again due to the changing epidemiological situation with new resistant variants. The benefit of several NRAs working in a consortium in emergency situations, such as the relatively new Access Consortium (Health Canada, Singapore HSA, Australian TGA, UK MHRA, and Swissmedic), was raised but the answer was unclear as it was an evolving situation.

The second presentation dealing with regulatory measures in public health emergencies was by **Dr D McManus** (Health Canada) entitled "**mAbs for Infectious Disease: Expedited Pathways, Extrapolation and Surrogate Endpoints".**

Dr McManus' review, based on publicly available information, compared normal and expedited submission pathways for mAbs against SARS-CoV-2, focusing on lessons learnt from the COVID-19 pandemic. He first described regular licensing pathways, with complete nonclinical and clinical data packages. In contrast, there were various expedited submission types offering a range of flexibility which had evolved to deal with, for example, fast track cancer therapies (urgent medical needs) and urgent public health needs, such as COVID-19. All had slightly different names and details (e.g., Emergency Use Authorization in USA, Conditional Licensing in Europe, and Interim Order in Canada). The expedited pathways were essentially based on promising evidence and smaller numbers of subjects / patients evaluated than regular pathways and there was a commitment to provide additional results following authorization; they were often based on surrogate endpoints and extrapolation of use was possible.

It was explained that most mAbs against SARS-CoV-2 were directed against the receptor binding domain of the spike protein although increasing attention was now being given to the N-terminal and other domains in an attempt to overcome the issue of variant evasion. Four examples of authorized mAbs by different manufacturers were described, the first being authorized on the basis of phase II data, but subsequent mAbs had been authorized on phase III studies. They were all indicated for the treatment of mild to moderate COVID-19 disease confirmed by direct SARS-CoV-2 viral testing and used in high-risk groups. It appeared that the

US FDA was more open to the use of early phase clinical data for authorization than other agencies.

Dr McManus described reliance on a surrogate marker, a reduction of viral load measured using in vitro pseudo virus assays, in comparison to placebo, as clinical evidence and support of authorization. He also reviewed the emergence of variant strains which has negatively impacted the activity of mAbs as well as vaccines against SARS-CoV-2. However, it was pointed out that in vitro activity may not always correlate with real world effectiveness and is only one component of clinical decision making. The basis of extrapolation of indication from adults to adolescent by the US FDA was explained as due to fact that the since the mAb was directed towards the virus, and not the host response to the viral infection, it was considered reasonable to anticipate similar clinical performance in the adolescent group compared with adults.

In summary, it was clear that authorization of anti-SARS-CoV-2 mAbs via expedited pathways had enabled marketing to proceed at a time when the pandemic was especially widespread and severe and where the product was likely to have been beneficial and safe. However, benefit-risk assessment became less certain over time due to the rapid evolution of antibody-resistant SARS-CoV-2 virus stains. Combination therapies were not always the most effective. Clinical decisions were heavily based on surrogate markers, such as reduction in viral load, impacted by in vitro pseudo-virus assays. SARS-CoV-2 mAbs had also been authorized despite not being studied in the intended patient populations but there were commitments for follow up studies, although this seemed to be up to individual NRAs.

Points raised in discussion touched on the issue of rational drug design and modelling, the impact of time limited authorization of EUA processes and, in the case of SARS-CoV-2, the pressure of obtaining relevant data to support conversion to regular authorization. The relevance of an official declaration of a pandemic by the WHO was also discussed and considered to be important to both NRAs and manufacturers in relation to setting priorities and supply chains and, for vaccines, independent lot release activities. Monitoring the decision-making process for a final WHO declaration of a pandemic was important in order to anticipate the final decision and plan accordingly.

Dr McManus was thanked for his presentation and Dr Isbrucker indicated that all of the comments received on the first draft of the document had now been reviewed by the drafting group and discussed at the Consultation. The few comments received on the Appendix had been discussed on Day 2 (above).

Having come to the end of reviewing the comments received on the draft guidelines Dr McManus thanked Dr Isbrucker, speakers and meeting participants for their invaluable contribution to the meeting. The current draft document would now be amended by the drafting group along the lines indicated and a second draft posted for public consultation prior to presentation to the ECBS at the end of March 2023. All objectives of the Consultation had been met (Table 1).

He thanked Sue Jenner and other colleagues for their support of the meeting which had been an interesting mixture of face to face and virtual but had actually worked very well.

The meeting was then closed.

Authors

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WHO staff: Ms D. Pirgari, WHO, Denmark; and Dr R. Isbrucker, Ms S. Jenner, Dr I. Knezevic, Dr C. Ondari, Dr E. Sparrow and Dr T. Zhou, WHO, Switzerland.

TABLE 1 Meeting the Objectives of the Consultation

1. To review the comments received on the first draft of the guidelines, to discuss the key issues identified, as well as to propose revisions to the text.
    - *All met. A second draft of the Guidelines taking account of the outcomes of the Consultation would be prepared and posted.*
2. To exchange scientific and regulatory experiences and perspectives pertinent to the guidelines.
    - *Met through discussion at the Consultation*
3. To provide WHO with some feedback on the strengths / weaknesses of the guidelines.
    - *Generally, the Guidelines were well received and considered important tools for improving global regulatory harmonization and access to mAb products against infectious diseases.*
4. To provide WHO with feedback on the future of these products.
    - *It is clear that this is an expanding and highly innovative field based on sophisticated biotechnologies with great expectations.*
5. To provide WHO with an awareness of potential further needs regarding mAbs against infectious diseases.
    - *Issues were identified that could affect preventive mAbs being considered for use for population health purposes or in routine immunization programmes in the USA. It is unclear if this is an issue in other countries. Whilst not for inclusion in the current Guidelines, the issues should be noted for further discussion and action, as appropriate, by the WHO ECBS and WHO's IVB Department, as well as the WHO Prequalification group. It was mentioned that WHO's IVB Department would be convening future meetings on clinical endpoints which might also identify the need for further work. Questions about the PQ process for preventive mAbs against rabies also need to be resolved.*