Oncology Pharmaceuticals: Streamlined Nonclinical Safety Studies for Biologics and Conjugated Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OCE) OCE-Guidances@fda.hhs.gov or (CDER) Tiffany Ricks or Haleh Saber at 240-402-0380.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
May 2026

Pharmacology/Toxicology

Oncology Pharmaceuticals: Streamlined Nonclinical Safety Studies for Biologics and Conjugated Products

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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

May 2026

Pharmacology/Toxicology

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

Oncology Pharmaceuticals: Streamlined Nonclinical Safety Studies for Biologics and Conjugated Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 certain oncology pharmaceuticals. This guidance is intended to facilitate drug development for biologics and conjugated products for the treatment of cancer while avoiding unnecessary animal use. The recommendations in this guidance are informed by data analysis of general toxicology studies[2,3,4,5] and practices developed during the COVID-19 pandemic to reduce use of non-human primates. By reducing animal testing and incorporating an integrated knowledge-based risk assessment, this guidance is anticipated to facilitate greater efficiencies in product development without compromising patients' safety.

This guidance provides recommendations for general toxicology studies with a primary focus on 3-month toxicology studies for certain oncology pharmaceuticals. This guidance supplements the International Council for Harmonisation (ICH) guidances for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (ICH S9) (as implemented by FDA in March 2010) and *ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals--Questions and Answers* (ICH S9 Questions and Answers) (as implemented by FDA in June 2018), and the FDA guidance for industry *Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling*

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE) and Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] Saber H, Del Valle P, Ricks TK, Leighton JK. An FDA oncology analysis of CD3 bispecific constructs and first-in-human dose selection. Regul Toxicol Pharmacol. 2017 Nov; 90:144-152.

[3] Kamperschroer C, Shenton J, Lebrec H, Leighton JK, Moore, PA, Thomas O. Summary of a workshop on preclinical and translational safety assessment of CD3 bispecifics. J Immunotoxicol. 2020 Dec; 17(1):67-85

[4] Saber H and Leighton JK. An FDA oncology analysis of antibody-drug conjugates. Regul Toxicol Pharmacol. 2015 Apr; 71(3):444-452.

[5] Saber H, Simpson N, Ricks TK, Leighton JK. An FDA oncology analysis of toxicities associated with PBD-containing antibody-drug conjugates. Regul Toxicol Pharmacol. 2019 Oct; 170:104429.

Recommendations (August 2019).[6] This guidance does not address nonclinical safety assessments for impurities or excipients.

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

ICH S9 and ICH S9 Questions and Answers provide recommendations for nonclinical testing of oncology pharmaceuticals, including general toxicology studies. These guidances recommend that assessment of such products' chronic effects may be based on 3-month studies in one or two animal species, which is sufficient to support continued clinical development and marketing for oncology pharmaceuticals.

Current guidances for oncology pharmaceuticals support approaches to streamline nonclinical testing. For instance, ICH S9 (March 2010) states "[i]n certain circumstances, determined case-by-case, alternative approaches can be appropriate (e.g., for genotoxic drugs targeting rapidly dividing cells, a repeat dose toxicity study in one rodent species might be considered sufficient, provided the rodent is a relevant species)." The FDA guidance *Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations* (August 2019) recommends a risk assessment, instead of an animal toxicology study, to evaluate toxicities associated with radioactive drugs, stating "[a] general toxicology study with the radiopharmaceutical usually is not warranted. The animal biodistribution study, together with the general knowledge of organ-specific radiation-induced toxicities, is usually sufficient to address toxicities from the radiation." The ICH guidance, S6(R1) Addendum to Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (May 2012) (ICH S6(R1)), further states "in certain justified cases one relevant species may suffice (e.g., when only one relevant species can be identified or where the biological activity of the biopharmaceutical is well understood)."

Sponsors may propose alternative approaches for a 3-month general toxicology study for product classes not described in this guidance, provided such approaches are sufficient to address product safety. Such approaches for a 3-month general toxicology study may include a non-sacrificial toxicology study, an alternative study design to reduce animal numbers, or a weight of evidence (WoE) risk assessment for products with well-understood targets to replace an animal study. These approaches could be supplemented with new approach methodologies (NAMs), as appropriate. Sponsors proposing alternative approaches not specifically addressed in this guidance should provide appropriate scientific justification and relevant supporting data. The Agency will consider whether the alternative approach is adequate to characterize the safety risks in each case. Sponsors are encouraged to discuss proposed alternative approaches with FDA

[6] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

early in development of toxicology studies. Sponsors are encouraged to discuss their nonclinical programs during appropriate meetings. The meeting types are described in the FDA guidance Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products.[7] Additionally, sponsors may consider conducting 3-month toxicology studies early in development, in lieu of separate 1-month and 3-month toxicology studies, to reduce animal use.

III. RECOMMENDATIONS

A. General Toxicology

- For biologics, animal toxicology studies should use pharmacologically relevant species. Pharmacology studies should demonstrate binding of the oncology pharmaceuticals to molecular target(s) and elicit the intended pharmacologic 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 biologics that have pharmacological activity similar to humans in both rodent and non-rodent species, general toxicology (1- and 3-month) studies may be conducted in a single rodent species and supplemented with a WoE risk assessment, as appropriate.

- For PD-(L)1 blocking monospecific antibodies, an assessment of the products' chronic effects may be based on a WoE risk assessment in lieu of a 3-month toxicology study. In addition, with justification, the 1-month toxicology study may be non-sacrificial and supplemented with a WoE risk assessment.

- For CD3 bispecific T-cell engagers, an assessment of products' chronic effects may be based on a WoE risk assessment in lieu of a 3-month toxicology study.

- For antibody-drug conjugates (ADCs) with cytotoxic payloads, when the safety of the payload is well-characterized (e.g., same payload as in approved ADCs) and the payload is the main driver of toxicities, the 3-month toxicology study may be conducted in rodents only, irrespective of ADC binding to the target antigen. The rodent study may use the ADC or the payload, as appropriate. When the target of the antibody is novel and binding to the target does not occur in the rodent species, a WoE risk assessment should also be submitted.

B. Weight of Evidence Risk Assessment

- A WoE risk assessment may include the following information:

[7] Draft guidance for industry titled "*Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products"*, available at https://www.fda.gov/media/172311/download (September 2023).

- Nonclinical and clinical data generated with the investigational product, such as pharmacology, safety, and pharmacokinetics

- 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, in healthy and disease states)

- Toxicity findings in animals and humans, such as when the investigational product is in a class of pharmaceuticals with extensive information published on toxic effects

- Other data, as appropriate, e.g., fit-for-purpose NAMs[8]

CDER oncology review divisions will determine whether the information included in the WoE risk assessment is sufficient to address the safety risks based on the totality of evidence.

[8] Draft guidance for industry titled "General Considerations for the Use of New Approach Methodologies in Drug Development", available at https://www.fda.gov/media/191589/download (March 2026).