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Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases

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Annex 2

Guidelines on the nonclinical and clinical evaluation of monoclonal antibodies and related products intended for the prevention or treatment of infectious diseases

1.	Introduction	5
2.	Purpose and scope	6
3.	Terminology	7
4.	General considerations	8
5.	Nonclinical evaluation	11
5.1	General considerations in nonclinical evaluation	12
5.2	Pharmacodynamics and biological activity	14
5.3	Pharmacokinetics and toxicokinetics	16
5.4	Toxicology studies	17
5.5	Additional considerations in nonclinical evaluation	19
6.	Clinical evaluation	20
6.1	General considerations in clinical evaluation	20
6.2	Phase I studies	22
6.3	Clinical pharmacology	23
6.4	Efficacy – Phase II and III studies	25
6.5	Safety	28
6.6	Special populations	29
6.7	Manufacturing and formulation changes	31
6.8	Phase IV and post-marketing studies	31
6.9	Statistical considerations	31
6.10	Pharmacovigilance systems and risk-management planning	32
7.	Authors and acknowledgements	32
8.	References	33
Appendix	Considerations regarding abbreviated submissions for mAbs against an infectious disease during a public health emergency	40

Guidelines published by the World Health Organization (WHO) are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, these WHO Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It is recommended that modifications to these Guidelines are made only on condition that such modifications ensure that the product is at least as safe and efficacious as that prepared in accordance with the guidance set out below.

Abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADE	antibody-dependent enhancement (of disease)
ADR	adverse drug reaction
CDC	complement-dependent cytotoxicity
COVID-19	coronavirus disease 2019
Fab	fragment antigen-binding (region)
Fc	fragment crystallizable (region)
FIH	first-in-human
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
mAb	monoclonal antibody
MED	minimum effective dose
NRA	national regulatory authority
PD	pharmacodynamic(s)
PEP	post-exposure prophylaxis
PK	pharmacokinetic(s)
PrEP	pre-exposure prophylaxis
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TK	toxicokinetic(s)

1. Introduction

Monoclonal antibodies (mAbs) represent the largest class of therapeutic proteins in clinical use. However, the majority of currently marketed mAbs are used for the treatment of noncommunicable diseases such as cancer or autoimmune disorders. Although only a small number of mAbs have to date been licensed to treat or prevent infectious diseases, the number of such products in development is growing (1–4).

Advances in recombinant biotechnology and protein chemistry, combined with a greater understanding of mAb structure and function, have led to growing interest in recombinant varieties of mAbs such as chimeric mAbs, mAb fragments, single domain mAbs and multispecific mAbs. These mAb variants may offer significant production, formulation and clinical advantages, including improved production yields, greater stability, the potential for alternative routes of administration, multiple antigen targeting, prolonged half-lives, increased bioavailability, enhanced functional activity and/or altered tissue penetration. These technological advances in mAb engineering have led to the revision of the WHO nomenclature system to accommodate the growing diversity of mAb products (5).

Due to their established history of safe use, the rapid onset of their clinical effect and the relatively short time required to bring them to production, mAbs potentially offer a real-time response to emerging infectious diseases. As a result, they are considered to be a high priority for development due to their potential impact during public health emergencies such as coronavirus disease 2019 (COVID-19) (6), and in the treatment of chronic infectious diseases such as acquired immunodeficiency syndrome (AIDS). However, this will require that national regulatory authorities (NRAs) have the expertise, capacity and regulatory processes in place needed to review mAb products under such circumstances.

In 2020, the WHO Expert Committee on Biological Standardization discussed the advances being made in mAb engineering and production technologies, and the growing importance of such products in the management of infectious diseases (6). The Committee noted that although a range of WHO documents relevant to mAbs had already been published, these focused primarily on their use as biotherapeutics for noncommunicable diseases, with little guidance provided on nonclinical or clinical evaluation specific to pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP) or to post-infection treatment with mAbs. It was envisaged that the provision of such guidance on the evaluation of mAbs against communicable diseases would help to clarify regulatory expectations during their development and licensure processes, facilitate international regulatory harmonization efforts and thus improve access to such products. The Committee therefore endorsed a proposal to develop a WHO Guidelines document that would be broadly applicable to mAb products intended for prophylaxis and/or treatment of infectious diseases.

Following a detailed review of existing WHO documents to identify where additional guidance and clarity was required on the nonclinical and clinical evaluation of pathogen-directed mAbs and related biological products, the current WHO Guidelines document was developed through a process of international and public consultation. The Guidelines should be read in conjunction with the relevant sections of the existing WHO documents referenced throughout the text. A number of non-WHO documents are also cited where these may provide additional supporting information. In addition, a number of considerations regarding nonclinical and clinical approaches to abbreviated regulatory submissions for mAbs are provided in the Appendix to these Guidelines. It is envisaged that, where required, individual supplements to the Guidelines may also be developed in the future on disease-specific regulatory considerations for these products.

2. Purpose and scope

These Guidelines are intended to provide guidance to NRAs, sponsors, manufacturers and investigators on the nonclinical and clinical evaluation of mAbs directed against the antigens of invading pathogens or their toxins, and which are used specifically in the pre- and post-exposure prevention or treatment of human infectious diseases. It should be noted that the general principles outlined in the document would also apply to mAbs that target endogenous human proteins with the intention of preventing or treating infections (for example, a mAb to a cell surface receptor that prevents viral entry to the cell) – however, such products may require additional nonclinical and clinical studies depending on the protein target(s). Immunomodulatory antibodies are not within the scope of these Guidelines as they are not directed against the infectious agent itself, or against a toxin antigen, but towards components of the host immune response, such as T-cells or cytokines.

The guidance provided is intended to apply to mAbs regardless of their isotype, as well as to other recombinant mAb-related antigen-binding proteins based on an immunoglobulin scaffold. These products can include, but are not limited to:

- antibody fragments, such as single-chain variable fragments and fragment antigen-binding (Fab) fragments;
- single domain antibodies;
- bispecific or multispecific antibodies;
- mAbs or related antibody proteins which have been chemically modified, such as through conjugation;
- mAbs which have been modified (such as through sequence substitutions, additions, and/or altered glycosylation) for the purposes of extending the half-life, or reducing or enhancing the effector function; and
- multiple mAb substances co-formulated within a final product (“antibody cocktail”).

It should be noted that for the purposes of this document the term “monoclonal antibody” or “mAb” is used to encompass the breadth of the substances and products listed above, unless otherwise stated.

Small recombinant proteins intended to mimic mAb binding activity, but which have little or no immunoglobulin structure (for example, DARPin, affimers and anticalins), can differ significantly from mAbs in their pharmacological profiles (for example, in their bioavailability, pharmacokinetics (PK) and/or distribution) as well as in their formulation. With regard to convalescent serum immunoglobulins, although the basic principles for evaluating their pathogen-directed effects are similar to those described in the current document, there will be differences in their nonclinical and clinical evaluation, and such products would need to comply with regulations for testing blood-derived products. As a result, only parts of this document may be applicable to both small recombinant mAb mimetic proteins and pathogen-specific plasma-derived immunoglobulins, and sponsors of such products are encouraged to consult with the NRA on possible additional requirements. Similarly, these Guidelines do not apply to nucleic-acid-based platforms which use DNA, RNA or viral vector technology to deliver genetic sequences that encode for mAb production in vivo following administration. Such products face their own unique regulatory challenges that are best addressed in separate guidance.

Guidance on the production and quality control aspects of mAbs is provided in the WHO Guidelines for the production and quality control of monoclonal antibodies and related products intended for medicinal use (7). These Guidelines take into account the extensive

technological advances made in the field of mAb manufacturing since the original murine-hybridoma-derived mAbs were produced in the 1970s. Such advances include greatly improved production and purification methods, conjugation technologies, mAb fragments and mAbs derived from plant-based production systems. For mAb products developed as biosimilars, reference should be made to the WHO Guidelines on evaluation of biosimilars (8).

3. Terminology

The following definitions apply to the terms as used in these WHO Guidelines. These terms may have different meanings in other contexts.

Antibody cocktails: see **co-formulated mAbs**.

Antibody-dependent cellular cytotoxicity (ADCC): an effector function of the immune response in which fragment crystallizable (Fc) receptor-bearing effector cells can recognize and lyse an antibody-coated target cell expressing pathogen-derived antigens on their surface. Also called antibody-dependent cell-mediated cytotoxicity.

Antibody-dependent cellular phagocytosis (ADCP): an effector function of the immune response in which Fc receptor-bearing macrophages, or other phagocytic cells, phagocytose an antibody-coated target cell or microorganism.

Antibody-dependent enhancement (ADE): a phenomenon that occurs when antibodies promote, rather than inhibit, the infectivity of a microorganism and may occur through a number of possible mechanisms. Also called “antibody-dependent disease enhancement”.

Antibody mimetic proteins: peptides or proteins that are not structurally related to antibodies but which recognize and bind to specific antigens. Such proteins usually have a molar mass of 3–20 kDa. Also called “antibody mimetics”.

Anti-drug antibodies (ADAs): host antibodies that are capable of binding to the administered mAb therapeutic. This may or may not inactivate the administered mAb and/or induce serious adverse effects (see also **neutralizing antibodies** below).

Biological activity: the ability or capacity of a mAb to elicit a defined biological effect in vitro (for example, in cultured cells, bacteria or viruses) or in vivo (that is, in animal models and/or in humans).

Co-formulated mAbs: a final product formulated to contain two or more mAbs, mAb conjugates and/or mAb fragments, each of which recognizes a different epitope or antigen. These may also be referred to as “antibody cocktails”, “antibody mixtures”, “pooled antibody products” or “oligoclonal products”. Co-formulated mAbs are not the same as individual mAb products that may later be co-administered during treatment.

Complement-dependent cytotoxicity (CDC): an immune response in which an antibody–antigen complex activates complement and induces the formation of a terminal lytic complex that is inserted into a cell membrane, resulting in lysis and cell death.

Effector function: the capacity of the **fragment crystallizable (Fc) region** of a mAb, following binding to the antigen, to engage with elements of the immune system through interactions with Fc receptors to generate functional responses. Effector functions include ADCC, ADCP and **opsonization**.

Fragment antigen-binding (Fab) region: a region on an antibody that binds to antigens. It is composed of one constant and one variable domain of each of the heavy and the light chain.

Fragment crystallizable (Fc) region: the tail region of an antibody derived from the second and third constant domains of the two heavy chains. This region is responsible for the effector functions of antibodies through its interactions with cell surface Fc receptors and some

proteins of the complement system; however, such effector functions require the Fc region to be appropriately glycosylated.

Human challenge trial: a clinical trial involving the inoculation of healthy volunteers with a challenge agent before or after the administration of an investigational product.

Immunoconjugates: antibodies conjugated to a second molecule. Such molecules may include a toxin, anti-infective agent (antibiotic, antiviral or antifungal), radioisotope, label or non-bioactive compound. Immunoconjugates may be used in diagnosis and in targeted immunotherapy. Also called “antibody-drug conjugates”.

Neutralizing antibodies: can refer to antibodies which neutralize the infecting organism or toxin by preventing it from binding to and/or infecting the host cell. However, neutralizing antibodies may also refer to antibodies formed against the mAb product that render it inactive against its intended target (see also **anti-drug antibodies (ADAs)** above).

Opsonization: the effector function in which antibodies bind to the surface of the antigen rendering it more readily identified and engulfed by phagocytic cells (for example, macrophages) for destruction.

Platform technology: an existing technology, or group of technologies, that are applied to the development and/or production of similar mAb products by a manufacturer. A given manufacturer might have one or more platforms on which they will develop various mAbs. A platform would be considered when the elements of the manufacturing methods and/or processes, the mAb protein scaffold, and the compliance with good manufacturing practices are unchanged. The experience and knowledge gained, data generated (on manufacturing, control and stability), and the validation of unchanged methods can all be used as supportive data for the more rapid assessment and development of a new mAb product candidate that fits within the boundaries of the platform.

Prophylaxis: a passive immunization or treatment intended to prevent an infection or an infectious disease, and given either as pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP).

Therapeutic index: ratio of the median toxic dose to the median effective dose (TD₅₀:ED₅₀).

Therapeutic window: the range of mAb dosage, or its concentration in blood, that is sufficient to provide an effective response without significant adverse effect.

4. General considerations

The administration of antibodies for the prevention or treatment of infectious diseases is not a new concept. Human convalescent and immune animal sera were first used during the late 19th century as immunotherapies against both bacterial and viral infections (9–12). Human and equine plasma-derived immunoglobulins (such as anti-rabies, anti-hepatitis B and anti-tetanus immunoglobulins) continue to be used (12), with some included in the current WHO Model List of Essential Medicines. However, serum products can face issues of standardization, safety, supply and access (13). The introduction of mAb products offers the advantages of a more reliable and larger commercial supply, along with the potential for products that have better consistency between lots, are safer, can be engineered to have longer half-lives and which offer greater specificity and functionality than immune antisera and polyclonal antibodies (9, 10, 12, 14).

The mAb bioengineering and production technologies now available also potentially allow for the rapid development of new products directed against emerging infectious diseases for which there are no available vaccines or therapeutics. Passive immunization through the administration of mAbs can provide rapid and direct benefits in preventing or treating an infectious disease – unlike active immunization through vaccination which may take weeks

and may require multiple doses for the emergence of a protective effect. This is particularly important: (a) for immunocompromised individuals and those who cannot be vaccinated due to contraindications; (b) for those who are working or living in zones of high transmission during rapidly evolving epidemics or pandemics; and/or (c) when vaccination or other antimicrobial agents may not yet be available. As a result, mAbs are becoming an important addition to the repertoire of therapeutic and prophylactic products for infectious diseases, along with preventive vaccines and small-molecule antimicrobials (10, 12, 15, 16).

Anti-infective mAbs

Currently, anti-infective mAbs are mostly full-length immunoglobulin G (typically abbreviated to “IgG”) molecules – though immunoglobulin A (IgA) and immunoglobulin M (IgM) mAb isotypes are also under investigation. These mAbs can act directly by neutralizing the pathogen and inhibiting its ability to bind to human cell receptors, with fragment crystallizable (Fc)-receptor-dependent uptake by Kupffer cells and sinusoidal endothelial cells in the liver removing the toxin, bacterium, virus or other pathogen from the bloodstream (17). Such products may also act through their Fc-mediated effector function mechanism by stimulating immune responses such as antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC) or opsonophagocytosis. Due to this potential range of functions, an understanding of the mechanism(s) of action of the mAb is crucial in evaluating its activity in both nonclinical and clinical studies.

Along with understanding the intended mechanism of action of mAbs, it is also important to characterize their physicochemical properties, which may include their size and charge variants, post-translational modifications, conjugations, hydrophobicity, potential for aggregation, glycosylation patterns or C-terminal heterogeneity (7). All of these biochemical properties can significantly impact upon mAb half-life, tissue distribution, stability, susceptibility to enzyme degradation, excretion, and their pharmacological and/or reactogenic potential. For example, engineering amino acid changes in the Fc region of mAbs can lead to longer half-lives, as well as to enhanced or decreased effector functions such as their interactions with host Fc receptors or proteins of the complement system (18–20). Differences in post-translational glycosylation can also lead to functional changes and alterations to half-life (21, 22). Therefore, each individual mAb product may present a unique biochemical and biophysical profile which should be taken into consideration during their evaluation. Nevertheless, due to structural similarities among mAb products, the knowledge and technological experience of a manufacturer may be used to develop platform manufacturing processes that could be applicable to other mAbs produced by the same manufacturer using the same technologies and processes (7). Information from other manufacturers, or the products of other production processes, would not necessarily be supportive of such a proposal. Careful consideration is required in this regard, and an individual case-by-case approach may be justified but should be discussed and agreed with the relevant NRA(s).

Monoclonal antibody delivery

The biodistribution and ability of a mAb to reach site(s) of pathogen activity are other important considerations during product development. The physicochemical properties of the mAb, along with its formulation and route of administration, will all influence the compartments which it can access. To date, most mAbs have been administered by the intravenous route, often in specialized health-care settings and with administration times ranging from 30 minutes to several hours. However, considerable attention is now being given to the subcutaneous or intramuscular administration of highly concentrated mAbs which can be administered in only

a few minutes. Other alternative mAb delivery routes are also being explored, including nasal, inhaled, oral, intraocular, intrathecal and dermal routes, some of which are of particular interest for the administration of mAbs directed against infectious diseases. Specifications, formulations and safety issues for mAbs delivered by these alternative routes may differ from those for products to be administered by the intravenous route due to issues related to immunoglobulin concentration, viscosity, aggregation and stability – and this will need to be borne in mind during both nonclinical and clinical evaluation (23). In recent years, several mAb fragments and small mAb mimetic proteins based on non-immunoglobulin scaffolds have been generated using affinity selection technology. These highly engineered proteins are significantly smaller than full-length mAbs and have physicochemical properties which may be designed to influence their bioavailability and tissue penetration range. Despite offering several advantages, such mAb fragments and mimetic proteins may have reduced half-lives and are usually unable to elicit effector functions such as ADCC or CDC.

Potential adverse effects

Two potential adverse impacts of mAbs should be assessed throughout the product development programme, and should be monitored following their marketing approval – namely the emergence of antimicrobial resistance, and antibody-dependent enhancement (ADE) of disease. These effects may have significant impacts on product efficacy and safety, and should be considered during benefit–risk and/or safety assessments of mAb products to infectious diseases.

As has been observed with small-molecule antimicrobials, selection for resistance of the infecting pathogen to the mAb may occur and should be monitored for throughout the product life-cycle. For example, bacteria can be induced to produce antibody-degrading proteinases (24–26) or changes to the target antigen can occur through natural mutagenic selection processes – either of which could reduce the efficacy of mAb therapies (24, 27, 28). Similarly, the emergence of multiple strains and escape mutants among viruses can lead to new variants that may evade mAb therapies, for example through alteration of the antigenic structure of an epidemic pathogen in real time (29–31).

The potential emergence of organisms resistant to mAbs necessitates rational drug design approaches including the exploration of mAbs that target highly conserved antigens or epitopes, the combination of a mAb with one or more small-molecule drugs, or the use of co-formulated mAbs (antibody cocktails) that contain mAbs targeting separate antigens or epitopes (16, 29, 32, 33). The development of bispecific mAbs through bioengineering to combine the epitope specificities of two antibodies and simultaneously interact with different antigens or epitopes is also being explored (34).

ADE is also an important aspect to consider as part of the nonclinical and clinical programmes of any mAb against infectious diseases, particularly if the functions of the epitope are not clearly understood. Disease enhancement may occur through facilitation of the pathogen life-cycle (for example, by easing viral entry into a cell, promoting replication in target cells or facilitating cell-to-cell transmission) or through the enhancement of physiological responses (for example, complement activation). In the case of the former, antibody-mediated enhancement is classically defined as Fc γ -receptor–mediated enhanced disease, which may occur in the presence of non-neutralizing antibodies, sub-neutralizing antibody concentrations or low-affinity antibodies. Although ADE is more classically observed with viral infections (35–37), the ADE of bacterial infections has also been reported (38–40) and may be linked to antibody isotype and glycosylation patterns (24).

The assessment of potential ADE can be difficult during nonclinical and clinical development programmes as its mechanisms are not always fully understood, and may or may not translate between its nonclinical observation and occurrence, or risk, in the clinic. Cell

culture methods may provide an effective model in which to explore the potential mechanisms of ADE but may not be predictive of clinical outcome, and detecting its impact in clinical studies might be difficult if its occurrence is rare (37, 41).

Regulatory considerations

The nonclinical and clinical sections of these Guidelines describe a traditional path for evaluating the safety and efficacy of mAbs against infectious diseases and are likely to apply to the majority of products developed. However, a benefit–risk assessment of some epidemiological circumstances may warrant, or require, that the sponsor and NRA consider alternative approaches to evaluating product safety and efficacy, while balancing the regulatory requirements for safety and efficacy against ensuring product accessibility during a time of critical need. Such circumstances may occur, for example, for rare or neglected diseases, localized and/or short-lived outbreaks, an infection with a high fatality rate or during a public health emergency. Consideration of any alternative nonclinical and/or clinical plan will require good communication with the NRA, with discussions occurring as early as possible during product development. NRAs are encouraged to use good regulatory reliance practices and other collaborative approaches with regulatory partners when assessing submissions for mAb products for which alternative review strategies may be warranted.

In the case of the rapid development of products against a priority pathogen, such as during a public health emergency, consideration may be given to abbreviating the nonclinical and/or clinical requirements by deferring or omitting certain studies in order to expedite product development and regulatory evaluation. However, the benefit–risk ratio of such an approach must always be considered and early consultation with the NRA is strongly advised under such circumstances. Further discussion of this topic is provided in the Appendix to these Guidelines.

Standards and other reference materials

Standards and other reference materials play a vital part in the quality control and regulatory authorization processes of all biological products, including mAbs. Where they are available, such materials may be included in antigen quantification or bactericidal assays, or used in the determining of antibody concentrations or in methods for monitoring serological end-points. The standardization of assay methods used to support the nonclinical and clinical evaluation of mAbs will also be important in ensuring the comparability of laboratory results within and between countries, and between different clinical trials.

WHO international standards, reference reagents and other reference materials are the primary standards in use worldwide, and when available should be included in bioassays. In addition, NRAs and manufacturers should establish secondary (regional, national), working standards for use in assays supporting nonclinical and clinical studies, as well as for the purpose of testing mAb quality on a lot-to-lot basis (7).

5. Nonclinical evaluation

This section sets out a flexible approach to the nonclinical evaluation of mAbs intended for use in the prevention or treatment of infectious disease. The approach includes the use of both *in vitro* and *in vivo* (animal) studies. The guidance provided is intended to be complementary to, and should be read in conjunction with, Part B and Appendix 5 of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (42) and the WHO guidelines on nonclinical evaluation of vaccines (43). Additional guidance can be found in section 5 of the WHO Guidelines on evaluation of monoclonal

antibodies as similar biotherapeutic products (SBPs) (27), as well as in the WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products (28). ICH guidance on the preclinical safety evaluation of biotechnology-derived pharmaceuticals (44) and on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (45) should also be consulted, along with any relevant guidance from NRAs.

The initial discovery and characterization of a mAb typically involves the assessment of numerous mAb candidates in a variety of assays that evaluate their effectiveness in pathogen or toxin neutralization and determine their likely mechanism(s) of action. Although these tests will generally be performed using research materials, subsequent mechanistic and efficacy studies should be carried out using clinically relevant mAb product lots if possible. Where this is not feasible, the lots studied should be comparable with respect to their physicochemical characterization data, biological activity, stability and formulation (7). Such studies may include preliminary in vitro or animal tests performed with mAb product lots produced by a polyclonal cell population expressing the mAb as the first step in isolating a stable, high-expressing clone for the final manufacturing step. The continued comparability of the test material should be demonstrated whenever a new or modified manufacturing process is used or when other significant changes in the product or its formulation are made in an ongoing development programme. Comparability can be evaluated based on biochemical and biological characterization (that is, identity, purity, stability and potency) (7, 27). In some cases, additional studies may be needed (for example, nonclinical pharmacokinetic (PK) studies, pharmacodynamic (PD) studies and/or toxicology studies). The scientific rationale for the approach taken should be provided. It should be noted that the mAb product lots used in pivotal nonclinical studies must adequately represent the quality and formulation intended for use in subsequent clinical investigations.

Pivotal nonclinical toxicity studies should comply with good laboratory practices (44, 46). Data integrity should be maintained where internal standard operating procedures are not used, such as for dose-ranging studies or early toxicity studies that are not compliant with good laboratory practices.

All studies conducted in animals should follow the 3Rs principles (“Replace, Reduce, Refine”) and minimize the use of animals in research. Although animal study end-points need to best reflect those expected during clinical evaluation, such studies should terminate as early as possible to minimize suffering, particularly in the case of studies in which animals are infected. Where available, consideration should be given to the use of validated alternative in vitro methods for toxicological evaluation.

5.1 General considerations in nonclinical evaluation

The primary objectives of both in vitro and animal nonclinical studies are to define the pharmacological and toxicological effects of investigational products prior to the initiation of human studies (43). This will involve:

- Functional characterization of the product, such as its ability to prevent disease, reduce pathogen load, impair toxin activity, promote pathogen clearance from the blood and tissues, improve clinical signs, prevent or reduce weight loss, or reduce severity of infection.
- Identification of possible toxicities, their potential for reversibility and likelihood of potential adverse or undesirable effects.
- Identification of a safe starting dose for first-in-human (FIH) studies and of safe dose escalation when possible.

There are several important factors to consider when designing nonclinical studies for mAbs intended to prevent or treat a human infectious disease. Knowledge of the mAb target antigen of the infecting pathogen and its biology is expected, as is characterization of the binding site/epitope and evaluation of the specificity and selectivity of the mAb to the pathogen. Unwanted and unexpected cross-reactivity with animal or human cells and/or tissues need to be explored. In addition, naturally occurring changes to the antigen (that is, through antigenic drift or shift) may occur through the course of some epidemics and result in reduced affinity of the mAb to the target antigen. The potential for such reduced affinity through epitope mutation should therefore be considered and prospectively evaluated, if relevant, before a mAb is committed to clinical study, and should be monitored by the sponsor (for example, through *in vitro* tests using antigens derived from circulating and emerging strains).

Nonclinical study design should be guided by, and tailored to, the type of data needed, and by whether it is a PK, PD or safety study. Data derived from PD, PK and short-term toxicity studies help to approximate the FIH dose and dosing margins. PD studies in animals help to define the lower range of the efficacious therapeutic dose (for example, minimum effective dose) whereas short-term toxicity studies provide an indication of the upper range for a safe FIH dose. PK studies provide information on the blood concentration–time profile of the mAb following administration that can help refine the therapeutic dose range. In some cases, PK data may also provide an estimate of the lower dose range for use in FIH studies where PD data are not available. *In vitro* and modelling studies for mAbs for which there are sufficient data and experience may be acceptable alternatives for estimating FIH doses, but this should be discussed with the NRA in advance. *In vitro* and modelling studies for estimating FIH doses may not be sufficient for novel mAb products for which there is limited experience.

The selection of a suitable animal species for use in evaluating mAbs against an infectious disease could prove challenging, and may not necessarily be the same species across the different study types. Scientific justification should be provided for the animal species selected for use in each study and should take into account the likely suitability of the resulting data in guiding human clinical studies. Selection of the animal species, and the potential to combine end-points within one study, should be discussed with the NRA. This is particularly important where established animal models of infection do not exist, are not relevant to human physiology or do not reflect the pathology of the infection in humans.

The nature of the mAb product itself should also inform species selection since this may also influence the study results. Although the target antigen for anti-infective mAbs is unique to the infecting pathogen, regardless of the host, the subsequent response by the host to the mAb-bound pathogen can vary significantly in nonclinical studies depending on the host species and on the species from which the mAb has been derived. For example, the use of a humanized mAb in a mouse model would not necessarily predict the activity or safety of the same humanized mAb in humans. For this reason, understanding the impact of host species and mAb differences will be crucial in the preclinical development programme and in the translation of nonclinical data to the clinical situation.

The induction of anti-drug antibodies (ADAs) is species specific, and their occurrence in animal studies is generally not relevant in terms of predicting the potential immunogenicity of mAb products in humans. Nevertheless, the detection of ADAs in animals may provide some insight as to potential complications, particularly for mAb-related products, and may also assist in the interpretation of data derived from animal toxicity studies. For example, ADA formation can increase the clearance of the mAb and impact its PK and/or toxicokinetics (TK), which in turn can reduce its pharmacological and/or toxicological effects. The induction of ADAs could also result in other pharmacological and/or toxicological changes including the emergence of

new toxic effects. Therefore, all such PK and TK effects of ADA formation should be considered (see sections 5.3 and 5.4 below).

In addition, consideration should be given to situations where the mechanism of action of the mAb involves a secondary response such as ADCC, ADCP or CDC, which may vary greatly depending on antibody Fc and animal model Fc receptors. Such pharmacological properties, and whether or not they are species specific, should be considered when interpreting exposure–response relationships, PK parameters and tissue toxicity in animal studies. The degree of similarity of the animal infection model to human infection must also be taken into consideration.

In all animal studies it is important to sequence, characterize and standardize the pathogen challenge strain and its dose on administration. Where the passage of pathogenic strains may lead to the development of variants – as for example in the case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – it is vital to use challenge material at defined and standardized passage levels (47). It may also be informative to genotype pathogens isolated from animals that succumb to infection despite mAb exposure in order to assess whether the susceptibility to such infection correlated with antigenic drift or shift in the pathogen.

5.2 Pharmacodynamics and biological activity

5.2.1 In vitro studies

Biological activity may be evaluated using in vitro assays to determine which effects of the product may be related to clinical activity. Several concentrations of the product should be tested during in vitro pharmacology studies. If a mAb fragment or immunoconjugate is used it should be tested in that form. Appropriate newer assay technologies should be employed as they become available and validated.

In vitro studies for demonstrating mechanism of action can include assays that characterize the binding site(s), binding affinity to the exogenous target, infecting organism or bacterial toxin, mechanism of pathogen inactivation/destruction (for example, bactericidal, opsonophagocytic or neutralizing activity that includes effects on variants) and effector function of the mAb. Structural biology approaches can also be used to map the mAb-antigen complexes at the atomic level. In vitro studies may also help to evaluate the impact of: (a) antigenic variations such as those which occur naturally through genetic drift or shift; (b) bacterial capsule switching; and (c) escape mutations in the pathogen. These antigenic variants may be isolated in the laboratory or derived from clinical isolates. The sponsor should also consider the potential for cross-resistance with other marketed antibodies/drugs.

5.2.1.1 Cell culture studies

Cell culture models can be invaluable tools for the early screening of mAb product candidates, for assessing the effects of mAbs against pathogens of interest and for exploring mAb mechanism(s) of action. Cell culture systems are an integral component of the in vitro assessment of mAb neutralizing activity and antibody effector functions such as ADCC, ADCP or opsonization. However, cell culture systems may not have been established for all infectious agents, particularly during the early stages of a pandemic or when a pathogen is recalcitrant to cell culture methodologies or environments. Where cell culture models do exist, care should be taken to ensure that the environmental conditions are suitable for maintaining proper functionality of the mAb, and to minimize the interference of assay reagents. The use of tissues or cells from different species in cell culture models may also provide insight into the most relevant animal model to use in PD studies.

For co-formulated mAbs, the neutralizing activity of each of the constituent mAbs should be tested and any potential synergistic or antagonistic effect of the combination determined.

5.2.1.2 Tissue cross-reactivity studies

The non-target tissue binding of mAbs may have serious consequences, particularly when certain immunoconjugates are used. Therefore, cross-reactivity studies should usually be conducted prior to FIH studies to detect any non-target tissue binding or other cross-reactions.

Any unintended reactivity of an investigational mAb with human tissue should be determined using a frozen panel of tissues or representative cell cultures (44). Several concentrations of the candidate product should be tested as the ability to detect cross-reactions may depend on the concentration of the mAb. The NRA should be consulted on the requirements for the human tissue panel. Likewise, the possibility of evaluating off-target reactivity with human proteins using a validated cell and/or protein microarray assay should be discussed with the NRA. When cross-reactivity signals are detected, studies should be expanded to more tissues. Although the use of animal tissues may help interpret some findings from animal studies, tissue cross-reactivity testing in a full panel of animal tissues is not recommended (44).

5.2.2 Animal studies

In vivo animal PD studies are important in understanding the biological activity of the mAb in a living system. As animal PD studies are also used for the approximation of FIH doses they should be conducted where possible. However, as the requirements for PD studies to be conducted on mAbs against infectious diseases may vary between countries, and as in vitro and/or modelling studies may be acceptable alternatives for mAbs with sufficient associated data and experience, this should be discussed with the NRA as early as possible in the mAb development pathway. PD studies should be based on assays that ensure that the mAb is functional against the targeted infectious agent. However, classic PD/PK assessment may be of limited relevance in animal models. For most pathogens there will be a wealth of knowledge and experience of relevant assays amassed from work on the disease and its prevention. Existing knowledge of natural and/or vaccine-induced immunity may also provide additional insights during the nonclinical evaluation of the mAb product under development.

An attempt should be made to study the dose-dependence of PD effects when an animal model for the infection is available. The use of a broad range of doses, including high doses, may allow for better prediction of the therapeutic index. When two or more mAbs are co-formulated in the final product, only the intended combination should be evaluated in animals. The PD of each individual mAb and its co-formulation should be evaluated in vitro.

For proof-of-concept studies demonstrating anti-pathogen activity, preference should be given to studying the mAb in a model in which the infection in the animal is similar to that in humans. Consideration should be given to establishing how similar the infection is in the chosen animal model to human infection and disease. Due to the wide range of mAbs and infectious diseases that fall within the scope of the current document, the choice of animal species should be decided on a case-by-case basis and a scientific rationale justifying the model selected should be provided.

Animal studies may be useful in evaluating the proof of concept or providing evidence of potential efficacy, and (where relevant) in identifying the potential therapeutic window. Studies of mAbs intended for prophylaxis will be designed differently from those of therapeutic mAbs and, where possible, should be based on relevant experience from studies of the

infectious disease and pathogen in question. Candidate mAb products should be assessed with the view to establishing the most effective treatment protocol.

Where animal models of the infection do not exist or are not available for use due to supply or ethical reasons, alternative approaches will need to be justified and the NRA consulted. Supporting evidence of the functionality of the mAb might then be derived from human convalescent serum in which serum antibodies could, for example, recognize similar antigens and neutralize or remove the infecting agent.

5.2.3 Safety pharmacology

The purpose of a safety pharmacology study is to investigate the functional effects of the candidate mAb product on vital functions and major physiological systems. These usually include the cardiovascular, respiratory and central nervous systems. However, in accordance with ICH guidance (44, 48), safety pharmacology studies might not be necessary – though a justification for their omission should be provided. Investigations of cardiovascular, respiratory and central nervous system parameters could instead be incorporated into the design of toxicity studies.

The tissue distribution of the mAb may be influenced by a number of its physicochemical properties (for example, molecular size and glycosylation) and by its source or formulation. Therefore, such factors should be taken into consideration when assessing the impact of the product on vital functions and physiological systems.

5.3 Pharmacokinetics and toxicokinetics

PK and TK studies are undertaken in order to understand exposure in animals, to allow animal-to-human extrapolation and to predict margins of safety for clinical trials based on exposure. Additional guidance can be found in section B.3 of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (42). Although PK and TK evaluations may be integrated into broader pharmacology and/or toxicology studies, there may be limitations when interpreting PK and/or TK data due to the lack of a relevant animal model when the mAb is directed against an infecting agent.

PK and TK study design, and the interpretation of PK and TK data, should also take into consideration the nature of the mAb or immunoconjugate, its stability, ability to bind serum proteins, the presence or absence of the infection, and/or target antigen expression and level in the recipient animal model, as well as the route of administration (see also section 5.1 above).

5.3.1 Assays

Selecting the assay for use in PK and TK studies needs careful case-by-case consideration and the scientific rationale should be provided. The assay format should, preferably, be the same for animal and human studies, using validated techniques that are appropriate for the matrix and species. The possible influence of plasma-binding proteins and/or antibodies in plasma/serum on the performance of the chosen assay should be investigated and taken into consideration.

Product-specific assays should:

- cover the pharmacological/toxicological or PK aspects;
- represent and/or predict the clinical situation;
- broadly cover all functional aspects (for example, half-life); and
- be tailored to the product and be fully justified.

5.3.2 Other considerations

- **Absorption:** absorption studies are not required for intravenously administered mAbs. However, for mAbs administered via other routes (for example, intramuscular or subcutaneous) an evaluation of absorption and bioavailability should be conducted before the start of human Phase I studies.
- **Distribution:** should be investigated as appropriate and the physicochemical and kinetic properties of the mAb taken into consideration, along with the fact that its distribution will vary depending on the route of administration. Although mAbs may initially be confined to the vascular system, they may subsequently distribute to the extravascular space as a result of various factors, including bulk flow and active transport.
- **Metabolism:** classic biotransformation studies, as performed for pharmaceuticals, are not needed for mAbs. However, conjugated mAbs would require an understanding of the metabolic fate of the conjugated molecule following its deconjugation.
- **Elimination:** information on clearance/elimination in relevant animal models should be available prior to clinical studies in order to predict margins of safety based on exposure and dose. For an immunoconjugate, information on the elimination of the conjugated molecule should also be available.

5.4 Toxicology studies

Due to the wide range of mAbs and infectious diseases that fall within the scope of the current document, the choice of animal model and toxicological studies should be decided on a case-by-case basis and justified. When animal models of the disease are used for proof-of-concept studies, a toxicological assessment can be included to provide additional information on any potential target-associated toxicity. Where this is not feasible, appropriate risk mitigation strategies should be considered and discussed with the NRA.

For mAbs that show off-target binding to human tissues and/or produce toxicity in animal studies, additional toxicological testing may be justified.

A published review of the nonclinical safety evaluation of therapeutic antibodies highlights important considerations in planning a nonclinical programme, the types of nonclinical safety studies needed and a general timeline for their conduct in relation to clinical trials (49).

5.4.1 General considerations

A short-term repeat-dose toxicity study that investigates more than one dose level should be performed. For mAbs intended for multiple dosing during prophylactic treatment or during the course of infection, the dosing regimen investigated should reflect the dosing used in the worst-case clinical scenario. The study recovery period should be justified and may need to reflect the length of elimination time of the mAb (for example, 5 half-lives). Justification should be provided when a single-dose toxicity study is proposed (for example, for mAbs with a long half-life). The selection of species should also be justified by the sponsor.

Toxicity testing requirements should be discussed with the NRA. Ideally, testing should be conducted in healthy animals to allow for clearer interpretation of toxicity in the absence of disease, and to represent healthy subjects administered the mAb for prophylactic purposes. Testing should be performed in both male and female animals and at a stage in their development that reflects the most sensitive in the proposed target human population (for

example, young, middle-aged or elderly). The number of animals tested may vary depending on whether the study is conducted in rodent or non-rodent species. Likewise, the route of administration of the mAb product should reflect the intended route of its administration in clinical studies. When two or more mAbs are co-formulated, or otherwise developed to be used in combination, testing should be conducted on the combined mAbs. Any adverse responses noted may warrant further evaluation of each mAb individually. For immunoconjugate products, nonclinical safety studies should be performed on the immunoconjugate. In addition, the safety of the conjugate molecule (that is, the “payload”) should be understood and acceptable; otherwise further studies may be required and conducted according to appropriate guidance.

The potential development of ADAs may complicate the study and interpretation of the toxicology effects observed in animals and should be considered if immune-mediated reactions occur (44). The predictive values of repeated-dose studies for potential outcomes in humans should take the formation of ADAs and associated immunogenicity issues into account and may be discussed with the NRA. It should also be taken into account that infectious diseases in humans may not require repeated long-term treatment with mAbs and, therefore, the risk of inducing an anti-mAb immune response in the clinic may be reduced.

Local tolerance should be evaluated according to established methods (for example, evaluation of erythema/eschar and oedema). If feasible, the potential local adverse effects of the product can be evaluated in the toxicity studies, thus obviating the need for separate local tolerance studies.

5.4.2 Genotoxicity and carcinogenicity

Genotoxicity and carcinogenicity studies are generally not applicable to mAbs (42). However, such studies may be required for an immunoconjugate and should be considered on a case-by-case basis.

5.4.3 Developmental and reproductive toxicity

Developmental and reproductive toxicity studies may not be necessary for a mAb targeting an infectious agent (that is, a non-human antigen) but this requirement may vary by country and should be discussed with the NRA in advance. National guidelines may or may not be aligned with other guidelines in which additional considerations on the requirements for developmental and reproductive toxicity studies are discussed – see for example ICH S6(R1) (44). An NRA may require developmental and reproductive toxicity studies for mAbs intended for administration in women of childbearing potential – particularly if the product is an immunoconjugate or non-traditional mAb protein for which there is little clinical experience.

When conducted, the specific study design and dosing schedule may be modified on the basis of issues related, for example, to species specificity, immunogenicity, biological activity and/or a long elimination half-life. The species-specific profile of embryo-fetal exposure during gestation should also be considered when interpreting results. High molecular weight proteins (> 5 kDa) do not cross the placenta by simple diffusion. For antibodies with a molecular weight as high as 150 kDa, there exists a specific transport mechanism involving the neonatal Fc receptor which determines fetal exposure, with the expression of this receptor varying across species. In humans and non-human primates, immunoglobulin G placental transfer is low in the period of organogenesis and begins to increase in the early second trimester, reaching its highest levels late in the third trimester. Further discussion of this can be found in the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (42). The results of any prenatal and postnatal developmental studies should be submitted as part of the application for marketing

approval. Evaluation of potential effects of the product on female and male fertility, when appropriate, should also be completed before the start of Phase III trials.

5.5 Additional considerations in nonclinical evaluation

- ***Antibody-dependent enhancement (ADE)***: the potential for ADE should primarily be evaluated through in vitro mechanistic studies. A dedicated animal study for ADE assessment is not warranted – though the potential for ADE may be assessed as part of the PD/proof-of-concept study if an animal model of the disease is available (37).
- ***Impurities***: safety concerns may arise as a result of the presence of impurities in the final product. These impurities may be product-related (for example, mAb molecular variants, aggregates or fragments) with properties not comparable to the desired product, or process-related (for example, media components or host cell proteins). There are potential risks associated with host cell contaminants, whether derived from bacterial, yeast, insect, plant or mammalian cells. The presence of cellular host contaminants can result in allergic reactions and other immunopathological effects. Adverse effects associated with nucleic acid contaminants are theoretical, but include potential integration into the host genome. However, it is preferable to rely on quality control and manufacturing processes to minimize the amount of impurities present rather than to establish a nonclinical testing programme to evaluate their potential effects. Additional information can be found in Part A of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (42).
- ***Ecotoxicity/environmental fate***: mAbs are generally not considered to be a particular hazard for the environment and are expected to be fully metabolized via catabolic pathways, with negligible renal excretion. No special precautions are expected in terms of product use and disposal. Nevertheless, for some chemically modified or conjugated mAbs, a full environmental risk evaluation should be undertaken, unless otherwise justified.
- ***Anaphylaxis***: although uncommon in humans, the intravenous injection of protein-based products such as mAbs can lead to various hypersensitivity-type reactions ranging from mild to severe – the molecular mechanisms of which may differ and are mostly unknown. Similar hypersensitivity and infusion reactions may also be observed during animal studies but these may not be reflective of a risk of such reactions occurring in humans. The results of guinea-pig anaphylaxis tests, which are generally positive for protein products, are usually not predictive of reactions in humans and should not be conducted.
- ***Immunotoxicity studies***: are generally not required but should be considered if any adverse effects of mAbs on the immune system were noted during PD or toxicity studies and which resulted in potential decreased host resistance to infectious agents (42).

6. Clinical evaluation

The guidance provided in this section on the clinical evaluation of mAbs for potential use in the prevention or treatment of infectious disease is intended to be complementary to Part C of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (42) and section 6 of the WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs) (27). The WHO

Guidelines on clinical evaluation of vaccines: regulatory expectations (50) may also provide useful information, particularly when considering the clinical trial design for mAbs intended for prophylactic use.

All clinical trials must be conducted under the principles of good clinical practice (47, 51). Additional guidance on the implementation of good clinical practice principles can be found in the WHO Handbook for good clinical research practice (GCP) (52).

In some cases, clinical development could proceed by combining Phase I and Phase II, or Phase II and III, studies into Phase I/II, Phase II/III or platform studies. Although the nuances of such combined or platform clinical study designs are not specifically addressed here, the principles outlined below remain applicable.

6.1 General considerations in clinical evaluation

Each infectious disease has unique characteristics depending on the nature of both the invading microorganism and the host. Infectious diseases can be categorized by:

- microorganism type (bacterial, viral, fungal or parasitic), serotype or variant;
- the minimum infective dose;
- site of infection (for example, lung, urinary tract, bone or skin);
- host factors (such as prior infection, and whether they are immunocompromised, newborn, pregnant or elderly); and
- epidemiological features (for example, nosocomial, foodborne or waterborne, sexually transmitted, seasonal or geographically restricted).

Indications for the prophylaxis or treatment of infectious diseases are usually defined by the nature of the infectious process and/or symptoms of the disease. Each infectious disease also needs to be considered in terms of its severity, stage of pathogenesis (colonization, tissue invasion, latency and dissemination), rate of replication/multiplication, and the acute and chronic clinical phases of the disease. Participants enrolled in clinical trials must be appropriately identified according to these variables.

Clinical trial design and site selection for evaluating mAbs against infectious diseases must also reflect the epidemiological status of the pathogen. Clinical trial size and duration can vary depending on the biological half-life of the mAb product, whether the pathogen is in circulation and the number of people at risk within a community. The circulation of pathogen serotypes, subtypes or variants should also be noted, particularly if the mAb has differing affinities to each. For some highly lethal pathogens (for example, anthrax bacterium or rabies virus) it may not be ethical or feasible to conduct clinical safety and efficacy trials. In such cases, product safety and efficacy would need to be estimated from animal models of the disease and from safety and PK studies in healthy, uninfected volunteers. Discussions with the NRA are crucial when considering approaches to the evaluation of mAbs against such diseases.

Clinical evaluation and product development programmes for mAbs against infectious diseases should be specific and take into consideration whether the product to be evaluated is intended to be used as a prophylactic (PrEP and/or PEP), as a therapeutic or both. If a new mAb is to be evaluated for its ability to prevent an infection, then the goal of prophylaxis should be clearly stated in the protocol. Primary prophylaxis (that is, prevention of the acquisition of an infectious organism or of the development of an invasive infection of an organism already present in a patient) should be distinguished from secondary prophylaxis (that is, prevention of the reactivation of an infectious agent already harboured by a patient subsequent to a primary infection).

The activity of a treatment may be muted for those infectious diseases in which the symptoms appear or remain after the pathogen load has peaked (for example, as observed for COVID-19 following infection with SARS-CoV-2, or whooping cough following infection with *Bordetella pertussis*). This may have a significant influence on the clinical development of a mAb intended for PEP or therapy, especially with regard to the timing of product administration, and the selection of end-points and timing of their assessment. In such cases, rapid point-of-care diagnostics may be important in the evaluation and ultimate use of the intervention. An understanding of the epidemiology, pathology and transmission of the infecting agent may inform the introduction and use of the treatment prior to the emergence of clinical symptoms or diagnosis. Such rapid initiation of the therapy should be considered among those at greater risk of infection and/or at risk of developing a serious illness.

In general, participants in clinical trials of therapeutic products should be representative of the population targeted for eventual product use. Because of the functionality of the mAb, healthy volunteers may not be suitable candidates for therapeutic trials – but may be appropriate for prophylactic studies. Healthy volunteers may also provide useful data on product safety, PK and potential for ADA induction. Therefore, the nature of the mAb, the target antigen and the proposed clinical application should all be considered before deciding to enrol healthy volunteers in a trial.

Sponsors and investigators should carefully consider the clinical benefits against the risks for mAbs intended to be administered as a single dose, multiple doses in a single course or multiple courses of therapy. Repeat administration of the mAb may alter its safety and activity profiles. Changes in antigen modulation by the mAb and immune responses to the mAb may prevent extrapolation of single-dose data to multiple-dose schedules. Furthermore, where there is an ADA response against the mAb product, repeated administration may lead to loss of therapeutic benefit and potential toxicity. In addition, participants with known hypersensitivity to proteins or other components contained within the clinical trial materials, or with a history of relevant allergies, should be excluded from product development clinical studies.

6.1.1 Inclusion and exclusion criteria

Establishing the inclusion and exclusion criteria for subjects of any clinical trial requires careful consideration. The criteria will be product dependent and should be based on a risk assessment which takes into consideration the nonclinical study results, any prior clinical experience with the same or similar mAb of the same class and/or target antigen/epitope, the product dose and dosage, knowledge gained from PK and PD studies and the type of infectious disease. Both inclusion and exclusion criteria should be rational and scientifically justified in the clinical trial application.

In general, as product development advances through clinical studies the exclusion criteria should diminish to broaden the range of study subjects, and to include subjects from the intended target population. FIH studies would thus have the most conservative criteria for subjects, with broadening of the inclusion criteria during Phase Ib and II trials. Modelling from PK and PD study data may help to generate dosing information for expanding inclusion to certain subgroups in larger Phase III trials. Open-label safety studies might also be considered with a special population subset during Phase III or post-licensure studies in order to obtain additional safety information to supplement the product indications. Additional guidance on special populations is provided in section 6.6 below.

6.2 Phase I studies

Phase I and FIH trials are conducted to determine the initial safety and tolerability of the investigational product following completion of the essential nonclinical studies. Clinical experience has demonstrated that most humanized mAbs are, in general, well tolerated. However, mAb fragments, single domain and bispecific mAbs, and chemically modified and/or conjugated mAbs may have little or no clinical background information. Therefore, the safety assessment will be key when planning FIH trials for such products.

Initial studies of a therapeutic mAb in Phase I are generally single-dose escalation studies. Along with investigating product safety, the goal of Phase I clinical studies for mAb products should be to determine the minimum effective dose (MED) to be further pursued in Phase II trials. The MED can be considered to be the lowest mAb dose that provides an observable beneficial effect, and is usually defined by its pharmacokinetic or pharmacodynamic measurements (for example, degree of antigen binding or as determined during nonclinical studies) and, where appropriate, by the tolerability of the product (for example, the maximally tolerated dose). However, in the case of an unconjugated mAb, studies to identify the maximally tolerated dose may not be necessary.

Initial safety and tolerability studies at different doses may be conducted in healthy volunteers, where appropriate, to determine the mAb safety profile and potential physiological responses. Subjects with infections might also be considered, where appropriate, to obtain early PK/PD and safety data for mAbs intended for a treatment indication. However, the inclusion of infected patients in FIH and Phase I studies should be discussed with the NRA. If the product is intended to be given for an infectious disease in the elderly, in children or in other specific groups, safety and tolerability data may be required within those populations. However, this would also depend on a benefit–risk assessment and the type of infectious disease, as well as the extent of clinical familiarity with the mAb. In some cases, it may be more appropriate to start Phase I trials in young, healthy subjects and then consider expanding the investigations in later (Phase Ib) trials to broader age ranges and/or other specific populations. The expectations and requirements for safety and tolerability studies conducted in special populations should be discussed with the NRA.

Traditionally, the starting dose for FIH studies is based on the safety and toxicity information derived from testing in a relevant animal model. For biological therapeutics such as mAbs other approaches may be considered, and may be necessary, particularly if no relevant animal model of the infectious disease exists. As the effect of a mAb is often species specific and is targeting a non-native antigen, it may be more appropriate to base the FIH doses on a minimal anticipated biological effect level, the MED or possibly on predictive computer simulation and modelling.

When extrapolating from animal doses to human doses, information on the dose required for prevention or treatment of the infection may be of great value. The target dose in humans, or concentration range, should be based on both in vitro studies in which the mAb-antigen activity has been measured and studies of a relevant animal model if available. If animal models of the disease are judged to be impossible or of no relevance, and the initial in vivo studies are to be performed in humans, then testing should begin at a low dose based on extrapolation from in vitro tissue culture studies and/or from information gathered in clinical trials of a similar mAb. However, in such cases the toxicity studies in animals would be important for providing supportive safety information prior to FIH administration. In all such cases, the NRA should be consulted.

If use of a multiple-dose mAb regimen is anticipated, then multiple-dose schedules should be explored after basic data on toxicity, peak levels, clearance, distribution and biological effects are available from single-dose studies. Multiple-dose studies may also be assessed as part of Phase IV trials, and following marketing authorization, if the indication is to be expanded later from single-dose. The time required for recovery from the biological

effects of single doses should also be well understood prior to initiation of multiple-dose regimens. The rationale for dosing schedules should be provided and should take into account dose tolerance, available PK and PD data in humans, and relevant animal models of safety and efficacy. PK studies to determine the relationships between human ADA titres and circulating antigen levels and organ distribution, clearance and toxicity may be necessary.

Before undertaking the repeated administration of conjugated antibodies, all organ toxicities and pathology resulting from single-dose administration should be characterized. The timing of recovery from all toxic effects should be determined. Intra-patient dose escalation may be appropriate if no toxicity is seen at the initial dose levels or if it is possible to use initial safe “test” doses and if cumulative toxicity is deemed unlikely.

6.3 Clinical pharmacology

6.3.1 Pharmacogenomics

Pharmacogenomics have little impact on mAbs directed towards antigen epitopes on infectious organisms except, perhaps, in individuals who may develop ADAs.

6.3.2 Pharmacokinetics

The PK profile is an essential part of the basic description of a prophylactic or therapeutic product and should always be investigated. PK studies should be performed for the intended dose range and route(s) of administration. Additional information may be found in section C.2.3 of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (42).

The design of PK studies should take into consideration:

- the structure of the product (for example, whether it is a whole mAb, Fab or immunoconjugate) and its route of administration (for example, subcutaneous, intravenous or intramuscular);
- the potential impact of age, sex, immune status, weight and body mass index, as well as other physiological or disease status aspects which may impact the PK of a mAb;
- determination of plasma concentration profiles, distribution, clearance and elimination of the mAb;
- determination of doses for further study based on dose-concentration effect relationship and correlation with desired concentrations estimated from in vitro studies;
- determination of the organs and sites in which the mAb is distributed (including sites of infection), metabolized and eliminated;
- relationships between the elimination rate/disposition and the route of administration;
- relationship between the elimination rate and the antigen load;
- presence and load of a circulating antigen; and
- presence and nature of ADAs.

Multiple-dose PK studies may not be required if the mAb is intended to be given only in a single dose. However, they should be conducted when multiple-dose strategies are to be implemented as part of product development. The dose proportionality should be evaluated in single-dose or multiple-dose studies and the clinical consequences discussed. Time-dependent changes in PK parameters may occur during multiple-dose treatment, either due to elimination

or due to formation of ADAs. The effect of ADAs on PK should be evaluated, preferably by ensuring that sampling times for PK and ADAs coincide. The clinical relevance of ADAs for PK/PD should also be discussed. It is recommended that PK should be determined at several dose levels on several occasions during long-term studies, particularly if the mAb has been modified to extend its half-life.

In some cases, dedicated PK studies may not have been performed for the approval of some mAbs. Instead, population PK data from long-term trials could have been considered and used to establish the PK profile and the impact of other factors (based on sparse PK samples in clinical trials). The use of population PK and modelling/simulation applications may be acceptable to NRAs as a tool in guiding drug development.

As with all pharmaceuticals, one potential limitation of mAbs used for the treatment of infections is the unknown distribution of the passively infused mAb into tissues affected by the disease. The mAb isotype, its subclass and glycosylation pattern may significantly impact upon its bioavailability at the site of infection. Although similar limitations may also apply to mAb fragments, their smaller molecular size may permit greater tissue penetration than full-sized mAb products, albeit at the cost of more rapid clearance.

For conjugated mAb products, PK studies should consider both the intact substance as well as its components following deconjugation *in vivo*. For the development of co-formulated mAb products for infectious diseases, the intended combination of substances should be evaluated in PK/PD studies and early clinical trials. The PK of the individual mAb substances should also be analysed, if feasible.

6.3.3 Pharmacodynamics

The bioanalytical sampling necessary for PD studies (for example, for viral load or colony forming units) is usually conducted throughout the clinical development programme depending on the outcomes. The potential PD mechanism of action will largely depend on the nature of the antigen target, its role in the pathogenesis of the infecting organism, and the mAb isotype and structure (that is, whether it is an intact mAb or mAb fragment, conjugated or bispecific).

PD are usually investigated in the context of combined PK/PD studies. Such studies may provide useful information on the relationship between dose/exposure and effect, particularly if performed at different dose levels.

6.3.4 PK/PD relationships

The relationship between the administered dose, serum concentration and PD response (PK/PD relationship) and antigen load should be evaluated as part of the mAb development programme. PK and safety can initially be assessed in healthy volunteers. The PK, combined with nonclinical PD target levels, should guide the doses to be evaluated in infected subjects. If feasible, markers for both mAb activity and safety should be measured, preferably in the same study. Such studies may involve the *ex vivo* assessment of the neutralizing activity in serum collected at different time points following mAb administration.

Therapeutic mAbs often demonstrate nonlinear PK, where the area under the curve (AUC) is not proportional to the dose administered. The extent of such nonlinearity can depend upon the total body load of the target antigen, the accessibility of the target antigen to the mAb, mAb–antigen affinity and mAb dose(s). Antibacterial mAbs may also exhibit PK properties which reflect target-mediated drug disposition due to opsonophagocytosis or through the formation of antibody–toxin complexes. This may potentially lead to complicated tissue distribution patterns during bacterial infections.

MABs that have been modified to provide extended half-lives allow for less-frequent dosing and longer-term prophylaxis against an infection. However, the high affinity of such

mAbs and the involvement of the host immune system in their pharmacological actions may lead to complex and nonlinear PK and PD.

6.4 Efficacy – Phase II and III studies

The clinical trial design of Phase II and III studies for efficacy determination will depend on whether the mAb is intended as a prophylactic or therapeutic product. Clinical trials for prophylactic mAbs may have much in common with those used to assess vaccine efficacy in that the clinical evaluation would primarily focus on disease prevention. However, the onset of mAb activity would be more rapid than that of vaccines and the duration of effect may be shorter.

The efficacy of a mAb should be evaluated in terms of its ability to prevent the disease, prevent disease progression (that is, prevent deterioration in overall clinical status, hospitalization or death) and/or reduce clinically relevant end-points following diagnosis. Depending on the type of infection, efficacy might also include the ability to eliminate the pathogen, or reduce its shedding, from the body. An emphasis should be placed on designing randomized controlled trials that take into account the intended target population, the selected clinical end-point(s), and case definitions and detection. The stage of infection in a participant when entering a clinical trial (that is, the clinical starting point) may also influence efficacy outcomes, and it will be important to establish clinical criteria or clinical markers for entering the study. For example, anti-SARS-CoV-2 mAbs were generally found to be more effective when administered early to patients with symptomatic COVID-19 and prior to hospitalization (53, 54). The local epidemiology of circulating pathogen strains or variants may also affect efficacy outcomes, particularly if the mAb has different binding affinities to such variants or binds targets which are not universally present in all strains of the pathogen. For this reason, sequencing of the infecting pathogen or identification of the strain or variant present in clinical study samples may be needed.

Along with the primary clinical outcomes, biomarkers may provide useful secondary and complementary information for consideration and analysis. Biomarkers may include pathogen burden (for example, viral load, colony forming units or antigens linked to chronic parasitic infections) or host-response factors (for example, CD4 T-cell levels) that can be shown to be relevant to the pathophysiology and/or recovery from an infection. Such biomarkers may be considered once identified and once the assays for their detection have been validated – however, their selection should be discussed with the NRA. Further discussion of biomarker evaluation processes and steps to follow are outlined in section C3.3 of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (42).

Some mAbs may be intended for the treatment of rare infectious diseases for which the target population is very small. Consequently, trials that are considered confirmatory for rare disease indications are often based on a limited number of subjects. While such studies must still be designed with the rigour of traditional trials and should be conducted to a high standard in order to provide reliable and valid data for assessing product efficacy and safety, some flexibility is needed with regard to the statistical methods to be used. Single-arm studies (for example, in which reduction of clinical symptoms and/or viral load are evaluated) may sometimes be justified when there is no known effective therapeutic product, and standard of care is only supportive – however, this approach should be discussed with the NRA in advance.

The selection of an appropriate comparator for use in efficacy trials will also require careful consideration. A double-blind trial design should be used in efficacy studies intended to prevent or treat infections. An appropriate comparator would be an approved mAb to the pathogen or small-molecule antimicrobial agent – however, a placebo control may be

considered when no known agent is effective or when the natural history of the untreated infectious disease is relatively benign or self limiting. Any other current standard of care practices for the prevention or treatment of the infection must be provided to all participants regardless of the treatment arm. For example, this might include routine counselling and advice on prevention of infection transmission, provision of hydration and electrolyte solutions during episodes of diarrhoea and use of anti-inflammatory medications.

6.4.1 Clinical end-points

The selection of both primary and secondary end-points for mAbs intended to treat infectious diseases can be difficult as they may not necessarily include the reduction or elimination of an infecting pathogen, will likely be product specific and will also depend on the prophylactic or therapeutic indication for the mAb product. End-points are usually explored and clarified during Phase II trials – however, the end-points selected may change over time with increased knowledge and clinical experience with the mAb, and/or may even differ between countries. In all cases, both the primary and secondary end-points will need to be established before initiating Phase III studies.

End-points selected for efficacy studies should be as clinically meaningful and patient oriented as possible, and able to demonstrate a benefit relative to an appropriate comparator (which may be an active therapeutic or placebo) or, if available, the current standard of care. There should be sufficient supporting evidence that the primary end-point can provide a valid and reliable measure of clinically relevant treatment or prophylactic benefit in the targeted patient population. Laboratory-confirmed case ascertainment is encouraged, even if conducted in a sub-population. It is important to discuss the proposed end-point(s) with the NRA early in the trial design process. In some cases, a biomarker (for example, CD4 levels in the case of infection with human immunodeficiency virus) might be considered acceptable as a study end-point in chronic infections when based on biological plausibility and the mechanism of action of the product. However, the selection of surrogate end-points may have limited value if their predictive capacity is not well established, or if used for acute infectious diseases in which relevant clinical outcomes can be readily measured.

The timing of product administration relative to the start of infection is also important in relation to expected outcomes and clinical end-points, and should be pre-specified and standardized where possible. For some infections, it may be difficult to demonstrate benefit in patients with more severe or advanced disease.

The end-points chosen should be able to distinguish between the mAb product under investigation and the comparator, and to account for confounders which may be related to immune responses or immune status (for example, following vaccination or prior exposure to the infection). It may be permissible to combine the results obtained for patients who have received no prior therapy with those for patients who have received other anti-infective therapies, but this should be pre-specified in the protocol and a rationale provided as to why no differences in outcomes are expected between the two groups. If such clinical designs are being considered, it is advisable to also incorporate appropriate statistical considerations, including hierarchical testing strategies. If a pre-specified subset analysis demonstrates no difference between outcomes in the two groups (that is, no influence of prior therapy) then the results obtained for each group could be combined.

6.4.2 Phase II studies

Phase II studies provide the first evaluation of the activity and potency of a mAb product in patients. These studies aim to determine the correct dosage, identify common short-term side-

effects and determine the best regimen and clinical measures to be used in subsequent pivotal clinical trials.

Comparative randomized Phase II trials are generally preferred for demonstrating that the mAb interacts correctly with its target, and in turn alters the progress of the infectious disease or its symptoms. These trials may involve placebo and/or active comparator agents such as antibiotics or antivirals. In studies into the prevention or treatment of infectious diseases, placebo controls may only ethically be considered within most study populations when no known effective agent has full regulatory approval, or when the natural history of the untreated disease is relatively benign or self limiting. If used, the placebo should, whenever possible, be identical in appearance to the study drug.

Phase II studies usually explore a variety of possible end-points. Defining clinically meaningful end-points in protocols will lend greater credibility and validity to the study. The timing of clinical end-point determination for trials of a prophylactic or therapeutic mAb needs specific consideration. For a therapeutic product, both clinical variables (for example, resolution of symptoms) and laboratory results showing a decrease in infectious viral/bacterial load can be considered as end-points.

If the mAb product shows a promising clinically relevant end-point in Phase II trials for a serious or life-threatening condition for which no other treatment option exists, or is intended for use during a public health emergency, then approval based on limited data may be possible, with further confirmatory efficacy data to be provided through post-marketing studies. Further discussion of this issue is provided in the Appendix to these Guidelines.

6.4.3 Phase III studies

Controlled Phase III clinical studies are designed to evaluate the benefit of the mAb in a patient population that is either at risk of acquiring the infection or which has a confirmed diagnosis of the infection. These studies are conducted to establish efficacy at the chosen dose(s) and dosing regimen against the primary and secondary end-points established during Phase II studies, and to further evaluate product safety and monitor its potential side-effects.

Specific decisions on the size of the study group will depend on factors which may include: (a) the magnitude of the effects of interest (the end-points) in comparison to the active comparator or placebo; (b) the incidence of the infectious disease within the community at the time of the clinical study; (c) the characteristics of the study population; and (d) the study design. Confirmatory Phase III clinical studies must be adequately sized and powered to meet the primary end-points, and to accord with the statistical analysis plan.

As a general principle, two confirmatory studies are preferred which demonstrate that the results can be replicated in relevant and diverse populations. In some cases, one well-controlled pivotal Phase III study with statistically compelling and clinically relevant results could be sufficient for product marketing authorization. However, such results should be supported by the mechanism of action, Phase II study results and any complementary information obtained from other trials with the same mAb product that might help to define the target populations and indications. In other cases, a second confirmatory study may be necessary to demonstrate that the results can be replicated. The requirements for both single and repeat studies should be discussed with the NRA.

6.4.4 Human challenge trials

Human challenge trials are clinical trials in which participants are intentionally challenged with an infectious agent in order to evaluate the efficacy of a prophylactic or therapeutic pathogen-directed mAb. Such trials have proven useful in the clinical evaluation of some vaccines and may provide similar clinical support for mAbs against some infectious diseases, particularly

where there are insufficient cases within a population to conduct large Phase III studies or to provide support for an emergency use authorization, or when animal models are not available (55). The use of human challenge trials in the clinical development plan should be discussed with the NRA in advance for consideration and feedback regarding their potential role.

The use of such trials requires a strong and thorough risk assessment and ethical evaluation prior to commencement. For infections with lower risk (such as those with low mortality, an acute onset which can be readily and objectively detected, or an absence of any indication of long-term or late-onset harm) and/or for which efficacious treatments exist, a human challenge trial may be feasible. However, for infections associated with high fatality rates and/or in the absence of an effective treatment, this approach is not recommended. To reduce the risks associated with the infection, it may be possible to use less-virulent or attenuated strains of the disease agent, but if so the binding affinity of the mAb to the strain in comparison to the wild-type organism should be determined and the results included in the submission. Regardless of the pathogen used in human challenge trials, it is important that they are well characterized and that a standardized challenge strain and dose are used throughout.

Additional information on human challenge trials is provided in WHO Human challenge trials for vaccine development: regulatory considerations (55). Guidance on the ethical considerations of such studies is provided in WHO guidance on the ethical conduct of controlled human infection studies (56).

6.5 Safety

The continual evaluation of mAb product safety is an important component within all phases of clinical studies. Although mAbs generally have a very good safety profile, each product is unique and should be considered independently. Animal testing conducted during nonclinical development may not reveal all adverse events that might occur in humans – the lack of a safety signal in animals does not exclude the potential for safety issues in humans. Therefore, FIH studies should include risk-mitigation and risk-management strategies which may include the use of well-spaced and gradual dose-escalation, ad hoc review of emerging data and stop criteria. For mAbs against infectious diseases, attention should be given to potential hypersensitivity, autoimmune and immune-complex issues, and to the potential for ADE – though potential problems of this nature should have been ruled out as far as possible during nonclinical evaluation (42).

Safety data should be obtained from a sufficient number of subjects during the clinical trials to characterize and quantify the product safety profile, which can include the type, frequency and severity of adverse drug reactions (ADRs). In some cases, it may be possible to consider safety data from multiple clinical studies if both the product tested and the study conditions are sufficiently similar.

To assess potential changes in the ADR profile over time and to capture potentially delayed ADRs, the safety evaluation should continue for a reasonable length of time following product administration, taking into account the intended duration of the mAb activity and its half-life. However, rare adverse events are unlikely to be detected at this stage of product development and evaluation.

In the case of mAbs conjugated to a toxin, undesired tissue targeting and toxin release due to degradation are major safety concerns. Therefore, patients receiving such conjugated mAbs should be monitored more frequently for potential toxic effects.

General guidance on safety as well as on required cardiac studies is provided in the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (42). Additional requirements for mAb product safety evaluation should be discussed with the NRA.

6.5.1 Reactogenicity

The reactogenicity of a prophylactic or therapeutic mAb can be a significant problem and should be monitored in all phases of clinical development. Immune responses to the mAb can vary greatly among subjects and may have little or no clinical effect, or may interfere significantly with the safety and/or activity of the product. Therefore, the monitoring of ADA titres and of immune activity is of great importance in evaluating the safety and activity of mAbs and in designing protocols involving their repeat administration (57).

Product reactogenicity can be influenced by patient, disease and product factors. Patient-related factors that might predispose an individual to a particular type of immune response include their genetic makeup, pre-existing immunity, immune status and history of immunomodulating therapy. Treatment-related factors include dosing schedule and route of administration. Product-related factors that may influence the likelihood of an immune response include the similarity of the mAb to endogenous human immunoglobulins, the manufacturing process, and product post-translational modifications, formulation and stability characteristics.

Developing assays to test for ADAs can be methodologically challenging as standard assay formats involving anti-immunoglobulin reagents are not appropriate for this product class. Depending on the mAb construct, assays for ADAs will need to be developed that can distinguish them from the administered mAb product.

6.6 Special populations

As in any clinical development programme, studies in special populations would be expected where relevant to the indications. This may include, for example, in the elderly or children who may be more susceptible to the disease (such as COVID-19 or respiratory syncytial virus, respectively). Therefore, it is important to define both the nature of the infectious disease in these special populations and the features of the population which make them unique. In all cases, the inclusion of special populations in clinical studies should be discussed with the NRA.

6.6.1 Paediatric population and children

The extent of safety studies needed in children will depend on whether or not extrapolation from adults and children of other age groups is possible. Some mAbs may be designed for use in children from the beginning of product development, such as those targeting diseases which pose a greater risk to newborns, infants and/or children. Evaluation should be carried out in the appropriate age group, and it is usually recommended to begin with older children before extending the trial to younger children and then to infants.

Where justified, extrapolation of efficacy data from adult to paediatric patients may be based on PK and/or PD data (for example, when a similar effect can be expected with similar mAb exposure). However, safety data for children cannot always be extrapolated from adult studies and additional studies may be required. The adverse event profile may differ in paediatric populations compared to adults. Data on the safety of the mAb in the paediatric population should therefore be generated unless its use is clearly inappropriate.

During clinical development, the timing of paediatric studies will depend on the product, the type of disease being prevented or treated, safety considerations (including the need for a juvenile toxicity study in animals) and the efficacy and safety of alternative treatments (58). The justification for the timing and approach of a clinical programme which may include the paediatric population should be discussed in advance with the NRA.

6.6.2 Elderly population

The safety of mAb products should be investigated in elderly patients during clinical development unless there is no intention of using them in this age group. Adverse effects in the elderly population can be more severe, or less well tolerated, and may have more serious consequences than in younger populations. Therefore, it is important to determine whether the PK profile, efficacy, potency and safety of a mAb are different in the elderly compared to younger adults. If so, the elderly sub-population should be sufficiently represented in the main Phase III or Phase II/III clinical trials to permit the comparison of treatment effects, dose response and safety between older and younger patients – or investigated in separate studies. Population PK modelling and simulation PK data may also be used to support dosing in the elderly population.

6.6.3 Evaluation during pregnancy

The conducting of clinical trials in pregnant subjects may not be permitted in some countries and should be discussed with the NRA in advance. Where clinical trials during pregnancy are permitted, the inclusion of pregnant subjects should be based on an assessment of the potential benefits and risks for the mother, fetus and newborn, as well as on safety data gathered from nonclinical studies (including tissue cross-reactivity studies that include embryo-fetal and pregnancy protein targets) and from clinical trials in adults.

Understanding the process and likelihood of placental transfer of the mAb can also help in evaluating the risk of their administration during pregnancy. For mAbs that contain a constant region (Fc) of immunoglobulin G1 (IgG1) there is likely to be minimal active placental transfer during the first 20–22 weeks of pregnancy, due to the absence of the neonatal Fc receptor. However, the transport of mAbs across the placenta increases significantly towards the third trimester of pregnancy.

Longer-term observational studies are recommended to confirm the efficacy and safety of any mAb administered during pregnancy. Such studies would help assess whether gestational exposure to the mAb product poses a risk to the newborn, and whether such risk depends on the trimester of exposure. In all cases, the inclusion of pregnant women in clinical trials should be discussed with the NRA. Should the investigational mAb be inadvertently administered during pregnancy or pregnancy is confirmed soon after mAb administration, follow-up of the mothers and infants should be continued following birth and the findings supplied as part of the product submission package. Additional notes on testing during pregnancy are provided in the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (42).

6.7 Manufacturing and formulation changes

While manufacturing and formulation changes may be expected during product development, the Phase III studies should be conducted using mAbs manufactured according to the final manufacturing (commercial) process. If the product intended for commercial use is not available or has changed, a comparability exercise between the clinical and commercial product may be necessary to ensure that the change has not impacted the clinical performance of the product. Such a comparability exercise should normally follow a stepwise approach, starting with a comparison of the quality attributes of the active substance and relevant intermediates. However, this should not be limited to the routine release testing of the product but should also include more-extensive characterization parameters using a range of suitable analytical methods appropriate to the product and process changes in question. If differences are detected that might influence the clinical properties of the product, then nonclinical and/or clinical

bridging studies (such as PK/PD studies and possibly immunogenicity studies) may be required. Further information can be found in the WHO Guidelines for the production and quality control of monoclonal antibodies and related products intended for medicinal use (7) and in the WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products (28).

6.8 Phase IV and post-marketing studies

Phase IV studies may be required to further evaluate a mAb in order to obtain additional information on its safety or effectiveness, or both – especially if the product has been authorized for emergency use or was evaluated through a non-traditional regulatory pathway in which post-approval commitments were made. Such studies also provide an opportunity to evaluate the mAb in more diverse populations (for example, with regard to ethnicity or geographical location) and/or in groups with prior exposure to the infecting agent. Real-world evidence, such as that provided through the literature or derived from studies in other countries, may also provide supporting information. Post-marketing surveillance should also be conducted when it is anticipated that escape variants will emerge in order to test the activity of the mAb against newly recognized variant strains of the pathogen, or to monitor ADE. The requirements and plans for Phase IV studies and the use of real-world evidence and real-world data should be discussed with the NRA.

6.9 Statistical considerations

A number of general and specific statistical considerations, including the need for a statistical analysis plan, are outlined in section C.4 of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (42). Additional statistical considerations can be found in the ICH E9 Statistical principles for clinical trials guideline (59).

6.10 Pharmacovigilance systems and risk-management planning

Pharmacovigilance systems and risk-management plans should be developed by sponsors to include activities which reflect the risks associated with a specific mAb product and its intended use. Such risks may include potential reactogenicity, toxicity, ADE or reduced efficacy against circulating virus variants or antibiotic-resistant bacteria. A risk-management plan should be submitted and agreed with the NRA. This plan should note whether specific surveillance will need to be done and where relevant information may minimize risk.

Sponsors and prescribers are encouraged to facilitate the utilization of mAb products among those patients most likely to benefit from them. In addition, the genomic identification and characterization of mAb targets in locally circulating pathogens can augment antimicrobial stewardship and pharmacovigilance.

Further discussion of the key components of a risk-management plan can be found in the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (42).

7. Authors and acknowledgements

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recommendations) provided by Dr K. Kourad, consultant, Ottawa, Canada. The draft was then reviewed and revised by a drafting group comprising: Dr A. Chia, Health Sciences Authority, Singapore; Dr S. Desain, Lankenau Institute for Medical Research, the USA; Dr E. Griffiths, consultant, Kingston upon Thames, the United Kingdom; Dr V. Kayser, University of Sydney, Australia; Dr B. Klug, Paul-Ehrlich-Institut, Germany; Dr D. McManus, Health Canada, Canada; Dr E. Pelfrene, European Medicines Agency, the Netherlands; Ms D. Situ, Health Canada, Canada; Dr D Sok, International AIDS vaccine initiative, the USA; and Dr R. Isbrucker, World Health Organization, Switzerland.

The resulting draft document was posted on the WHO Biologicals website from 22 August to 28 October 2022 for a first round of public consultation. Comments were received from Ms E. Coates, Regeneron Pharmaceuticals Inc., the USA; Ms R. Coe, Biotechnology Innovation Organization, the USA; Dr N. de Clercq, GSK, Belgium; Ms K. Flanagan, Therapeutic Goods Administration, Australia; Dr M. Gencoglu, International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), Switzerland; Dr B. Haenen, Janssen Pharmaceuticals, Belgium; Ms A. Karsten, Paul-Ehrlich-Institut, Germany; Dr E. Lilly, National Centre for the Replacement, Refinement and Reduction of Animals in Research, the United Kingdom; Dr E. Pelfrene, European Medicines Agency, the Netherlands; Dr S. Ponzano, European Medicines Agency, the Netherlands; Dr V. Sintchenko, University of Sydney, Australia; Ms D. Situ, Health Canada, Canada; Mr D. Stoss, Vir Biotechnology, the USA; Dr B. Styr, Center for Drug Evaluation and Research, US Food and Drug Administration, the USA; Dr C. Tipple, Drugs for Neglected Diseases initiative, Switzerland; and Dr D. Yeskey, Coalition for Epidemic Preparedness and Innovation, the USA.

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Appendix

Considerations regarding abbreviated submissions for mAbs against an infectious disease during a public health emergency

During a public health emergency, some NRAs may consider reviewing mAb products against the infectious agent supported by abbreviated submissions, and/or providing conditional marketing authorization, in order to expedite product availability. This process requires that an appropriate regulatory framework is in place that allows for the review of abbreviated submissions and outlines the conditions under which they may be considered.

Although it is not possible to outline a common regulatory pathway detailing the minimum nonclinical and clinical study requirements applicable to all situations and all regulators, one strategy that has evolved to reduce product development time during a public health emergency is the conducting of parallel nonclinical and clinical studies, as well as overlapping or combined Phase I/II and/or Phase II/III clinical trials. Such a condensed strategy may be acceptable to some NRAs under appropriate circumstances for supporting the issuing of a limited or temporary form of marketing authorization. However, as expectations and regulatory capacities for reviewing abbreviated submissions vary greatly between countries, and may differ for each outbreak, regular communication between the sponsor and NRA is strongly advised and should begin as early as possible. Ongoing discussions should be held to clarify commitments and their timelines, as well as post-authorization expectations, on the understanding that the full nonclinical and clinical programmes are continued until the requirements for full licensure are met. Additional points to consider during discussions will be situation dependent, but may include requirements to: (a) monitor the affinity of the mAb for the circulating pathogen strain; (b) review mAb product development plans during an evolving pandemic (for example, due to the difficulties of completing confirmatory trials as variant strains emerge); and/or (c) use real-world evidence and real-world data in supporting clinical data packages.

The use of platform technology in the manufacturing of mAbs may reduce the development time required for establishing and validating production processes and quality control methods (1). However, although mAbs produced within established platform technologies may provide some level of confidence with regard to product safety, most NRAs would still regulate such mAbs as any other new biological product. Therefore, platform technology might not reduce the nonclinical and clinical regulatory expectations or requirements for marketing authorization.

During a public health emergency, it is important to determine the minimum nonclinical studies which can reasonably support the start of Phase I clinical trials of mAbs against the infectious disease. The characteristics and novelty of the candidate mAb product should be taken into consideration, along with the biology of the infection and target antigen. For a candidate product for which there is little or no clinical experience, NRAs may require a greater amount of toxicity data. In such cases, the nonclinical studies should focus on any unexpected direct and indirect consequences that might result from administration of the product. It is important to note that any limited nonclinical toxicity dataset must be of good quality, and be generated from relevant animal species following the principles of good laboratory practices to the fullest possible extent.

Interim data from ongoing toxicity studies and the submission of draft unaudited toxicity study reports may be sufficient to support proceeding to Phase I clinical trials. NRAs may require that the toxicity studies include the immediate effect on survival, vital physiological functions, histopathology data, safety pharmacology, local tolerability and/or TK

assessments. In cases where clinical trials were initiated on a minimum safety data package, the nonclinical programme should continue in parallel with clinical development. An abbreviated nonclinical package should contain tissue cross-reactivity studies, PD proof-of-concept studies and a pivotal toxicity study. It is emphasized that the pivotal nonclinical toxicity study should be conducted in a pharmacologically relevant animal species at an age that reflects the proposed clinical target population for emergency treatment (for example, adult animals for pandemic pathogens primarily affecting the elderly, or juvenile animals for pandemic pathogens that primarily affect young children).

PK evaluation in animal models may be omitted if sufficient human PK data is anticipated or becomes available. The abbreviated submission may also omit reproductive toxicity studies and carcinogenicity risk assessments – however, the provision of a scientific rationale for their omission is encouraged. Juvenile toxicity studies can be omitted when the target population for emergency treatment is not children, and on the understanding that the data gap would need to be addressed with a nonclinical juvenile toxicity study and/or clinical data/experience at a later time and prior to approval of the mAb for use in children (2). Similarly, large-scale Phase III efficacy trials may be approved in endemic regions without enrolling pregnant women – however, NRAs may require that developmental toxicity studies be conducted in parallel in order to support their eventual inclusion, either prior to the conclusion of the Phase III study or through their enrolment in a separate clinical study.

Since the use of a reduced toxicity dataset during a public health emergency provides less certainty about the safety of the mAb product, additional nonclinical data should be submitted as they become available, including data on any delayed effect observed at later time points in repeat-dose toxicity studies, histopathological data and the final signed audited reports. At the time of the full licensing application, the completed nonclinical data appropriate for the mAb should be submitted, or the application should be otherwise adequately justified.

Phase I and II studies of investigational mAbs against infectious diseases are, in general, expected to provide initial safety information and determine optimal dose(s). During a public health emergency, NRAs may consider recommending larger Phase I clinical studies to increase the early safety database, as well as the use of study populations similar to the eventual target population, thus facilitating timely initiation of Phase II clinical studies. This might be done by enrolling more trial sites than usual.

The epidemiology of the disease is likely to have a major impact on the timing and design of Phase III studies. In the face of an outbreak, and without any available preventive vaccines or other medications, mAb evaluation should still adhere to the principles of the phased approach but the intervals between clinical trial phases may be compressed to the point of overlap. For example, compressed timelines for clinical development may be achieved by initiating Phase III studies based on interim safety data from earlier-phase studies rather than on data from final study reports.

As the mAb product is intended for a foreign (non-endogenous) antigen, the early benefit–risk considerations may favour its safety profile in humans with underlying medical conditions. Therefore, under the circumstances of an emerging outbreak, epidemic or pandemic, consideration should be given to adjusting the trial-inclusion criteria to include those populations at higher risk from the emerging pathogen (for example, the immunocompromised, or those with cardiac, respiratory or renal diseases).

Phase II and Phase III clinical trials may be designed with prospectively planned adaptive features that allow for changes in design or analyses based on examination of the accumulated data at pre-specified interim points in the trial. Such adaptive features may make trials more efficient but also risk introducing complexities that would require advanced statistical plans and additional consultations with NRAs.

If the nature of a public health emergency affects the benefit–risk balance of a mAb product in such a way as to justify its accelerated development and conditional approval, the product sponsor would still be required to complete the full development work to the same standard required for a new mAb under non-emergency conditions should it be decided to subsequently submit the product for full licensure. The required supplementary data and expected timelines for their submission should be agreed between the sponsor and the NRA.

Regulatory processes and national requirements for the emergency assessment of products to be used during public health emergencies vary greatly between NRAs. For some NRAs, experience in considering products within an abbreviated development pathway may be limited and their capacities stretched due to the greater burden placed on resources. As part of good reliance practices (3), NRAs are strongly encouraged to implement evidence-based reliance on the assessments and decisions of trusted partner NRAs, WHO and regional regulatory bodies. This may be particularly valuable for NRAs with limited experience in reviewing applications for mAbs or with limited resources that may be further stressed during an epidemic or pandemic.

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