Provision Translation (as of January 2026)*

Administrative Notice
October 24, 2025

(To industry groups)

Pharmaceuticals and Medical Devices Agency
Center for Product Evaluation

Use of the Weight of Evidence approach as an alternative to nonhuman primate developmental and reproductive toxicity testing for biopharmaceuticals (Early Consideration)

Pharmaceuticals and Medical Devices Agency (PMDA) had exchanged views with relevant parties on alternatives to nonhuman primate developmental and reproductive toxicity testing for biopharmaceuticals at the annual meeting of American College of Toxicology in November 2021. This was summarized in the International Journal of Toxicology (Int J Tox. 2023; 42: 467-79. DOI: 10.1177/10915818231200859). PMDA's Center for Product Evaluation has summarized the current concept regarding the use of the Weight of Evidence Approach as an alternative for the developmental and reproductive toxicity testing in nonhuman primates for biopharmaceuticals. This Early Consideration is one example of "Thoughts on the Use of Weight of Evidence Approach in Nonclinical Safety Evaluation" dated 24 October 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 advances.

* 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.

Use of the Weight of Evidence approach as an alternative to nonhuman primate developmental and reproductive toxicity testing for biopharmaceuticals

(Early Consideration)

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1. Background

For biotechnology-derived pharmaceuticals (hereinafter referred to as "biopharmaceuticals") with high target specificity and species specificity, the nonhuman primate (NHP) is often the only species used as laboratory animal in which binding affinity to the target molecule and similar pharmacological effects to those in humans can be expected. In addition, the similarity of phylogenetic and physiological characteristics and placental transfer of antibodies to those of humans[1] makes NHPs a frequent choice for developmental and reproductive toxicity (DART) testing for biopharmaceuticals. On the other hand, the use of NHP DART testing may be limited to hazard assessment[2] because of the small group size, the wide variability across groups, and the high background pregnancy loss.[1] In view of the limitations of NHP DART testing and the 3Rs in animal experiments (reduce, refine, replace), the need for NHP DART testing should be determined more carefully.

2. Alternatives to NHP DART Testing

When the biopharmaceutical is pharmacologically active only in NHPs, DART testing should be conducted in NHPs.[2] However, even in that case, an alternative scheme shown below (Figure 1) can be used in place of NHPs if appropriate scientific justification is provided.

This Early Consideration presents PMDA's view on the use of the Weight of Evidence (hereinafter referred to as "WOE") approach as an alternative to NHP DART testing for the DART risk assessment for biopharmaceuticals when the NHP is the only relevant species to evaluate safety in humans.

1) Assessment by using the WOE approach

Biopharmaceuticals are generally highly specific to their targets and less likely to have off-target DART compared with chemically synthesized drugs. Therefore, DART evaluation approaches based on the placental transfer, the mechanism of action, or the biological characteristics of the target may be considered. A comprehensive review of the publicly available information (e.g., mechanism of action, detailed information on the biological properties of the target molecule, reproductive and developmental findings in the existing genetically modified animals, reproductive and developmental

information on humans treated with similar drugs) may provide sufficient information for DART risk assessment. Examples include the following:

- When there are serious concerns in embryo/fetal development

There may be a case that a clinical dose may cause serious concerns in embryo/fetal development (e.g. fetal malformation, embryo/fetal lethality, abortions) due to the intended pharmacological effects (e.g. inhibition of angiogenesis) on the basis of nonclinical studies of efficacy (mechanism of action), evaluation using literature and databases, and assessment of placental transfer. In this case, information on embryo/fetal development toxicity should be provided to healthcare professionals and patients without conducting animal studies,[2] and the administration to pregnant women should generally be avoided.

- When the existing information is considered sufficient for risk assessment

In case of a biopharmaceutical targeting an endogenous protein with well-characterized biological properties or when several similar products with the same target are already approved and their substantial information on DART in pregnant women treated is available, it may be possible to judge that the DART risk in humans is low based on the overall assessment of these available information. However, the reliability, appropriateness, and consistency of the obtained data should be considered,[3] and DART evaluation should be carefully conducted.

For an antibody drug, the clinical pharmacokinetic data will be generally available prior to the DART testing because it is generally conducted before the marketing application for approval.[4] In case of locally administered biopharmaceuticals such as intravitreal administrations, for example, the systemic exposure to the drug can be very low. If the systemic exposure in humans is less than the minimum anticipated biological effect level, DART associated with the pharmacological effect is not expected to occur. In such cases, the DART risk is low, and DART testing is not considered necessary.

2) Assessment using homologous protein or genetically modified animals

When sufficient information on DART cannot be obtained by the WOE approach, it is necessary to consider conducting DART testing. In such cases, evaluation by an alternative approach using homologous proteins of clinical candidates (e.g., surrogate antibodies) or genetically modified animals expressing human target proteins may be considered instead of an NHP testing. When a sponsor chooses to conduct an assessment using a homologous protein or genetically modified animals, it is necessary to explain its appropriateness in terms of the target specificity of the homologous protein, the biodistribution of the target molecule in genetically modified animals, the species-specific differences in pharmacological action of the test substance, and the effects on the physiological function. Note that risk assessment will be difficult in testing using homologous proteins or genetically

modified animals because the quality characteristics of homologous proteins and clinical candidates are not identical and the expression levels and functions of human target molecules in genetically modified animals are not necessarily equivalent to those in humans.

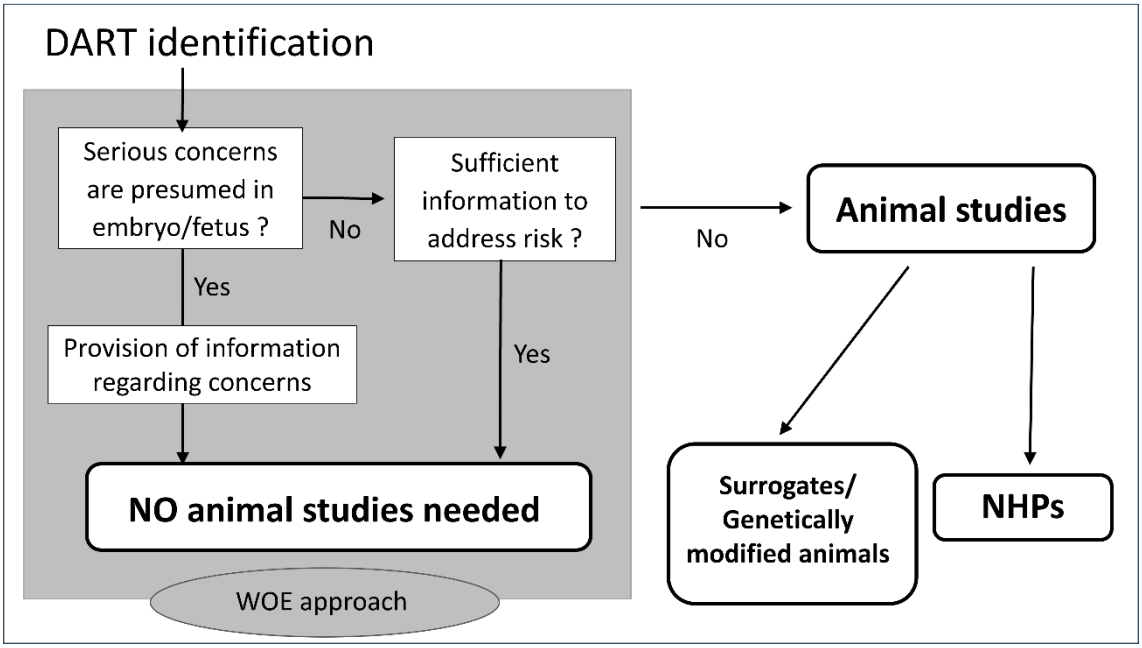

Figure 1. Scheme for DART testing when the clinical candidate is pharmacologically active only in NHPs

3. Conclusion

Considering the limitations of DART testing in NHPs and ethical issues of animal studies, there may be room for the active use of WOE assessment based on the information on the mechanism of action of the clinical candidate and the DART of similar drugs as well as the accumulated information on phenotypes of genetically-deficient animals, and DART testing using homologous proteins. In addition, the necessity of DART testing may vary depending on the characteristics of the population that affects the fertility rate (e.g., age, disease), seriousness of the target disease, and treatment options in Japan. It is recommended that these approaches be agreed upon with PMDA through active use of consultation services to avoid any negative impact on the application for marketing approval.

[References]

1. ICH S5 (R3) “Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals” (PSEHB/PED Notification No. 0129-8 issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare on January 29, 2021)
2. ICH S6 (R1) “Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals”

(PFSB/ELD Notification No. 0323-1 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare on March 23, 2012)

3. EFSA, Guidance on the use of the weight of evidence approach in scientific assessments, 2017, doi: 10.2903/j.efsa.2017.4971
4. ICH M3 (R2) “Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals” (PFSB/ELD Notification No. 0219-4 issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare on February 19, 2010)

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