U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

# Drug-Drug Interaction Assessment for Therapeutic Proteins

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**SBIA**

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# Agenda

- Raajan Naik
  - Background
  - Guidance Recommendations
    A. DDI Mechanisms Related to Pro-Inflammatory Cytokines
- Lin Zhou
  - Guidance Recommendations
    B. DDI Mechanisms Unrelated to Pro-Inflammatory Cytokines
    C. Types of DDI Assessment, Study Design Considerations
    D. Labeling Recommendations
    E. Decision Tree for Summary
- Q&A
  - Panelists: Elimika Pfuma Fletcher, Lin Zhou, Raajan Naik, Xiaofei Wang

# History of Guidance Development

- Therapeutic protein (TP) DDI – previously addressed in 2012 DDI guidance
  - TP DDI was excluded in the revised draft and final guidances for in vitro DDI studies and clinical DDI studies (January 2020)

- Goal of new TP DDI Draft Guidance (August 2020):
  - Provide a systematic, risk-based approach based on current scientific knowledge and experience

- TP DDI Final Guidance (June 2023)
  - Considerations for assessing DDIs for TPs – situations where determining the DDI potential of a TP is warranted
  - DDI assessments – considerations for study design and recommendations for labeling

# Draft vs. Final Guidance Changes

- Changes from draft to final guidance:
  - FDA review divisions should be consulted related to novel modalities (e.g., cellular and gene therapies)
  - Clarifying that limitations exist in knowledge related to effect of TPs on transporters
  - Adding literature references for clarifications
  - Limiting text related to antibody-drug conjugates (ADCs) due to an ADC draft guidance being published (February 2022)
  - Including language about potential use of various modeling approaches

# Assessing DDIs for Therapeutic Proteins

- **TP definition**: any alpha amino acid polymer with a specific, defined sequence that is >40 amino acids in size
  - Examples: monoclonal antibody (mAb), ADC, cytokine, enzyme, fusion protein, growth factor, hormone

- When evaluating the potential for a DDI between a TP and small molecules or between TPs consider:
  - Potential mechanism for the interaction
  - Disease type and severity (if DDI related to disease condition)
  - Product type
  - Clearance pathways of the TP
  - Commonly co-administered medications in patient population(s)

Ref: Federal Register – TP Definition (URL)

# A. Mechanisms Related to Proinflammatory Cytokines

1. TP is a proinflammatory cytokine

   – Proinflammatory cytokines (e.g., peginterferon) are well known to potentially inhibit CYP enzymes
     - Evaluation of such DDI potential for TPs is important and clinically relevant

   – Proinflammatory cytokine-transporter DDIs:
     - Data only available in animal or in vitro models
     - Cytokines may inhibit multiple transporters
     - Clinical relevance unknown
     - Recommend investigating cytokine-transporter DDIs in clinical studies

| CYP enzyme | Cytokines/cytokine modulators |
|---|---|
| CYP1A2 | IFN-α, IFNα-2b, IFN-β, IL-2, IL-6, hGH[a] |
| CYP2C8 | IL-1 |
| CYP2C9 | IL-2, IL-10 |
| CYP2C19 | Tocilizumab[b], IFNα-2b, FN-β, IL-2, TNF-α, IL-6, hGH |
| CYP2D6 | IFNα-2b |
| CYP2E1 | IL-2, IFNα-2b |
| CYP3A | Basiliximab, muromonab-CD3, tocilizumab[b], IL-1, IL-2, IL-6, IL-10 |

[a]The effect of hGH is an increase in activity. [b]The effect of tocilizumab, an anti-IL-6 receptor monoclonal antibody, is an increase in activity.

Ref: Huang SM et al., Clin Pharmacol Ther. 2010, 87, 497.

Ref: Sun Q & Kuo L, Clin Pharmacol Ther. 2019, 105(Suppl. 1), S73.

# A. Mechanisms Related to Proinflammatory Cytokines

2. TP is a proinflammatory cytokine modulator

a) TP causes an increase in proinflammatory cytokine levels (stimulator)

- Increase could be transient or persistent
- The need and design of a DDI study is informed by the time course and extent of the increase in cytokine levels in clinical studies
- Examples: glofitamab

**Glofitamab**: approved in 2023, a bispecific CD20-directed CD3 T-cell engager, for treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), associated with cytokine release syndrome (CRS) and cytokine related DDI

| **Labeling Section 7 - Drug interactions** |
| --- |
| For certain CYP substrates where minimal concentration changes may lead to serious adverse reactions, monitor for toxicities or drug concentrations of such CYP substrates when coadministered with glofitamab.<br><br>Glofitamab causes the release of cytokines that may suppress the activity of CYP enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur after the first dose on Cycle 1 Day 8 and up to 14 days after the first 30 mg dose on Cycle 2 Day 1 and during and after CRS. |

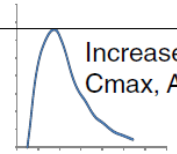
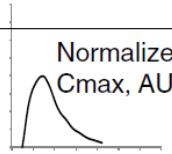
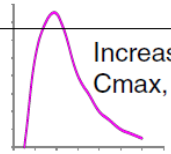
Ref: glofitamab USPI (URL)

# A. Mechanisms Related to Proinflammatory Cytokines

2. TP is a proinflammatory cytokine modulator

b) TP modulates proinflammatory cytokines in conditions associated with elevated cytokine levels (inhibitor)

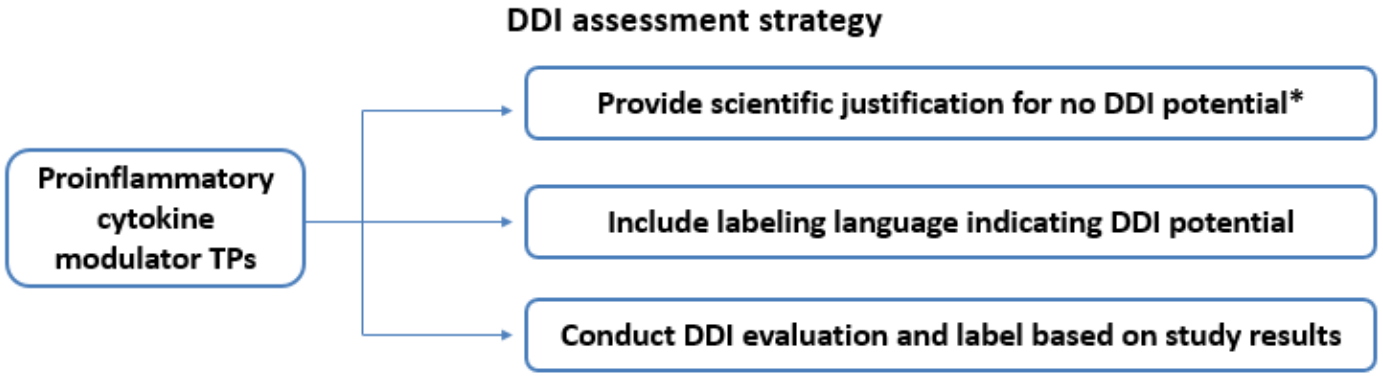
- Levels of proinflammatory cytokines differ by disease and severity of disease
- If a TP is being developed for multiple indications, the potential for DDI should be evaluated in patients with indications manifesting the most severe inflammatory burden, when clinical DDI study is conducted

| | **Inflammatory disease state (e.g., psoriasis)** → Disease improvement → **Healthy state** → Disease return or worsening → **Disease relapse or rebound** | | |
|---|---|---|---|
| **Pro-inflammatory cytokine expression** | Elevated | Normalized | Elevated |
| **CYP Enzymes expression and activity** | Suppressed | Normalized | Suppressed |
| **CYP substrate exposure** |  Increased Cmax, AUC |  Normalized Cmax, AUC |  Increased Cmax, AUC |

Ref: Wang J et al., AAPS J. 2014, 16, 938; Coutant DE et al., J Clin Pharmacol. 2018, 58, 849.

# A. Mechanisms Related to Proinflammatory Cytokines

2. TP is a proinflammatory cytokine modulator
   - 2a) TP causes an increase in proinflammatory cytokine levels (stimulator)
   - 2b) TP modulates proinflammatory cytokines in disease conditions (inhibitor)




*Examples of justifications:

- DDI effects seen with other agents or the same agent in other disease states with similar or more inflammatory burden
- Differences in exposure level of sensitive CYP substrate in healthy subjects vs. the indicated population considering other covariates
- The magnitude of cytokine modulation by the TP

# B. Mechanisms Unrelated to Proinflammatory Cytokines

Scenarios in which DDI evaluation should be considered include:

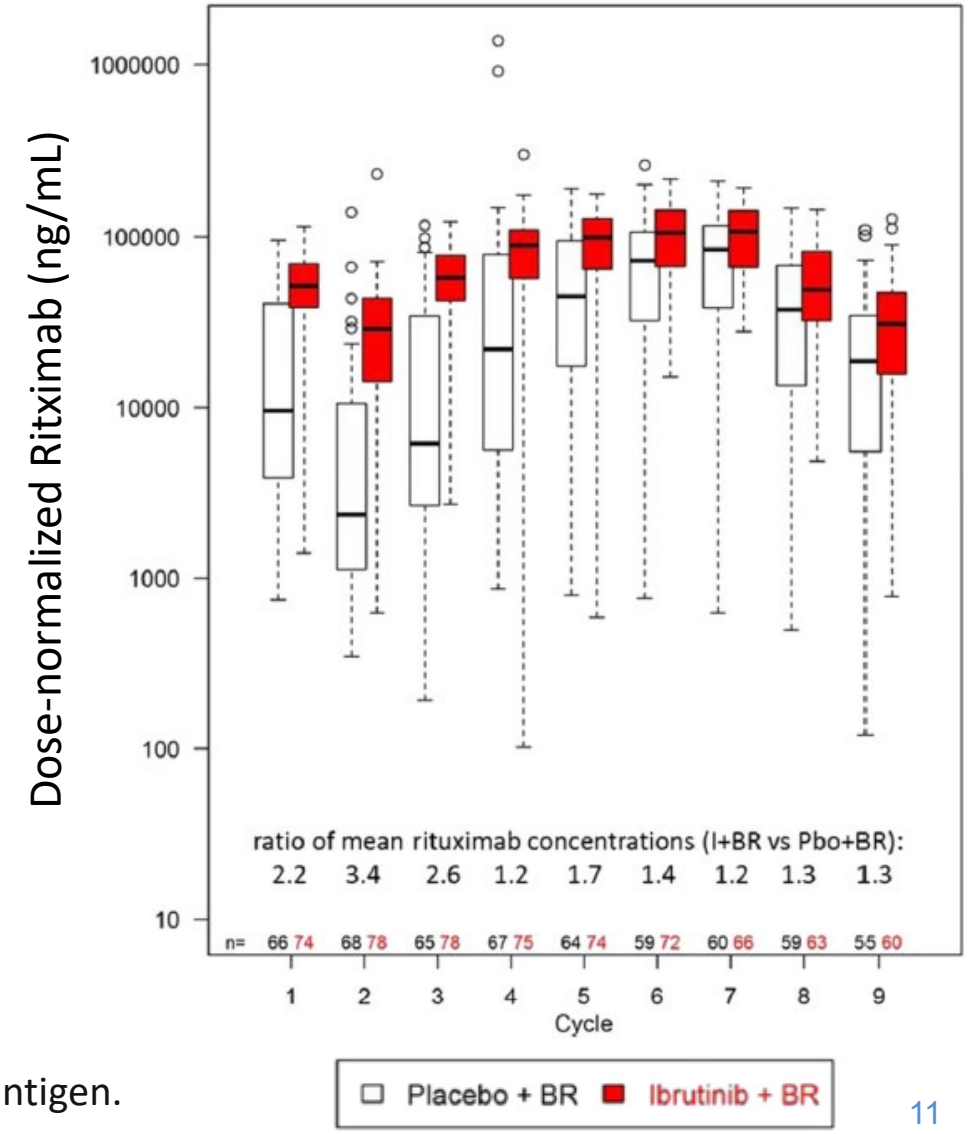
1. A TP affects human physiological process and thereby alters the PK of co-administered drugs.
   - GLP-1 receptor agonists (e.g., dulaglutide and albiglutide) result in delayed gastric emptying[1, 2].

Ref 1&2: USPI of dulaglutide and albiglutide

# B. Mechanisms Unrelated to Proinflammatory Cytokines

2. A co-administered drug impacts the distribution of the TP to the site of target or TMDD of the TP.

- Anti-VEGF mAb decreased the distribution of anti-CEA mAb into colorectal tumor xenografts in mice[3].
- Systemic exposure of rituximab increased by ibrutinib[4].

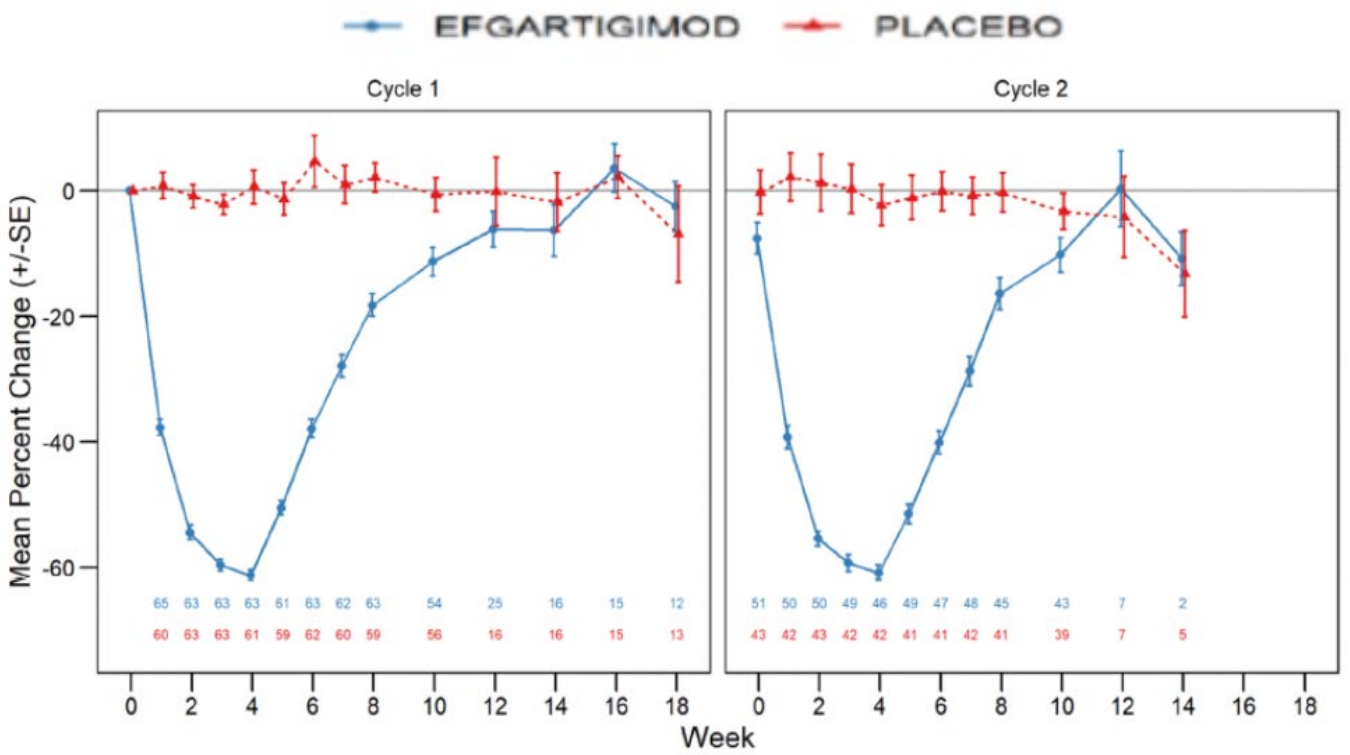



TMDD: target-mediated drug disposition
Anti-VEGF: anti-vascular endothelial growth factor; anti-CEA: anti-carcinoembryonic antigen.
Ref 3: Abuqayyas L et al, 2012; Ref 4: Lavezzi SM et al, 2019

# B. Mechanisms Unrelated to Proinflammatory Cytokines

3. A co-administered TP affects another TP's interaction with the FcRn and decrease the exposure of the TP.

- IV immunoglobulin therapy increases antibody elimination via saturation of FcRn in mice[5].
- Efgartigimod alfa: an FcRn blocker, approved in 2021.




**Percent Change From Baseline in Total IgG Levels** (*URL*)

FcRn: neonatal crystallizable fragment receptor

Ref 5: Hansen RJ et al., 2002

# B. Mechanisms Unrelated to Proinflammatory Cytokines

4. A co-administered immunosuppressor alters the PK of a TP whose PK is affected by immunogenicity.

- ADA affect adalimumab PK in multiple patient populations[6].
- Concomitant use of methotrexate increased adalimumab concentrations[6, 7].

**Table 2** Adalimumab levels for patients on different dosages of MTX

| Group | Group dose | Median MTX-dose (mg/week) | IQR | N | Median adalimumab level (µg/mL) | IQR |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0–0 | 51 | 4.1 | 1.3–7.7 |
| 1 | 5–10 | 10 | 6.9–10 | 34 | 8.0 | 4.0–10.5 |
| 2 | 12.5–20 | 15 | 15–20 | 49 | 6.9 | 4.8–11.1 |
| 3 | ≥22.5 | 25 | 25–25 | 87 | 7.7 | 5.5–10.5 |

p Values between group 1 and 2: p=0.835; groups 1–3: p=0.474; group 2–3: p=0.279.
MTX, methotrexate.

Ref 6: USPI of adalimumab Section 12.3; Ref 7: Pouw MF et al., 2015; ADA: Anti-drug antibodies

# C. Types of DDI Assessments and Study Design Considerations

1. Dedicated clinical studies
   - Population selection: *consider DDI mechanism and TP safety profile*
   - Parallel vs. crossover:
     - *for TP as a substrate of an interaction, a parallel design might be appropriate if TP has a long half-life;*
     - *for TP as a precipitant of an interaction, a single-sequence, crossover design can be used.*
   - Timing and duration of administration: *consider the time course for cytokine modulation by the TP in the specific disease state*
   - Substrate selection: *a cocktail approach is an efficient means where multiple CYPs could be impacted*

# C. Types of DDI Assessments and Study Design Considerations

2. PopPK modeling (nested DDI studies)
   - Need to have well-designed procedure and protocol, appropriate PK sampling, documentation of the timing of administration and type of concomitant medications.
   - In general, this approach is used to evaluate the effect of other agents on the investigational TP.
   - The approach can also be used to evaluate the effect of the investigational TP on the substrate of interest, if planned prospectively and data for a substrate collected.

# C. Types of DDI Assessments and Study Design Considerations

3. Other modeling approaches:
   - PBPK modeling for evaluating DDI potential of a TP is an emerging area.
   - May help understand the underlying mechanism.

4. In vitro and animal models:
   - Not predictive of clinical DDI risk, may provide mechanistic understanding

PBPK: Physiologically based pharmacokinetic

# C. Types of DDI Assessments and Study Design Considerations

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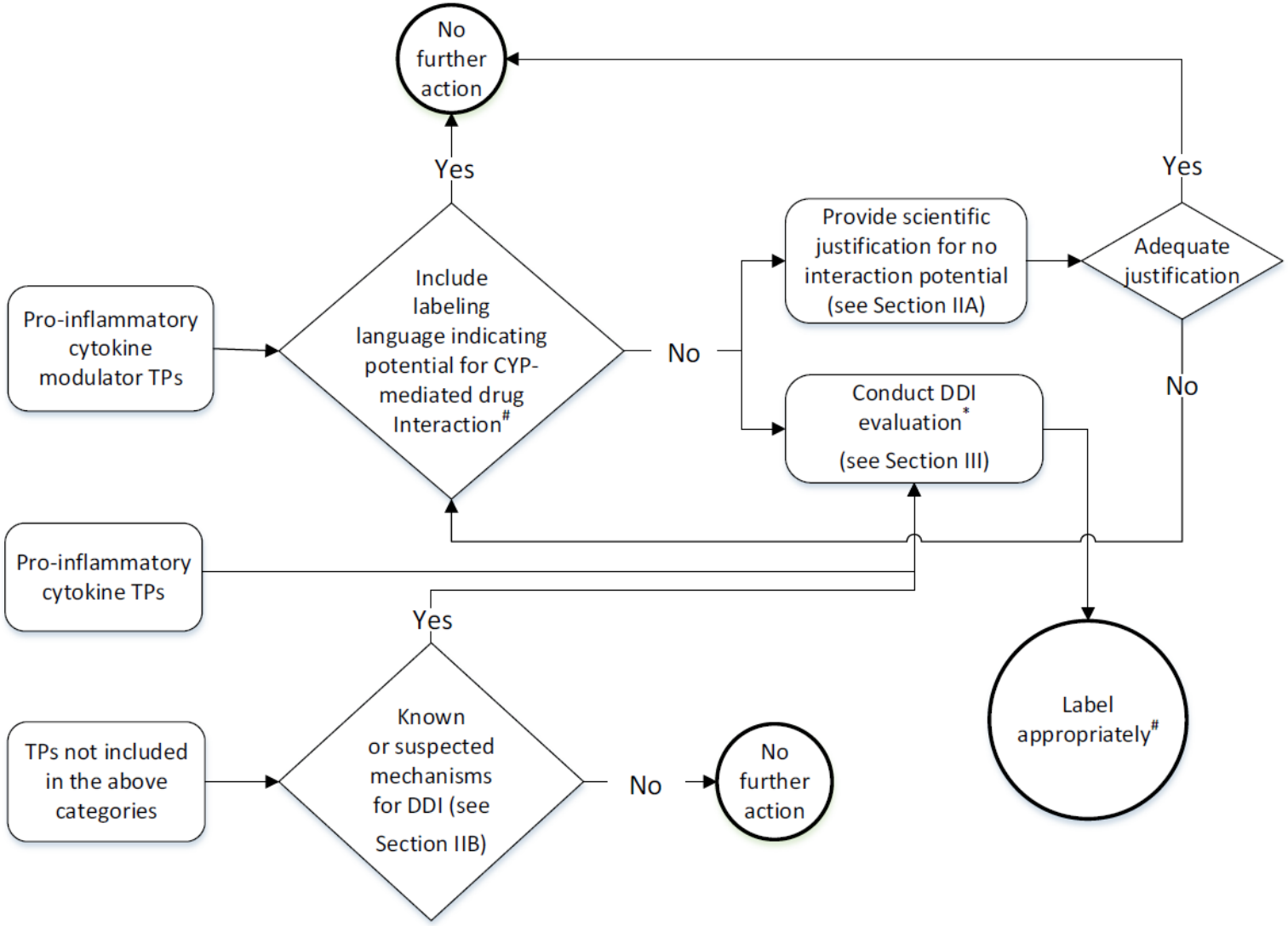
PBPK: Physiologically based pharmacokinetic

# D. 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.
- 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)*

# E. Decision Tree




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

#: Refer to Section IV. Labeling recommendations of the guidance.

# Knowledge Check

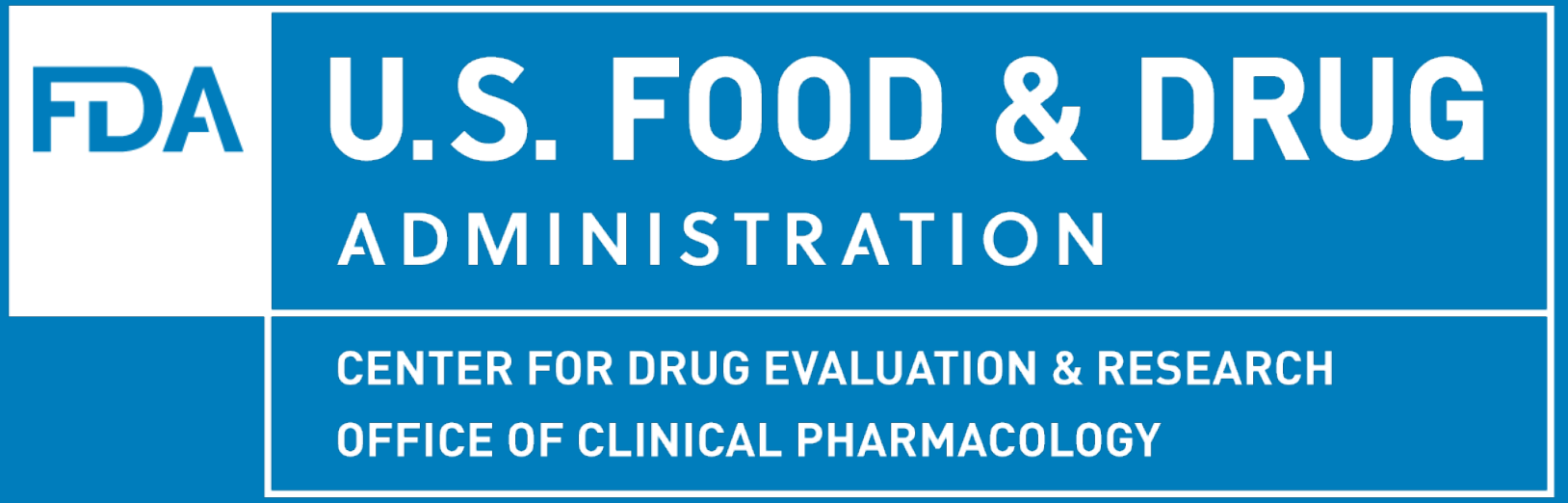
The 2023 FDA guidance: *Drug-Drug Interaction (DDI) Assessment for Therapeutic Proteins* (TPs) recommends evaluating the DDIs for:

a) Proinflammatory cytokines

b) Proinflammatory cytokine modulators

c) Therapeutic proteins involved in known or suspected mechanisms unrelated to proinflammatory cytokines (e.g., co-administered TP that affects another TP's interaction with FcRn)

d) All the above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