Clinical Pharmacology Considerations for Antibody-Drug Conjugates

Guidance for Industry

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

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Contains Nonbinding Recommendations

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This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to assist industry and other parties involved in the development of antibody-drug conjugates (ADCs) with a cytotoxic small-molecule drug or *payload*. Specifically, this guidance addresses the FDA's current thinking regarding clinical pharmacology considerations and recommendations for bioanalytical methods, dosing strategies, dose- and exposure-response analysis, intrinsic factors, QTc assessments, immunogenicity, and drug-drug interactions (DDIs). The principles discussed in this guidance might not be applicable to the development of other types of ADCs (e.g., ADCs with payloads other than cytotoxic small molecule drugs and/or for indications other than oncology).

This guidance specifically outlines clinical pharmacology considerations of ADC development programs and references other relevant guidances when appropriate.[2] ADCs are subject to all pertinent laws and regulations for biological products, including those governing product development, testing, and approval as outlined in section 351 of the PHS Act (42 U.S.C. 262). Given that ADCs include a small-molecule drug,[3] there are other guidances that are applicable to ADCs that would not necessarily apply to other biological products. Of note, this guidance does not focus on the development of any particular ADC, and questions about regulatory recommendations and development programs for a particular ADC should be addressed to the appropriate FDA review division. Also, for both clinical and non-clinical data, applicants for so-called "stand-alone" applications (e.g., biologics license applications (BLAs) submitted pursuant

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

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

[3] The FDA considers an ADC to be a combination product composed of a biological product constituent part and a drug constituent part (see 21 CFR 3.2(e)(1); 70 FR 49848, 49857-49858 (August 25, 2005; effective November 23, 2005)). As explained in Q.II.3 of the guidance for industry, *Questions and Answers on Biosimilar Development and the BPCI Act (Revision 2),* (September 2021), the Center for Drug Evaluation and Research considers submission of a BLA under section 351 of the PHS Act to provide the more appropriate application type for ADCs.

to section 351(a) of the Public Health Service Act (PHS Act)) generally must own or have a right of reference to all information used to support licensure of their applications.

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

A. ADCs

An ADC is generally composed of a small-molecule drug, also known as a payload, and an antibody or antibody fragment, conjugated together by a chemical linker. The antibody or antibody fragment (herein referred to as the antibody) is selected or engineered against a specific antigen of interest present on the target cell surface, which is ideally unique to the disease state being treated (e.g., a tumor-specific antigen). In general, when the antibody binds to its target antigen, the ADC is internalized through physiological mechanisms (e.g., endocytosis), at which point the payload is released via a specifically designed release mechanism (e.g., reduction, pH-dependent hydrolysis, enzyme-mediated linker cleavage). The released payload then exerts its effect in the targeted cell (e.g., the cells expressing the specific antigen of interest) while ideally minimizing the effect on non-targeted cells (e.g., the cells that do not express the specific antigen of interest). Given that the mechanism of action (MOA) of ADCs aims to deliver the payload directly to tissues guided by the target specificity, the systemic exposure of the payload can be relatively low compared to use of these payloads as oral and intravenous monotherapy.

The following terminology is used in this guidance:

- **ADC** – an antibody, or antibody fragment (herein referred to as the antibody) conjugated to at least one payload molecule via a chemical linker (i.e., drug to antibody ratio (DAR) of at least one).

- **Total antibody** – the collection of antibodies that are both unconjugated (i.e., not conjugated to any payload molecules) and conjugated to at least one payload molecule.

- **Unconjugated antibody** – a free antibody not conjugated to any payload molecules (i.e., DAR equal to 0).

- **Unconjugated payload** – a free small-molecule drug that is not conjugated to an antibody.

- **Chemical linker** – the linkage between the payload and the antibody.

- **Constituent parts of the ADC** – includes the total antibody, as defined above, the unconjugated payload, the pharmacologically active metabolite (if any), and the ADC catabolized products (if relevant).

- **Pharmacologically active metabolite** – a pharmacologically active metabolite from the metabolism of the unconjugated payload that impacts the efficacy and safety profile. Also see FDA's guidance entitled *Safety Testing for Metabolites* (March 2020) for additional definition of metabolites.

B. Key Considerations for ADC Dosing Strategies

ADCs combine the selectivity of an antibody for a specific target with the potency of a small-molecule drug. Therefore, selection of optimal dosing strategies for ADCs requires careful consideration of the differences between the pharmacokinetics (PK) and pharmacodynamics (PD) of the antibody and the payload, because the different constituent parts of the ADC can independently impact safety and/or efficacy. A relatively small increase in the systemic exposure of the cytotoxic payload and/or the ADC can cause significant adverse reactions that are dose limiting from a safety perspective. Due to these challenges, gaining a thorough understanding of the PK and PD of the ADC and its constituent parts early in development and their relationships to safety and efficacy outcomes is crucial to optimize the ADC dosage. The data contributing to this understanding could include findings from nonclinical studies.

1. Dosage Selection During Clinical Development

The FDA strongly encourages evaluating a broad dosage range that includes multiple dosage levels and/or dosing regimens (e.g., single or fractionated dosing) for ADCs in early drug development to fully characterize the relationship between the exposure of both the ADC and its active constituent parts to the safety and activity of the ADC. Assessing both fixed and weight-based dosing should also be considered when appropriate. Selection of the dosing strategy or strategies used in later stage development can be informed by exposure-response analyses using data from early clinical studies. In general, tolerability characterized in early development plays a key role in justifying the dosing strategy or strategies used in later stage development. Additionally, exposure-response analyses can be used to select dosing strategies for specific subsets of patients in pivotal studies (e.g., study participants with organ impairment). To help select dosing strategies for a pivotal study or studies and/or specific patient subsets, an integrated data analysis package from relevant nonclinical and clinical data, pharmacodynamic biomarker data and receptor occupancy (target engagement) data, and exposure-response analyses for efficacy and safety should be leveraged.

2. Considerations for Dosing Strategies for Intrinsic and Extrinsic Factors

It is challenging to determine the recommended dosage based on intrinsic and extrinsic factors (e.g., renal or hepatic impairment, DDIs) because the different constituent parts of the ADC can independently impact safety and/or efficacy. For example, modifying the ADC dosage in a specific patient subset to achieve a similar exposure of one constituent part (e.g., usually the payload) to that observed in the overall population could lead to altered ADC exposure and,

subsequently, altered efficacy. Hence, the labeling for ADCs could recommend avoiding use in a specific population.

The impact of intrinsic and extrinsic factors on PK, safety, and efficacy should be evaluated in ADC development programs to inform labeling, which should include risk mitigation strategies, as appropriate, for use in specific patient subsets.

Pharmacokinetic, efficacy, and safety information that can inform dosage recommendations for ADCs can be obtained from:

- Patients with organ impairment or interacting concomitant medications enrolled in the dose-escalation studies (e.g., as a staggered cohort at lower doses compared to patients with normal organ function or no interacting concomitant drug)

- Patients with organ impairment or interacting concomitant medications enrolled in safety and efficacy studies

- Dedicated organ impairment or DDI studies

Of note, enrollment of patients based on various intrinsic or extrinsic factors in safety and efficacy studies should be based on the absorption, distribution, metabolism, and excretion (ADME) of the payload and the safety/efficacy profile of the ADC in early studies. Eligibility criteria for patients with organ impairment in cancer clinical trials is outlined in the FDA's guidance entitled *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020). Also, while human mass balance studies might not be feasible with ADCs, efforts to assess or predict human elimination pathways of the payload can include assessment of excreted metabolites in urine and feces in early clinical trials, animal studies, and/or in vitro assays of the payload. See the relevant sections below for more information on intrinsic and extrinsic factors.

III. CLINICAL PHARMACOLOGY CONSIDERATIONS

A. Bioanalytical Approach

All bioanalytical methods should be validated and reported as outlined in the FDA guidance entitled *M10 Bioanalytical Method Validation* (November 2022). In general, beginning with first-in-human studies, the ADC and its constituent parts should be measured with validated assays. Later in development, the ADC, its constituent parts, and its pharmacologically active metabolites that are quantifiable in systemic circulation should be measured to inform exposure-response analyses as described in section III.B Dose- and Exposure-Response. Any decisions to exclude measurements of constituent parts of the ADC in later development should take into consideration:

- Their pharmacokinetic characteristics from early clinical trials (e.g., the correlation between the total antibody and ADC concentrations, the systemic exposure of the unconjugated payload, and pharmacologically active metabolites)

- Relevant nonclinical pharmacology, PK, or safety data (e.g., nonclinical data regarding the MOA of the ADC, pharmacologic activity of the unconjugated antibody, pharmacological activity of metabolites)

- Preliminary exposure-response data on the contribution of the ADC's constituent parts to safety and/or efficacy

For example, if the unconjugated payload is undetectable with a sufficiently sensitive assay, measuring the unconjugated payload may not be necessary. If the ADC only serves to selectively deliver the payload (i.e., acts as a carrier), and the total antibody concentrations are highly correlated to the ADC, quantifying the total antibody may not be necessary.

Of note, bioanalytical assays for the unconjugated payload should be sufficiently sensitive to detect small changes in systemic exposure that could be clinically meaningful. Additionally, if the antibody's target is shed into the systemic circulation to a significant extent, bioanalytical assays could be recommended to distinguish the target-unbound ADC (i.e., free) from the target-bound ADC. See section III.B Dose- and Exposure-Response for additional information.

The following is a list of some dedicated clinical pharmacology studies that describe when the ADC and its constituent parts should be considered for quantification via validated bioanalytical methods.

- For organ impairment studies, the ADC, the unconjugated payload, and pharmacologically active metabolites should be measured. The total antibody should be measured if mechanistically relevant. See section III.C.1 Organ Impairment for more information.

- For QTc assessments, measuring the unconjugated payload and pharmacologically active metabolites is usually sufficient. See section III.D QTc Assessment for more information.

- For DDI studies, measuring the unconjugated payload and pharmacologically active metabolites could be adequate if the unconjugated payload is detectable using a sufficiently sensitive bioanalytical assay. Also, if the antibody is expected to be mechanistically involved in a DDI either as an inhibitor, inducer, or a substrate,[4] measuring the ADC or total antibody in relevant studies could also be recommended. See section III.F DDIs for more information.

[4] Please see the FDA's guidance *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) for more information.

- For pharmacokinetic comparability studies (e.g., manufacturing process changes, formulation changes), concentrations of the ADC and its constituent parts should be measured.

B. Dose- and Exposure-Response

In addition to evaluating the dose-response relationship of the ADC, exposure-response analyses should be conducted for safety and efficacy with the ADC and its constituent parts. These analyses help support dosage selection and dosage adjustments as outlined by the FDA guidances, *Exposure-Response Relationships - Study Design, Data Analysis, and Regulatory Applications* (April 2003) and *Population Pharmacokinetics* (February 2022). Of note, ADC average DAR can be used as one constituent part in the analysis. In later development, justification can be provided for not conducting exposure-response analyses with an ADC constituent part (e.g., low systemic exposure of the payload or pharmacologically active metabolites, no pharmacological activity of the antibody, total antibody concentrations are highly correlated with that of the ADC). See sections II.B.1 Dosage Selection During Clinical Development and II.B.2 Considerations for Dosing Strategies for Intrinsic and Extrinsic Factors for more information.

Also, if the antibody target is known to shed into the systemic circulation to a clinically meaningful extent, exposure-response analyses should be conducted with the ADC and/or total antibody that is not bound to the shed target in circulation. Considerations for such analyses can include:

- The relative concentrations of the target-bound ADC compared to target-unbound ADC in circulation.

- Correlations between the target-bound ADC and target-unbound ADC concentrations.

- The potential for the target-bound ADC to retain pharmacological activity.

C. Intrinsic Factors

Intrinsic factors (e.g., renal or hepatic impairment, pharmacogenomics, body weight, age, sex, race, ethnicity) that have the potential to influence exposure of the ADC or its constituent parts should be evaluated in either: 1) clinical studies, through population pharmacokinetic analysis, or 2) dedicated studies. Some special considerations for organ impairment and pharmacogenomics are elaborated below.

1. Organ Impairment

The unconjugated payload and pharmacologically active metabolites, if any, can undergo renal or hepatic elimination. Impaired renal or hepatic function can lead to changes in unconjugated payload exposure that could alter the safety and/or efficacy profile of the ADC. Therefore, the impact of renal and hepatic impairment on the PK of the unconjugated payload should be assessed in all ADC development programs per the principles outlined in the FDA guidances

Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (May 2003).[5]

Assessing the effect of organ impairment on the exposure of the ADC or the total antibody could be relevant. For example, the ADC could be eliminated through the renal route if an antibody fragment is used, and the molecular weight of the ADC is less than 69 kDa. Also, altered ADC exposure has been observed in patients with hepatic impairment.[6]

The sponsor should provide a rationale for including or not including the ADC or its constituent parts in the organ impairment assessment. Recommending ADC dosage modifications for organ impairment, when appropriate, should be made by considering the pharmacokinetic, safety, and efficacy data in the target population. See sections II.B.1 Dosage Selection During Clinical Development and II.B.2 Considerations for Dosing Strategies for Intrinsic and Extrinsic Factors for more information.

A population pharmacokinetic approach can be used to assess the effects of organ impairment on the unconjugated payload, pharmacologically active metabolites, if any, and/or total antibody if patients with organ impairment are enrolled in pivotal studies, and pharmacokinetic data coupled with safety and efficacy information in those patients are available. Specifically, the FDA recommends:

- Sufficient ADME information of the unconjugated payload and pharmacologically active metabolites from non-clinical and early clinical studies to inform inclusion of varying degrees of organ impairment in pivotal studies. For additional information, refer to the FDA guidances *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020) and *Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies* (July 2020).

- Adequate pharmacokinetic sampling during pivotal studies to allow for accurate estimation of the effect of organ impairment on clearance of the unconjugated payload, pharmacologically active metabolite, and/or total antibody. Refer to the FDA guidance *Population Pharmacokinetics* (February 2022) for additional information on pharmacokinetic sampling.

- Sufficient safety and efficacy information in patients with organ impairment to understand the impact of an exposure change, if any. Of note, the number of enrolled patients with organ impairment to provide sufficient safety and efficacy information should be prospectively discussed with the FDA on a case-by-case basis.

[5] See also the draft FDA guidance *Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing* (September 2020). When final, this guidance will represent the FDA's current thinking on this topic.

[6] Sun Q, S Seo, S Zvada, C Liu, and K Reynolds, 2020, Does Hepatic Impairment Affect the Exposure of Monoclonal Antibodies?, Clin Pharm Ther, 107(5):1256-1262.

Dedicated studies in subsets of patients with organ impairment (e.g., a dose-escalation study, a pharmacokinetic study) can also be conducted to guide dosing recommendations for these patient subsets. The need for such a study and the study design is determined by characteristics of the ADC, such as:

- ADME and potential changes in the systemic exposure of the ADC and/or unconjugated payload (e.g., an expectation of a clinically significant change in the systemic exposure of the unconjugated payload could inform the need for a dedicated study)

- The nature of dose- or exposure-response relationships of the ADC with efficacy and of the unconjugated payload with safety and the anticipated clinical consequences of the systemic exposure changes to the ADC and/or unconjugated payload

- Safety signals that can be correlated with exposure changes detected in study participants included in efficacy and safety studies, especially those with organ impairment

2. Pharmacogenomics

Evaluation of genotype information on exposure or response to an ADC could be recommended as outlined in the FDA guidance *Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling* (January 2013). For ADCs, a recommendation for a pharmacogenetic evaluation depends on ADME information, the systemic exposure of the unconjugated payload, and the role of the antibody in the MOA of the ADC, for example:

- Genetic variants and/or expression of the target for the antibody can affect patient response to the ADC.

- Functional genetic variants of metabolic enzymes (e.g., cytochrome P450 2D6 (CYP2D6)) and transporters (e.g., breast cancer resistant protein (BCRP)) can impact the pharmacokinetic clearance of the unconjugated payload.

- Functional genetic variants of Fc-gamma receptors (FcγRs) can affect the binding of IgG molecules to FcγRs, leading to altered antibody-dependent cellular cytotoxicity (ADCC), which can be a contributing factor to the MOA of the ADC.

D. QTc Assessment

An assessment of QT prolongation risk and a proposed QT assessment plan should be submitted for all ADC development programs as outlined by the FDA guidances, *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2012) and *E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential--Questions and Answers* (August 2022) as well as the *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers (R3)* (June 2017). In general, the antibody part of the ADC has a low likelihood of direct ion channel interactions and QT assessment for this

component is not necessary unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or nonclinical studies. Therefore, the QTc assessment should focus on the unconjugated payload, linker, and any pharmacologically relevant metabolites, and the characterization of QT prolongation risk should be conducted similar to that for a small-molecule drug. All proposals in the QT assessment plan should be adequately justified and discussed with the Agency.

E. Immunogenicity

An immune response to an ADC can be generated to any part of the ADC, including the antibody, the conjugated payload, or epitopes created by the conjugation linker. Given that ADCs generally have a relatively narrow therapeutic range, it is important to evaluate immunogenicity to ADCs and the potential impact on PK, safety and efficacy. A multitiered immunogenicity assessment should be conducted as outlined in the FDA guidances *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014) and *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019), including a confirmatory assessment detecting anti-drug antibodies (ADAs) against the ADC. Additionally, it could be appropriate to develop multiple assays to measure the immune responses to the constituent parts of the ADC, such as additional epitopes or domains resulting from the conjugation of the constituent parts.

F. DDIs

ADC development programs should include an in vitro DDI risk assessment for the unconjugated payload and relevant constituent parts of the ADC as an inhibitor, inducer, and a substrate using both CYP enzyme- and transporter-related assays as outlined in the FDA guidance *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020). Based on in vitro characterization of the metabolic enzymes and transporters involved in the clearance of the payload and its pharmacologically active metabolites, payload toxicity, and/or the potential contribution to efficacy, the FDA could recommend that the sponsor conduct an in vivo DDI evaluation of the unconjugated payload as a substrate. Characterizing the systemic exposure of the unconjugated payload, though possibly relatively low, is important for determining its DDI potential as an inhibitor and inducer.

In vivo DDI characterization should be conducted as outlined in the FDA guidance *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020). Conducting an in vivo DDI characterization and developing a risk mitigation strategy due to DDIs should be based on early characterization of in vitro DDIs and an understanding of the concomitant medications of the target patient population. Additionally, physiologically based pharmacokinetic modeling could be appropriate as outlined in the FDA's guidance *Physiologically Based Pharmacokinetic Analyses — Format and Content* (September 2018).

Alternatively, adequate in vivo DDI characterization could be achieved from large clinical studies when prospectively designed. For specific considerations when performing such nested-DDI assessments please refer to the FDA guidances, *Clinical Drug Interaction Studies —*

Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020) and *Population Pharmacokinetics* (February 2022).

Also, under certain circumstances, the FDA could recommend an assessment of the DDI potential for the antibody component. For more information, please see the FDA guidance *Drug-Drug Interaction Assessment for Therapeutic Proteins* (June 2023). A DDI evaluation should generally be considered if the ADC is administered with:

- Medications that share the same pharmacodynamic target with the ADC
- Medications that block or interfere with the interaction between an ADC containing an Fc region of human IgG and FcRn
- Immunosuppressors if the ADC's PK are affected by immunogenicity