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Meeting Report

WHO Informal consultation on the guideline for the safe production and quality control of monoclonal antibodies for use in humans

Virtual meeting
13 – 15 December, 2021[1]

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Summary
The ability to quickly develop safe and effective monoclonal antibodies (mAbs) makes them a priority for the treatment of emerging infections such as COVID-19. However, existing WHO guidance on mAbs focuses on products targeting noncommunicable diseases and offers little advice on mAbs intended for the treatment of infectious diseases. In the context of the COVID-19 pandemic, draft guidance was developed to address this limitation and the resulting document was subject to public consultation towards the end of 2021. An informal consultation involving the drafting group and manufacturers' representatives was held between 13th and 15th December 2021 to review the comments elicited by the public consultation. Overall, the draft document was well-received and resulted a number of positive general comments from reviewers. In total there were 198 comments from nine respondents representing mAb developers, manufacturers and regulators. The majority of suggestions were addressed in a revised version of the document, enabling the drafting group to correct errors and make significant improvements to the prospective guidance.

Introduction

Therapeutic monoclonal antibody (mAb) products have become increasingly important over the last 25 years and are now the predominant form of treatment for a wide variety of diseases. Although the majority of approved therapeutic mAbs have been developed for the treatment of noncommunicable diseases, the short development time, rapid impact and safety of mAbs make them a high priority for the treatment of emerging infections such as COVID-19. However, existing WHO guidance on mAbs focuses on products targeting noncommunicable diseases and offers little advice on the development, production, quality control and evaluation of mAbs used to treat infectious diseases.

During its meetings in October and December 2020, the WHO Expert Committee on Biological Standardization (ECBS) expressed its support for the development of updated guidance to address this limitation as well as take into account technological advances and innovative production methods for mAbs. A drafting group was established early in 2021 to develop a WHO Guideline for the safe production and quality control of mAbs for use in humans, which is intended to replace Annex 3 of Technical Report Series, No. 822 from 1991. A draft document was subject to a first round of public consultation during October/November 2021 and a meeting of the drafting group was held over three consecutive days, from the 13th to 15th December, to address the issues raised. The meeting was held by Zoom video conferencing due to the restrictions imposed during the COVID-19 pandemic and in addition to drafting group members was attended by representatives of biopharmaceutical manufacturers associations.

The meeting was opened by Dr Clive Ondari, Director, Health Product Policy and Standards at WHO, who began by welcoming meeting participants and continued by explaining the significance of the current project to update existing guidance on mAbs. The first WHO *Guidelines for assuring the quality of monoclonal antibodies for use in humans* were adopted by the WHO ECBS at its forty-second meeting in October 1991 and published in January 1992. These early guidelines largely focused on mAbs produced from hybridomas and provide little information relevant to modern methods of mAb development and production, or for the assessment of their quality and safety. Since the early 1990s there has been extensive use of recombinant DNA technology to express mAbs and related antibody-like products in alternative systems. Similarly, there have been important technological

advances in the purification and quality control of such biotherapeutics. Subsequently, WHO *Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology* were published in 2014. These contain useful information relevant to the production of new mAbs for human use but this is not their primary focus and stakeholders have requested specific, detailed guidance for antibody-based products.

Because of the technological developments in this area, recombinant mAbs have rapidly become a large class of therapeutics used to treat a wide range of diseases. At present these are predominantly noncommunicable diseases, especially cancers; however, mAbs are increasingly being used to treat or prevent infectious diseases. Their potential for addressing challenging diseases such as malaria and Ebola makes recombinant mAb products particularly important in LMICs, where access to modern biotherapeutics remains a problem. Updated guidance on the production and quality control is expected to facilitate access in LMICs by harmonizing regulatory processes and supporting WHO prequalification recommendations. It is currently anticipated that the revised guidelines will be presented to ECBS for adoption in April 2022. Dr Ondari concluded by thanking the drafting group and external experts for their time and commitment to this project. He also thanked Dr Simon Hufton and Dr Ian Feavers for serving as chair and rapporteur respectively, Dr Richard Isbrucker for his leadership and coordination of the project, and Teija Katajainen for administrative support.

Noting that six participants were nominated by manufacturers' associations, declaration of interests of all participants were reviewed. None were perceived to be an influence on the content of this meeting.

Background

Dr Ivana Knezevic updated meeting participants on the broader WHO biological standardization activities. There are currently 105 global written standards: 11 general documents that apply to all biologicals; 12 general documents that apply to vaccines; 73 that are vaccine specific; and 9 that are specific for biotherapeutics. Given the importance of scientific evidence in the development of WHO written standards, they are subject to a rigorous public consultation and review process that strengthens the documents with input from stakeholders worldwide. In addition, WHO International Standards, as measurement standards, play an essential role the development, licensing and lot release of biologicals. These are held and distributed worldwide by a small number of custodian laboratories, with NIBSC playing a significant role as the custodian of >90% of International Standards. WHO endeavours to produce written and corresponding measurement standards at the same time as far as practicable. There are eight WHO collaborating centres for biological standardisation: NIFDC, NIBSC and PEI were re-designated in 2021. All the collaborating centres have made important contributions to COVID-19 related standardisation issues in addition to other on-going projects.

She explained that WHO guidelines provide key principles for the evaluation of biologicals as a basis for setting national requirements and WHO prequalification. They are sufficiently flexible and non-prescriptive that NRAs can formulate additional or more specific requirements for their own jurisdiction. They are regarded as "living" documents that can be developed further to incorporate advances in scientific knowledge and experience. In developing guidelines, WHO considers guidance offered by other bodies so as to complement and harmonise advice. WHO also helps to implement guidelines into regulatory and manufacturers' practices through: global, regional and national workshops involving

regulators, manufacturers and other relevant experts; training; and advisory groups. She went on to summarise the WHO written standards that support the regulatory evaluation of vaccines and biotherapeutics including guidelines on the nonclinical and clinical evaluation of vaccines, good practices (e.g., GMP, GLP and GCP), cell substrates for vaccine production, stability evaluation, lot release, and post-approval changes.

Noting that the development and adoption of WHO written standards is always a key element of an ECBS meeting agenda, Dr Knezevic summarized the outcomes of the 71st and 72nd ECBS meetings held in August and October 2020 respectively. Documents that were particularly relevant to COVID-19 prevention and treatment were highlighted. In addition, information on the application of existing guiding principles to COVID-19 vaccines had been made available on the WHO biologicals webpage on COVID-19 vaccine standardization. In addition, ECBS had adopted revised guidelines on DNA vaccines at its 71st meeting and regulatory considerations for RNA vaccines at its 74th meeting. The subject of the present meeting, WHO guideline for mAbs for use in humans, is expected to be presented to ECBS at its 75th meeting in April 2022. Updated guidelines for similar biotherapeutic products (SBPs), which include addition explanation regarding the flexibility for reducing data required for approval, are also expected to be presented at the 75th meeting. Other WHO written standards that would be under consideration from 2022 and the recent measurement standards pipeline were also briefly reviewed.

Reflecting on the speed with which measurement standards for COVID-19 had been produced to support the development of molecular and antibody assays, Dr Knezevic highlighted their importance in comparing results from different assays and laboratories, thereby harmonizing the evaluation of diagnostics, vaccines and other products. Three new WHO international reference preparations were established by ECBS at its 73rd meeting in December 2020: the 1st WHO International Standard for SARS-CoV-2 RNA for NAT-based assays; 1st International Standard for anti-SARS-CoV-2 immunoglobulin; and an anti-SARS-CoV-2 immunoglobulin international reference panel. At the same meeting ECBS endorsed a proposal to develop a standard for SARS-CoV-2 antigens to support the development, assessment and comparability of antigen-based rapid diagnostic tests.

Looking ahead, the WHO would continue to provide technical support to manufacturers and regulators on the use of standards, encouraging the appropriate use of IU and BAU when reporting assay results. A WHO manual for the development of national and other secondary standards for antibodies had been produced to complement the existing manual for secondary standards for vaccines, and would be presented to ECBS for adoption in April 2022. The WHO was also providing technical assistance to the users of standards through COVAX, participating in Blueprint workshops on immunobridging and variants of concern as well as collaborating with COVAX SWAT teams for enabling sciences, clinical development and manufacturing.

Dr Richard Isbrucker outlined the objectives of the meeting and provided participants with the background to the project. The first guideline for assuring the quality of monoclonal antibodies for use in humans was adopted in 1992 and focused on the production of antibodies from hybridomas. The main concerns addressed in this document were the specificity of the mAb and potential contamination with adventitious agents. Its emphasis was primarily on the quality aspects of production. The WHO Guideline on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology was published in 2014. It is general in nature making it applicable to mAbs as well as other biotherapeutic proteins; however, it is limited in its details and applicability to current manufacturing

technologies for mAbs, and focusing on treatments for non-communicable diseases largely ignores mAbs aimed at the treatment of infectious disease.

Other relevant WHO Guidelines include the evaluation of similar biotherapeutic products and of monoclonal antibodies as similar biotherapeutic products published in 2013 and 2014 respectively. The purpose of these guidelines is to provide internationally acceptable principles for licensing biotherapeutic products that are claimed to be biosimilar. Consequently, they provide advice on ensuring the comparability of a prospective similar biotherapeutic with the originator product. The current guideline is being developed to provide guidance on the production and quality of mAbs and, therefore, does not address biosimilarity. In addition, there are several other more general WHO Guidelines that may be applicable in the production of recombinant mAbs including: GMP for pharmaceutical products (TRS 986, Annex 2, 2014); GMP for biological products (TRS 999 Annex 2, 2016); recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks (TRS 978, Annex 3, 2013); guidelines on TSEs in relation to biological and pharmaceutical products (2003); general requirements for the sterility of biological substances (TRS 530, Annex 4, 1973); sterility test for mycoplasma (TRS 872, Annex 3, 1998); guidelines for national authorities on quality assurance for biological products (TRS 822, Annex 2, 1992); as well as other WHO guidelines listed in the draft document and ICH quality guidelines. It was noted that the current draft guidelines should as far as possible be self-contained and avoid the duplicating other WHO guidance. Reference to non-WHO guidance, which may not be widely available globally, should be limited to ensure the utility of the WHO Guideline internationally.

Equitable global access to mAb-based products is very limited, with 80% of all mAb therapeutics sold in U.S., Canada, and Europe. The causes of the disparity in availability to low- and middle-income countries are complex but include: cost and capacity; limited health policies; limited experience in the regulation of mAbs; and lack of regulatory harmonization. To address the regulatory issues, there is a need for updated guidelines offering more detail and greater clarity on both the production and control of mAbs irrespective of their therapeutic or prophylactic indication. Given the growing number of mAbs for infectious diseases in clinical development, there is also a need for guidance on the preclinical and clinical evaluation of mAbs targeting infectious diseases. Two separate guidelines are, therefore, in development: the current document providing guidance on the production and control of mAbs for use in humans, irrespective of therapeutic use or biosimilarity; the other on the preclinical and clinical evaluation of mAbs and related proteins for pre-exposure prophylaxis and treatment of infectious diseases. Each will be supplemented with additional disease-specific information such as relevant reference standards, animal models, assays, clinical experience, and human challenge models.

The scope of the current draft guideline was reviewed. Irrespective of intended therapeutic mechanism of action it includes: all types of mAbs regardless of isotype, whether they are humanized, human, or chimeric; biosimilar mAbs; antibody fragments, such as single-chain variable fragments (scFv's) and antigen-binding fragments (Fab); single domain antibodies; bispecific or multispecific mAbs; conjugated and chemically modified mAbs; and multiple mAb substances pooled to produce a final product. Antibody mimetic proteins based on non-immunoglobulin scaffolds and nucleic acid-based platforms for the expression of antibody *in vivo* following administration are outside the scope of the guideline.

The aim was to submit the guideline to ECBS for adoption in April 2022. The purpose of the current meeting was for the drafting group to review comments received from the first public consultation and prepare a final draft that would be posted for a second round of public consultation between January and March. Reminding the drafting group that the guideline should be relevant to all WHO member states and be sufficiently detailed but not too prescriptive, Dr Isbrucker concluded by outlining the objectives for the three days of the meeting. Although the agenda was flexible, it was anticipated that the general and regulatory considerations would be covered on the first day, while the manufacturing recommendations and recommendations for NRAs would be reviewed during the remainder of the meeting.

Review of comments received form the first round of public consultation

Following the first round of public consultation, a total of 198 comments had been received, of which more than 70 were considered minor or editorial and there was a consensus amongst the drafting group that these did not need further review. Overall, the draft document was well-received and elicited a number of positive general comments from reviewers. It was noteworthy that even though there was lengthy discussion on some of the issues raised by reviewers, a strong consensus was invariably reached on how they should be addressed in the document.

Unless explicitly stated, this meeting report refers to the section numbering in the revised draft of the guideline, which may differ from the version that was subject to public consultation because of addition or deletion of text.

Overall comments on the document

Noting the extensive attention given to plant-based expression systems, it was questioned whether the guideline could offer authoritative advice given the limited experience of plant-based expression systems for mAb production to date. The drafting group acknowledged the concern but supported the view of ECBS that mAbs expressed in plants were being developed in countries that would welcome such guidance. In the revised document the rationale for including plant-based expression systems is explained in the introduction.

In response to other comments, antibody-based products such as Fc-fusion proteins, immunocytokines, and immunotoxins were added to the scope of the revised document. In addition, one reviewer had suggested that the document should include guidance on cell-free expression systems for the production of mAbs. The drafting group agreed to include “novel expression systems” in the revised document to cover cell-free and any other expression system that might be developed in the future providing the principles set out in the guideline were applicable. Following some discussion, a suggestion to include guidance on the use of small-scale models to develop control strategies for manufacturing processes was considered to be beyond the scope of the guideline.

Introduction

There were six minor/editorial suggestions on the introduction section of the document, all of which were incorporated into the revised version of the draft guideline.

Terminology

The principal issues raised in this section concerned harmonizing the terminology used for cell lines and making it consistent with other WHO and ICH guidelines. After a detailed discussion, the drafting group agreed that the use of the term “original cell line” was not typical and should be replaced with “parental cell line”. There was a consensus that it was important to emphasize

that cell lines originate from a single clone by using the term “clonally derived” where applicable throughout the guideline, including in the existing definitions of production cell line and master cell bank.

Additional definitions were included in the terminology section as a result of discussions during the meeting. These were for biological activity, co-formulated mAbs, and platform technology.

General and Regulatory Considerations

This section covers a number of topics that are likely to arise during the development and production of mAb products. It starts with a brief overview of mAb technology and continues with a range of issues that require careful consideration, particularly from a regulatory perspective, including: cell substrates used for mAb expression; downstream processing; the application of quality by design; pegylation and conjugation to therapeutic payloads; potential causes of heterogeneity; and approaches to characterization.

There were 40 comments on this section of the draft guideline. Many comments raised relatively minor or editorial issues that were accepted by the drafting group and incorporated into the revised version of the guideline. Comments included a suggestion that the scope of the document be expanded to provide more guidance on the use of prior knowledge in process development. The drafting group agreed it was important to encourage the application of existing experience with one product to the development and production of other similar products. As a result, the paragraph describing platform technology was expanded to provide more detail and clarity. The section on cell substrate was modified to address criticism that it appears to prescribe particular cell lines. To address various comments on the conjugation of mAbs and related proteins to other molecules, the sub-section on conjugation was extensively redrafted to reduce its emphasis on pegylation and broaden it to include other possible therapeutic payloads. Text in the characterisation subsection of the draft document was edited to clarify that only the expected immunobiological activity of the mAb is included in the characterization package and expanded to include examples of Fc-effector function assays.

Based on comments made during the public consultation, the drafting group discussed at length whether to remove the table summarizing potential sources of heterogeneity in recombinant mAbs and methods of detection. Concluding that the table was useful and noting that it was not intended to be prescriptive, the drafting group agreed that it should be moved to an appendix and be expanded to be more comprehensive.

Special considerations

This section of the guideline addresses the importance of ensuring the comparability of the mAb product throughout the development programme and the need to accommodate anticipated changes in product characteristics. It also considers the analytical procedures and specifications to be used in assuring the quality and consistency of the product by in-process and final product testing.

The first round of public consultation raised five comments on this section, most of which were straightforward and accepted by the drafting group. As ICH Q13 introduces concept of continuous process verification for continuous processes compared with more traditional process validation for batch processes, it was suggested that this section should include a statement to capture this concept and the paragraph on process validation in the previous section was edited accordingly. In addition, it was suggested that the text be modified

to take account of increasing interest in patient-centric product specifications and the application of a broader range of relevant knowledge in establishing specifications. Having discussed this at some length, there was a consensus amongst the drafting group that product consistency is crucial to ensuring the safety and efficacy of the mAb. The penultimate paragraph of the section was, therefore, redrafted to emphasize the critical importance of product consistency.

International standards and reference materials

As in WHO Guidelines for other biological products, this section documents the availability of biological reference materials used in bioassays for some mAbs and how to source them. Two reviewers highlighted the risk that mentioning biosimilar mAbs in this section might cause confusion and be inappropriately interpreted that WHO reference preparations can be used as the reference product when assessing biosimilarity. The drafting group agreed, editing the text to remove the word "biosimilar" and clarify the use of reference preparations in bioassay development.

Part A: Manufacturing recommendations

Part A of the mAb production and quality control guideline adopts a format similar to the corresponding section of other manufacturing guidelines for biological medicines. In addition to general manufacturing recommendations, it includes guidance the control of source materials, production, the final bulk, and the final product, as well as advice on documentation, stability and logistics. The majority of comments arising from the first round of public consultation were on this section, although many were minor or editorial and were accepted by the drafting group without extensive discussion.

Several comments were raised on the number of batches used for process performance qualification (PPQ). Consequently, for clarity the drafting group modified the text relating to PPQ for both marketing authorization and post-approval changes in section A.2 to provide 13 -0 more flexibility. This included suggesting that the number of batches for a PPQ relating to post-approval changes should be justified on risk- and science-based principles, allowing for fewer batches to be used where changes were expected to have a minimal impact on quality.

The section A.4 on the control of raw materials was edited to address several minor issues raised during the public consultation, including the need to standardise the language to be consistent with other regulatory guidance. In addition, the text concerning comparability studies required when changing the mAb production cell line or cell type was modified for clarity and consistency with ICH Q5E, and to reflect the application of risk-based principles.

The drafting group discussed at some length a request for additional guidance on the use of transient expression systems for the commercial production of clinical grade mAbs. There was a consensus that the use of a transient expression system could facilitate the rapid introduction of the product into clinical development, which could prove particularly useful in a public health emergency and to address unmet medical needs. However, the drafting group remained unconvinced that such an approach would be used to manufacture a commercial product and felt it would be difficult to provide specific guidance. The wording of section A.4.4 was modified to reflect the potential for transient expression to be used early in product development and, as it would inevitably be considered on a case-by-case basis, to recommend the use of transient expression should be discussed with the NRA. In the same section, the text on how cells at the limit of *in vitro* production should be characterized was edited for clarity and consistency with ICH Q5B and Q5D.

Several reviewers challenged the text that suggested a change of WCB manufacturing facility would warrant a different testing approach to the original WCB manufacturing facility, since both facilities operate under GMP control. To address this the drafting group agreed a redrafted version of section A.4.5 that acknowledged WCBs have to be replaced from time to time and should be characterized and qualified according to ICH Q5B and Q5D guidance.

The drafting group accepted criticisms that parts of section A.5 on the control of mAb production may be subjective or too prescriptive and modified the text where appropriate. Text was added on the sort of data that informs particular processes and edited to appear more flexible and risk-based. Accepting that the bulleted list in this section was not comprehensive, the drafting group felt that it was, nevertheless, useful for less experienced regulators and should be retained. There were numerous detailed comments on section A.5.3 which provides guidance on purification processes and their validation. The corresponding section of other WHO guidelines typically shorter and provides less detail. With this in mind, a new version of this section was produced that is informative and addresses the majority of comments, which were primarily raised by manufacturers and regulators. In addition, the section providing guidance on in-process hold times was moved into section A.5.3 from the stability section of the draft guideline (section A.12) and edited for clarity to address comments raised by manufacturers.

A new section (A.5.5) was introduced to provide guidance on the stability and storage of the drug substance. This section also addresses a concern that the draft guideline did not offer guidance on the assessment of extractable and leachable material from product contact surfaces of containers and closure systems.

Guidance on the control of the drug substance (section A.5.6) was modified to remove specific ranges for acceptance criteria, which might be interpreted as regulatory expectations in some jurisdictions, as well as to meet concerns about text regarding the assessment of heterogeneity profiles of purified bulk mAbs and mAb conjugates. The latter was addressed by shortening the original text and introducing the idea that the selection of appropriate methods should be risk-based and product-specific. In addition, the subsection A.5.6.6 on the heterogeneity profile was edited to clarify these issues and suggest the criteria that should be considered and discussed with the NRA. There was also a wide-ranging discussion on the acceptable level of substance- and process-related impurities. Accepting the manufacturers' recommendation to make the guidance on impurities and their impact on patient safety more explicit, the text of subsection A.5.5.8 on in-process impurities was edited to be clear that limits for impurities should be based on clinical safety and the methods used for their detection should be sufficiently sensitive to detect unsafe levels.

Following the public consultation, the start of section A.6 on the preparation and control of the final bulk was been expanded to provide more explicit advice on the inclusion of excipients and their quality specifications. A second paragraph was also added to provide more clarity on the development of control strategies for the final bulk and cross-reference the ICH Q11 guideline. The drafting group was in agreement not to include a specific subsection on inherent protein particles, as suggested by manufacturers, preferring to elaborate on the issue of visible particles in the guidance on verifying appearance of the final product later in the document (section A.8.2.1).

Several minor and editorial suggestions were incorporated into section A.8 on the control of the final product. Additional text was provided offering more comprehensive guidance on when control tests may be omitted. As mentioned above, text on appearance testing was modified and guidance on the identity test for the final product was edited for consistency with similar guidance for the drug substance earlier in the document. The drafting group noted that it preferred the term "co-formulated" to "cocktail" when referring to formulations containing multiple mAbs and "co-formulated mAbs" has also been added to the list of terminology in the revised document. Acknowledging that non-consensus glycosylated species and translational modifications are widely regarded as heterogeneity rather than impurities, the drafting group agreed that the text on product related impurities (A.8.2.7) should be corrected. It also agreed that to be consistent with changes in section A.6, the text on testing excipients (A.8.2.9) should be less prescriptive and focus on those excipients that are critical for product stability. There was a consensus that the testing strategy for excipients should be risk-based and agreed with the NRA. Cognisant of aim of the WHO/NC3Rs project to remove the rabbit pyrogen test (RPT) from all WHO TRSs, the drafting group agreed that although the guideline would have to allow for current use of the RPT in some jurisdictions, its use should be discouraged.

The public consultation elicited several comments on the issue of hold times. The drafting group discussed the use of the term "hold time" at some length and agreed that the concept was better addressed in the context of process validation rather than stability. In the revised draft guideline, the hold time subsection (formerly A.12.1) was removed from the section on stability. There was also a suggestion from the public consultation that the guideline might include expectations for the stability of combination products but the drafting group was unanimously of the view that this would add unnecessary confusion and risked misleading less experienced regulators. Other suggestions on the stability section (A.13) were largely incorporate in the revised document, including the modification of the language on leveraging platform technology and gathering stability data during the product development.

Part B: Recommendations for NRAs

As official control authority batch release is not generally required for mAb products, statements suggesting the contrary were removed from Part B of the revised guideline. There were no other significant comments on Part B.

Conclusion

The first round of public consultation elicited more 198 helpful comments on the draft guideline, most of which were incorporated into a revised draft that was submitted to a second round of public consultation in February 2022. Such consultations are a crucial part of developing WHO guidelines. The drafting group was in unanimous agreement that the first public consultation on the draft WHO Guideline for the safe production and quality control of monoclonal antibodies and related proteins for use in humans had been instrumental in the development of a significantly improved version of the document. This document only provides guidance on the manufacturing and quality aspects of mAb production, and in due course is expected to be used in conjunction with a second guideline covering the non-clinical and clinical aspects of mAb development.

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