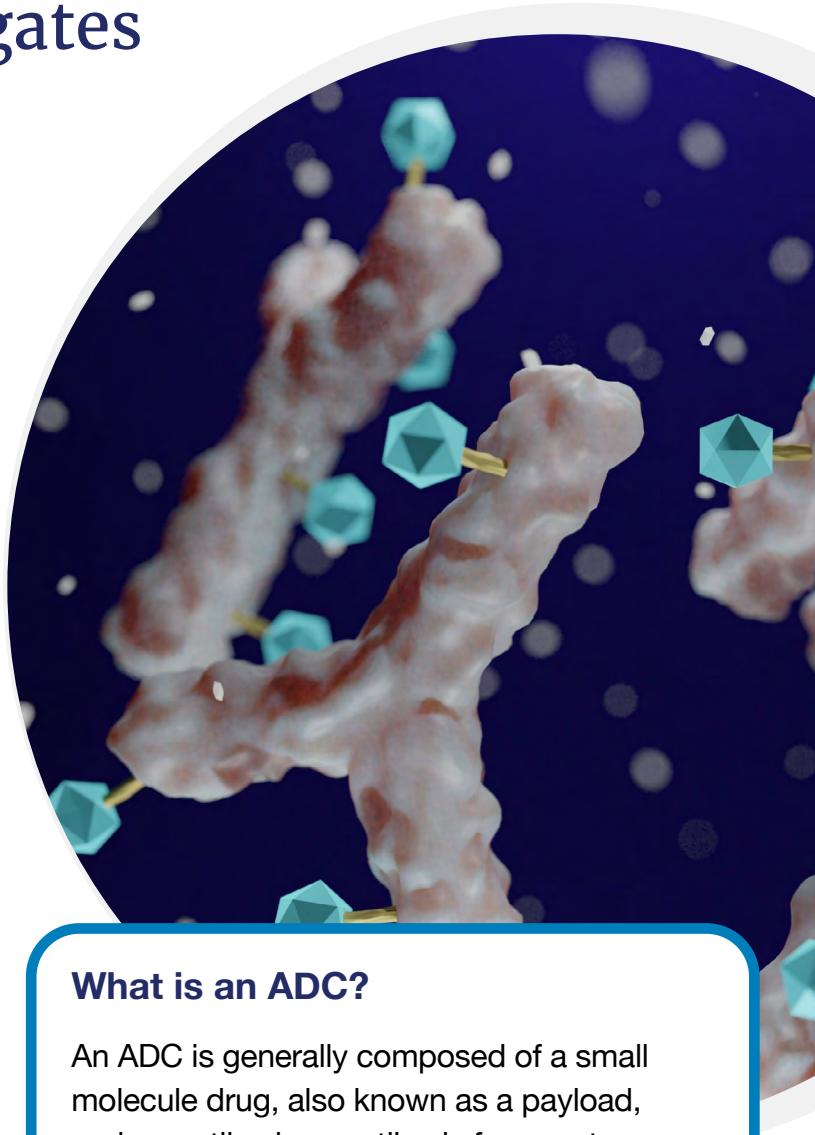
U.S. FOOD & DRUG ADMINISTRATION

Guidance Snapshot

Clinical Pharmacology Considerations for Antibody–Drug Conjugates

Final Guidance for Industry



What is Recommended in This Guidance?

This guidance discusses clinical pharmacology considerations for the development of antibody-drug conjugates (ADCs) with small molecule drugs that are cytotoxic.

Why Is This Guidance Important?

ADCs are distinct from both biologics and small molecule drugs. There are special considerations for ADCs due to their unique structure and mechanism of action. This guidance provides comprehensive clinical pharmacology recommendations specific for ADCs to support the growing number of ADCs under development. Topics covered in the guidance include dosing strategies, the bioanalytical approach, intrinsic factors, drug-drug interactions (DDIs), and more.

What is an ADC?

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. As such, an ADC has multiple constituent parts. ADCs are designed to target specific cells, such as cancer cells, while minimizing effects on non-targeted cells. When the antibody binds to its target antigen on the cell surface, the ADC is internalized and the cytotoxic payload is released to kill the tumor cells.

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about clinical pharmacology considerations for antibody-drug conjugates, **read the guidance**. To see additional Guidance Snapshots, **check out the pilot program**.

Clinical Pharmacology Considerations During ADC Development

Dosing Strategies

The payload and antibody parts of an ADC can independently contribute to safety and/or efficacy. Therefore, selection of optimal dosing strategies for ADCs requires careful consideration for the pharmacokinetics (PK) and pharmacodynamics of the ADC, the antibody, and the payload. This guidance recommends assessing a broad dose range early during drug development to inform dose selection of the ADC.

Bioanalytical Approach

The bioanalytical assay should be validated. The guidance provides recommendations regarding which analytes should be measured in different dedicated clinical pharmacology studies. If the antibody's target is shed into the systemic circulation, the assay should distinguish the target-bound vs. target-unbound ADC.

Dose- and Exposure-Response

Exposure-response analyses support dosage selection and dosage adjustments. Evaluation of the ADC and its constituent parts early in drug development is recommended to fully characterize the exposure-response relationship. If the target is known to shed into circulation, exposure-response analyses should be conducted with the ADC and/or total antibody that is not bound to the shed target in circulation as well as those bound to the shed target in circulation.

Intrinsic Factors

Any intrinsic factor that has the potential to affect exposure of ADC or its constituent parts should be evaluated. These intrinsic factors can be evaluated through population PK analysis or in dedicated studies. Although dosage adjustment is challenging for ADCs, the assessment of intrinsic factors (e.g., organ impairment) is essential to inform labeling strategy, such as, to avoid dosing in a specific population.

QTc Assessment

QTc assessment is recommended for all ADC development programs. In general, the antibody part of ADC has a low likelihood of direct ion channel interactions; therefore, the QTc assessment should focus on the unconjugated payload, linker, and any pharmacologically relevant metabolites. The principles for characterization of QT prolongation risk are similar to those for small-molecule drugs.

Immunogenicity

It is important to evaluate immunogenicity to ADCs and the potential impact on PK, safety, and efficacy given that ADCs generally have a relatively narrow therapeutic range. A multi-tiered immunogenicity assessment is recommended. In addition, multiple assays may be needed to evaluate where the anti-drug antibodies bind to.

Drug-Drug Interactions

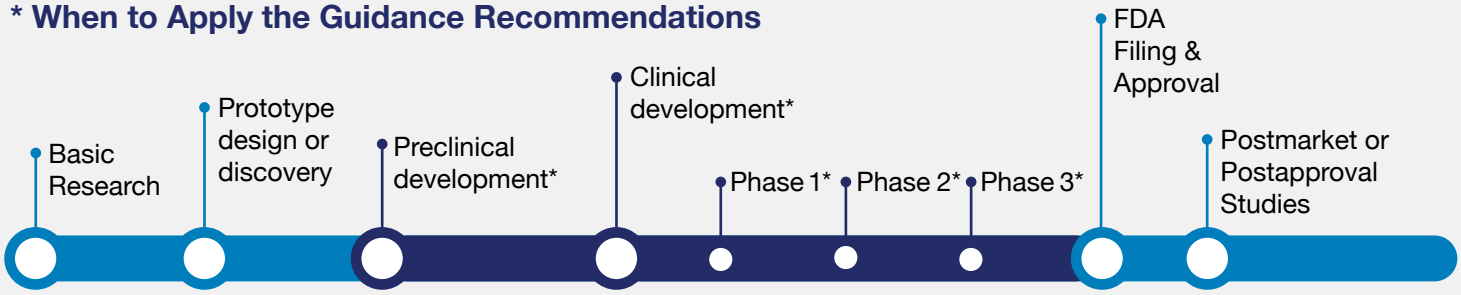
An in vitro assessment of DDI risk associated with drug metabolizing enzymes and/or transporters should be conducted for the unconjugated payload and relevant ADC constituent parts, both as a precipitant and as a substrate. In vivo studies may be recommended by the FDA based on the outcomes of the in vitro characterization. Assessment of the unconjugated payload as a substrate can be recommended even if systemic exposure is low, as a relatively small increase in systemic exposure of the cytotoxic payload could have an impact on safety.

Background of This Guidance

This is FDA's first guidance document providing clinical pharmacology recommendations specifically for ADCs. FDA has accumulated decades of experience evaluating a large variety of ADC applications and has approved 11 ADCs for oncology as of January 2024. This guidance provides FDA's current thinking regarding the clinical pharmacology considerations to facilitate the development and approval of ADCs. ADCs are subject to all pertinent laws and regulations for biological products. Given that ADCs also include a small-molecule drug component, there are recommendations that are applicable to ADCs that would not necessarily apply to other biological products.

Drug Development Timeline

*** When to Apply the Guidance Recommendations**



Recommendations in the guidance are applicable from preclinical development through clinical development: Information and data collected in preclinical assessment and early clinical studies will inform the development strategy and design of studies in the later stages of ADC development programs. For example, in vitro DDI risk assessement for the unconjugated payload uisng both drug metabolizing enzyme- and transporter-related assays will inform the need for and design of in vivo DDI studies. Absorption, distribution, metabolism, and excretion information of the unconjugated payload from preclinical and early clinical studies will inform whether organ impairment should be evaluated in pivotal studies or in dedicated studies.

Guidance Recap Podcast

Hear highlights from FDA staff

Speakers:
Qin Sun, PhD, Biologics Lead, and Sarah Ridge, PhD, Policy Analyst, in the Center for Drug Evaluation and Research (CDER),Office of Clinical Pharmacology.

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