
NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the proposed document – WHO Guideline on the nonclinical and clinical evaluation of monoclonal antibodies and related biological products intended for the prevention or treatment of human infectious diseases – to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Written comments proposing modifications to this text MUST be received by 28 October 2022 in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Health Products Policy and Standards. Comments may also be submitted electronically to the Responsible Officer: Dr Richard Isbrucker at email: isbruckerr@who.int

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide, second edition" (KMS/WHP/13.1).

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Appendix 1
Abbreviations

ADAs anti-drug antibodies (anti-mAb antibodies)
ADCC antibody-dependent cellular cytotoxicity
ADCP antibody-dependent cellular phagocytosis
ADE antibody-disease enhancement
ADR adverse drug reaction
AUC area under the curve
CARPA complement activation related pseudo-allergy
CDC complement-dependent cytotoxicity
CRS cytokine release syndrome
CFU colony forming units
DARTs dual-affinity re-targeting antibodies
Fab fragment antigen binding
FIH first in human
HIV human immunodeficiency virus
mAb monoclonal antibody
MABEL minimal anticipated biological effect level
MED minimally effective dose
MTD maximally tolerated dose
NABs neutralizing antibodies
NRA national regulatory authority
OBD optimum biological dose
PD pharmacodynamics
PEP post-exposure prophylaxis
PK pharmacokinetics
PrEP pre-exposure prophylaxis
RSV respiratory syncytial virus
SAE serious adverse event
TK toxicokinetic studies
1. Introduction

Monoclonal antibodies (mAbs) represent the largest and, perhaps, the predominant
class of therapeutic proteins in clinical use. However, the majority of currently marketed
mAbs are for use in the treatment of noncommunicable diseases, such as cancer or
autoimmune disorders, and only a few have been licensed to treat infectious diseases.
Nevertheless, at the time of writing this guidance document, there is a growing number of
mAbs in development intended for the prevention and/or treatment of infections (1-3).
Because of 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 are considered a high
priority for their potential impact in the control and treatment of infectious diseases,
especially those for public health emergencies, such as COVID-19 (4).

Advances in recombinant biotechnology and protein chemistry, combined with a
greater understanding in mAb structure and functions, has led to a growing interest in
modified mAbs, such as mAb fragments, as well as mAb mimetic proteins based on non-
immunoglobulin scaffolds. These variants of mAbs and related proteins may offer significant
clinical advantages, such as better penetration of tissue, improved secretion, and greater
stability and bioavailability allowing for alternate routes of administration.

The WHO Expert Committee on Biological Standardization (ECBS) discussed the
advances in mAb engineering and production technologies and their growing importance in
the treatment of infectious diseases at their 72nd and 73rd meetings in 2020 (4). The
Committee noted that although a range of WHO guidance documents relevant to mAbs had
been published previously, these focused primarily on their use as biotherapeutics for
noncommunicable diseases and there was little advice on nonclinical or clinical evaluation
specific to the pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), or to post-
infection treatment with mAbs. It was envisaged that clarifying issues unique to the
evaluation of mAbs against communicable diseases would help to harmonize the regulatory
expectations during their development and licensure process and thereby improve access to
such products. Therefore, ECBS endorsed a proposal to develop WHO guidance on the
nonclinical and clinical evaluation of mAbs and mAb mimetic proteins which would be
broadly applicable to those products intended for prophylaxis and/or treatment of infectious
diseases. In addition, individual supplements to the guidance will be drafted as required to
provide further disease-specific regulatory considerations for these products.

This guideline was developed through international consultation and following a
detailed review of existing WHO documents in order to identify where additional guidance
and clarity was required which may be specific to mAbs and related biological products
directed towards infecting microorganisms. The current guideline should be read in
conjunction with relevant sections of other WHO guidance documents, which are referenced
throughout the text. Some non-WHO guidelines are also cited where they provide additional
supporting information.

2. Scope

This current guideline is intended to apply to mAbs and other antigen binding proteins
based on an immunoglobulin scaffold, as well as a range of mAb mimetic proteins with
unique structures. These mAbs and mAb mimetics can include, but are not limited to:
antibody fragments, such as single-chain variable fragments (scFvs) and antigen-binding fragments (Fab),

- single domain antibodies,

- bispecific or multispecific antibodies,

- DARPin, affimers, and anticalins,

- mAbs or related antibody proteins which have been chemically modified, such as

- through conjugation,

- multiple mAb substances co-formulated within a final product (“antibody cocktail”).

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

This document is intended to provide flexible guidance to National Regulatory Authorities (NRAs), sponsors, manufacturers and investigators on the nonclinical and clinical evaluation of mAbs directed against the antigens of invading pathogens, or their toxins, and used specifically in the pre- and post-exposure prevention or treatment of human infectious diseases. It does not address the evaluation of mAbs or related biologicals that target endogenous human proteins, such as cytokine responses to an infection, nor does it apply to mAbs or related biologicals used for the diagnosis of infections. Therefore, immunomodulatory antibodies are not within the scope of this guideline as they are not directed against the infectious agent itself, nor against a toxin antigen, but towards the host immune response, such as T cells or cytokines. It should be noted that the general principles within this guideline would apply to mAbs which target endogenous human proteins with the intention of preventing or treating infections (e.g., mAbs to a cell surface receptor which prevents viral entry to the cell); however, such products may require additional nonclinical and clinical studies depending on the protein target(s).

Although originally considered for inclusion in this document, 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 better addressed in a separate guidance document.

Guidance on the manufacture and quality control of mAbs is provided in a separate WHO Guideline for the production and quality control of monoclonal antibodies and related products for medicinal use (5). That guideline takes account of the extensive technological advances in the field of mAb manufacturing since the original murine hybridoma-derived mAbs were produced in the 1970s such as improved production and purification methods, conjugation technologies, mAb fragments, and mAbs from plant-based production systems.

3. Terminology

The following definitions apply to the terms used in this document. They may have different meanings in other contexts.

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

**Antibody-dependent cellular cytotoxicity (ADCC):** an immune response in which Fc receptor-bearing effector cells can recognize and kill an antibody-coated target cell. Also
called antibody-dependent cell-mediated cytotoxicity or antibody-dependent cellular cytotoxicity.

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

**Antibody mimetic proteins (antibody mimetics):** Peptides or proteins which are not structurally related to antibodies, but which recognize and bind to specific antigens. They usually have a molar mass between 3 to 20 kDa.

**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 may induce serious adverse effects.

**Biological activity:** The ability or capacity of a mAb substance and/or product to elicit a defined biological effect *in vitro* (e.g., in cultured cells, bacteria or viruses) or *in vivo* (in animal models and/or humans).

**Biosimilar:** a biological product that is highly similar in terms of quality, safety and efficacy to an already licensed reference product.

**Co-formulated mAbs:** A final product formulated to contain two or more mAbs, mAb conjugates and/or mAb fragments which each recognize different epitopes or antigens. 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 which may later be co-administered during treatment.

**Complement-dependent cytotoxicity (CDC):** the 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, thereby resulting in its lysis and cell death.

**Cytokine release syndrome (CRS):** Uncontrolled release of cytokines.

**Fragment antigen binding (Fab):** 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.

**Humanised immunoglobulins:** are recombinant DNA-derived antibodies from non-human species whose genetic sequences have been modified to produce immunoglobulins with increased similarity to antibody variants produced naturally in humans.

**Human challenge trial:** Involves healthy volunteers being inoculated with a challenge agent and this can be done either before or after the administration of investigational product.

**Immunoclonocjugates:** are antibodies conjugated to a second molecule, usually a toxin, radioisotope or label; however, they could also be conjugated to non-bioactive compound such as polyethylene glycol (PEG). They may be used in diagnosis and targeted immunotherapy. They are often known as antibody-drug conjugates.
Neutralizing antibodies (NAbs): prevent the infecting organism from binding to and/or infecting the host cell. NAbs have the potential for both therapeutic and prophylactic applications.

Optimal biological dose (OBD): usually defined by pharmacokinetics or pharmacodynamic measurements (e.g., degree of antigen binding or saturation or target blood levels, determined on the basis of nonclinical studies) and, where appropriate, by the tolerability to the agent (e.g., the maximally tolerated dose).

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 GMP are unchanged. The experience and knowledge gained, data generated (from 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 treatment intended to prevent an infection (pre-exposure prophylaxis (PrEP)) or to prevent pathogenesis following exposure or infection (post-exposure prophylaxis (PEP)).

4. General and regulatory considerations

The administration of antibodies for the prevention or treatment of infectious diseases is not a new concept. The use of human convalescent and immune animal sera in immunotherapy against both bacterial and viral infections was first developed during the late 19th century (6-9). Human and equine plasma derived immunoglobulins, such as anti-rabies, anti-Hepatitis B and anti-tetanus immunoglobulins, continue to be used, although these products face issues of standardization, safety, supply and access (10). Some plasma-derived immunoglobulins are also listed in the current WHO List of Essential Medicines (9). The introduction of mAb therapies offers the advantage of a more reliable and larger commercial supply along with the potential for products which have better consistency between lots, are safer, can be engineered for longer half-lives, and offer greater specificity than immune antisera and polyclonal antibodies (6, 7, 9, 11). For bacterial infections, mAb – antibiotic immunoconjugates are under development, as are radioimmunoconjugates which link radionuclides to mAbs for target delivery of bactericidal radiation to infected cells (12). Similar radioimmunotherapy is being considered for selective killing of HIV infected human cells (12).

The bioengineering and production technologies currently available for mAbs and mAb mimetic proteins also provide a potential for rapidly developing new products directed against emerging novel infectious diseases for which there are no available vaccines or therapeutics. For many diseases, mAbs thus offer the possibility of being developed faster than vaccines and could be used prior to the availability of suitable vaccines or can be complementary to vaccine usage (7, 13). The administration of mAbs also provides immediate activity in preventing or treating an infection, unlike vaccines which can take weeks for the emergence of a protective effect. This is particularly important for immunocompromised individuals and those who cannot be vaccinated, for those being
deployed into zones of high transmission, and during rapidly evolving epidemics or pandemics. Therefore, mAbs could form part of an overall armamentarium along with other therapeutics and vaccines (7, 9, 13, 14).

As has been experienced with small molecule antimicrobials, mAbs and mAb mimetic proteins may also be susceptible to the emergence of drug resistance by the infecting pathogen. For example, bacteria can be induced to produce antibody-degrading proteinases (12, 15, 16) or changes to the target antigen through natural mutagenic selection processes, either of which could impede the efficacy of mAb therapies (12, 17, 18). Similarly, the emergence of multiple strains and escape mutants among viruses can lead to new variant strains which have the potential to evade mAb therapies (19-21). This has the potential to alter the antigenic structure of an epidemic pathogen in real time.

This potential emergence of organisms resistant to mAbs and mAb mimetic proteins favours the exploration of combined therapies, either through the combination of a mAb with one or more small molecule drugs or the use of co-formulated mAbs (antibody cocktails) which combine mAbs that target separate antigens or epitopes (14, 19, 22, 23). The development of bispecific mAbs through bioengineering which can combine the specificities of two antibodies and simultaneously interact with different antigens or epitope is also being actively pursued (24).

Currently, anti-infective mAbs are mostly full-length IgG molecules, although other mAb isotypes (IgA, IgM) are also under consideration. MAbs can act directly by neutralizing the pathogens and inhibiting their capacity to bind to human cell receptors. Fc-receptor dependent uptake by Kupffer cells in the liver can rapidly reduce the burden of toxins, bacteria, virus, or other pathogens in the bloodstream. MAbs may also act by stimulating immune responses such as ADCC, ADCP, CDC, or opsonophagocytosis. Therefore, an understanding of the mechanism(s) of action of the mAb is crucial in evaluating its efficacy in both nonclinical and clinical studies.

Although the target antigen for anti-infective mAbs is unique to the infecting organism, regardless of the host, the subsequent response by the host to the mAb-bound infecting agent can vary significantly in nonclinical studies depending on the host species and the species from which the mAb has been derived. For example, the use of humanized mAbs in a mouse model would not necessarily induce the same efficacy or safety as a murine mAb in mice, or a humanized mAb in humans. For this reason, understanding the impact of species differences between the mAb and the host is critical in the preclinical development program and translation of the data to the clinical situation.

In certain infections, there is concern for mAb - disease enhancement (ADE) (12). Categories of possible enhancement include antibody-mediated facilitation of viral entry and replication in target cells (e.g., Fc-bearing monocytes or macrophages) and virus-antibody immune complexes and the associated cytokine release. For the former, antibody-mediated enhancement is classically defined as Fcγ-receptor–mediated enhanced disease in the presence of sub-neutralising concentrations of antibodies or non-neutralising antibodies. ADE of bacterial infection has been reported less frequently and is sometimes linked to antibody isotype and glycosylation patterns (12). For example, anti-capsular IgA1 mAb dependent enhancement of IgA1 protease-secreting S pneumoniae binding to pharyngeal epithelial cells, possibly promoting colonization, has been reported by Weiser et al 2003 (25). Similarly, mAb IgG3 directed against anti capsular antigens of Acinetobacter baumannii has been shown
to enhance adherence / invasion of macrophages and human lung epithelial cells leading to significantly increased mortality in a mouse pneumoniosis infection model (26). Also, some human isotype-dependent mAbs directed against *Mycobacteria tuberculosis* antigens have been reported to promote mycobacterial invasion of epithelial cells (27). Therefore, ADE is an important aspect to assess as part of the nonclinical program for any mAb to infectious diseases, particularly if the functions of the epitope are not clearly understood. The absence of enhancement should be confirmed in clinical studies.

Along with understanding the intended mechanism of action of mAbs, it is important to characterize their size and charge variants, post-translational modifications and conjugations, hydrophobicity and potential for aggregation, glycosylation patterns, and N- and C-terminal heterogeneity (5). All of these biochemical properties can significantly impact the mAb half-lives, tissue distribution, stability, susceptibility to degrading enzymes, secretion, and their immunogenic potential. Therefore, each individual mAb may present a unique biochemical and biophysical profile which should be taken into consideration during the evaluation of such products. Nevertheless, due to structural similarities amongst mAb products, the knowledge and technological experience of a manufacturer may be used to develop platform manufacturing processes which could be applicable to other mAbs produced by the same manufacturer using the same technologies and processes (5).

Information from other manufacturers, or products of other production processes, would not necessarily be supportive of such a proposal. Careful consideration is required and an individual case-by-case approach may be justified but should be discussed and agreed with the relevant NRA(s).

The ability of the mAb to reach site(s) of pathogen activity is another important consideration during its development. For example, an intravenously administered mAb product may have limited access to mucosal, CNS, or intestinal infections. In recent years, several small mAb mimic proteins on non-immunoglobulin scaffolds and mAb fragments have been generated using affinity selection technology. These mAb mimic proteins have significantly lower molecular weights (often in the range of 3-20 kDa) and exhibit better tissue penetration than full-length mAbs. MAb fragment products, although still much smaller than full-length mAbs, tend to be greater than 30 kDa in size which can impact their tissue penetration range.

In the past, most mAbs have been administered by the intravenous route (IV infusion, often in hospital settings taking several hours) but considerable attention is now being given to subcutaneous or intramuscular administration of highly concentrated mAbs which can be administered in only a few minutes. A number of licensed plasma derived immunoglobulins for the prevention or treatment of infectious diseases (e.g., tetanus, hepatitis B) are given by the intramuscular route (10). Other alternative mAb delivery routes are also being actively explored, including nasal, inhaled, oral, intra-ocular, 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 IV route due to issues related to immunoglobulin concentration, viscosity, aggregates and stability and this needs to be borne in mind during both nonclinical and clinical evaluation (28).

In the case of the rapid development of products against a priority pathogen, such as during a public health emergency, considerations 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. Consultation with the NRA is strongly advised under such circumstances, and further discussion on the topic is provided in Appendix 1.

5. Nonclinical evaluation

This section is intended to provide a flexible approach to the nonclinical evaluation of mAb products which are intended to be used in the prevention or treatment of human infections. It includes both in vitro and in vivo (animal) studies.

The guidance outlined in this section is 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 (29), and the WHO Guidelines on nonclinical evaluation of vaccines (30). Additional guidance can be found in Section 5 of WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (17), as well as in the WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products (18). The ICH S6(R1) guidance on Pre-clinical safety evaluation of biotechnology-derived pharmaceuticals (31) and ICH M3(R2) guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (32) should also be consulted, as should any relevant guidelines from national regulatory authorities (NRAs).

The mAb product lots, used in nonclinical studies should be adequately representative of the quality and formulation intended for use in subsequent clinical investigations and, ideally, nonclinical testing should be done on the same lot as that proposed for the clinical trials. The initial discovery and characterization process of a mAb typically involves assessing many mAb candidates in a variety of assays that evaluate their effectiveness in viral neutralization and determine their likely mechanism(s) of action. These tests will generally not be performed with clinical grade mAbs; clinically relevant mechanistic and efficacy studies should be validated with 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 (5). This may include preliminary in vitro or in vivo tests performed with mAb product lots produced by a polyclonal population of cells expressing the mAb, established as the first step in isolating a stable, high-expressing clone for the final manufacturing step. The comparability of the test material should be demonstrated when a new or modified manufacturing process or other significant changes in the product or formulation are made in an ongoing development program. Comparability can be evaluated based on biochemical and biological characterization (i.e., identity, purity, stability and potency) (5, 17). In some cases, additional studies may be needed (e.g., PK, PD and/or safety). The scientific rationale for the approach taken should be provided.

Nonclinical toxicity studies should comply with good laboratory practices (GLP) (31, 33). Internal SOPs should be maintained for any non-GLP compliant studies that have been conducted. All relevant studies, whether GLP or non-GLP compliant, should be included in submissions for marketing authorization.

All studies conducted in animals should follow the principles of 3Rs (Replace, Reduce, Refine) and minimize the use of animals in research. Consideration should be given to the use of appropriate in vitro alternative methods for safety evaluation. Selected
endpoints, particularly for studies in which animals are infected, should minimize the suffering of animals.

### 5.1 General considerations

The primary objectives of both *in vitro* and *in vivo* nonclinical studies are to define the pharmacological and toxicological effects of investigational products prior to the initiation of human studies (30). This includes:

- Functional characterization of the product, such as its ability to reduced pathogen load, impair the function of toxins, promote pathogen clearance from the blood circulation and tissues, improve clinical signs, reduce weight loss, or reduce severity of infection,
- Identification of possible toxicities and likelihood of potential adverse events or undesirable effects,
- Identification of a safe starting dose for Phase I clinical studies and dose escalation when possible.

There are several important factors to consider when designing nonclinical studies for mAbs relevant to preventing or treating a human infectious disease. Knowledge of the mAb target antigen on the infecting pathogen and its biology is expected, as is the characterization of the binding site/epitope and the specificity and selectivity of the mAb to the infecting agent. Unwanted and unexpected cross reactivity with other human or animal cells and/or tissues need to be explored. Also, resistance to a mAb can emerge through antigenic drift of the target antigen and is an important issue in the case of some pathogens. The potential for mAb resistance through epitope mutation should be considered and prospectively evaluated, if relevant, before a mAb is committed for clinical study. This potential for resistance should be monitored by the manufacturer (e.g., with *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, proof of concept (functionality), pharmacokinetic (PK), pharmacodynamic (PD) or safety. 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 for proof of concept, PD, PT and toxicology studies. The former, proof of concept studies, demand an infection model whereas toxicology needs to be carried out in healthy animals to represent possible prophylactic use as well as to reduce confounding signals due to tissue damage from infection and disease state, allowing for a clearer interpretation of any toxicity signals. Where possible, preference should be given to studying mAb functionality in an animal model where the mechanism of the infection and pathology is similar to that in humans.

Scientific justification should also be provided for the selection of the animal species used for PK and toxicokinetic (TK) evaluation, taking into account that the PK profile in the chosen animal species should ideally reflect the PK profile in humans. The nature of the mAb product itself, whether murine, humanized or human, or a mimetic based on a non-immunoglobulin scaffold, should be kept in mind since it may influence study results, as should the stability of a mAb or immunoconjugate.

The induction of anti-mAb antibodies in animals is generally not relevant in terms of predicting the potential immunogenicity of mAb products in humans, although it may provide some insight as to potential complications for the mAb-related products. Furthermore,
infectious diseases may not require chronic treatment with mAbs thereby reducing the risk of inducing an anti-mAb immune response. Nevertheless, immunogenicity studies if undertaken may assist in the interpretation of in vivo animal studies.

In addition, consideration should be given to situations where the mechanism of action of the mAb under investigation involves a secondary response such as the activation of complement or cell induced killing. The pharmacological properties of the mAb and whether it may be species-specific, particularly for antibody-dependent cellular cytotoxicity (ADCC) or phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC), always need to be considered in exploring exposure-response relationships in animal models and in developing the initial estimate of PK parameters. The similarity of animal infection model to human infection, or otherwise, also needs to be borne in mind when interpreting the data. Monoclonal antibodies with ADCC activity (with an Fc region that is recognised by the animal species or mAb preparations with pseudo-allergens) require more extensive non-clinical testing in more than one animal species over a range of doses.

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 of conjugate is used, and if feasible, it should be tested in that form. Appropriate newer technologies should be employed as they become available and validated.

Tissue cross reactivity studies

The unintended reactivity of an anti-infectious agent mAb with human tissue should be determined using frozen panel of adult tissues, or representative cell cultures. Several concentrations of the product should be tested as the ability to detect cross-reactions may depend on the concentration of the antibody. When cross reactions are encountered, studies should be expanded to more tissues.

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 Phase I human studies to search for non-target tissue binding or any cross-reactions.

Cell culture studies

Cell cultures can be used to study the prophylactic effect of mAbs (where cultures are treated with the mAb prior to inoculation of the infectious agent; pre-exposure) as well as their ability to treat infections (where the cultures are treated with mAbs after inoculation of the infectious agent; post-exposure). For co-formulated mAbs, the neutralising activity of each of the constituent mAbs should be tested and any potential synergistic effect of the combination reported. However, preference should be given to the study of the co-formulated mAbs in a suitable animal model. In vitro activity studies using tissues or cells from different species is also important in order to determine the most relevant animal model to use for toxicology work and in aiding the selection of appropriate animal model(s).
In addition, *in vitro* studies might be used early on to assess the potential for enhancement of infection, if such an assay has been developed. Animal models might also be used, but only if they closely resemble human responses (e.g., in NHPs).

For co-formulated mAbs, the neutralising activity of each of the constituent mAbs should be tested and potential synergism reported. However, preference should be given to the study of a mAb in a suitable animal model.

### 5.2.2 In vivo studies

Pharmacodynamics should be studied where possible, but classic PD/PK assessment may be of limited relevance in animal models in most situations. The focus should be on assays that ensure the mAb is functional against the targeted infectious agent. In most cases 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 form the basis for the nonclinical evaluation of mAbs.

For proof-of-concept studies demonstrating anti-pathogen activity, preference should be given to studying a mAb in an animal model where the infection in the animal and human is similar. Consideration should be given to establishing how similar the infection is in the chosen animal model in comparison with the human infection and disease. Due to the wide range of mAbs and related biologicals being considered in this general document, as well as infections, the choice of animal species should be decided on a case-by-case basis. The development and use of animal models based on transgenic and humanized mice could be considered when an animal model is not available for a particular infection.

*In vivo* studies could be useful for characterizing potential clinical use, whether prophylaxis or treatment, or both, and where relevant, identifying the potential therapeutic window. Studies of mAbs for prophylaxis will be designed differently from those of therapeutic mAbs and where possible based on relevant experience from studies of the infectious disease and pathogen in question. MAbs should be assessed with the view to establishing the most effective treatment protocol.

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 a better prediction of the therapeutic index. When two or more mAbs are co-formulated in the final product the PD of each mAb should be evaluated separately as well as in the intended combination.

In all such studies it is important to characterize and standardize the pathogen challenge strain and its dose. Where passage of pathogenic strains may possibly lead to the development of variant strains, such as in the case of SARS-CoV-2, it is critical to use challenge material at defined and standardized passage levels (34). It may also be informative to genotype pathogens isolated from animals that succumb to infection despite mAb exposure, in order to assess whether resistance correlated with antigenic-drift or mutation.

### 5.2.3 Special considerations

Where animal models of the infection do not exist or are not available for use due to
supply or ethical reasons, alternative approaches need to be justified and the NRA should be consulted. Supporting evidence of the functionality of the mAb might then be derived from human infections in which serum antibodies could, for example, recognize similar antigens and neutralize or remove the infecting agent. The mechanism of action of the mAb is dependent on binding to the infecting organism or bacterial toxin and could be confirmed in vitro. Functional aspects, if part of the mechanism of action, could also be determined in other ways, such as with bactericidal, opsonophagocytic, or viral neutralization assays.

5.2.4 Safety pharmacology

The aim of these studies is to measure the functional effects on major physiological systems. These usually include the cardiovascular, respiratory, CNS and renal systems.

However, in accordance with ICH guidelines S6(R1) and S7A (31, 35), no stand-alone safety pharmacology studies might be necessary. Instead, functional indices of potential toxicity could be incorporated in the design of toxicity studies.

Differences in tissue distribution between mAbs and low molecular weight mAb mimetics due to significant differences in their molecular weights should always be borne in mind and could be an important factor in this respect.

5.3 Pharmacokinetics and toxicokinetics

PK and TK studies are undertaken in order to understand exposure in safety studies, to allow cross-species comparisons 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 (29).

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

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 method should, preferably, be the same for animal and human studies, one validated method usually being sufficient. The possible influence of plasma-binding proteins and/or antibodies in plasma/serum on the performance of the chosen assay should be borne in mind and investigated.

Product-specific assays should:

- cover the pharmacological/toxicological or pharmacokinetic aspect,
- represent and/predict the clinical situation,
- broadly cover all functional aspects,
- be tailored to the product and need to be fully justified,
- represent all modes of action of the product.
5.3.2 Other considerations

**Absorption:** Absorption studies are not required for intravenous administered mAbs. However, the evaluation of absorption should be conducted during human Phase I studies of mAbs administered via the intramuscular or sub-cutaneous routes.

**Distribution:** Should be investigated as appropriate. Due to their molecular weight, mAbs do not usually distribute well and, following intravenous application, are initially confined to the vascular system. However, with time they may distribute to the extravascular space as a result of various factors, including bulk flow and active transport.

In contrast, mAb mimetic products with their significantly lower molecular weights can have considerably better tissue penetration and behave differently from mAbs or mAb fragments in this respect.

**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 small molecule following its deconjugation.

**Elimination:** Apart from absorption and disposition, 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.

5.4 Toxicology studies

Due to the wide range of different types of mAbs and related biologicals, as well as infections, the choice of animal model and safety testing that can usefully be carried out should be decided on a case-by-case basis and justified. Ideally, the NRA should be consulted. Nevertheless, safety testing of the mAbs, as described in existing guidance documents (29, 32), is essential.

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

A practical review of nonclinical safety evaluation of therapeutic antibodies by Lynch et al (36) highlights important considerations for planning a non-clinical program, the types of nonclinical safety studies needed, and a general timeline for their conduct in relation to clinical trials.

5.4.1 General considerations

Generally, a short-term study that investigates 2 or more doses with a minimum of 2-week dosing period should be considered. For mAbs that are intended for multiple dosing during prophylactic treatment and/or during the course of infection, the dosing regimen should reflect dosing in the worst-case clinical scenario. The study recovery period should reflect the exposure to mAb (e.g., 5 half-lives).

Toxicity testing should be carried out in healthy animals to allow for a clearer interpretation of toxicity and to represent prophylactic conditions. Testing should be
performed in both male and female animals and at an age that covers the proposed target human population, but the number of animals tested may vary depending on the species. Likewise, the route of administration of the product should reflect the intended route of administration of the mAb in clinical studies. When two or more mAbs are developed to be used in combination, the combined mAbs should be tested individually and in combination. For mAb conjugates, nonclinical safety studies should be conducted on the unconjugated mAb, the toxic agent (antibiotic, radionuclide), as well as on the combined antibody-drug conjugate.

The development of anti-immunoglobulin antibodies greatly complicates the study and interpretation of the effects of repeated dose studies in animals. Murine antibodies are non-immunogenic in mice but are immunogenic in humans, making it difficult to extrapolate the results of repeated dose studies in mice to planned repeated dose administration in humans. The reciprocal problem will occur with fully human, chimeric or "humanized" mAb if tested in animals. Repeated dose studies in rodents may therefore be of little predictive value as to what might happen in humans, although they might be useful in establishing safety margins.

Local tolerance should be evaluated according to established methods (e.g., evaluation of erythema/eschar and oedema according to dermal Draize score). If feasible, the potential 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 studies are generally not applicable to mAbs nor to related biologicals (29). Any product specific issues, such as a toxic molecule conjugated to a mAb, should be addressed on a case-by-case basis.

Carcinogenicity is less of an issue when the mAb target is exogenous. Standard carcinogenic studies are therefore generally inappropriate for these products. However, careful consideration should be given to bi-specific mAbs which may include an endogenous host antigen.

5.4.3 Developmental and reproductive toxicity

The need for reproductive/developmental toxicity studies will depend upon the product type (mAb, mAb fragment or very low molecular weight mAb mimetic), the clinical indication and the intended patient population. The specific study design and dosing schedule may be modified on the basis of issues related to species specificity, immunogenicity, biological activity and/or a long elimination half-life. Reproductive and developmental studies including teratogenicity in an appropriate animal species should be carried out in instances in which the product is intended for repeat or chronic administration to women of childbearing potential. However, the species-specific profile of embryo-foetal exposure during gestation should be considered in interpreting results. High molecular weight proteins (>5,000 D) do not cross the placenta by simple diffusion. For mAbs with molecular weight as high as 150,000 D, there exists a specific transport mechanism, the neonatal Fc receptor, which will determine foetal exposure and varies across species. The fact that in NHPs and humans, IgG placental transfer is low in the period of organogenesis and begins to increase in the early second trimester, reaching highest levels late in the third trimester should be taken

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into consideration. Further discussion can be found in the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (29). The results of such pre- and post-natal developmental studies should be submitted for marketing approval. Evaluation of male fertility, when appropriate, should be completed before Phase III trials.

Other toxicity studies

Assessment of antibody formation / immunogenicity should be conducted only to assist in the interpretation of study results and to improve the design of subsequent studies. Such analyses in animal studies are usually not relevant in terms of predicting potential immunogenicity of mAbs in humans. See Section C.7 of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (29).

Antibody dependent enhancement (ADE): It might be possible to test for the potential of ADE in a suitable animal model of disease although the mAb-mediated mechanisms may not be the same in humans. Regardless, such animal models may provide valuable insight into better understanding the infectious agent and the mAb mechanism of action.

Impurities: Safety concerns may arise as a result of the presence of impurities or contaminants. There are potential risks associated with host-cell contaminants, whether derived from bacteria, yeast, insect, plant or mammalian cells. The presence of cellular host contaminants can result in allergic reactions and other immunopathological effects. The 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 rather than to establish a nonclinical testing programme to evaluate their potential effect. 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 (29) as well as the ICH Q3 guideline on impurities in new drug products (37).

Ecotoxicity / environmental fate: mAbs are not considered as a particular hazard for the environment. They are expected to be fully metabolized via catabolic pathways, with negligible renal excretion. No special precautions are expected in terms of use and disposal. In these circumstances it can be justified not to submit a full environmental risk evaluation.

Anaphylaxis: Although uncommon in humans, the intravenous injection of a variety of protein-based products such as mAbs can lead to anaphylactoid reactions ranging from mild to severe, the molecular mechanisms of which may differ and are mostly unknown.

The possible role of complement activation has been implicated in some cases (38) and should be considered and evaluated in animal studies. However, the results of guinea pig anaphylaxis tests, which are generally positive for protein products, are usually not predictive of reactions in humans and are usually not conducted.

Immunotoxicity studies should be conducted to determine the possible adverse effects of mAbs on the immune system resulting in decreased host resistance to infectious agents (29).
6. Clinical evaluation

This section discusses approaches to the clinical evaluation of mAbs that may be used in the treatment or prevention of infectious diseases. These considerations are complementary to Part C of the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (29) and section 6 of the WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (39). The WHO Guidelines on clinical evaluation of vaccines: regulatory expectations (40, 41) may also provide useful information, particularly when considering the clinical trial design for mAbs intended for prophylactic use.

All human clinical trials must be conducted under the principles of good clinical practice (34, 42). Additional guidance on the implementation of good clinical practice principles can be found in the WHO Handbook on Good Clinical Research Practice (43).

6.1 General considerations

Each infectious disease has unique characteristics that depend on the nature of both the invading microorganisms and the host. Infectious diseases can be categorized by microorganism type (bacterial, viral, fungal, parasitic) and serotype or variant; by site of infection (e.g., lung, urinary tract, bone, skin); by host factors (such as prior infection, whether they are immunocompromised, new-born, pregnant or elderly); and by epidemiological features (e.g., nosocomial, food- or water-borne, 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 symptoms of the disease. Each infectious disease also needs to be addressed in terms of severity and stage of pathogenesis. The various stages include the microbiological stages of colonization, rate of replication/multiplication, tissue invasion and dissemination, as well as the acute and chronic clinical phases. Participants enrolled in clinical trials must be appropriately identified according to these variables.

Clinical trial design and site selection for mAbs to infectious diseases must also consider the epidemiological status of the pathogen. Clinical trial size and duration can vary depending on the mAb product’s biological half-life, whether the disease 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.

Clinical evaluation and product development programs for mAbs to infectious diseases should be specific and take into consideration whether the product to be evaluated is intended to be used as a prophylactic (either pre- and/or post exposure), 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 (i.e., 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 (i.e., prevention of the reactivation of an infectious agent already harboured by a patient subsequent to a primary infection).
The apparent efficacy of a treatment may be muted for those infectious diseases where the symptoms appear or remain after the pathogen load has peaked (e.g., as observed for SARS CoV-2, or pertussis). This may have a significant influence on the clinical development of a mAb for post-exposure prophylaxis or therapy, especially with regards to the timing of product administration and the selection of endpoints. In such circumstances, rapid point-of-care diagnostics may be important to the success in the evaluation and ultimate use of the intervention. An understanding of the epidemiology, pathology, and transmission of the infecting agent may help in the introduction and use of the treatment prior to the emergence of clinical symptoms or diagnosis. This 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 appropriate for prophylactic studies. Healthy volunteers may also provide useful data on the product safety, PK and potential for the induction of ADAs. Therefore, the nature of the mAb, the target antigen, and the proposed clinical application should be considered before deciding to enrol healthy volunteers in a trial.

Sponsors and investigators should carefully consider the clinical benefits over the risks of whether the mAbs are 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 efficacy 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, if there is an antibody response against the mAb product, repeat administrations may lead to loss of therapeutic benefit and potential toxicity. Similarly, participants with prior parenteral exposure to any components or proteins contained within the clinical trial material, to the comparator product, or with a history of relevant allergies, should be excluded from product development clinical studies.

Inclusion and exclusion criteria

Establishing the inclusion and exclusion criteria for subjects within any clinical trial requires careful consideration. The criteria will be product-dependent and should also be based on a risk assessment which considers 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 within the clinical trial applications.

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 within the intended target population. As such, the FIH studies would have the most conservative criteria for the subjects, with a broadening of the inclusion criteria during the Phase Ib and II trials. Modelling from PK and PD study data may help predict dosing information for expanding the inclusion of 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. Some additional discussion can be found in Section 6.6 on Special populations.
6.2 Phase I studies

Phase I and the first-in-human (FIH) trials are conducted in order to determine the initial safety and tolerability after the completion of essential nonclinical studies with the investigational product. Clinical experience has demonstrated that most humanized mAbs are, in general, well-tolerated. However, mAb fragments, single domain and bispecific antibodies, chemically modified and/or conjugated mAbs, and antibody mimetic agents (e.g., DARPin, affimers and anticalins) may have little, or no, clinical background information. Therefore, the safety assessment is 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 an optimal biologic dose (OBD) and/or to establish the minimum effective dose (MED) to be further pursued in Phase II trials. The OBD can be considered as the lowest mAb dose which provides the greatest efficacy and is usually defined by its pharmacokinetics or pharmacodynamic measurements (e.g., degree of antigen binding or as determined during nonclinical studies) and, where appropriate, by the tolerability to the agent (e.g., the maximally tolerated dose). However, in the case of an unconjugated mAb, studies that 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. If the product is intended to be given for an infectious disease in the elderly, in children, or in other specific groups, the safety and tolerability data may be required within those populations. However, this would also depend on a benefit-risk assessment, the type of infectious disease, as well as the 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 into broader age ranges and/or other specific populations. The expectations and requirements for safety and tolerability studies within special populations should be discussed with the NRA.

Classically, the Phase I 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 that it is targeting a non-native antigen, it may be more appropriate to base the FIH doses on a minimal anticipated biological effect level (MABEL), its MED, or possibly through the use of predictive computer simulation and modelling.

If extrapolating from animal doses to human doses, information about the dose required for treatment or prevention of the infectious agent may be of great value. The target in vivo dose, or concentration range, should be based both on in vitro studies of cells for which the mAb-antigen activity has been measured, as well as on studies of a relevant animal model, if available, to assess in vivo activity. If animal studies are judged to be impossible or of no relevance and initial in vivo studies are to be performed in humans, testing should begin at a low dose that is based on extrapolation from in vitro tissue culture studies or else from available information gathered in clinical trials of a similar mAb. Toxicity and other safety studies in animals could then be supportive information for FIH administration.
If a multiple-dose regimen of a mAb is anticipated, multiple-dose schedules should be explored after basic data on toxicity, peak levels, clearance, distribution, and biologic effects are available from single-dose studies. Multi-dose studies may also be assessed as part of Phase IV trials, and after 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 accounting for dose tolerance, available pharmacokinetic and pharmacodynamic data in humans, and on relevant animal models of safety and efficacy. Pharmacokinetic studies to determine the relationships of human anti-mAb antibody titres and circulating antigen levels with organ distribution, clearance, and toxicity may be necessary.

Before undertaking repeat 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 towards antigen epitopes on infectious organisms except, perhaps, in individuals who may develop ADAs.

6.3.2 Pharmacokinetics

The pharmacokinetic (PK) profile is an essential part of the basic description of a therapeutic or prophylactic product and should always be investigated. PK studies should be performed for the intended dose range and routes 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 (29).

Design of PK studies should consider:

- the structure of the product (e.g., whether it is a whole mAb, Fab fragment, antibody mimic, immunoconjugate) and its route of administration,
- The potential impact of age, gender, immune status, weight and body-mass index, as well as other physiological or disease status 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 where the mAb is distributed, metabolized, and eliminated,
- relationships between the elimination rate and the route of administration, and antigen load, and
- presence of a circulating antigen or 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 the 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 on the PKs should be evaluated and the clinical relevance discussed. It is recommended that PKs 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 instances, dedicated PK studies may not have been performed for the approval of some mAbs. Instead, population PK data from long-term trials could be considered and have been used to establish the PK profile and the impact of other factors (based on sparse PK samples in clinical trials). Population PKs and modelling/simulation applications may be acceptable by NRAs as a tool in guiding drug development.

A potential limitation of mAbs for the treatment of infections is the unknown bioavailability of the passively infused mAb into tissues affected by the disease. The mAb isotype, its subclass, and glycosylation pattern may have a large impact on its bioavailability at the site of infection. Similar limitations may apply to the mAb mimetic products, although their smaller molecular size may permit greater tissue penetration than full-sized mAb products.

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. In some cases, it may be valuable to assess the PK of the substances individually.

### 6.3.3 Pharmacodynamics

Samples and data necessary for PD studies are usually conducted throughout Phase I or Phase II trials but may also extend into Phase II studies 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 (i.e., whether it is an intact mAb or mAb fragment, conjugated, bispecific, or a mAb mimetic protein).

PDs 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 Pharmacokinetic/pharmacodynamic relationships

The relationship between concentration and PD response (PK/PD relationship) should be evaluated as part of mAb development program in both healthy subjects and patients with infection. If feasible, markers for both efficacy and safety should be measured, preferably in the same study. Such studies may consider the in vitro assessment of antimicrobial activity of plasma isolated at different time points following the 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 the nonlinearity can be dependent on 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 pharmacokinetic properties which reflect target-mediated drug disposition due to opsonophagocytosis or through the formation of antibody-toxin complexes. This may lead to some potential for complicated tissue distribution during bacterial infections.

MAbs which have been modified to provide extended half-lives allow for less frequent dosing and longer-term prophylaxis to 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 pharmacokinetics and pharmacodynamics.

6.4 Efficacy

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 mostly focus on disease prevention although for mAbs the onset of activity would be more rapid than vaccines and the duration of effect much shorter.

In trials of therapeutic mAbs, efficacy should be evaluated in terms of their ability to eliminate the pathogen from the body and/or to reduce the clinical symptoms following diagnosis. The emphasis should be on designing randomised controlled trials that account for the intended population of use, the selected clinical endpoint(s), case definitions and detection. The stage of infection in a participant when entering a clinical trial (i.e., the clinical starting point) may also influence the efficacy outcomes and it will be important to establish clinical criteria or clinical markers for entering the study. For example, the administration of anti-SARS CoV-2 virus mAbs were only effective when administered early to patients with symptomatic Covid-19 infections and prior to hospitalisation (44, 45). The nature of circulating variant strains of the infecting pathogen may also impact efficacy outcomes if the mAb binding affinity differs between the variants.

Biomarkers may provide equally important outcomes to be considered. Examples of some relevant biomarkers include viral load, colony forming units (CFU), antigens linked to chronic parasitic infections, and CD4 levels. Such biomarkers may be considered once identified and the assays for their detection validated; however, their selection should be discussed with the NRA. Further discussion of biomarker evaluation process and steps to follow are outlined in Section C3.3 of WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology (29).

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 with high quality in order to provide reliable and valid data for assessing efficacy and safety, some flexibility is needed with regard to the statistical methods that will be utilized in these trials. Single-arm studies (for example, when reduction of clinical symptoms and or viral load are evaluated) can sometimes be justified when there is no known effective therapeutic, and
standard of care is only supportive.

The selection of an appropriate comparator agent for use in efficacy trials will also require careful consideration. Placebo controls may be used in studies intended to treat or prevent infections only when no known agent is effective or when the natural history of the untreated infectious disease is relatively benign or self-limiting. Otherwise, the comparator agent should be an approved anti-microbial agent. However, 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 cases of diarrhoea, or use of anti-inflammatory medications.

Clinical endpoints

The selection of both primary and secondary endpoints for mAbs 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. Endpoints are usually explored and clarified during Phase II trials; however, the endpoints selected may change over time with increased knowledge and clinical experience with the mAb and/or may even be different between countries. Regardless, both primary and secondary endpoints need to be established before initiating Phase III studies.

Endpoints selected for efficacy studies should be clinically meaningful patient-oriented as best possible and able to demonstrate a benefit relative to a placebo or the current standard of care. There should be sufficient evidence that the primary endpoint 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 measured in a sub population. In some cases, a biomarker (for example, CD4 levels in HIV) could be considered acceptable as a study endpoint based on the biological plausibility and mechanism of action of the product. Examples of other endpoints may be the time from diagnosis to negative blood culture, reduction in hospitalization rates following a positive diagnosis, time to resolution of fever, or decrease in the occurrence of inflammation or coagulopathy.

The timing of product administration relative to the start of infection is also important in relation to expected outcomes and clinical endpoints. For some infections, it may be difficult to demonstrate benefit in patients with more severe or advanced disease. This was evidenced during the COVID-19 pandemic where mAbs were more effective when administered early during the disease and before patients had severe illness or were hospitalized (44, 45).

Endpoints should also be able to account for efficacy of the treatment versus induction of a primed immune response to the infection. It is permissible to combine the results for patients who have received no prior therapy with those for patients who have received brief anti-infective therapy unless there is evidence of a difference between the outcomes for these groups. If a pre-specified subset analysis demonstrates no difference between outcomes in the two groups (i.e., no influence of prior therapy) then the results could be combined for consideration.
6.4.1 Phase II studies

Phase II studies provide the first evaluation of a mAb product’s efficacy and potency 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 to demonstrate 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 (e.g., antibiotic or antiviral medication). Within most study populations, placebo controls may be ethically considered in studies of the treatment or prevention of infections only when no known agent is effective for these purposes and has full regulatory approval, or when the natural history of the untreated disease is relatively benign or self-limited. Whenever possible, the placebo should be visually identical to the study drug in appearance.

Phase II trials usually explore a variety of possible endpoints. Defining clinically meaningful endpoints in protocols will lend greater credibility and validity to the trials. The timing of clinical endpoint determination for trials of a prophylactic or therapeutic mAb needs specific consideration. Clinical variables for a therapeutic (e.g., resolution of symptoms) and laboratory assays showing a decrease in infectious viral/bacterial load can be considered as endpoints.

If the mAb product shows promising efficacy in Phase II trials for a serious or life-threatening condition where no other treatment option exists, or under situations of a public health emergency, approval based on a limited amount of data may be possible with further confirmatory efficacy data being provided through post-marketing studies (see Appendix 1).

6.4.2 Phase III studies

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

Specific decisions about the size of the study group will depend on factors which may include the magnitude of the effect of interest (the endpoints) in comparison to the active comparator or placebo, the incidence of the infectious disease within the community at the time of the clinical trial, characteristics of the study population, and study design. Confirmatory Phase III clinical trials must be adequately sized and powered to meet the primary endpoints, and according to the statistical analysis plan.

One well-controlled Phase III study with statistically compelling and clinically relevant results may be sufficient for a product marketing authorisation, particularly if supported by the mechanism of action and Phase II study results. However, a second confirmatory trial may be necessary in some cases to demonstrate that the results can be replicated. The requirements for a single or repeat study should be discussed with the NRA.
6.4.3 Human challenge studies

Human challenge studies are clinical trials in which participants are intentionally challenged with an infectious disease organism in order to evaluate the efficacy of a prophylactic or therapeutic agent. Such studies have proven useful in the clinical evaluation of some vaccines and may provide similar clinical support for mAbs to some infectious diseases, particularly in instances where there are insufficient cases within a population to conduct large Phase III trials, to provide support for an emergency use authorization, or when animal models are not available (46).

The use of such studies requires a strong and thorough risk assessment and ethical evaluation prior to starting. For infections with lower risk, such as those with low mortality, an acute onset which can be readily and objectively detected, and with existing efficacious treatments, a human challenge study may be feasible; however, infections with high fatality rates and/or absence of an effective treatment are not recommended. To reduce the risks associated with the infection, it may be possible to use less virulent or attenuated strains of the disease but the binding affinity of the mAb in comparison to the wild type organism should be understood and reported. Regardless of the pathogen used in human challenge studies, it is important that they are well characterized and that a standardized challenge strain and dose are used throughout the study.

Additional information on human challenge studies are provided in the WHO Regulatory Considerations for Human Challenge Trials for Vaccine Development (46). Guidance on the ethical considerations is available in the WHO Guidance on the Ethical Conduct of Controlled Human Infection Studies (47).

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 management strategies which may include the use of well-spaced, gradual dose-escalation, rolling review of emerging data, and stop criteria. For mAbs to infectious diseases, attention should be given to potential hypersensitivity, autoimmune and immune-complex issues, although problems of this nature should have been eliminated as far as possible during nonclinical evaluation (29).

Safety data should be obtained from a sufficient number of subjects during the clinical trials in order 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.

The safety evaluation should cover a reasonable length of time following production administration, taking into account the intended duration of the mAb activity and half-life so as to assess potential changes in the ADR profile over time and to capture potential delayed ADRs. Shorter-term safety data may be appropriate for mAbs to infectious diseases if the product is not intended for chronic treatment. However, rare adverse events are unlikely to be

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detected at this stage of product development and evaluation.

In the case of mAbs conjugated to a toxin, undesired tissue targeting and release of toxin due to degradation are major safety concerns. Therefore, patients receiving such conjugated mAbs should have more frequent monitoring of 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 (29). Additional requirements for mAb product safety evaluation should be discussed with the NRA.

6.5.1 Immunogenicity

Immunogenicity towards 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 efficacy of the product. Therefore, monitoring of ADA titres and immune activity is of great importance in evaluating the safety and efficacy of mAbs and in designing protocols involving their repeat administration (48).

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

Developing assays to test for anti-mAb-antibodies can be methodologically challenging since standard assay formats involving anti-immunoglobulin reagents are inappropriate for this product class. Depending on the construct of the mAb, assays for anti-immunoglobulins will need to be developed that distinguish between the ADAs and the presence of the administered mAb product.

6.6 Special populations

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

Paediatric population and children

The extent of safety studies needed in children depends on the possibility of extrapolation from adults and children of other age groups. Some mAbs may be designed for use in children from the early stages 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 (e.g., when a similar effect can be expected with similar exposure). However, safety data in children cannot always be extrapolated from adult studies and additional studies may be required. The adverse event profile may differ in paediatric population as compared to adults. Data on the safety of the mAb in the paediatric population should therefore be generated unless their use is clearly inappropriate.

During clinical development, the timing of paediatric studies will depend on the product, the type of disease being treated, safety considerations, and the efficacy and safety of alternative treatments. Justification for the timing and approach for a clinical program which may include the paediatric population and children should be clearly addressed with the regulatory authorities.

**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. Elderly patients are more prone to adverse effects of infection or treatments since they often have comorbidities and are taking concomitant medication that could impact the clinical performance of the investigational product. In addition, the adverse effects themselves can be more severe, or less well tolerated and may have more serious consequences than in the younger population. Therefore, it is important to determine whether the PK profile, efficacy, potency and safety of a mAb is different in the elderly as compared to younger adults. If so, the elderly sub-population should be represented sufficiently in the main Phase III or Phase II/III clinical trials to permit comparison of treatment effects, dose response and safety between older and younger patients, or investigated in separate studies.

**Evaluation during pregnancy**

In general, conducting clinical trials in pregnant subjects is not recommended due to ethical reasons; however, as the administration of prophylactic or therapeutic mAbs may be proposed for pregnant patients during clinical practice, their inclusion in clinical trials may be considered where reasonable. Including pregnant subjects should be based on safety data gathered from nonclinical studies, from clinical trials in adults, as well as an assessment of the potential benefits and risks for the mother, foetus and the newborn.

Understanding the process and likelihood of placental transfer of the mAb can help in evaluating the risk of their administration during pregnancy. For mAbs which contain a constant region (Fc) of 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 toward the third trimester of the pregnancy.

Longer-term observational studies are recommended to confirm the efficacy and safety of any mAb administered during pregnancy. Such studies would help determine 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. 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* (29).

### 6.7 Manufacturing and formulation changes

While manufacturing and formulation changes may be expected during product development, the Phase III studies should be conducted with mAbs, manufactured according to the final manufacturing (commercial) process. If this is not feasible, 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 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 include more extensive characterization parameters, using a range of suitable analytical methods as appropriate to the product and process changes in question. If differences are detected that may possibly influence the clinical properties of the product, 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 on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology* (29) and in the *WHO Guidelines on procedures and data requirements for changes to approved biotherapeutic products* (18).

### 6.8 Post marketing: Phase IV studies

Phase IV studies may be required to evaluate further an approved mAb to obtain more information about safety or effectiveness, or both, especially if the product has been approved for emergency use authorization and information is lacking. Further data may also be required to monitor the emergence of resistance or test the efficacy against newly recognized variant strains of the pathogen. Plans for Phase IV studies should be discussed with the NRA.

### 6.9 Statistical considerations

General statistical considerations, methodology applied to clinical trials and recommendations for the Statistical Analysis Plan (SAP) are outlined in the *WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology* (29). Additional statistical considerations can be found in the ICH E9 Statistical Principles for Clinical Trials guideline (49).

### 6.10 Pharmacovigilance and risk management planning

Pharmacovigilance and risk management plans should be developed by manufacturers to include activities which reflect risks associated with the specific mAb products such as its potential immunogenicity, toxicity or efficacy against circulating virus variants or antibiotic resistant bacteria. A pharmacovigilance plan should be submitted and agreed by the NRA. This plan should note whether specific surveillance needs to be done and where relevant information may minimize risk.

For the key components of a risk management plan, refer to the *WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology* (29).
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References


APPENDIX

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

During a public health emergency some NRAs may consider the review of mAb products supported by an abbreviated submission and/or the provision of a conditional marketing authorization in order to expedite product availability to the public. 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, a common strategy has evolved to reduce the product development time through the use of parallel nonclinical and clinical studies as well as overlapping or combining Phase I and II and/or Phase II and III clinical trials. This condensed strategy can be used to issue a limited, or temporary form of marketing authorization with the condition that the full nonclinical and clinical programmes are continued until the requirements for full licensure are completed. As the expectations and regulatory capacity for reviewing abbreviated submissions vary greatly between countries and may be different with each epidemic, early consultations with NRAs are strongly advised.

The use of platform technology in the manufacture of mAbs may reduce the development time required for establishing and validating their production processes and quality control methods (5). MAbs produced within established platform technologies may provide some level of confidence in the product safety; however, 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 to the infectious disease. This should consider the characteristics and novelty of the candidate mAb product as well as the biology of the infection and target antigen. For a candidate product for which there is little (or no) clinical experience, such as a novel mAb mimic, 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 dataset must be of good quality, generated from relevant animal species, and follow GLP principles as best possible.

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 toxicokinetic assessments. In cases where clinical trials were initiated on a minimum safety data package, the nonclinical program should continue in parallel with clinical development. An abbreviated nonclinical package should contain pharmacodynamic 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 (e.g., adult animals for pandemics primarily affecting the elderly, juvenile animals for pandemic illnesses that affect young children).
PK evaluation *in vivo* 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, a scientific rationale is encouraged for their omission. Juvenile toxicity studies can be omitted when the target population for emergency treatment is not in children, and with the understanding that the data gap would need to be completed with a nonclinical juvenile toxicity study and/or clinical data/experience at a later time and prior to the approval of the mAb for children (50). 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 with their enrollment 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 to infectious diseases are, in general, expected to provide initial safety information and determine optimal dose(s). During a public health emergency, NRAs may consider 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 is usually considered.

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 adhere to the principles of this phased approach but intervals between clinical trial phases of evaluation may be compressed and 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 favor its safety profile in humans with underlying medical conditions. Therefore, under the circumstances of an emerging outbreak or epidemic, consideration should be given to adjust the trial inclusion criteria for those populations who are at higher risk from the emerging infection (e.g., 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.
as 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 emergency assessments of products to be
used during public health emergencies vary greatly among NRAs. Similarly, their experience
in considering products within an abbreviated development pathway may be limited, and
their capacities stretched due to the greater burden on resources. NRAs with limited
experience in reviewing applications for mAbs, or with limited resources are strongly
encouraged to practice evidence-based reliance on the assessments and decisions of trusted
partners and NRAs with more longstanding experience and expertise in the review of the
same, or similar mAb products.