Clinical Drug Interaction Studies With Combined Oral Contraceptives

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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I. INTRODUCTION

This guidance is intended to help sponsors of investigational new drug applications (INDs) and new drug applications (NDAs) evaluate the need for drug-drug interaction (DDI) studies of their investigational drugs with combined oral contraceptives (COCs), design such studies, and determine how to communicate DDI study results and mitigation strategies to address potential risks associated with increased or decreased exposure of COCs in labeling. This guidance focuses on evaluating the DDI potential of an investigational drug (i.e., perpetrator) on a COC (i.e., victim).

Reference is made to the FDA final guidances for industry entitled *Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020)[2] for general principles in assessing the clinical DDI potential and *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) for in vitro experimental approaches to evaluate the interaction potential for investigational drugs that involve metabolizing enzymes and/or transporters. This guidance focuses solely on specific recommendations relevant to metabolism-based drug interactions with COCs. Other mechanisms that can cause an interaction (e.g., absorption-based) are not addressed in this guidance but should be considered by sponsors and investigators. In addition, this guidance does not discuss DDIs with progestin-only pills (POPs) and contraceptives administered via non-oral routes (e.g., transdermal systems). However, a DDI study with a COC could inform the impact of other types of contraceptives containing the same progestin.

In general, the 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

[1] This guidance has been prepared by the Office of Clinical Pharmacology, Office of Translational Sciences, in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

the word *should* in the Agency's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

COCs usually contain two synthetic steroid hormones, a progestin and an estrogen. COCs are highly effective in preventing pregnancy when used correctly. However, drug interactions with concomitant therapies can adversely impact the efficacy and/or safety of COCs by affecting enzymes involved in the metabolism of progestins and estrogens. For example, decreased progestin concentrations can lead to unintended pregnancy (loss of efficacy), whereas increased estrogen and/or progestin concentrations can increase the risk of venous thromboembolisms (VTEs), a rare but severe adverse event.

Because COCs are widely used in women of childbearing potential, and many investigational drugs are co-prescribed with COCs after approval, clinically relevant DDIs between an investigational drug and COCs should be: (1) evaluated during drug development of the investigational drug; (2) understood via in vitro and/or clinical assessment at the time of the investigational drug's approval; and (3) communicated in the labeling, as needed.

III. WHEN COC DDI STUDIES SHOULD BE CONDUCTED

Cytochrome P450 3A (CYP3A) is responsible for the metabolism of most commonly used progestins, although the relative contribution of CYP3A to the clearance of different progestins varies. Other metabolic enzymes, including CYP2C19, uridine 5'-diphospho-glucuronosyltransferases (UGTs), and sulfotransferases (SULTs), are also involved in the metabolism of certain progestins.[3] These enzymes are known to share gene expression regulation pathways (e.g., pregnane X receptor) with CYP3A, although the induction of UGTs and SULTs is less well understood compared to CYPs. In general, CYP3A is very sensitive to induction. Therefore, an investigational drug's induction effect on CYP3A can inform its potential to affect the pharmacokinetics of progestins in vivo.

The metabolism of ethinyl estradiol (EE), the most commonly used estrogen in COCs, involves multiple enzymes (i.e., CYP3A, CYP2C9, UGT1A1, and SULT1E1). Although the relative contribution of each of these enzymes in the elimination of EE remains unclear, available information from in vivo DDI studies suggests that moderate or strong inhibition of CYP3A combined with inhibition of other metabolic pathways of EE can significantly increase EE exposure (i.e., on average 40 percent or more for COCs containing ≥ 35 μg EE) to the level that can increase the risk of serious adverse reactions, including VTEs.

When the investigational drug for chronic use is expected to be co-administered with a COC in women of childbearing potential, and in vitro studies suggest that it is a CYP3A inducer or inhibitor, the sponsor can opt to directly conduct a COC DDI study or consider the following

[3] Zhang N, J Shon, M Kim, C Yu, L Zhang, S Huang, L Lee, D Tran, and L Li, 2018, Role of CYP3A4 in Oral Contraceptives Clearance, Clin Trans Sci, 11:251-260.

(See Section III.A-III.B) to determine whether a clinical DDI study is needed. Also, for an investigational drug that is given for short-term use, sponsors can discuss with the appropriate FDA review division whether a DDI study with a COC is needed.

A. CYP3A Inducers

When in vitro studies suggest that the investigational drug is a CYP3A inducer, the sponsor should address the DDI potential via one of the pathways below (see also Figure 1 in the Appendix):

- If the investigational drug does not affect the area under the plasma concentration-time curve (AUC) of a sensitive CYP3A substrate, then it is not expected to markedly affect the systemic exposures of COCs. Therefore, a COC DDI study is not necessary. There could be situations where a drug is both a potent inducer and an inhibitor of CYP3A so that the net effect on a sensitive CYP3A substrate is minimal. However, other enzymes (e.g., UGT) involved in the metabolism of COCs can also be induced via a shared gene regulation pathway with CYP3A. Therefore, if the drug does not inhibit these enzymes, it could still decrease the AUC of COCs. Sponsors are encouraged to consult with review divisions on whether to conduct a DDI study with a COC in such cases.

- If the investigational drug is a moderate or strong CYP3A inducer (i.e., it reduces the AUC of a sensitive CYP3A substrate by ≥ 50 percent), then significant reduction in exposures of COCs may occur, potentially leading to reduced efficacy of the COC. Therefore, the labeling should recommend avoiding concomitant use with COCs. Alternatively, for moderate CYP3A inducers (i.e., it reduces the AUC of a sensitive CYP3A substrate by ≥ 50 to < 80 percent), sponsors can consider conducting a dedicated study with a COC to evaluate the magnitude of exposure change of the COC to determine whether the tested COC can be used concomitantly.

- If the investigational drug is a weak CYP3A inducer (i.e., it reduces the AUC of a sensitive CYP3A substrate by ≥ 20 to < 50 percent), then the sponsor should conduct a clinical DDI study with a COC to evaluate the effect of the investigational drug on the COC to determine whether the tested COC can be used concomitantly. If the sponsor plans to request a waiver of the COC DDI study, the following factors (not limited to these) should be taken into consideration: (1) the projected magnitude of the interaction based on the study with a sensitive CYP3A substrate or other scientific evidence; and (2) whether the investigational drug shows any nonclinical reproductive and developmental toxicity.

B. CYP3A Inhibitors

Exposures at or above 50 µg EE have been reported to be associated with clinically meaningful increases in the risk of serious adverse reactions, such as VTEs.[4] Therefore, an approximately 40 percent increase in EE concentration for COCs containing 35 µg EE resulting in exposures

[4] Gerstman BB, JM Piper, DK Tomita, WJ Ferguson, BV Stadel, and FE Lundin, 1991, Oral Contraceptive Estrogen Dose and the Risk of Deep Venous Thromboembolic Disease, Am J Epidemiol, 133(1):32-37.

similar to COCs containing 50 µg EE could be clinically meaningful. The sponsor should conduct a clinical COC DDI study (see Figure 2 in the Appendix) to quantify the magnitude of the DDI if in vivo studies suggest that the investigational drug is a moderate or strong CYP3A inhibitor (i.e., it increases the AUC of a sensitive CYP3A substrate by 2-fold or more) and also inhibits one or more other enzymes involved in the metabolism of EE (e.g. CYP2C9, UGT1A1, and SULT1E1).

C. Teratogenic Drugs for Use in Women with Childbearing Potential

If the investigational drug has teratogenic potential,[5,6] then regardless of the in vitro or in vivo DDI study results, a COC DDI study should be conducted, unless an in vivo DDI study using a CYP3A probe substrate has already shown that the investigational drug is a moderate or strong CYP3A inducer, in which case the labeling should recommend avoiding concomitant use with COCs (see section IIIA).

IV. DESIGN AND CONDUCT OF CLINICAL COC DDI STUDIES

A. Study Population

- Either premenopausal or postmenopausal women can be included in the DDI study; however, including premenopausal females allows for the assessment of pharmacodynamic (PD) endpoints that cannot be studied in postmenopausal subjects.

- The number of subjects included in a COC DDI study should be sufficient to provide a reliable estimate of the magnitude and variability of the interaction.

B. Choice of COC

- Sponsors should use COCs that contain the most commonly used progestins in the United States, such as norethindrone (NET), norgestimate (NGM), levonorgestrel (LNG), or drospirenone (DRSP), combined with EE, so that the study results can directly inform the most likely clinical use. Alternatively, we recommend studying COCs containing DRSP as a worst-case scenario for CYP3A inhibition (see section VI).

[5] Ahn MR, L Li, J Shon, ED Bashaw, and M-J Kim, 2016, Teratogenic Drugs and Their Drug Interactions with Hormonal Contraceptives, Clin Pharmacol Ther, 100:217-219.

[6] Akbar M, E Berry-Bibee, DL Blithe, RS Day, A Edelman, J Höchel, J Roxanne, M Kim, L Li, VS Purohit, JA Turpin, PE Scott, DG Strauss, H Sun, NK Tepper, L Zhang, and C Yu, 2018, FDA Public Meeting Report on Drug Interactions With Hormonal Contraceptives: Public Health and Drug Development Implications, J Clin Pharmacol, 58:1655-1665.

C. Dose

- The investigational drug (perpetrator) should be given at the highest proposed therapeutic dose and should be dosed for a sufficient duration to ensure maximal modulation of the drug's metabolizing enzymatic pathways.

- The COC can be dosed as either a single dose or as multiple doses for the pharmacokinetic (PK) assessment. For PD assessments, multiple doses of a COC are needed.

D. Food Intake

- For instructions on how to administer the perpetrator drug in relation to food intake in DDI studies with COCs, sponsors should follow the proposed perpetrator's product label or the instructions used in pivotal clinical trials to reflect the clinically relevant conditions.

E. Study Design

- Fixed sequence or randomized crossover studies are preferred. If these designs are not feasible, a parallel study design is acceptable.

F. PK Sampling

- Intensive PK sampling should be conducted for progestins and estrogens of the COC on PK assessment days. In addition, PK sampling of the investigational drug is useful to ensure that adequate systemic exposures are achieved.

G. PD Assessments

- Currently, the dose/exposure-response relationships of progestin and estrogen for contraceptive efficacy are not fully established. An approach assessing PD parameters (i.e., luteinizing hormone, follicle stimulating hormone, and progesterone) in addition to PK parameters can be considered, as it could provide supportive information when the PK results reside outside of the no-effect boundaries (see sections V and IX).

Sponsors are encouraged to seek feedback from the appropriate FDA review division when they plan to conduct PK assessments using alternative study designs, including PD assessments.

V. INTERPRETING THE RESULTS OF CLINICAL COC DDI STUDIES

- The primary systemic exposure parameters should be reported, for example, $AUC_{0\text{-}TAU}$ for multiple-dose studies, $AUC_{0\text{-}inf}$ for single-dose studies, and the maximum concentration (C_{max}).

- If the 90 percent confidence intervals (CIs) for the geometric mean systemic exposure ratios fall entirely within the no-effect boundaries of 80 to 125 percent for the COC, no significant DDI is considered to be present. If the 90 percent CIs are outside of the 80 to 125 percent boundaries, the totality of evidence (e.g., safety and efficacy of the COC) should be considered when determining the clinical impact of the DDI on the COC. For certain drugs, such as teratogenic drugs, the clinical context and individual PK changes might need to be considered besides the CIs.

VI. EXTRAPOLATING THE RESULTS OF CLINICAL COC DDI STUDIES

- Although progestins including NET, LNG, NGM, or DRSP usually have the same direction of exposure change (increase vs. decrease) when taken with the same perpetrator (i.e., a CYP3A inhibitor or inducer), quantitative extrapolation of DDI results from one progestin in a COC to another should not be performed due to the different extents of CYP3A-mediated metabolism of each of these progestins.[7]

- DRSP is a more sensitive CYP3A substrate compared to other approved progestins such as NET and LNG. In general, if a clinical DDI study with a DRSP-containing COC shows no interaction, the DDI results for DRSP can be extrapolated to NET and LNG. The specifics of this strategy should be discussed and agreed upon with the Agency prior to initiating the study.

VII. LABELING RECOMMENDATIONS

In general, the magnitude of the interaction will guide clinical interpretations and labeling recommendations. For example:

- If EE exposures increase to those observed at an EE dose of ≥ 50 µg, the investigational drug's labeling would likely recommend avoiding concomitant use with COCs containing EE or recommending to not use a COC with EE exceeding a specific dose.

- If the investigational drug is an enzyme inducer that will decrease progestin exposure to an extent that can lead to reduced effectiveness of the COC, the investigational drug's labeling should recommend the use of a back-up or alternative method of contraception.

COC DDI information in the DRUG INTERACTIONS section of the investigational drug's labeling:

[7] See footnote 3

- Must describe clinically significant DDIs[8] and the mechanism of the clinically significant DDIs[9] (e.g., PK metabolism/transporter-based, PD interaction), if known, and should cross reference to the CLINICAL PHARMACOLOGY section of labeling for details of the DDI study results

- Should include the clinical effects of the clinically significant DDI

- Must include specific practical instructions for preventing or managing the clinically significant DDI[10] and should cross reference to the DOSAGE AND ADMINISTRATION section of labeling for detailed dosage modification information, if applicable

When the COC DDI study results show no clinically significant DDI between an investigational drug and the tested COC, the *Pharmacokinetics* subsection of CLINICAL PHARMACOLOGY section of the investigational drug's labeling should include the following statement or similar statement: *No clinically significant differences in [drug substance] pharmacokinetics were observed when Drug-X was used concomitantly with Drug-Y.*[11]

When drug interaction information appears in multiple sections of labeling, applicants should cross-reference DDI information in accordance with the recommendations in the FDA final guidance entitled *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013).

[8] 21 CFR 201.57(c)(8)(i).

[9] Ibid.

[10] Ibid.

[11] For more information, see the FDA final guidance for industry entitled *Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products – Content and Format* (December 2016).

VIII. ABBREVIATIONS

AUC_{0-t}	Area under the plasma concentration-time curve integrated from time of administration (0) to time of last quantifiable observation (t)
AUC_{0-INF}	Area under the plasma concentration-time curve from time of administration extrapolated to infinity from AUC_{0-t}
AUC_{0-TAU}	Area under the plasma concentration-time curve integrated across the dosing interval
COC	Combined oral contraceptive
CIs	Confidence intervals (CIs)
CYP	Cytochrome P450
DDI	Drug-drug interaction
DRSP	Drospirenone
EE	Ethinyl estradiol
FDA	Food and Drug Administration
IND	Investigational new drug
LNG	Levonorgestrel
NDA	New drug application
NET	Norethindrone
NGM	Norgestimate
PD	Pharmacodynamic
PK	Pharmacokinetic
PLR	Physician labeling rule
POP	Progestin-only pill
SULTs	Sulfotransferases (SULTs)
UGTs	Uridine 5'-diphospho-glucuronosyltransferases

VTE	Venous thromboembolism

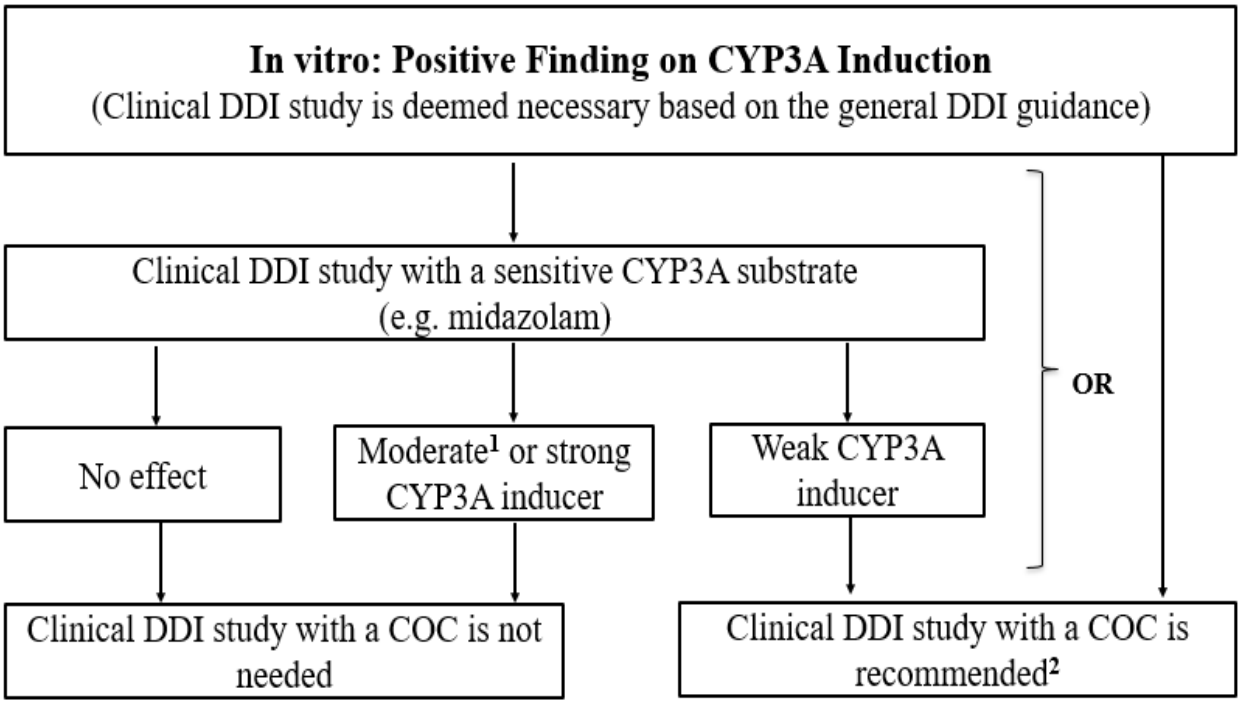
IX. DEFINITIONS

Inducer	An inducer is a drug that decreases the AUC of substrates (i.e., victim drug) of a given metabolic pathway.
Inhibitor	An inhibitor is a drug that increases the AUC of substrates (i.e., victim drug) of a given metabolic pathway.
No-effect boundaries	No-effect boundaries represent the interval within which a change in a systemic exposure measure is considered not significant enough to warrant clinical action (e.g., dose or schedule adjustment, or additional therapeutic monitoring).
Perpetrator	A perpetrator is a moiety that can induce or inhibit an enzyme or a transporter.
Victim	A victim is a substrate whose exposure changes due to inhibition or induction of an enzyme or transporter by a perpetrating moiety.

X. APPENDIX

Figures 1 and 2 show decision trees for determining when clinical COC DDI studies should be conducted.

Figure 1: COC DDI Study Decision Tree Based on CYP Induction Potential



[1] For strong and moderate CYP3A inducers, labeling should recommend avoiding concomitant use with COCs due to an expected significant reduction in systemic exposures of COCs. For moderate CYP3A inducers, sponsors can consider conducting a dedicated study with a COC. If the results suggest no significant decrease in exposure of the COC, concomitant use with the COC studied could be allowed.

[2] Sponsors can make the decision, in conjunction with the FDA's input, on whether to conduct a study with a COC. If the sponsor plans to request a waiver of the COC DDI study, the following factors (not limited to these) should be taken into consideration: (1) the projected magnitude of the interaction based on the study with a sensitive CYP3A substrate or other scientific evidence; and (2) whether the investigational drug shows any nonclinical reproductive and developmental toxicity.

Figure 2: COC DDI Study Decision Tree Based on CYP Inhibition Potential