U.S. FOOD & DRUG ADMINISTRATION

Guidance Snapshot

# Drug-Drug Interaction Assessment for Therapeutic Proteins

## Final Guidance for Industry

## What is recommended in this guidance?

This final guidance provides recommendations on evaluating the drug-drug interaction (DDI) potential for an investigational therapeutic protein (TP). This guidance focuses on when TP DDI studies could be warranted and the relevant study type and study design. The DDI evaluation for antibody-drug conjugates is covered by a separate guidance: *Clinical Pharmacology Considerations for Antibody-Drug Conjugates* (February 2022).[1]

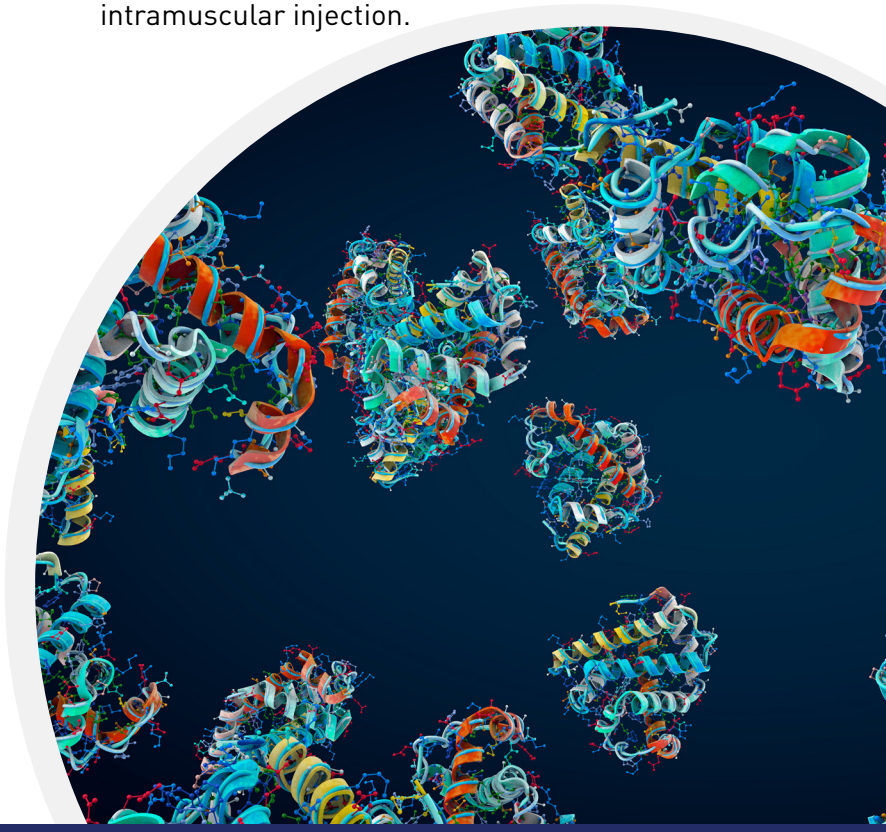
## Why is this guidance important?

Patients frequently use more than one medication at a time. Unanticipated, unrecognized, or mismanaged DDIs could lead to increased adverse events or decreased efficacy associated with prescription TP use. The guidance provides recommendations for evaluating DDIs during TP development and outlines when and how TP DDIs should be evaluated.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page.

## What are TPs?

TPs are large, complex amino acid-based molecules derived from living cells. Currently, FDA defines the term "protein" as any alpha amino acid polymer with a specific defined sequence that is >40 amino acids in size. TPs include purified monoclonal antibodies, cytokines, enzymes, and other novel proteins. They are usually administered through intravenous, subcutaneous, or intramuscular injection.



Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about drug-drug interaction assessment for therapeutic proteins, read the guidance.

## Background About the Guidance

With the continued market growth and increased clinical use of TPs, it is important to understand the nature of and the potential for DDIs with these products. This guidance supplements the final FDA guidances for industry *In Vitro Drug Interaction Studies–Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) and *Clinical Drug Interaction Studies–Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) by providing a systematic, risk-based approach to determining the need for DDI studies for TPs. Although this guidance applies to TPs, the general concepts could be applicable to other biological products, including biological products regulated by CBER such as cellular and gene therapies.

## Example scenarios in which DDI studies could be warranted:

- **Mechanisms Related to Proinflammatory Cytokines**
  - TPs that are proinflammatory cytokines or that cause increases in proinflammatory cytokine levels can downregulate cytochrome P450 (CYP) enzymes that metabolize certain drugs
  - TPs that reduce cytokine levels can also impact CYP activity, but background levels of proinflammatory cytokines differ by disease and can influence the magnitude of effect
- **Mechanisms Unrelated to Proinflammatory Cytokines**
  - TPs that affect physiological processes (e.g., delayed gastric emptying)
  - TP disposition, distribution, or binding interactions can be impacted by concomitantly administered medications or other TPs
  - Concomitantly administered immuno-suppressors can affect the immunogenicity and pharmacokinetics of a TP

## Types of DDI assessments

- **In Vitro and Animal studies:** may help provide mechanistic information
- **Clinical Studies**
  - **Parallel Design:** might be appropriate when evaluating the effect of other drugs on a TP and when the TP has a long half-life.
  - **Single Sequence Crossover:** can evaluate the effect of the TP on other drug(s)
  - **Population PK Modeling:** pprospective designs can assess the effect of other drugs on a TP, or the effect of a TP on other drugs if necessary data are collected
  - **Other Modeling Approaches (e.g., physiologically based PK modeling)**[2]

[2] This is an emerging area, and sponsors are encouraged to discuss the proposed approach with FDA.

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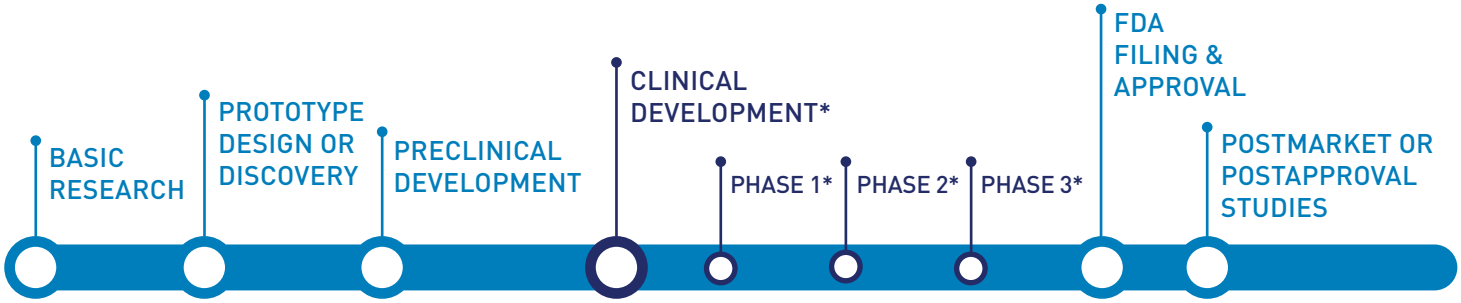
# Labeling Recommendations

Prescribing Information must include a summary of essential DDI information needed for the safe and effective use of the drug by the health care provider. For specific requirements and recommendations regarding how to incorporate DDI information in labeling, refer to 21 CFR 201.57 and the following FDA guidances:

- *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013)
- *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011)
- *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016)
- *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2014)

## Drug Development Timeline

### When to Apply the Guidance Recommendations




### Apply to Clinical Development Phases 1 through 3:

Sponsors should consider the DDI risk of their TPs early in clinical development and summarize their DDI evaluation program at milestone meetings with the FDA. Potential discussion topics at these meetings include the need for and planning, timing, and study design of DDI evaluations for the investigational TP. Currently in vitro or animal data have not been predictive of the potential for clinical DDI with TPs, although some data could provide mechanistic understanding of the DDI potential of a TP.

### Guidance Recap Podcast

Hear highlights from FDA staff

**Speaker(s):** Elimika Pfuma Fletcher, PhD, and Qin Sun, PhD,
Policy Leads in the Center for Drug Evaluation and Research, Office of Clinical Pharmacology

**Click here to listen**

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To learn more about drug-drug interaction assessment for therapeutic proteins, **read the guidance**.
To see additional Guidance Snapshots, **check out the pilot program**.