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# Drug-Drug Interaction Assessment for Therapeutic Proteins Guidance for Industry

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**June 2023  
Clinical Pharmacology**

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# **Drug-Drug Interaction Assessment for Therapeutic Proteins Guidance for Industry<sup>1</sup>**

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**

The purpose of this guidance is to help sponsors of investigational new drug (IND) applications and applicants of biologic license applications (BLAs) determine the need for drug-drug interaction (DDI) studies for a therapeutic protein by providing recommendations for a systematic, risk-based approach.<sup>2,3</sup>

For this guidance, a therapeutic protein refers to a protein that is being developed for licensure, or is licensed, as a biological product under section 351 of the Public Health Service Act (42 U.S.C. 262).<sup>4,5</sup> Therapeutic proteins include purified monoclonal antibodies, cytokines, enzymes, and other novel proteins for in vivo use. Therapeutic proteins do not include proteins intended to act as vaccines or allergenic products, cellular and gene therapy products, and/or human cells, tissues, and cellular and tissue-based products.<sup>5</sup> Although this guidance applies to therapeutic proteins, many of the general principles may be applicable to other biological products, such as novel products regulated by CBER (e.g., cellular and gene therapies). Due to the evolving knowledge of novel products, sponsors should consult corresponding review divisions for detailed information regarding a specific DDI assessment.

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<sup>1</sup> This guidance has been prepared by the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research in collaboration with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

<sup>2</sup> Schrieber SJ, EP Fletcher, XF Wang, YM Wang, S Sagoo, R Madabushi, SM Huang, and I Zineh, 2019, Considerations for Biologic Product Drug–Drug Interactions: A Regulatory Perspective, *Clin Pharmacol Ther*, 105:1332-1334.

<sup>3</sup> Hereafter, the term *sponsors* will refer to either applicants or sponsors.

<sup>4</sup> Section 351 of the Public Health Service Act, 42 U.S.C. § 282.

<sup>5</sup> More information on therapeutic proteins regulated by CDER and CBER can be found on the FDA web page *Transfer of Therapeutic Products to the Center for Drug Evaluation and Research* available at: <https://www.fda.gov/combination-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research>.

## ***Contains Nonbinding Recommendations***

This guidance supplements the FDA guidances entitled *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* and *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).<sup>6,7</sup>

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 guidance means that something is suggested or recommended, but not required.

## **II. CONSIDERATIONS FOR ASSESSING DDIs FOR THERAPEUTIC PROTEINS**

When evaluating the potential for a DDI between a therapeutic protein and small molecules or between therapeutic proteins, sponsors should take into account various factors including the potential mechanism for the interaction, disease type and severity (if the DDI mechanism is related to the disease condition), biological product type, clearance pathways of the therapeutic protein, and commonly co-administered drugs in the proposed patient population(s).<sup>8,9</sup>

Below are examples for which DDI studies of a therapeutic protein could be warranted. This list is not all-inclusive, as the development of novel therapeutic proteins will continue to inform the DDI risk. Also, refer to the decision tree in the Appendix.

### **A. Mechanisms Related to Proinflammatory Cytokines**

Therapeutic proteins that are proinflammatory cytokines (e.g., peginterferon) or therapeutic proteins that cause increases in proinflammatory cytokine levels (e.g., IL-6) can downregulate the expression of cytochrome P450 (CYP) enzymes (e.g., blinatumomab), thereby decreasing the

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<sup>6</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

<sup>7</sup> For recommendations on assessing the DDI potential of antibody-drug conjugates, please refer to the FDA draft guidance entitled *Clinical Pharmacology Considerations for Antibody-Drug Conjugates* (February 2022). When final, this guidance will represent the Agency’s current thinking on this topic.

<sup>8</sup> Kraynov E, SW Martin, S Hurst, OA Fahmi, M Dowty, C Cronenberger, CM Loi, B Kuang, O Fields, S Fountain, M Awwad, and D Wang, 2011, How Current Understanding of Clearance Mechanisms and Pharmacodynamics of Therapeutic Proteins Can Be Applied for Evaluation of Their Drug-Drug Interaction Potential, *Drug Metab and Disp*, 39:1779-1783.

<sup>9</sup> Jing X, P Ji, SJ Schrieber, EP Fletcher, C Sahajwalla, 2020, Update on Therapeutic Protein-Drug Interaction: Information in Labeling, *Clin Pharmacokinet*, 59:25-36.

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metabolism of drugs that are CYP substrates and increasing their exposure levels.<sup>10</sup> Conversely, therapeutic proteins that reduce cytokine levels (e.g., TNF inhibitors) can relieve the CYP downregulation from an inflammatory environment (e.g., rheumatoid arthritis), thereby increasing CYP expression and activity and reducing exposure of drugs that are CYP substrates.

Although there are data suggesting potential effects of cytokines on transporters based on information from in vitro assays or animal models, the translation to clinical significance is unknown.<sup>11</sup> Investigating the potential for DDIs between cytokines or products that modulate cytokines and transporters in clinical studies will help inform risk mitigation strategies.

### *1. Therapeutic Protein is a Proinflammatory Cytokine*

Sponsors should evaluate the DDI potential for therapeutic proteins that are proinflammatory cytokines (see Appendix).

### *2. Therapeutic Protein is a Proinflammatory Cytokine Modulator*

- a. Therapeutic protein causes an increase in proinflammatory cytokine levels

The increase in cytokine levels following administration of a therapeutic protein can be transient or persistent. Transient elevation of cytokines might not lead to a clinically relevant interaction. Sponsors should determine the time course and extent of any increase in cytokine levels in clinical studies to inform whether a DDI study is warranted, the design of a study, and an appropriate risk mitigation strategy, if necessary. If the sponsor determines that the DDI potential of a therapeutic protein is low, the sponsor should discuss that with the appropriate FDA review division and provide a justification for this determination (see Appendix).

- b. Therapeutic protein modulates proinflammatory cytokines in conditions associated with elevated cytokine levels

Levels of proinflammatory cytokines differ by disease and severity of disease, leading to variability in CYP expression, which makes it challenging to design a DDI study that can be extrapolated beyond the study population. Hence, the labeling for such proinflammatory cytokine modulators should include language indicating the potential for a DDI in conditions associated with elevated cytokine levels.

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<sup>10</sup> Lee J, L Zhang, AY Men, LA Kenna, and SM Huang, 2010, CYP-Mediated Drug-Therapeutic Protein Interactions: Clinical Findings, Proposed Mechanisms and Regulatory Implications, *Clin Pharmacokinet*, 49:295-310.

<sup>11</sup> Cressman AM, V Petrovic, and M Piquette-Miller, 2012, Inflammation-mediated Changes in Drug Transporter Expression/activity: Implications for Therapeutic Drug Response, *Expert Rev Clin Pharmacol*, 5:69-89.

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Sponsors should provide justification for the exclusion of labeling language indicating the potential for a DDI if the data support that the potential for clinically significant DDI is low.<sup>12,13</sup> Examples for justifications could include a discussion of:

- DDI effects observed with other agents or the same agent in other disease states with similar or more inflammatory burden
- Differences in exposure levels of sensitive CYP substrates in healthy subjects versus the indicated population considering other covariates
- Magnitude of cytokine modulation by the therapeutic protein

Alternatively, sponsors can assess the DDI potential in a clinical study to further inform labeling. The clinical study can be a stand-alone DDI study or a nested DDI study as part of a larger clinical study in which the primary objective is not to evaluate DDIs (see section III.C). The disease type and severity and dosage(s) are important considerations. If a therapeutic protein is being developed for multiple indications, the potential for DDIs should be evaluated in patients with the indication manifesting the most severe inflammatory burden.<sup>12</sup>

### **B. Mechanisms Unrelated to Proinflammatory Cytokines**

There are observed or postulated DDIs with therapeutic proteins that are not caused by proinflammatory cytokines. Depending on the expected mechanism of the DDI, sponsors should evaluate the effect of a therapeutic protein on other drugs or the effect of other drugs on the therapeutic protein. Scenarios in which DDI evaluation should be considered include:

- A therapeutic protein that affects human physiological processes (e.g., GLP-1 receptor agonists such as dulaglutide and albiglutide result in delayed gastric emptying) and thereby alters the pharmacokinetic profiles of co-administered drugs. In such cases, sponsors should evaluate the potential for a therapeutic protein to affect the other drug(s).
- A concomitantly administered medication that impacts the distribution of the therapeutic protein to the site of target<sup>14,15</sup> or the target-mediated disposition of the therapeutic

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<sup>12</sup> Coutant DE and SD Hall, 2018, Disease-Drug Interactions in Inflammatory States Via Effects on CYP-Mediated Drug Clearance, *J Clin Pharmacol*, 58:849-863.

<sup>13</sup> Sathe AG, AA Othman, MF Mohamed, 2021, Therapeutic Protein Drug Interaction Potential in Subjects With Psoriasis: An Assessment Based on Population Pharmacokinetic Analyses of Sensitive Cytochrome P450 Probe Substrates, *J Clin Pharmacol*, 61:307-318.

<sup>14</sup> Abuqayyas L and JP Balthasar, 2012, Pharmacokinetic mAb-mAb Interaction: Anti-VEGF mAb Decreases the Distribution of Anti-CEA mAb into Colorectal Tumor Xenografts, *AAPS J*, 14:445-455.

<sup>15</sup> Pastuskovas CV, EE Mundo, SP Williams et al, 2012, Effects of Anti-VEGF on Pharmacokinetics, Biodistribution, and Tumor Penetration of Trastuzumab in a Preclinical Breast Cancer Model, *Mol Cancer Ther*, 11:752-762.

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protein.<sup>16</sup> In such cases, depending on the role of the therapeutic protein in the DDI, sponsors should evaluate the DDI potential of the therapeutic protein to affect the other drug(s) or be affected by the other drug(s).

- A concomitantly administered therapeutic protein that affects another therapeutic protein's interaction with the FcRn (e.g., saturating, blocking, or interfering with the interaction between therapeutic proteins containing an Fc region of human IgG and FcRn) and decreases the exposure of the therapeutic protein.<sup>17,18</sup> In such cases, depending on the role of the investigational therapeutic protein in the DDI, sponsors should evaluate the DDI potential of the therapeutic protein to affect the other drug(s) or be affected by the other drug(s).
- A concomitantly administered immunosuppressor with a therapeutic protein whose pharmacokinetics are affected by immunogenicity (e.g., methotrexate on the clearance of adalimumab).<sup>19,20</sup> In such cases, the potential of the other drug to affect the therapeutic protein should be evaluated. This type of DDI evaluation can be difficult to prospectively design, and as such, a descriptive analysis can often be considered adequate.

### **III. TYPES OF DDI ASSESSMENTS AND STUDY DESIGN CONSIDERATIONS**

Using a systematic, science-driven approach to evaluate the DDI potential of therapeutic proteins is highly recommended and can involve a combination of the assessment types listed below. Sponsors should consider the DDI risk of their therapeutic protein early in 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 therapeutic protein.

#### **A. In Vitro and Animal Studies**

In vitro or animal data have not been predictive of the potential for clinical DDIs with therapeutic proteins. However, such data could provide a mechanistic understanding of the DDI potential of a therapeutic protein. Sponsors are encouraged to discuss their specific DDI study plans with the FDA.

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<sup>16</sup> Lavezzi SM, JD Jong, M Neyens et al, 2019, Systemic Exposure of Rituximab Increased by Ibrutinib: Pharmacokinetic Results and Modeling Based on the HELIOS Trial, *Pharm Res*, 36:93.

<sup>17</sup> Hansen RJ and JP Balthasar, 2002, Intravenous Immunoglobulin Mediates an Increase in Anti-Platelet Antibody Clearance via the FcRn Receptor, *Thromb Haemost*, 88:898–899.

<sup>18</sup> USPI of VYVGART<sup>®</sup>, Sections 7.1 and 12.3.

<sup>19</sup> Pouw MF, CL Krieckaet, MT Nurmohamed, DV Kleij, L Aarden, T Rispens, and G Wolbink, 2015, Key Findings towards Optimising Adalimumab Treatment: the Concentration-effect Curve, *Ann Rheum Dis*, 74:513–518.

<sup>20</sup> USPI of Humira<sup>®</sup>, Section 12.3.



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### **B. Dedicated Clinical Studies**

Clinical studies designed to evaluate the potential for DDIs with a therapeutic protein should consider the mechanism for the DDI and safety when selecting the relevant study population and the interacting drugs.

The study design (parallel or crossover) should be informed by the mechanism for the DDI, the pharmacokinetic (PK) characteristics of the drugs (e.g., the drug's half-life), and the immunogenicity risk of the therapeutic protein, for example:

- When the effect of other drug(s) on the therapeutic protein is evaluated, a parallel design might be appropriate when the therapeutic protein has a long half-life.
- When evaluating the effect of the therapeutic protein on the other drug(s) (e.g., the effect of proinflammatory cytokines or proinflammatory cytokine modulators on CYP substrates), a single-sequence, crossover design can be used (i.e., substrate alone followed by the substrate plus the therapeutic protein).
  - The sponsor should determine the time course for cytokine modulation by the therapeutic protein in the specific disease state to guide the timing and duration of administration of the substrate and therapeutic protein in the study.
  - A *cocktail* approach (i.e., simultaneous administration of substrates of multiple CYP enzymes) is an efficient means of evaluating the DDI potential for therapeutic proteins where multiple CYPs could be impacted (e.g., proinflammatory cytokines and proinflammatory cytokine modulators).<sup>21</sup>

### **C. Population PK Modeling (Nested DDI Studies)**

Population PK analyses can be informative in evaluating the DDI potential of therapeutic proteins.<sup>22,23</sup> A population PK analysis for prospective DDI evaluation should have carefully designed study procedures and protocols for the collection of PK samples, as well as clear documentation of the timing of administrations and the types of concomitant medications for which DDI is being assessed. In general, this approach is used to evaluate the effect of other agents on the investigational therapeutic protein, as PK data are usually collected for the

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<sup>21</sup> Jing X, P Ji, SJ Schrieber, EP Fletcher, C Sahajwalla, 2020, Update on Therapeutic Protein-Drug Interaction: Information in Labeling, *Clin Pharmacokinet*, 59:25-36.

<sup>22</sup> Chow AT, JC Earp, M Gupta, W Hanley, C Hu, DD Wang, S Zajic, and M Zhu, 2014, Population PK TPDI Working Group: Utility of Population Pharmacokinetic Modeling in the Assessment of Therapeutic Protein-Drug Interactions, *J Clin Pharmacol*, 54:593-601.

<sup>23</sup> Kenny JR, MM Liu, AT Chow, JC Earp, R Evers, JG Slatter, DD Wang, L Zhang, and HH Zhou, 2013, Therapeutic Protein Drug-Drug Interactions: Navigating the Knowledge Gaps - Highlights from the 2012 AAPS NBC Roundtable and IQ Consortium/FDA Workshop, *AAPS J*, 15:933-940.

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investigational agent only. However, a sponsor can prospectively plan and collect the necessary data for a substrate of interest to support the evaluation of the effect of the investigational therapeutic protein on the substrate of interest. For a discussion on nested DDI studies, refer to the FDA guidances entitled *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) and *Population Pharmacokinetics* (February 2022).

### **D. Other Modeling Approaches**

The application of physiologically based PK (PBPK) modeling in the evaluation of the DDI potential of a therapeutic protein is an emerging area. PBPK modeling has a potential role in understanding the underlying mechanism of a DDI. For more information, see the FDA guidance entitled *Physiologically Based Pharmacokinetic Analyses — Format and Content* (September 2018).

Other modeling approaches could be considered, and sponsors are encouraged to discuss the proposed approach with the FDA.

## **IV. LABELING RECOMMENDATIONS**

Prescribing Information must include a summary of essential DDI information needed for the safe and effective use of the drug by the healthcare provider.<sup>24</sup> For specific requirements and recommendations regarding how to incorporate DDI information in labeling, refer to 21 CFR 201.57 and the following FDA guidances:<sup>25</sup>

- *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)

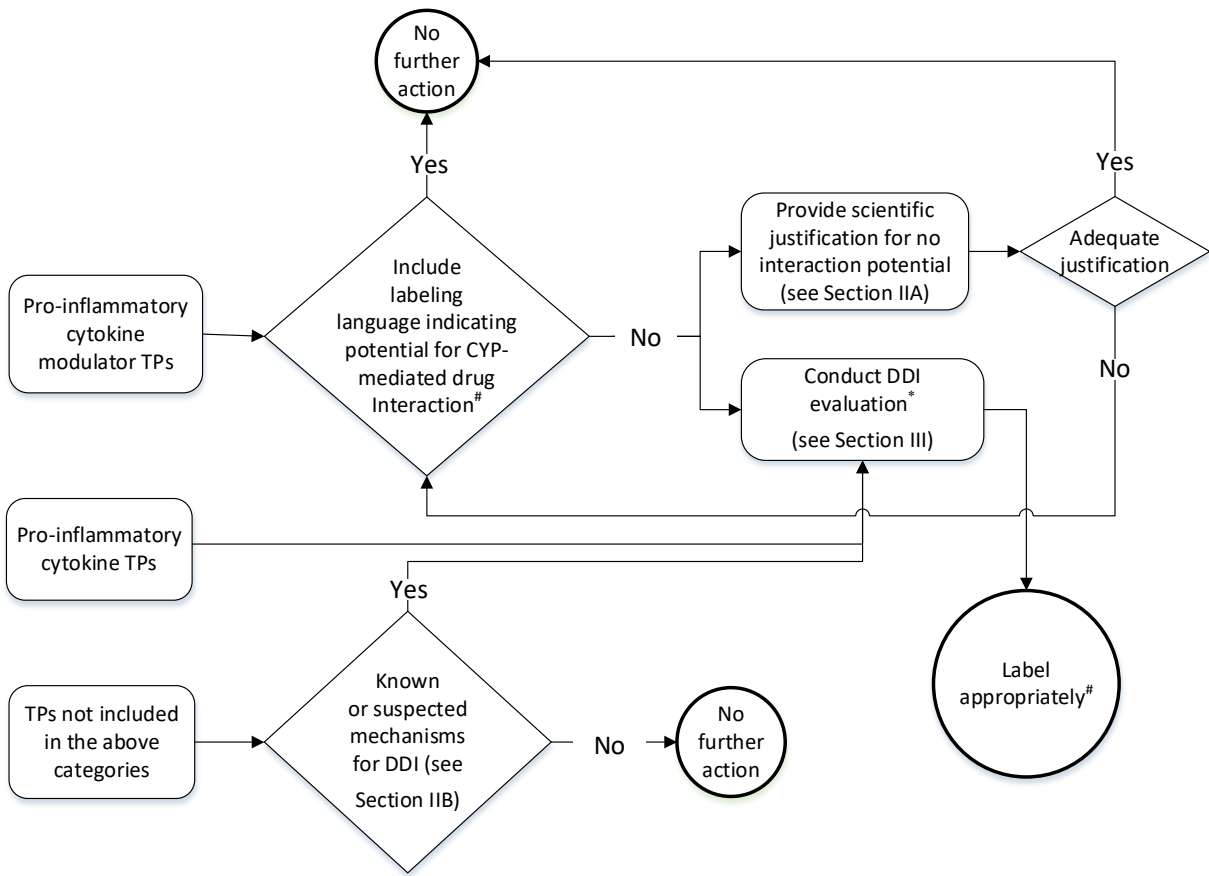
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<sup>24</sup> 21 CFR 201.56(a)(1).

<sup>25</sup> See also the FDA draft guidance entitled *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023). When final, this guidance will represent the Agency's current thinking on this topic.

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**V. APPENDIX. DECISION TREE**



CYP, cytochrome P450; DDI, drug-drug interaction; TP, therapeutic protein.

\*The Agency recommends that DDI evaluation proposals be discussed with the appropriate review division before initiating a study.

#Refer to Section IV.