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Administrative Notice

May 13, 2026

(To industry groups)

Pharmaceuticals and Medical Devices Agency

Center for Product Evaluation

Considerations for the General Toxicity Evaluation of Monoclonal Antibodies (Early Consideration)

Pharmaceuticals and Medical Devices Agency (PMDA) has organized its current thinking on the general toxicity evaluation of monoclonal antibodies, as attached, taking into account the promotion of the 3Rs of animal experiments (reduce, refine, replace), as well as recent advances in New Approach Methodologies (NAMs). This Early Consideration represents one example of the "Considerations on the Use of the Weight of Evidence Approach in Nonclinical Safety Evaluation" dated October 24, 2025

Early Consideration is reference information and point of view at this time for promoting the practical application of new technologies and the development of innovative pharmaceuticals, although scientific knowledge and information have not yet been fully accumulated. Please note that those reference information and point of view may change in the future based on new knowledge and scientific advance.

♦ This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Considerations for the General Toxicity Evaluation of Monoclonal Antibodies
（Early Consideration）

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1. Background

Monoclonal antibodies are characterized by high target specificity and species specificity. Consequently, in many cases, the experimental animal in which sufficient binding to the target molecule is confirmed and in which pharmacological effects comparable to those in humans can be expected is limited to non-human primates (typically monkeys). It is well recognized that most toxicities associated with monoclonal antibodies are related to their intended mechanism of action[1], and that the risk of off-target toxicity is low. In recent years, several studies have retrospectively compared and analyzed short-term and long-term general toxicity study results in monkeys for biotechnology-derived pharmaceuticals, including conventional monoclonal antibodies. These studies indicate that, in many cases, only predictable toxicity findings—such as exaggerated pharmacological effects and immunogenicity—are observed in both short-term and long-term general toxicity studies. The data suggest that a 3-month general toxicity study can provide sufficient information to support clinical development[2,3,4]. Taking into account these characteristics of biotechnology-derived pharmaceuticals and the accumulation of safety data, both the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have issued documents referring to the rationalization of toxicity testing for monoclonal antibodies and to alternative approaches for toxicity evaluation utilizing New Approach Methodologies* (hereinafter referred to as NAMs)[5,6,7].

2. General Toxicity Evaluation of Monoclonal Antibodies

In this Early Consideration, based on the background described above, the PMDA presents its current thinking on toxicity evaluation using a Weight of Evidence (hereinafter referred to as “WOE”) approach**, including the rationalization of general toxicity evaluation and the utilization of data obtained from New Approach Methodologies (NAMs), for conventional monoclonal antibodies (-tug, unmodified immunoglobulins)[8].

In the development of antibody therapeutics, it is required to ensure the safety of clinical trial participants by conducting general toxicity evaluations using animals, as well as additional studies such as tissue cross-reactivity studies, and, if appropriate, risk assessments of cytokine release mediated by immune activation and evaluations of potential secondary effects associated with off-target binding. Furthermore, the use of NAMs in these evaluations may also be considered.

In the general toxicity evaluation of biotechnology-derived pharmaceuticals, it is important, first, to assess whether there is an appropriate animal species in which the pharmacological activity of the product is exhibited[1]. The fundamental approach to general toxicity evaluation differs substantially depending on whether such an appropriate animal species exists. In this section, the considerations for the duration of repeated-dose toxicity studies are first described for cases in which monkeys are the only relevant species. This is followed by a description of the general approach to toxicity evaluation in cases where no appropriate animal species is available.

2.1 Considerations for the Duration of Repeated-Dose Toxicity Studies When Monkeys Are the Only Relevant Species

2.1.1 WOE Factors Relevant to the Need for a 6-Month Repeated-Dose Toxicity Study in Monkeys

In considering whether a 6-month repeated-dose toxicity study is necessary, the following factors should be comprehensively taken into account as elements of the WOE approach.

- ✓ Information on the monoclonal antibody under development
  - Toxicity study results obtained to date, including results from 3-month repeated-dose toxicity studies in monkeys (including toxicokinetic data)
  - Data on the mechanism of action and pharmacological characteristics
  - Literature/database information on potential toxicities associated with the target molecule
  - Other nonclinical data (e.g., data obtained from NAMs)
  - Available data on safety and pharmacokinetics from clinical studies conducted to date
- ✓ Information on other monoclonal antibodies targeting the same antigen
  - Results from nonclinical studies
  - Safety information in humans

2.1.2 Considerations on the Need for a 6-Month Repeated-Dose Toxicity Study in Monkeys

Based on the WOE factors described in Section 2.1.1, examples of considerations regarding the need for a 6-month repeated-dose toxicity study in monkeys are provided below.

In general, a 6-month repeated-dose toxicity study is likely to be required in the following cases:

- When toxicity findings are observed in toxicity studies that cannot be explained by the pharmacological effects or class effects, and for which the mechanism is unknown
- When toxicity findings are observed in toxicity studies that cannot be appropriately monitored in humans
- When the expression and distribution of the target molecule extend across multiple organs and tissues, and diverse toxic effects may occur

- When there is limited precedent for the pharmacological target and it is difficult to predict risks based on existing knowledge

On the other hand, if none of the above conditions apply, or if the impact of immunogenicity is substantial in repeated-dose toxicity studies in monkeys, making the interpretation of toxicity evaluation difficult, the additional value of conducting a 6-month repeated-dose toxicity study may be limited. Therefore, the scientific merit of conducting a 6-month repeated-dose toxicity study should be considered on a case-by-case basis, based on the results of risk assessment using the WOE approach.

2.2 General Approach to Toxicity Evaluation When No Appropriate Animal Species Exists

According to the ICH S6(R1) guideline, when no relevant species exists, the use of relevant transgenic animals expressing the human receptor or the use of homologous proteins should be considered[1]. Furthermore, if neither transgenic animal models nor homologous proteins can be utilized, the guideline refers to the conduct of a repeated-dose toxicity study of up to 14 days in a single animal species, including evaluations of critical functional endpoints (e.g., cardiovascular and respiratory systems)[1].

2.2.1 When the Target Molecule Is an Exogenous Factor (e.g., Bacteria or Viruses)

In general, toxicity attributable to the primary pharmacological action is not anticipated, and concerns to be evaluated are mainly related to off-target effects. Therefore, the relevance of conducting a stand-alone repeated-dose toxicity study using a single animal species in which pharmacological activity is not demonstrated, as described in the ICH S6(R1) guideline, is considered limited. Accordingly, it is considered sufficient to confirm, in animal studies conducted for the purpose of evaluating efficacy or pharmacokinetics, that there are no particular concerns regarding critical functional endpoints (e.g., cardiovascular and respiratory systems).

2.2.2 When the Target Molecule Exists Only in Humans, or When an Ortholog of the Pharmacological Target Exists but Sufficient Pharmacological Activity Is Not Observed in Animals

It may be appropriate to conduct toxicity studies using transgenic animals or homologous proteins in order to evaluate hazards related to the pharmacological activity. In addition, the concept of Target Safety Assessment[9,10], incorporating information such as biological data on the target molecule (e.g., physiological function of the target, involved pathways, and protein and gene expression) and genetic information (e.g., phenotypes of genetically modified animals and human gene annotations), may serve as a useful reference. Furthermore, evaluations utilizing NAMs, focusing on the assessment of specific endpoints, may be conducted in combination for the purpose of assessing potential risks anticipated from the pharmacological activity.

On the other hand, when neither toxicity studies using transgenic animals nor studies employing

homologous proteins can be conducted, the information available for general toxicity evaluation is limited. In such cases in particular, it is important to maximize the use of all relevant available information, including nonclinical and clinical safety data of related products, and to perform toxicity evaluation based on a WOE approach. In addition, as described in Section 2.2.1, it is necessary to confirm, in any available animal study, that there are no particular concerns regarding critical functional endpoints.

3. Conclusion

In light of advances in science and technology and the accumulation of safety information on conventional monoclonal antibodies, an environment is emerging in which the rationalization of nonclinical safety evaluation for such antibodies can be considered on a scientific basis. Sponsors are encouraged to proactively utilize consultation opportunities, such as consultation services, to discuss with the PMDA, as appropriate, the necessity of conducting long-term repeated-dose toxicity studies in monkeys and the application of toxicity evaluation using a WOE approach, including the use of data obtained from NAMs. The PMDA intends to promote the principles of the 3Rs, on the premise of ensuring human safety, and to advance case-by-case considerations regarding the rationalization of general toxicity evaluation for conventional monoclonal antibodies, as well as toxicity evaluation of conventional monoclonal antibodies utilizing a WOE approach.

【Glossary】

The following terms are defined as follows in this document.

* New Approach Methodologies

Tools to evaluate the efficacy, safety, and pharmacokinetics of medical products. without using the conventional animal models and encompasses all technologies and methodologies including *in silico*, *in chemico*, *in vitro*, and *ex vivo* approaches (ECHA, 2016. New approach methodologies in regulatory science. Proceedings of a scientific workshop. Helsinki: European Chemicals Agency. doi: 10.2823/543644).

** Weight of Evidence approach

Concept or method of comprehensive evaluation combining multiple available data and information (Ministry of Health, Labour and Welfare, Ministry of Economy, Trade and Industry, Ministry of the Environment 2025. Weight of Evidence implementation manual for biodegradation assessment in CSCL risk evaluation) to draw conclusions that are not clear from a single piece of data (OECD, 2010. OECD Environment, Health and Safety Publications Series on Testing and Assessment No. 129 GUIDANCE DOCUMENT ON USING CYTOTOXICITY TESTS TO ESTIMATE STARTING

DOSES FOR ACUTE ORAL SYSTEMIC TOXICITY TESTS).

【References】

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