Clinical Drug Interaction Studies With Combined Oral Contraceptives

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

June 2023
Clinical Pharmacology

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Contains Nonbinding Recommendations

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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 drug-drug interaction (DDI) effects of their investigational drugs on combined oral contraceptives (COCs), design DDI studies, and determine how to communicate DDI study results and risk mitigation strategies in labeling to address potential risks associated with increased or decreased exposure of COCs.

Reference is made to the FDA guidances 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 on other types of contraceptives containing the same progestin.

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[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.

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 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). In addition, decreased estrogen concentrations could cause breakthrough bleeding and may also adversely affect the efficacy of COCs. Increased estrogen or progestin concentrations can increase the risk of venous thromboembolisms (VTEs), a rare but serious adverse event.

Because COCs are widely used in females of reproductive potential, and many investigational drugs are co-prescribed with COCs after approval, the DDI potential between an investigational drug and COCs should be evaluated during drug development and communicated in the labeling.

III. SITUATIONS WHERE COC DDI STUDIES SHOULD BE CONDUCTED

Cytochrome P450 (CYP) 3A is responsible for the metabolism of most commonly used progestins, although the relative contribution of CYP3A to the clearance of different progestins varies.[3] Other metabolic enzymes, including CYP2C19, and certain isoforms of uridine 5'-diphospho-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs), are also involved in the metabolism of certain progestins.[4] These enzymes share gene expression regulation pathways (e.g., pregnane X receptor, PXR) with CYP3A, although the induction of UGTs and SULTs is less well understood compared to CYPs. In general, CYP3A is more sensitive to induction than other enzymes involved in the metabolism of progestins such as CYP2C19, UGTs, and SULTs. Therefore, an investigational drug's induction effect on CYP3A can inform its potential to affect the pharmacokinetics of progestins in humans.

The metabolism of ethinyl estradiol (EE), the most commonly used estrogen in COCs, involves multiple enzymes (i.e., CYP3A, CYP2C9, UGT1A1, and SULT1E1).[4] Available information from clinical DDI studies suggests that moderate or strong inhibition of CYP3A combined with inhibition of other metabolic pathways of EE can significantly increase EE exposure levels higher than 50 mcg EE, the level at which there is an increased risk of serious adverse reactions, including VTEs.[5]

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[3] Li L, X Yang, D Tran, SK Seo, and Y Lu. 2023, Combined Oral Contraceptives as Victims of Drug Interactions, Drug Metab Dispos, doi: 10.1124/dmd.122.000854 (online ahead of print).

[4] 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.

[5] 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.

When an investigational drug for chronic use is expected to be co-administered with a COC in females of reproductive potential, and in vitro studies suggest that it is a CYP3A inducer or inhibitor, the sponsor can consider the following (see sections III.A-III.B) to determine whether a clinical DDI study should be conducted. Also, for an investigational drug that is given for short-term use, sponsors should discuss whether to conduct a DDI study with a COC with the appropriate FDA review division.

A. CYP3A Inducers

When in vitro data suggest that the investigational drug has the potential to induce CYP3A in humans, the sponsor can address the DDI potential with COCs via one of the pathways below (see also Figure 1 in the Appendix):

- If the investigational drug does not significantly decrease the area under the plasma concentration-time curve (AUC) of a sensitive CYP3A substrate (i.e., reducing the AUC of a sensitive CYP3A substrate by < 20 percent), then:

    - A COC DDI study might not be warranted when the investigational drug (and/or its metabolite when relevant) is not a CYP3A inhibitor in vitro or is not expected to inhibit CYP3A in humans.[6] In this scenario, the lack of effect of the drug on a CYP3A substrate from the clinical DDI study indicates that the drug does not induce CYP3A in humans. Hence, the drug is not expected to markedly decrease the systemic exposures of progestins/estrogens.

    - Further evaluation of the DDI potential with COCs could be recommended if the drug (and/or its metabolite when relevant) inhibits CYP3A in vitro and is expected to inhibit CYP3A in humans. 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 or shown as inhibition. 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 other enzymes, it could still decrease the AUC of COCs. Sponsors are encouraged to consult with the appropriate FDA review division on whether to conduct a DDI study with a COC in such cases.

- If the investigational drug is a weak CYP3A inducer (i.e., reducing 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. If the sponsor does not intend to conduct a COC DDI study, adequate justification should be provided. Some factors that should be taken into consideration include: (1) the projected magnitude of the interaction based on the study with a sensitive CYP3A substrate and other scientific evidence, such as a lack of concurrent CYP3A inhibition; and (2) whether the investigational drug shows nonclinical reproductive and

[6] Refer to the FDA guidance entitled *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

developmental toxicity findings of concern to humans.[7] Sponsors are encouraged to consult with the appropriate FDA review division in such cases.

- If the investigational drug is a moderate CYP3A inducer (i.e., reduces the AUC of a sensitive CYP3A substrate by ≥ 50 to < 80 percent), sponsors should consider conducting a dedicated DDI study with a COC to evaluate the magnitude of exposure change of the COC. In the absence of a dedicated DDI study, labeling should recommend avoiding concomitant use with COCs. If concomitant use cannot be avoided, an alternative contraceptive that is not affected by enzyme inducers (e.g., intrauterine system) or additional nonhormonal contraception (e.g., condoms) should be recommended, since the drug has the potential to reduce the exposure, and possibly the efficacy, of COCs.

- If an investigational drug is a strong CYP3A inducer (i.e., reduces the AUC of a sensitive CYP3A substrate by ≥ 80 percent), then significant reduction in exposures of COCs are likely to occur. Therefore, the labeling should recommend avoiding concomitant use with COCs. Furthermore, if the use of the CYP3A inducer is unavoidable, an alternative contraceptive method (e.g., intrauterine system) or additional nonhormonal contraception (e.g., condoms) should be recommended.

When a drug is shown or anticipated to significantly reduce the systemic exposures of progestins/estrogens, further evaluations could be considered to characterize the time for the induction effect to disappear. These additional evaluations could be helpful in identifying the duration that an alternative contraceptive method or additional nonhormonal contraception should be used after cessation of the investigational drug.

B. CYP3A Inhibitors

COCs containing 50 mcg of EE or more have been reported to be associated with clinically meaningful increases in the risk of serious adverse reactions, such as VTEs, compared to products containing less than 50 mcg of EE.[5] Therefore, an approximately 40 percent increase in EE concentration for COCs containing 35 mcg EE resulting in exposures similar to COCs containing 50 mcg 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: (1) prior clinical DDI 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 (2) in vitro or in vivo data suggest that the investigational drug also inhibits one or more other enzymes involved in the metabolism of EE (e.g., CYP2C9, UGT1A1, and SULT1E1).

[7] For more information, see the FDA guidance entitled *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021 ICH Revision 3).

Inhibition of SULT1E1 could lead to a significant increase in EE exposures.[8,9] Therefore, for investigational drugs that inhibit SULT1E1, a clinical DDI study with COCs should be considered or appropriate mitigation strategies should be proposed in labeling. Due to very limited in vitro and clinical DDI studies conducted for SULTs so far, a cut-off value for in vitro-to-in vivo extrapolation using basic equations similar to those recommended for CYP enzymes has not yet been established.

C. Teratogenic Drugs for Use in Females of Reproductive Potential

For investigational drugs that have teratogenic potential,[10,11] even if the results of in vitro or clinical DDI studies using a sensitive CYP3A substrate probe suggest weak or no induction potential on CYP3A, a COC DDI study should still be conducted. For teratogenic drugs that are moderate or strong inducers of CYP3A, the approach of evaluating for DDIs with a COC is the same as that described in Figure 1 and section III.A. For drugs that do not have teratogenic potential but are intended to be used with teratogenic drugs as a combination therapy, the sponsor should address the interaction potential with COCs as for teratogenic drugs. Sponsors are encouraged to consult with the appropriate FDA review division.

IV. DESIGN AND CONDUCT OF CLINICAL COC DDI STUDIES

A. Study Population

Premenopausal and postmenopausal females 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 pharmacokinetic (PK) parameters.

B. Choice of COC

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[8] Schwartz J, T Hunt, WB Smith, P Wong, P Larson, T Crumley, A Mehta, K Gottesdiener, N Agrawal, 2009, The Effect of Etoricoxib on the Pharmacokinetics of Oral Contraceptives in Healthy Participants, J Clin Pharmacol, 49(7):807-15.

[9] Helmer E, N Karimian, K Van Assche, I Seghers, S Le Tallec, G Cherala, G Scott, FS Namour, 2022, Ziritaxestat Drug-Drug Interaction with Oral Contraceptives: Role of SULT1E1 Inhibition, Clin Pharmacol Ther, Jun 17. doi: 10.1002/cpt.2689.

[10] 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.

[11] 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.

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. Since DRSP is more sensitive to CYP3A modulation,[12] a negative DDI result can be extrapolated to COCs containing progestins that are less sensitive to CYP3A induction (e.g., NET and LNG). Alternatively, studying the COCs containing less sensitive progestin can maximize the chances of confirming the lack of impact of a drug as an inducer on the specific progestin but would limit the ability to extrapolate the study results to other progestins (see section VI).

C. Dose

The investigational drug should be given at the highest proposed dose for labeling and should be dosed for a sufficient duration to ensure maximal modulation effect of the drug on metabolizing pathways of COCs.

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

D. Study Design

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

E. PK Sampling

Intensive PK sampling should be conducted for progestins and estrogens of the COC on PK assessment days to adequately characterize the maximum concentration (C_{max}) and AUC. In addition, PK sampling of the investigational drug is useful to ensure that adequate systemic exposures are achieved.

F. PD Assessments

Currently, the dose/exposure-response relationships of progestin and estrogen for contraceptive efficacy are not fully established. An approach for assessing PD parameters (e.g., estradiol, follicle stimulating hormone, luteinizing hormone, progesterone, and Hoogland score[13]) in addition to PK parameters can be considered, as it could provide supportive information when the geometric mean ratios of the systemic exposure parameters fall outside of the no-effect boundaries (see sections V and IX).

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[12] Wiesinger H, S Klein, A Rottmann, B Nowotny, K Riecke, I Gashaw, M Brudny-Klöppel, R Fricke, J Höchel, and C Friedrich, 2020, The Effects of Weak and Strong CYP3A Induction by Rifampicin on the Pharmacokinetics of Five Progestins and Ethinylestradiol Compared to Midazolam, Clin Pharmacol Ther, 108(4):798-807.

[13] Hoogland HJ and SO Skouby, 1993, Ultrasound Evaluation of Ovarian Activity Under Oral Contraceptives, Contraception, 47(6):583-90.

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, the area under the plasma concentration-time curve (AUC) integrated across the dosing interval ($AUC_{0\text{-}TAU}$) for multiple-dose studies, the AUC from time of administration extrapolated to infinity ($AUC_{0\text{-}inf}$) for single-dose studies, and C_{max}.

If the 90 percent confidence intervals (CIs) for the geometric mean ratio of the systemic exposure parameters 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 should be considered in addition to 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 versus decrease) when taken with the same investigational drug (i.e., a CYP3A inhibitor or inducer), quantitative extrapolation of DDI results from one progestin in a COC to another is challenging due to the different extent of CYP3A-mediated metabolism for each of these progestins.

DRSP is a more sensitive CYP3A substrate compared to certain approved progestins such as NET and LNG.[12] Therefore, the magnitude of exposure changes in DRSP due to CYP3A induction is expected to be larger than that for NET and LNG. For an investigational drug that is a CYP3A inducer, if a clinical DDI study with a DRSP-containing COC shows no interaction, the investigational drug is less likely to affect the PK of progestins in NET- and LNG-containing COCs.

VII. LABELING RECOMMENDATIONS

In general, the magnitude of the interaction and clinical consequences will guide labeling recommendations. For example:[14]

[14] For more examples, see a related FDA draft guidance entitled *Labeling for Combined Hormonal Contraceptives* (December 2017). When final, this guidance will represent the Agency's current thinking on this topic.

- If the increase in EE exposures leads to exposure levels exceeding those observed at an EE dose of 50 mcg, the drug's labeling should recommend avoiding concomitant use with COCs containing EE or to avoid use with a COC when EE exceeds a specific dose.

- If the investigational drug is an enzyme inducer that will decrease progestin or estrogen exposure to an extent that can lead to reduced effectiveness of the COC, the drug's labeling should recommend avoiding concomitant use with COCs. If use of the enzyme inducer is unavoidable, an alternative contraceptive that is not affected by enzyme inducers (e.g., an intrauterine system) or additional nonhormonal contraception (e.g., condoms) should be recommended in the labeling.

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

- Must describe clinically significant DDIs[15] and the mechanism of the clinically significant DDIs[16] (e.g., PK metabolism-based, PD interaction) if known, and should cross-reference to the CLINICAL PHARMACOLOGY[17] section of labeling for details of the DDI study results

- Should include the clinical effects of clinically significant DDIs

- Must include specific practical instructions for preventing or managing clinically significant DDIs[15] 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 a drug and the tested COC, the *Pharmacokinetics* subsection of CLINICAL PHARMACOLOGY section of the 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.*[17]

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

[15] 21 CFR 201.57(c)(8)(i).

[16] 21 CFR 201.57(c)(8)(i).

[17] For more information, see the FDA guidance entitled *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016).

VIII. ABBREVIATIONS

$AUC_{0\text{-}INF}$	Area under the plasma concentration-time curve (AUC) from time of administration extrapolated to infinity
$AUC_{0\text{-}TAU}$	Area under the plasma concentration-time curve integrated across the dosing interval
COC	Combined oral contraceptive
CIs	Confidence intervals
CYP	Cytochrome P450
DDI	Drug-drug interaction
DRSP	Drospirenone
EE	Ethinyl estradiol
FDA	Food and Drug Administration
IND	Investigational new drug application
LNG	Levonorgestrel
NDA	New drug application
NET	Norethindrone
NGM	Norgestimate
PD	Pharmacodynamic
PK	Pharmacokinetic
PLR	Physician labeling rule
POP	Progestin-only pill
SULTs	Sulfotransferases
UGTs	Uridine 5'-diphospho-glucuronosyltransferases
VTE	Venous thromboembolism

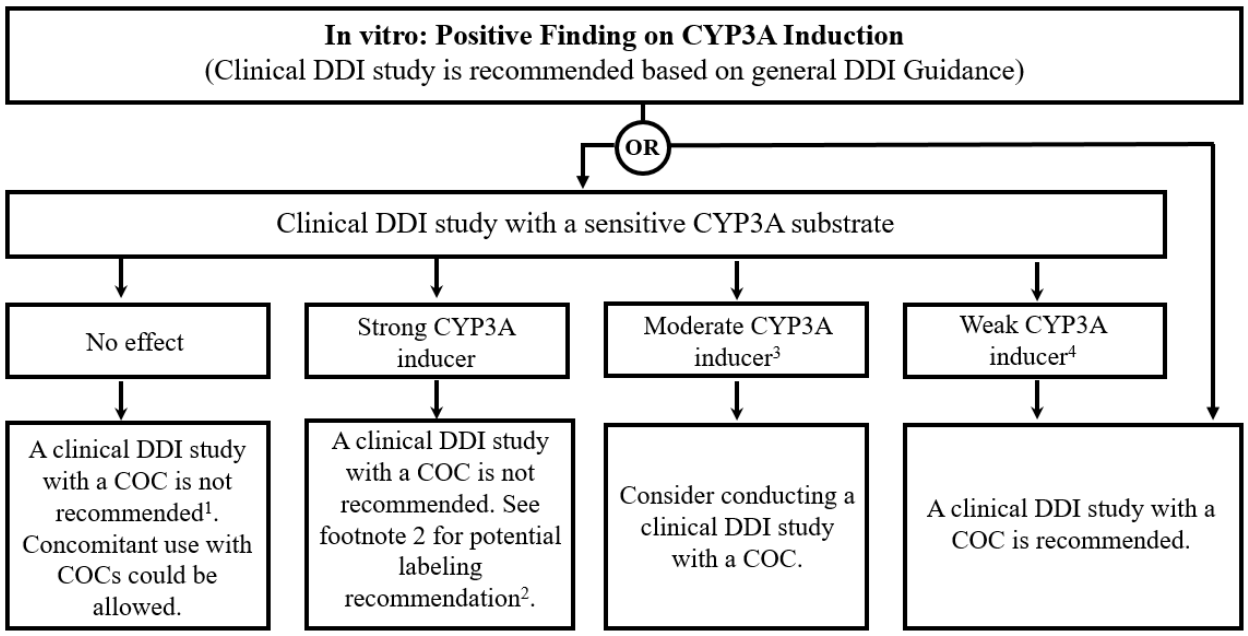
IX. DEFINITIONS

Inducer	An inducer is a drug that decreases the AUC of substrates of a given metabolic pathway.
Inhibitor	An inhibitor is a drug that increases the AUC of substrates 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).

X. APPENDIX

Figures 1 and 2 show decision trees for determining when clinical COC DDI studies should be conducted. It should be noted that these decision trees are not applicable for investigational drugs that have teratogenic potential or will be used in combination with teratogenic drugs (see section III.C).

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



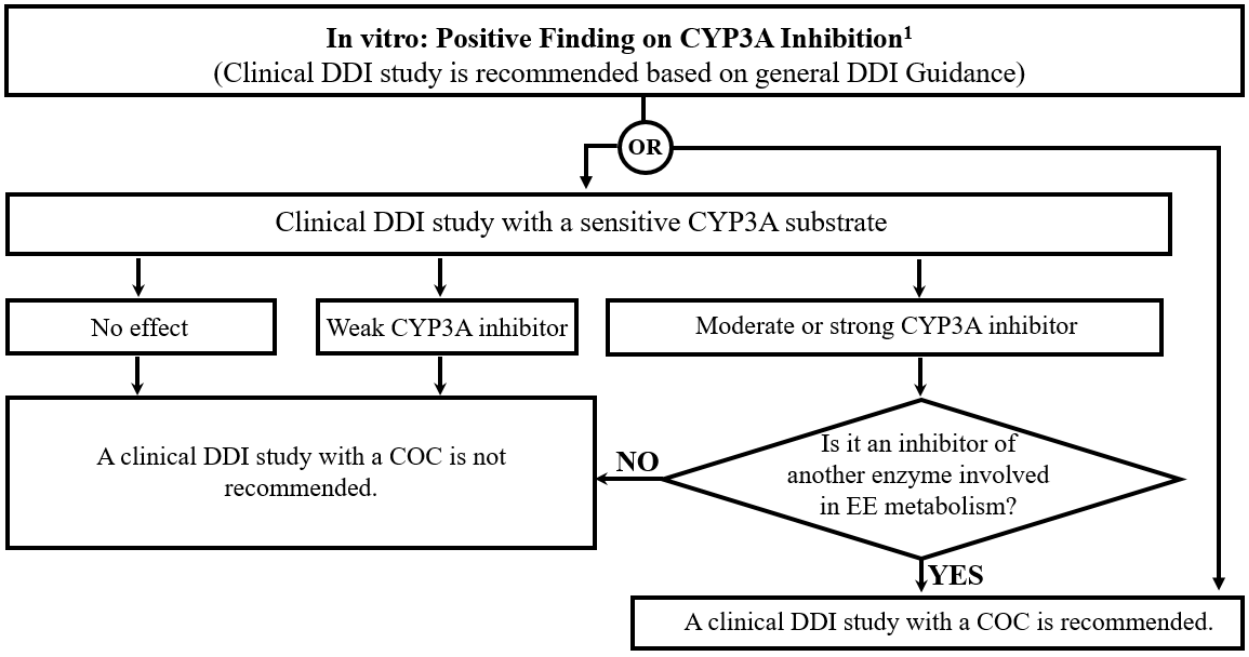
[1] A COC DDI study might not be recommended when the drug (and/or its metabolite when relevant) is not a CYP3A inhibitor in vitro or is not expected to inhibit CYP3A in humans; further evaluation of the DDI potential with COCs could be recommended if the drug (and/or its metabolite when relevant) inhibits CYP3A in vitro and is expected to inhibit CYP3A in humans, given the potential for the inhibitory effect to counteract the induction effect.

[2] For strong CYP3A inducers, labeling should recommend avoiding the use of this drug in patients taking COCs. If concomitant use cannot be avoided, use an alternative contraceptive that is not affected by enzyme inducers (e.g., intrauterine system) or additional nonhormonal contraception (e.g., condoms).

[3] 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. In the absence of a dedicated study, labeling should recommend avoiding the use of this drug in patients taking COCs. If concomitant use cannot be avoided, use an alternative contraceptive that is not affected by enzyme inducers (e.g., intrauterine system) or additional nonhormonal contraception (e.g., condoms).

[4] For weak CYP3A inducers, if sponsors do not intend to conduct a COC DDI study, adequate justification should be provided. Some factors that should be taken into consideration include: (1) the projected magnitude of the interaction based on the study with a sensitive CYP3A substrate and other scientific evidence such as a lack of concurrent CYP3A inhibition; and (2) whether the investigational drug shows any nonclinical reproductive and developmental toxicity. Sponsors are encouraged to consult the relevant review division in such cases.

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



[1] Inhibition of SULT1E1 *alone* can lead to a significant increase in EE exposures. For drugs that inhibit SULT1E1, regardless of its inhibitory effect on CYP3A, a clinical DDI study with COCs should be considered or appropriate mitigation strategies should be proposed in labeling.