Clinical Pharmacology Considerations for Antibody-Drug Conjugates

Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Clinical Pharmacology

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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 ADC development programs, including bioanalytical methods, dosing strategies, dose- and exposure-response analysis, intrinsic factors, QTc assessments, immunogenicity, and drug-drug interactions (DDIs).[2]

This guidance specifically outlines clinical pharmacology considerations of ADC development programs and references other relevant guidances when appropriate.[3] 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,[4] 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

[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] This guidance provides recommendations for ADCs with a cytotoxic small molecule drug or *payload*, which, thus far, are primarily in oncology indications. The principles discussed in this guidance might not completely be applicable to the development of other types of ADCs and should be discussed with the FDA.

[3] 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.

[4] 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 1)*, (December 2018), 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.

requirements and development programs for a particular ADC should be addressed to the appropriate FDA review division.

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II. BACKGROUND

A. ADCs

An ADC is composed of one type of 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 either upon exposure to the low pH of the lysosome or by degradation of the antibody/linker by lysosomal enzymes. 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 a specific site, the systemic exposure of the payload can be relatively low compared to use of these payloads as oral and intravenous monotherapy.

The following terminology will be 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 (e.g., 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 (DAR equal to 0)

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

- **Chemical linker** – the linkage between the small-molecule drug or payload and the antibody

- **Constituent parts of the ADC** –includes the total antibody and the unconjugated payload

- **Pharmacologically active metabolite** – a pharmacologically active metabolite from the metabolism of the unconjugated small molecule drug or payload that contributes to efficacy and safety. Also see FDA's guidance entitled *Safety Testing for Metabolites* (March 2020).

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. Given that payloads are cytotoxic, a relatively small increase in the systemic exposure of the payload can cause significant adverse reactions. Therefore, the toxicity of the payload is dose limiting from a safety perspective. Given 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 dose. The data contributing to this understanding can include the nonclinical program.[5]

1. Dose Selection During Clinical Development

The FDA strongly encourages broad dose-ranging in first-in-human studies for ADCs and the selection of multiple-dose levels for evaluation in early clinical development (e.g., cohort expansion in Phase I or Phase II studies) to characterize the safety and activity of the ADC. Overall tolerability in early studies should also be considered in the selection of the dosing strategies for a pivotal study or studies. Information from exposure-response analyses using data from these early clinical studies - that evaluates the relationship of the exposure of both the ADC and its constituent parts to safety and/or efficacy - can also be used to select dosing strategies for a pivotal study or studies. Furthermore, 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). Additional supportive data, such as pharmacodynamic biomarker data and receptor occupancy/target engagement data, should be leveraged to help select dosing strategies for a pivotal study or studies and/or specific patient subsets.

2. Considerations for Dosing Strategies for Intrinsic and Extrinsic Factors

Dose adjustments based on intrinsic and extrinsic factors (e.g., renal or hepatic impairment, DDIs) are challenging because the different constituent parts of the ADC can independently contribute to safety and/or efficacy. For example, adjusting the dose of the ADC in a specific

[5] Please see the FDA guidance entitled *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers* (June 2018).

patient subset to match the exposure of one constituent part (e.g., usually the payload) in the overall population could lead to altered ADC exposure and, subsequently, altered efficacy. However, the impact of the intrinsic and extrinsic factors on PK, safety, and efficacy should always be evaluated in ADC development programs to inform labeling instructions for use in specific patient subsets. For example, *no dose adjustment* would be recommended for a specific population where the PK and risk-benefit profile are not expected to be significantly changed from the overall population. Conversely, labeling recommendations could include *avoid dosing.* in a specific population where adverse events are expected to increase in severity and frequency in comparison to the overall population, but the dosage cannot be adjusted without adversely impacting efficacy.

Pharmacokinetic, efficacy, and safety information for recommendations on dose adjustments can be obtained from:

(1) 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 drug)

(2) Patients with organ impairment or interacting concomitant medications enrolled in safety and efficacy studies

(3) 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. 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 or animal studies and in vitro assays of the payload. See the relevant sections below for more information on intrinsic and extrinsic factors.

III. CLINICAL PHARMACOLOGY CONSIDERATIONS

Given that ADCs are composed of an antibody, a chemical linker, and a payload, evaluating the clinical pharmacology of ADCs can be more complex than for small or large molecules alone.

A. Bioanalytical Approach

All bioanalytical methods should be validated and reported as outlined in the FDA's guidance entitled *Bioanalytical Method Validation* (May 2018). In general, beginning with first-in-human studies, the ADC, its constituent parts, and its pharmacologically active metabolites, if any, should be measured. 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 or pharmacologically active metabolites 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, pharmacokinetics, 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, the FDA may not recommend measuring the unconjugated payload. If the antibody constituent part only serves to selectively deliver the payload (i.e., acts as a carrier), and the total antibody concentrations are highly correlated to the ADC, the FDA may not recommend measuring the unconjugated antibody.

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 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, its constituent parts, and pharmacologically active metabolites, if any, 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. If the exposure of the unconjugated payload is low and cannot be quantified, a time-based analysis, where detection of the ADC will verify administration of the product, should be conducted. 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 bioanalytical assays exhibit a sensitivity that adequately characterizes the relatively low systemic exposure of the unconjugated payload. Also, if the antibody is expected to be mechanistically involved in a DDI either

as a victim or perpetrator,[6] measuring the ADC or total antibody in relevant studies could also be recommended. See section III.F DDIs 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, its constituent parts, and pharmacologically active metabolites, if any. These analyses help support dose selection and dose adjustments as outlined by the FDA's guidance, *Exposure-Response Relationships - Study Design, Data Analysis, and Regulatory Applications* (April 2003). In later development, justification can be provided for not conducting exposure-response analyses with an ADC constituent part or pharmacologically active metabolites (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 Dose 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 significant extent, exposure-response analyses should only 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 (free) ADC in circulation

- Correlations between the target-bound ADC and target-unbound (free) ADC concentrations

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

C. Intrinsic Factors

Intrinsic factors (e.g., renal or liver impairment, pharmacogenomics, body weight, age, gender, race) that have the potential to influence exposure of the ADC, its constituent parts, and pharmacologically active metabolite, if any, 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.

[6] Victim is defined as an investigational product that is a substrate of metabolizing enzymes. Perpetrator is defined as an investigational product that is an inhibitor or inducer of a metabolizing enzyme. Please see the FDA's guidance *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) for more information.

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's guidance *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003). [7]

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.[8]

The sponsor should provide a rationale for including or not including the ADC, its constituent parts, and pharmacologically active metabolites, if any, in the organ impairment assessment. Recommending ADC dose adjustments 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 Dose Selection in 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 other ADC constituent parts 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, pharmacologically active metabolites and/or other ADC constituent parts, from non-clinical[9] and early clinical studies to inform inclusion of varying degrees of organ impairment in pivotal studies. For additional information, refer to the FDA's 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).

[7] See also the 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.

[8] 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.

[9] Please see the FDA guidance entitled *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers* (June 2018).

- 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 other ADC constituent parts. Refer to the FDA's 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.

Dedicated studies in subset 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. Whether or not to recommend - and the design of - a dedicated study 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 lead to a recommendation of a dedicated study)

- The dose- or exposure-response relationship of the ADC with efficacy and of the unconjugated payload with safety (e.g., a shallow exposure-response relationship for efficacy with a steep exposure-response relationship for safety would likely allow for testing a reduced starting dose in a dedicated study without compromising the risk/benefit ratio)

- 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's 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.

- Unconjugated payload could be metabolized or transported by metabolizing enzymes or transporters in the liver, which can exhibit functional genetic variants that impact the metabolism rate (e.g., cytochrome P450 2D6 (CYP2D6), or breast cancer resistant protein (BCRP)).

- 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's guidance *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2012). In general, the unconjugated payload is the only constituent part of the ADC considered to have potential risk for QT prolongation. Therefore, the QT assessment plan for an ADC development program should consider all the factors that would be part of an QT assessment for a small-molecule drug. Any analysis recommended for the QT assessment should be determined using information about the payload's ADME characteristics. Of note, electrocardiogram (ECG) monitoring during early clinical trials coupled with a sufficiently sensitive bioanalytical assay for the unconjugated payload could be deemed a sufficient QT assessment. If exposure of the unconjugated payload is low and cannot be quantified, a time-based analysis, where detection of the ADC will verify administration of the product, should be conducted.

E. Immunogenicity

An immune response to an ADC can be generated to any constituent part of the ADC, including the antibody, the payload, or epitopes created by the conjugation linker. Given that ADCs generally have a relatively narrow therapeutic window, 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 pharmacologically active metabolites, if any, as both a perpetrator and a victim using both CYP enzyme- and transporter-related assays as outlined in the FDA's 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 disposition and elimination 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 victim. Characterizing the systemic exposure of the unconjugated

payload, though possibly relatively low, is important for determining its DDI potential as a perpetrator.

In vivo DDI characterization should be conducted as outlined in the FDA's 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).

Of note, adequate in vivo DDI characterization could be achieved from the pivotal efficacy study when prospectively designed with the following considerations:

- Detailed classification of concomitant medications as sensitive substrates (if the unconjugated payload and/or pharmacologically active metabolites have the potential as a perpetrator based on in vitro risk evaluation), and strong or moderate inducers or inhibitors
- Timing of concomitant medications relative to the administration of the therapeutic product
- Dosing regimen and route of the concomitant medications
- Prespecified analysis
- Adequate pharmacokinetic sampling and measurement of the victim concomitant medications

Also, under certain circumstances, the FDA could recommend an assessment of the DDI potential for the antibody component.[10] In summary, a DDI evaluation could be recommended 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

Although there could be limitations in the ability to modify the dose of an ADC, the sponsor should seek to understand whether a drug can be safely used concomitantly with the ADC.

[10] For more information, please see the FDA guidance *Drug-Drug Interaction Assessment for Therapeutic Proteins* (August 2020). When final, this guidance will represent the FDA's current thinking on this topic.