Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications

Guidance for Industry

DRAFT GUIDANCE

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

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Clinical Pharmacology

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Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Elevation of gastric pH by acid-reducing agents (ARAs) can affect the solubility and dissolution characteristics of orally administered drug products. As a result, concomitant administration of a drug with an ARA could alter the bioavailability of the drug, potentially resulting in a loss of efficacy for weak-base drugs or increased adverse events for weak-acid drugs. ARAs such as antacids, histamine H_2-receptor antagonists (H_2 blockers), and proton pump inhibitors (PPIs) are widely used, and many of these drugs are available over the counter.[2,3] Consequently, there is an increased risk for clinically significant drug-drug interactions (DDIs) with concomitant administration of drugs with ARAs. Therefore, it is important to assess the susceptibility of an investigational drug to DDIs mediated by gastric-pH changes (referred to as pH-dependent DDIs) early in drug development, characterize the DDI effect with clinical studies when needed, and communicate the relevant findings in the drug product labeling.

This guidance describes the FDA's recommendations regarding: (1) when clinical DDI studies with ARAs are needed; (2) the design of clinical DDI studies; (3) how to interpret study results; and (4) communicating findings in drug product labeling.[4]

[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] Centers for Disease Control and Prevention's (CDC's) National Health and Nutrition Examination Survey, available at: https://www.cdc.gov/nchs/data/hus/hus16.pdf#079 (accessed May 16, 2018).

[3] Zhang L, F Wu, SC Lee, H Zhao, and L Zhang, 2014, pH-Dependent Drug-Drug Interactions for Weak Base Drugs: Potential Implications for New Drug Development, Clin Pharmacol Ther, 96(2):266-277.

[4] For general considerations regarding the evaluation of DDIs during drug development, see FDA's guidance for industry *Clinical Drug Interaction Studies – Cytochrome P450 Enzymes and Transporters-Mediated Drug Interactions* (January 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

This guidance does not cover other DDI mechanisms for some ARAs such as reduced absorption due to the formation of chelate complexes (e.g., aluminum or magnesium hydroxides, calcium carbonate) for weak-acid drugs and decreased renal elimination of certain drugs as a result of alkalization of urine (e.g., sodium bicarbonate). When appropriate, sponsors should evaluate the significance of these DDIs during drug development.

In general, FDA guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the current thinking of the Agency 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.

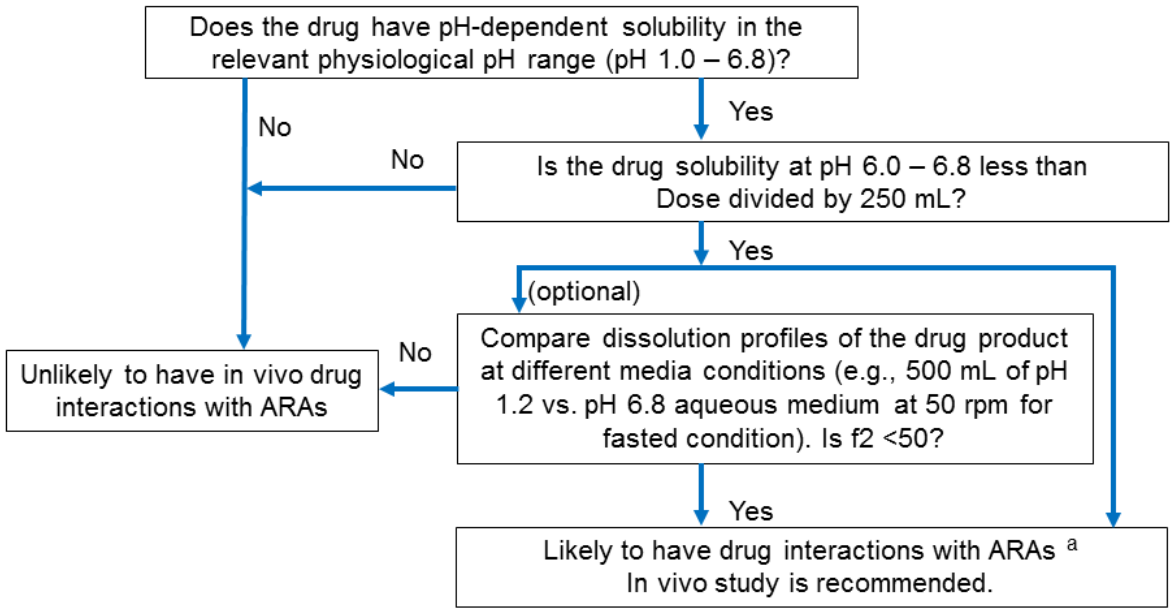
II. WHEN CLINICAL DDI STUDIES WITH ARAs SHOULD BE CONDUCTED

Sponsors should evaluate the potential of pH-dependent DDIs for a drug during early development to better inform dosing of the drug with ARAs in subsequent clinical trials, especially for those indications where a significant proportion of patients are likely to be taking ARAs.

A. Immediate-Release Products of Weak-Base Drugs

Most drugs that have demonstrated pH-dependent DDIs are weak bases with low intrinsic aqueous solubility compared to the solubility needed to dissolve the clinical dose (i.e., dose divided by 250 mL water). The potential for an interaction with an ARA for a new investigational drug can be assessed in a stepwise manner based on the physicochemical properties of the drug substance and dissolution data of the drug product (Figure 1). Sponsors should consult the appropriate review division if they pursue alternative strategies to evaluate pH-dependent DDIs.

Figure 1. A Framework to Assess Clinical DDI Risk With ARAs for Immediate-Release Products of Weak-Base Drugs



rpm – rounds per minute

f2 – similarity factor

[a] AUC or C_{max} of the investigational drug is anticipated to decrease on an average by 25% or more in the presence of an ARA. The clinical significance for an individual drug will be determined by the exposure or dose-efficacy relationship of individual drug.

The assessments should account for the following additional considerations:

- **Solubility**: It is important to characterize the aqueous solubility profile of the drug substance over a physiologically relevant pH range (e.g., 1.0 to 6.8), preferably in uniform increments (e.g., approximately one pH unit) such that any inflection in the profile is appropriately characterized. Since the pH of the medium for measuring solubility could be altered by a tested drug and deviate from the initial pH, the pH of the solution should be measured and adjusted, if necessary, to the original pH of the tested medium. The dose used to calculate the reference solubility (i.e., dose divided by 250 mL) should be the maximum single dose intended for registration.

- **Formulation and dose used in a dissolution test**: Dissolution data should be generated for the formulation intended for registration at the maximum dose.

- **Drugs intended to be taken only with food**: Gastric pH is elevated upon food intake. Thus, for a drug that is intended to be taken with food, the impact of a gastric-pH change should be evaluated by comparing solubility and dissolution profiles at conditions

representing the fed-state pH conditions to that of pH 6-6.8. For example, the evaluations can include pH 4-5 approximating the pH conditions after a high-fat and high-calorie meal and pH 2-3 approximating the pH after a light meal.[5,6,7] Besides elevating pH, food might increase the drug solubility in the GI tract due to the increase of bile salt concentrations under fed condition. Therefore, in vitro testing results might not be predictive of pH-mediated DDI under the fed condition.

B. Immediate-Release Products of Weak-Acid Drugs

There is limited experience with weak-acid drugs. It is possible that co-administration with a PPI or a H_2 blocker could result in a higher rate and/or extent (maximum concentration (C_{max}) and/or area under the concentration time curve (AUC)) of absorption for weak-acid drugs with low solubility at pH 1-2 and increased solubility at elevated pH. However, based on current data, the magnitude of pH-dependent DDIs for weak-acid drugs is generally modest. Thus, the need to conduct an in vivo study will depend on the safety profile of a drug.

C. Modified-Release Products

Extended-release or delayed-release products with pH-sensitive release mechanisms have the potential for DDIs with ARAs. There is very limited experience with in vivo pH-dependent DDIs for these modified-release products. Sponsors are encouraged to consult the appropriate review division.

In general, irrespective of the type of the product, if a drug is determined to have the potential for a pH-dependent DDI, the sponsor should conduct an in vivo study to characterize the effect of ARAs on the pharmacokinetics of the investigational drug (see section III) or provide a rationale justifying the lack of a pH-dependent DDI based on additional in vitro, in silico, and/or clinical information.

III. DESIGN AND CONDUCT OF CLINICAL DDI STUDIES

- **Study population:** Generally, standalone studies can be conducted in healthy subjects to characterize the interaction potential with ARAs. Safety considerations could preclude the use of healthy subjects for testing certain drugs (e.g., cytotoxic drugs). The number

[5] Surofchy DD, LA Frassetto, and LZ Benet, 2019, Food, Acid Supplementation and Drug Absorption-A Complicated Gastric Mix: A Randomized Control Trial, Pharm Res, 36(11):155.

[6] Koziolek M, F Schneider, M Grimm, C Mode, A Seekamp, T Roustom, W Siegmund, and W Weitschies, Intragastric pH and Pressure Profiles After Intake of the High-Caloric, High-Fat Meal as Used for Food-Effect Studies, 2015, J Control Release, 220(PT A):71-78.

[7] Simonian HP, L Vo, S Doma, RS Fisher, and HP Parkman, 2005, Regional Postprandial Differences in pH Within the Stomach and Gastroesophageal Junction, Dig Dis Sci, 50(12):2276-2285.

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

- **Study design:** Crossover studies (fixed-sequence or randomized) are preferred as they account for intersubject variability. A parallel study design can be considered if an investigational drug has a long half-life.

- **Choice of ARAs:** Selection of ARAs and associated dosing regimens for DDI studies depend on the purpose (e.g., characterization of a worst-case scenario or identification of an appropriate mitigation strategy such as staggered administration). Some considerations are discussed in detail below.

  - **PPIs:** Pre-treatment with PPIs for several days (e.g., 4 to 5 days) is needed to reach the pharmacodynamic steady-state of PPIs before administering the investigational drug. The effect of PPIs on gastric pH is long lasting, and thus staggered administration of an investigational drug with a PPI is not expected to mitigate the DDI risk (see section V for additional considerations).

    The elevating effect of PPIs on gastric pH (e.g., mean pH over 24 hours, percentage of the time when the pH $\geq$ 4.0 in a 24-hour interval) is dependent on the individual PPI and its dose. It is preferable to select a PPI and a dose that is expected to provide a near maximum effect on pH elevation (e.g., 40 mg esomeprazole, 20 mg rabeprazole).[8, 9]

  - **H_2 blockers:** In general, administration of H_2 blockers ahead (e.g., 2 hours) of the investigational drug can maximize the pH-elevating effect. Since H_2 blockers result in a relatively shorter duration of pH increase than PPIs, the pH-dependent DDI risk could be reduced or avoided for a drug with staggered administration of H_2 blockers. For example, administration of an investigational drug 2 hours before and 10 to 12 hours after dosing of H_2 blockers could mitigate the risk (see section V for additional considerations).

  - **Antacids:** A single-dose administration could be used for antacids due to their direct gastric acid neutralizing effect. Because of their short-lasting effect on gastric pH, administration of an investigational drug 2 hours before or after antacid dosing is generally not expected to result in a pH-dependent DDI (see section V for additional considerations).

  - **Additional considerations:** Interacting mechanisms other than gastric-pH changes should be taken into consideration when choosing an ARA to study. For example,

[8] Miner P, PO Katz, Y Chen, M Sostek, 2003, Gastric Acid Control With Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, and Rabeprazole: A Five-Way Crossover Study, Am J Gastronenterol, 98(12):2616-20.

[9] Kirchheiner J, S Glatt, U Fuhr, U Klotz, I Meineke, T Seufferlein, J Brockmöller, 2009, Relative Potency of Proton-Pump Inhibitors-Comparison of Effects on Intragastric pH, Eur J Clin Pharmacol, 65(1):9-31.

omeprazole is a known inhibitor of CYP2C19, and cimetidine inhibits multiple CYP enzymes and transporters (e.g., CYP2D6, CYP3A4, MATE1 and MATE2/K). It is preferable to select an ARA that does not exhibit other interacting mechanisms (see section I). Also, an ARA should not be used in a DDI study if its pharmacokinetics are anticipated to be affected by the investigational drug.

- **Dose:** To characterize the worst-case scenario, the sponsor should select the maximum recommended dose of an ARA. The maximum dose of an investigational drug that is intended for therapeutic use is recommended since it is more susceptible to gastric pH-dependent DDI effects. The sponsor should provide a justification if an alternative dose or dosing regimen is proposed.

- **Dosing frequency of investigational drug:** Single-dose administration of the investigational drug is acceptable, unless: (1) there is a change in drug absorption after multiple doses; or (2) the study has to be conducted in patients, and single-dose administration is not beneficial to patients who need continuous treatment.

- **Food intake:** If an investigational drug is intended to be taken in the fasted state, the study should be conducted under fasted conditions. If the investigational drug is intended to be taken without regard to food, the study should be conducted under fasted conditions as it is likely to represent the worst-case scenario. If the investigational drug is intended to be taken with food, the study should be conducted under fed conditions that are consistent with the procedures for late-phase clinical trials or approved labeling.

- **Pharmacokinetic sampling and data collection:** Pharmacokinetic (PK) sampling times should be sufficient to adequately characterize the $AUC_{0\text{-}INF}$ (or $AUC_{0\text{-}TAU}$ for multiple-dose studies), the C_{max}, the time to reach C_{max} (T_{max}), and if clinically significant, the minimal concentration (C_{min}) of an investigational drug administered alone and when co-administered with an ARA. The sponsor should also determine active metabolite concentrations if the metabolites contribute to the investigational drug's efficacy or safety.

IV. ALTERNATIVE APPROACHES FOR EVALUATING pH-DEPENDENT DDIs

- **Population pharmacokinetic (PopPK) analysis:** DDIs with ARAs can be evaluated within clinical trials using PopPK analyses. General design considerations for such analyses can be found in the FDA draft guidance for industry entitled *Population Pharmacokinetics* (July 2019).[10] Some considerations specific to ARAs are discussed below.

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

- **Record of the dosing information:** The pH-dependent DDI effect is sensitive to the time of administration of the investigational drug relative to the ARA (e.g., H_2 blockers or antacids) and can also be affected by the dose of ARAs and the intake of food. Thus, it is critical to have a prospective plan to ensure that relevant information such as dose, timing, and duration of administration of the investigational drug and ARAs as well as food intake and content (e.g., fasted, high-fat, normal, or light meal) are accurately captured.

- **PK sampling:** A pH-dependent DDI is expected to affect drug absorption; therefore, it is important to have sufficient blood sampling during the absorption phase of the investigational drug to better capture the potential DDI effect.

- **Data analysis:** Since the gastric pH-elevating effects of PPIs, H_2 blockers, and antacids have different durations, it is appropriate to evaluate these ARAs by different classes (e.g., using PPIs, H_2 blockers, and antacids as three separate covariates). If feasible, it can be useful to compare the systemic exposure of the drug between patients taking ARAs throughout the trial and patients taking ARAs periodically during the trial.

- **Physiologically based PK simulations:** In conjunction with the assessment framework outlined in Figure 1, physiologically based PK (PBPK) simulations can sometimes be used to further assess the potential for pH-dependent DDIs. PBPK approaches can also be useful to inform clinical study designs. The application of PBPK is still evolving, and new applications of PBPK simulation are continuously being evaluated by the FDA. Therefore, sponsors are encouraged to consult the appropriate review division.

V. EXTRAPOLATING CLINICAL DDI STUDY RESULTS

- In general, the effects observed with an investigational drug and one ARA from a dedicated DDI study can be extrapolated to other ARAs within the same class (i.e., from one PPI to other PPIs at dose levels that achieve a similar gastric-pH elevating effect).

- Extrapolation of the findings with an ARA to other in-class ARAs will be confounded when a dedicated DDI study is conducted with an ARA that has multiple interacting mechanisms besides a change in gastric pH.

- A framework is presented below as an example for how to extrapolate results from a dedicated study conducted with an immediate-release product of a weak-base drug and a PPI and develop labeling recommendations (Figure 2). Sponsors are encouraged to consult the appropriate review division if they pursue alternative strategies to evaluate pH-dependent DDIs.

- PPIs represent a worst-case scenario for pH-dependent DDIs due to their long-lasting effects on gastric pH. Thus, a negative result from a dedicated study with a PPI indicates

the lack of a pH-dependent DDI for an investigational drug. Whether PK results are considered as clinically significant should be determined based on the exposure-response (e.g., efficacy) relationship of an investigational drug.

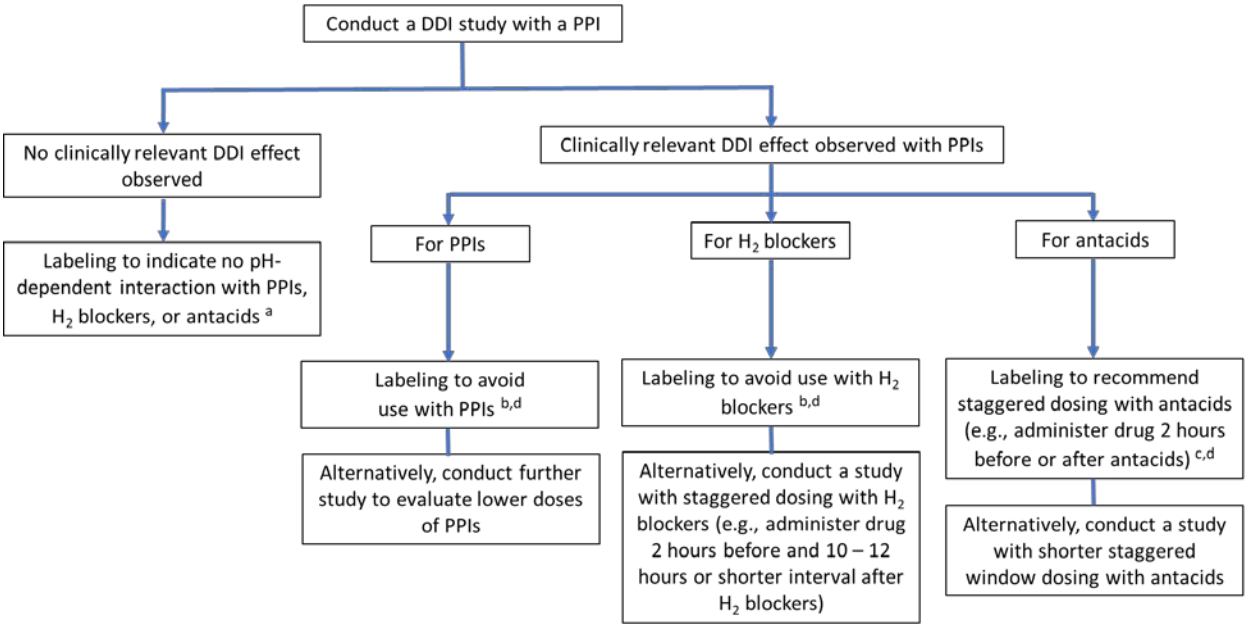
- If the study with a PPI demonstrates a clinically significant change in the exposure of an investigational drug, there are several implications for labeling and further considerations discussed below.

  - **PPIs:** The labeling should indicate to avoid the use of the drug with PPIs. Alternatively, the sponsor can consider conducting an additional study to evaluate the impact of a lower dose of a PPI. If the pH-dependent DDI risk is mitigated with the lower dose of the PPI, the labeling can provide more flexibility for patients.

  - **H_2 blockers:** The labeling should indicate to avoid the use of the drug with H_2 blockers. Alternatively, sponsors can conduct an additional study to evaluate the interaction potential of staggered dosing with H_2 blockers (e.g., administered drug 2 hours before and 10 to 12 hours after H_2 blockers). It could be challenging for patients to follow the above staggered dosing schedule, especially for drugs that are administered twice daily or more often. The sponsor can explore different staggered dosing schedules to identify a more clinically practical dosing regimen to mitigate the risk of pH-dependent DDIs.

  - **Antacids:** The labeling can indicate that the drug dosing can be staggered with antacids (e.g., administer drug 2 hours before or after antacids). Alternatively, sponsors can consider an additional study to evaluate a shorter staggered dosing window with antacids. If the pH-dependent DDI risk is also mitigated under these conditions, the labeling can provide more flexibility for patients.

Figure 2. Extrapolating Clinical DDI Study Results and Implications for Immediate-Release Products of Weak-Base Drugs



[a] Drug Interaction Studies heading under Section 12.3 of the Prescription Drug Labeling (PDL) stating the lack of clinically significant differences in drug pharmacokinetics when used concomitantly with PPIs, H_2 blockers, or antacids, without additional detail.

[b] Drug Interaction Studies heading under Section 12.3 of the PDL with essential study results, and Section 7 with a description of the interaction and a recommendation to avoid use with PPIs and H_2 blockers.

[c] Drug Interaction Studies heading under Section 12.3 of the PDL with essential study results, Section 7 with a description of the interaction and a statement recommending staggered dosing with antacids, and Section 2 with specific instructions for staggered dosing with antacids.

[d] Communication of this information in other labeling sections (e.g., WARNINGS AND PRECAUTIONS) could also be warranted.

- For more specific recommendations on content and format of the relevant labeling sections, refer to the following FDA guidances for industry:

  - *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2016)

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

  - *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Prescription Drug and Biological Products — Content and Format* (October 2011)

- *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (December 2014)