Monoclonal Antibodies: Streamlined Nonclinical Safety Studies

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2025
Pharmacology/Toxicology

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in implementing streamlined approaches for nonclinical safety assessments of monoclonal antibodies that recognize a single molecular target, referred to as monospecific antibodies. Most antibodies are pharmacologically active in nonhuman primates (NHPs) only, and this guidance is intended to facilitate drug development for monospecific antibodies while avoiding unnecessary use of animals, particularly NHPs, consistent with the 3R principles of reducing, refining, and replacing animal testing. By reducing animal testing and incorporating an integrated knowledge-based risk assessment, this guidance is anticipated to facilitate greater efficiencies in product development.

The streamlined approaches recommended in this guidance are intended to apply broadly to the development programs for monospecific antibodies in any indication except those reviewed by the Office of Oncologic Diseases (OOD). Oncology-specific guidances provide additional flexibility appropriate for oncology indications specifically. This flexibility is not described in this guidance.[2]

This guidance supplements the ICH guidances for industry *S6(R1) Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012) (ICH S6(R1)), *S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals* (May 2021) (ICH S11), and *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021) (ICH S5(R3)). This guidance also supplements the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), which provides guidance with

[1] This guidance has been prepared by the Office of New Drugs in Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For indications in OOD and related guidances, visit https://www.fda.gov/about-fda/oncology-center-excellence/oncology-center-excellence-guidance-documents.

regard to timing of nonclinical studies relative to clinical development. This guidance also supplements other streamlined approaches, such as those described in the guidances for industry *Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals* (March 2019) and *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023).[3]

This guidance does not address toxicology studies related to multispecific antibodies, conjugated antibodies (e.g., antibody-drug conjugates), or antibody constructs (e.g., single-chain variable fragments)

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended but not required.

II. BACKGROUND

Clinically relevant toxicities of antibodies are primarily due to their exaggerated pharmacological effects. Antibodies are large proteins with low tissue distribution and high specificity for their molecular targets; these features reduce the potential for off-target toxicities. Because monospecific antibodies are typically metabolized through protein catabolism and degradation rather than hepatic biotransformation, the metabolite safety concerns and species-specific metabolic differences that are relevant for small molecule drugs are generally not applicable to these products. Because of these product characteristics, knowledge of target biology and expression profile may inform approaches for assessing patient safety, and studies in animals (when warranted) could be streamlined.

Consistent with the Agency's commitment to reducing, refining, and replacing animal testing, this guidance provides broadly applicable recommendations for streamlined approaches to assess long-term safety from monospecific antibodies; describes when general toxicology studies are not warranted or may be limited to a short-term study; and addresses alternative approaches for reproductive, developmental, and juvenile toxicity assessments. Sponsors are encouraged to discuss their approach to nonclinical safety assessments of monospecific antibodies with the FDA review divisions before initiating their nonclinical programs.

To help advance the principles of the 3Rs, sponsors may propose nonclinical tests, including new approach methodologies (NAMs), as appropriate, and study designs that reduce the number of animals in toxicology studies. Sponsors are encouraged to discuss their nonclinical programs during appropriate meetings, for example, Type B meetings.[4] The Agency will evaluate whether

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023).

the proposed approaches and designs adequately address product safety and meet nonclinical regulatory requirements.

III. RECOMMENDATIONS

A. Chronic Toxicology Studies

1. Evaluating Safety From Chronic Administration of Monospecific Antibodies

In general, studies longer than 3 months in nonrodent species (e.g., NHPs, dogs, and mini-pigs) are not warranted to evaluate toxicities from chronic administration of monospecific antibodies when data from 3-month studies are supplemented with a weight-of-evidence (WoE) risk assessment.

A WoE risk assessment may include the following data:

- Mechanism of action and pharmacology data generated with the monospecific antibody.
- A literature-based assessment of potential toxicities associated with the molecular target, (e.g., based on the expression profile or roles of the molecular target in physiological processes).
- Results of toxicology and pharmacokinetic (PK) data in pharmacologically relevant species (also see sections III.A.2 and III.B).
- Results of an assay to detect human-relevant off-tissue binding and potential secondary effects. This is particularly recommended when a pharmacologically relevant species has not been identified and thus no toxicology studies are conducted.
- Clinical safety and PK data generated with the monospecific antibody (e.g., phase 1 or 2 data).
- Toxicity findings in animals and humans, such as when extensive information is published on toxic effects based on other monospecific antibodies against the same target.
- Other nonclinical data as scientifically justified (e.g., NAMs, transgenic models, data using surrogates).

For exceptional cases when a 3-month study and WoE risk assessment may be inadequate , sponsors should consult the appropriate FDA review division regarding whether a 6-month toxicology study is warranted. For duration of general toxicology studies in severely debilitating or life-threatening hematologic disorders see the guidance for industry *Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals*.

2. Examples of When 3-Month (or Longer Duration) Toxicology Studies Are Not Warranted

When an assessment of long-term safety is warranted (e.g., a monospecific antibody being administered weekly continuously to humans over many months), sponsors should decide whether a 3-month (or longer duration) toxicology study in animals will generate relevant information. Below are examples of when 3-month studies (or studies of longer duration) are not warranted. The concept may be applied to other safety studies, as appropriate, and sponsors should discuss their nonclinical development plans with the FDA review divisions before initiating a study in NHPs.

- When results of additional studies are likely to be confounded, for example, due to formation of neutralizing or clearing anti-drug antibodies (ADAs) observed in a completed short-term toxicology study conducted with the investigational monospecific antibody.

- When a 3-month toxicology study in animals is not feasible, for example, because severe immune suppression or anemia in a short-term toxicology study suggests that a longer duration study is likely to lead to mortality.

- When pharmacology data indicate that the monospecific antibody does not bind to the target in any nonclinical species or binding does not elicit pharmacological activity. In these cases, no toxicology studies are warranted (see section III.B).

- When substantial animal data with other monospecific antibodies against the same molecular target indicate that the animal data have not been predictive of human toxicities. In these cases, no toxicology studies are warranted.

B. Other Considerations for Nonclinical Safety Studies

- Animal toxicology studies should use pharmacologically relevant species. Pharmacology studies should demonstrate binding of the monospecific antibody to the molecular target and elicit the intended functional effects. In the absence of a pharmacologically relevant species, the safety assessment could be based on a WoE risk assessment in lieu of animal toxicology studies.

- For antibodies that have pharmacological activity similar to humans in both rodent and nonrodent species, general toxicology studies (short- and long-term) conducted in a single rodent species may provide sufficient and appropriate nonclinical data.

- A WoE based decision should be made first to determine whether additional nonclinical studies with the monospecific antibody are warranted in support of pediatric studies,

consistent with ICH S11.[5] For development programs that will include only pediatric subjects, sponsors should consult the appropriate FDA review division.

- Assessment of reproductive and developmental toxicities should begin with a WoE risk assessment.[6] A study in a relevant animal species may be warranted when a WoE risk assessment or other approaches (e.g., alternative assays) cannot adequately address safety. For products intended to directly or indirectly target gametes or have an indication for pregnancy-specific conditions, sponsors should consult the appropriate FDA review division regarding the appropriate approach for assessing risk.

- Sponsors should consider whether safety concerns identified based on a WoE risk assessment can be addressed in clinical studies of the investigational products.

[5] A WoE approach for pediatric risk assessment may contain additional factors not included in section III.A.1 of this guidance. See ICH S11.

[6] A WoE approach for reproductive risk assessment may contain additional factors not included in section III.A.1 of this guidance, for example, placental transfer, reproductive findings from genetically modified animals or models employing pharmacological inhibition, expression and the role of the molecular target during embryo-fetal development. Also see ICH S5(R3) and ICH S6(R1).