Drug-Drug Interaction Assessment for Therapeutic Proteins Guidance for Industry

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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I. INTRODUCTION

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

For the purpose of this guidance, a TP refers to a protein, licensed as a therapeutic biological product under section 351 of the Public Health Service Act (42 U.S.C. 262).[4,5] Although this guidance applies to therapeutic proteins, the general concepts could be applicable to other biological products, including biological products regulated by CBER such as cellular and gene therapies.

This guidance supplements the final FDA guidances entitled *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* and *Clinical Drug*

[1] This guidance has been prepared by the Therapeutic Protein DDI Working Group in 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.

[2] Schrieber SJ, E Pfuma-Fletcher, X Wang, YC Wang, S Sagoo, R Madabushi, S Huang, and I Zineh, 2019, Considerations for Biologic Product Drug–Drug Interactions: A Regulatory Perspective, Clin Pharmacol Ther, 105:1332-1334.

[3] Hereafter, sponsors will refer to either applicants or sponsors.

[4] Section 351 of the Public Health Service Act, 42 U.S.C. § 282.

[5] Please refer to the FDA web page, *Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research*, for more information about these products available at: https://www.fda.gov/combination-products/classification-and-jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research.

Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020).[6]

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. CONSIDERATIONS FOR ASSESSING DDIs FOR TPs

When evaluating the potential for a DDI between a TP and small molecules or between TPs, sponsors should consider the mechanisms of a potential DDI, taking into account the pharmacology and clearance of the TP as well as any co-administered medications in the patient population.[7]

Below, we provide examples of the types of situations in which an assessment of the DDI potential of a TP can be warranted. This list should not be considered all-inclusive, as the development of novel TPs will continue to inform the DDI risk. Also, refer to the decision tree in the Appendix for more information.

A. Proinflammatory Cytokine-Related Mechanisms

TPs that are proinflammatory cytokines (e.g., peginterferon) or TPs that cause increases in proinflammatory cytokine levels can down-regulate the expression of cytochrome P450 (CYP) enzymes, thereby decreasing the metabolism of drugs that are CYP substrates and increasing their exposure levels.[8] Conversely, TPs that reduce cytokine levels (e.g., TNF inhibitors) can relieve the CYP down-regulation from an inflammatory environment (e.g., rheumatoid arthritis), thereby increasing CYP expression and activity and reducing exposure for CYP substrates. Of note, therapies such as T-cell redirecting bispecific antibodies as well as certain cellular and gene therapies can cause cytokine release syndrome. Co-medication in some cases could be used to treat or prevent these increases in cytokines. These changes in cytokines have the potential to affect CYP expression as well as the activity and exposure for CYP substrates.

1. The TP is a Proinflammatory Cytokine

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

[7] 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.

[8] 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.

The sponsor should evaluate the DDI potential for TPs that are proinflammatory cytokines.

2. The TP is a Cytokine Modulator

a. The TP causes an increase in proinflammatory cytokine levels

The increase in cytokine levels as a result of TP treatment can be transient or persistent. Therefore, the sponsor should determine the time course and extent of this increase in cytokine levels to help determine the need for a DDI study, the design of a study, and an appropriate mitigation strategy, if necessary. If the sponsor determines that the DDI potential of the TP is low, they should contact the FDA and provide justification for this determination (see Appendix).

b. The TP modulates proinflammatory cytokines in conditions associated with elevated cytokine levels

Levels of proinflammatory cytokines differ by disease type and severity of disease, leading to variability in CYP expression. These considerations make 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.

A sponsor can provide justification why they would prefer to not include the labeling language if they believe that the potential for clinically significant DDI is low.[9] Justification can include a discussion of:

- Effects seen 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
- The magnitude of the drug effect or the extent of cytokine modulation by the TP

Alternatively, the sponsor can perform a DDI study in the relevant indicated population to further inform labeling. The disease type and severity and dose(s) used are important considerations. Therefore, if a TP is being developed for multiple indications, the potential for DDIs can be evaluated in the disease with the most severe inflammatory burden.

B. Mechanisms of DDIs Unrelated to Proinflammatory Cytokines

Mechanisms unrelated to proinflammatory cytokines have been observed or postulated where the TP acts as a perpetrator (e.g., an inhibitor or inducer) or a victim of a small molecule or other TP

[9] Coutant DE and SD Hall SD, 2018, Disease-Drug Interactions in Inflammatory States Via Effects on CYP-Mediated Drug Clearance, J Clin Pharmacol, 58(7):849-863.

DDI. Depending on the expected mechanism of the DDI, a TP could be evaluated as a victim or as a perpetrator. Scenarios when DDI evaluation should be considered include:

- When a TP affects human physiological processes that can in turn alter the pharmacokinetic profiles of co-administered medications (e.g., GLP-1 receptor agonists such as dulaglutide and albiglutide result in delayed gastric emptying). In this case, the sponsor should evaluate the TP as a perpetrator.

- Co-administered medications that impact the TP target or target-mediated disposition.[10, 11] In these cases, depending on the role of the TP in the DDI, the sponsor should evaluate the DDI potential of the TP either as a perpetrator or as a victim.

- Co-administered medications that compromise the function of the FcRn can affect TPs which interact with the FcRn (e.g., blocking or interfering with the interaction between TPs containing an Fc region of human IgG and FcRn).[12] In these cases, the sponsor should evaluate the DDI potential of the TP as a victim.

- Co-administration of immunosuppressors with a TP whose pharmacokinetics are affected by immunogenicity (e.g., methotrexate on the clearance of adalimumab).[5] Since immunogenicity (i.e., the formation of antibodies to TPs) can alter the clearance of some TPs, drugs that suppress immunogenicity can change the clearance of a TP. In these cases, the sponsor should evaluate the DDI potential of the TP as a victim. This type of DDI evaluation can be difficult to prospectively design, in which case a descriptive analysis can often be considered adequate.

C. Antibody-Drug Conjugates

For antibody-drug conjugates (ADCs), the small molecule drug component conjugated to the antibody component can be released into unconjugated form. Therefore, the DDI potential of both the antibody and the small molecule drug components should be evaluated as described below:

- For the antibody component, consider the categories described above (see Section II) to determine if a DDI assessment is warranted.

- For the small molecule drug component, follow the considerations described in the final FDA guidances for industry entitled *In Vitro Drug Interaction Studies — Cytochrome*

[10] Abuqayyas L, JP Balthasar JP, 2012, Pharmacokinetic mAb-mAb Interaction: Anti-VEGF mAb Decreases the Distribution of Anti-CEA mAb into Colorectal Tumor Xenografts, AAPS J, 14(3):445–55.

[11] 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(3):752-62.

[12] Kiessling P, R Lledo-Garcia , S Watanabe, et al, 2017, The FcRn Inhibitor Rozanolixizumab Reduces Human Serum IgG Concentration: A Randomized Phase 1 Study, Sci Transl Med, 9(414):1208.

P450 Enzyme- and Transporter-Mediated Drug Interactions and Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020).

It is important to understand the systemic exposure of the small molecule drug component of the ADC. In many cases, the systemic concentration might be too low to act as a perpetrator. It might be necessary to evaluate the small molecule component (administered as an ADC) as a victim drug. Understanding the exposure-response relationship of the various moieties is important in determining the need for and significance of DDI studies. For example, if systemic concentrations of the free small molecule drug are low, evaluating the effect of strong CYP3A inducers on the drug's pharmacokinetics might not be necessary if the free small molecule drug in circulation is not contributing to efficacy. However, a study with a strong inhibitor could be necessary due to the potential for safety concerns associated with the increase in concentration of the free small molecule drug in the circulation. Although there are 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.

III. TYPES OF DDI ASSESSMENTS AND STUDY DESIGN CONSIDERATIONS

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

A. In Vitro and Animal Studies

The translation of in vitro data or animal data to humans has been limited. However, some methods could provide mechanistic understanding of the DDI potential of a TP and in some cases be combined with physiologically based pharmacokinetic (PBPK) models. Recommendations on the use of in vitro and animal studies may be further updated once relevant models are validated for their intended use. In vitro DDI evaluation for the small molecule drug component of an ADC should be performed consistent with the final FDA guidance for industry entitled *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) (see Section IIC).

B. Clinical Studies

Clinical studies of TPs should consider the suspected mechanism for the DDI when selecting the relevant study population and the interacting drugs to evaluate. The study design (parallel or crossover) should be informed by the suspected mechanism of the DDI and the pharmacokinetic (PK) characteristics of the drugs (e.g., the drug's half-life).

For TPs with a long half-life, a parallel design might be appropriate in evaluating the TP as a victim. A single sequence crossover design (substrate followed by the substrate plus the TP) can be used when evaluating the TP as a perpetrator (e.g., the effect of proinflammatory cytokines or cytokine modulators on CYP substrates). The sponsor should determine the time course for cytokine modulation by the TP in the specific disease state to guide the timing and duration of administration of substrate and TP in the study. A cocktail approach is an efficient means of evaluating the DDI for TPs where multiple CYPs could be impacted (e.g., proinflammatory cytokines and cytokine modulators).

C. Population PK Modeling (Nested DDI Studies)

Population PK analyses can be informative in the evaluation of DDIs for TPs.[13,14] A population PK analysis for prospective DDI evaluation should have carefully designed study procedures and protocols for the collection of PK samples. In general, this approach can be used to evaluate the effect of other agents on the investigational TP as PK data are usually only collected for the investigational agent. However, a sponsor can prospectively plan and collect the necessary data for a substrate of interest to support the evaluation of the investigational TP as a perpetrator. For a discussion on nested DDI studies, refer to the final FDA guidance entitled *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) and the draft FDA guidance entitled *Population Pharmacokinetics* (July 2019).[15]

D. Physiologically Based PK Modeling

The application of PBPK modeling in the evaluation of the DDI potential of a TP is an emerging area. PBPK modeling has a potential role in understanding the underlying mechanism of a DDI. Sponsors are encouraged to contact the FDA when proposing to use PBPK modeling to evaluate the DDI potential of TPs. For more information, see the FDA final guidance entitled *Physiologically Based Pharmacokinetic Analyses — Format and Content* (September 2018).

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 health care provider.[16] For specific requirements and recommendations regarding how to incorporate DDI information in labeling, refer to 21 CFR 201.57 and the following final FDA guidances:

[13] 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.

[14] Kenny JR, MM Liu, AT Chow, JC Earp, R Evers, JG Slatter, DD Wang, L Zhang, and H 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, 15:993-940.

[15] When final, this guidance will represent the FDA's current thinking on this topic.

[16] 21 CFR 201.56(a)(1)

- *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013)

- *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (March 2010)

- *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)

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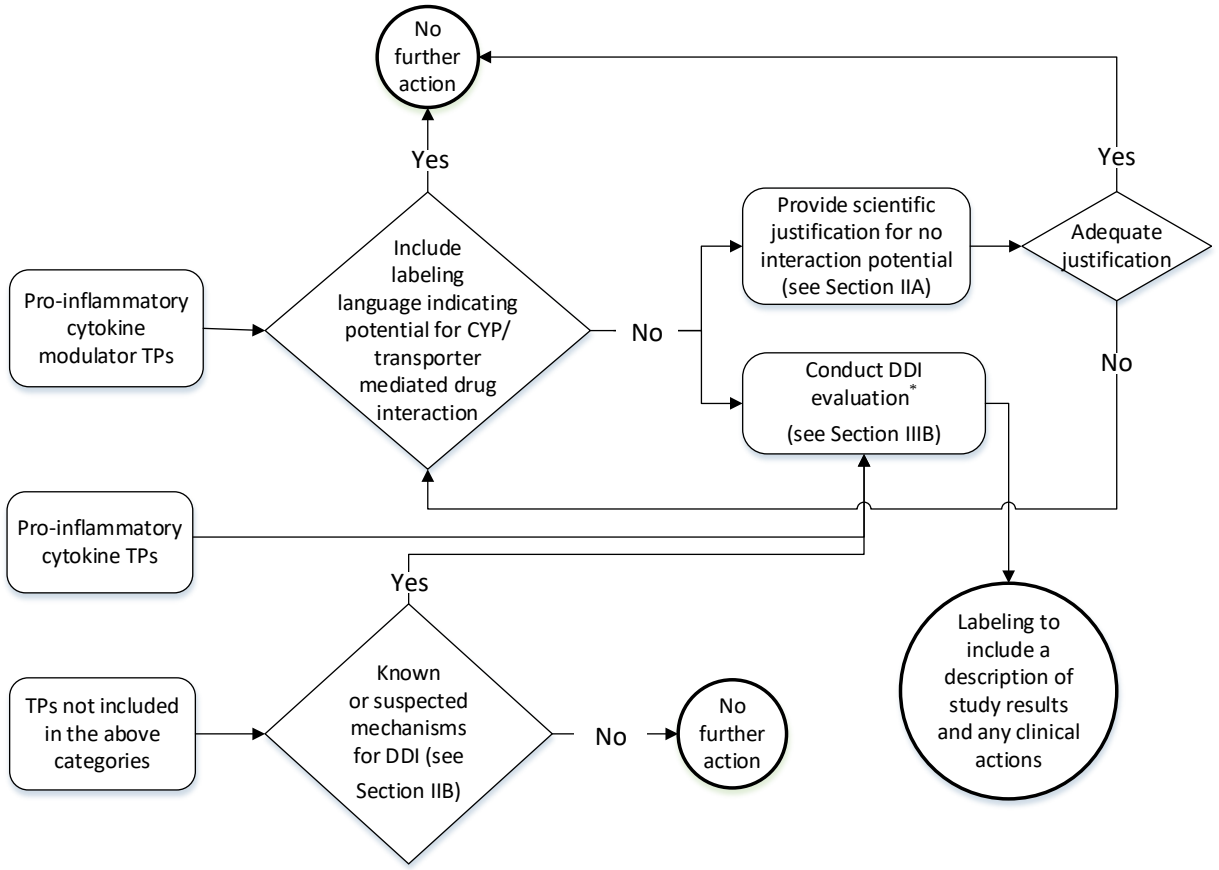

*The Agency recommends that DDI evaluation proposals be discussed with the appropriate review division prior to initiating a study.

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