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

Guidance for Industry

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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Guidance for Industry[1]

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I. INTRODUCTION

Elevation of gastric pH by acid-reducing agents (ARAs) can affect the solubility and dissolution characteristics of some orally administered drugs. 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 these drugs are available through prescription and also over the counter.[2,3] Consequently, there is a potential 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 and mitigation options where available 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 such clinical DDI studies; (3) how to interpret these study results; and (4) communicating these findings in drug product labeling.[4]

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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] 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 April 1, 2022).

[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 the FDA guidance entitled *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 the alkalinization of urine (e.g., sodium bicarbonate). When appropriate, sponsors should evaluate the significance of these DDIs during drug development.

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. WHEN CLINICAL DDI STUDIES WITH ARAs SHOULD BE CONDUCTED

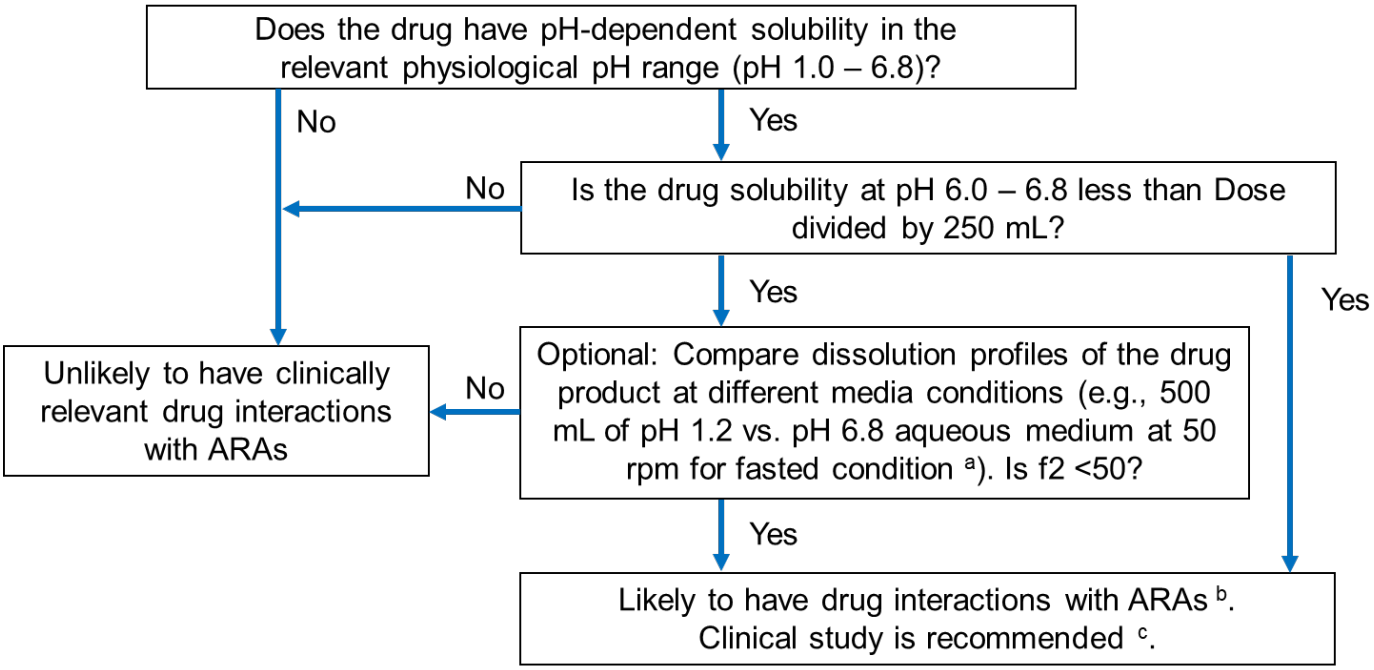
Sponsors should assess the potential of pH-dependent DDIs for a drug during early development to better inform dosing of the drug with ARAs in subsequent clinical trials, especially for those indications where a significant proportion of patients are likely to be taking ARAs. In general, if a drug is determined to have the potential for a pH-dependent DDI, the sponsor should conduct a clinical 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 in vitro, in silico, or clinical information.

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., the highest therapeutic dose divided by 250 mL). The potential for an investigational drug to have an interaction with an ARA can be assessed in a stepwise manner based on the physicochemical properties of the drug substance and dissolution profiles of the drug product.[5] A framework is presented below as an example for how to assess clinical DDI risk with ARAs (Figure 1). Sponsors should consult the appropriate review division if they pursue alternative strategies to evaluate pH-dependent DDIs.

[5] Miao L, F Wu, X Yang, YM Mousa, A Ramamoorthy, SC Lee, K Raines, L Zhang, and P Seo, 2022, Application of Solubility and Dissolution Profile Comparison for Prediction of Gastric pH-Mediated Drug-Drug Interactions, AAPS J, 24(35):https://doi.org/10.1208/s12248-022-00684-3.

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



rpm – revolutions per minute

f2 – similarity factor[6]

[a] When appropriate, with justification, other dissolution parameters (e.g., apparatus, speed) and biorelevant media can be selected based on the properties of the drug substance and product.[7,8,9,10]

[6] For more information, see the FDA guidance entitled *M9 Biopharmaceutics Classification System-Based Biowaivers* (May 2021).

[7] Markopoulos C, CJ Andreas, M Vertzoni, J Dressman, C Reppas, 2015, In Vitro Simulation of Luminal Conditions for Evaluation of Performance of Oral Drug Products: Choosing the Appropriate Test Media, Eur J Pharm Biopharm, 93:173-82.

[8] Mann J, J Dressman, K Rosenblatt, L Ashworth, U Muenster, K Frank, P Hutchins, J Williams, L Klumpp, K Wielockx, P Berben, P Augustijns, R Holm, M Hofmann, S Patel, S Beato, K Ojala, I Tomaszewska, J Bruel, J Bulter, 2017, Validation of Dissolution Testing With Biorelevant Media: An OrBiTo Study, Mol Pharm, 14(12):4192-4201.

[9] Dressman JB, M Vertzoni, K Goumas, C Reppas, 2007, Estimating Drug Solubility in the Gastrointestinal Tract, 2007, Adv Drug Deliv Rev, 59(7):591-602.

[10] Segregur D, T Flanagan, J Mann, A Moir, EM Karlsson, M Hoch, D Carlile, S Sayah-Jeanne, J Dressman, 2019, Impact of Acid-Reducing Agents on Gastrointestinal Physiology and Design of Biorelevant Dissolution Test to Reflect These Changes, J Pharm Sci, 108(11):3461-3477.

[b] The average AUC or C_{max} of the investigational drug is anticipated to decrease by 25 percent or more in the presence of an ARA.[11] The clinical significance of this decrease for an investigational drug should be determined based on the dose/exposure-efficacy relationship of individual drug.

[c] Alternative approaches (e.g., population pharmacokinetic or physiologically based pharmacokinetic modeling, see section IV) can be considered.

The assessments should account for the following additional considerations:

- **Solubility**: It is important to characterize the aqueous equilibrium solubility profile of the drug substance over a physiologically relevant pH range (e.g., 1.0 to 6.8).[12] The pH values to conduct solubility measurements should be chosen, for example, in uniform increments (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 reported. The dose used to calculate the reference solubility (i.e., dose divided by 250 mL) should be the maximum therapeutic dose intended to be marketed.

- **Formulation and dose used in a dissolution test**: Dissolution data can be generated for an initial formulation during early drug development to help assess the liability of pH-dependent DDIs for an investigational drug. In addition, the dissolution test should also be performed and reported for the formulation intended to be marketed at the maximum therapeutic dose.

- **Drugs intended to be taken only under fed condition:** Gastric pH is elevated upon food intake. Thus, for a drug that is intended to be taken under fed conditions, the impact of gastric-pH changes 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, pH 4-5 approximates the pH condition after a high-fat and high-calorie meal, and pH 2-3 reflects the pH condition after a light meal.[13,14,15] However, assessing pH-dependent DDI liability based on in vitro pH-solubility and -dissolution profiles can be

[11] 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.

[12] See the FDA guidance entitled *M9 Biopharmaceutics Classification System-Based Biowaivers* (May 2021).

[13] 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.

[14] 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.

[15] 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.

challenging because besides elevating pH, food intake stimulates secretion of bile acid which could increase drug solubility in the gastrointestinal tract. Under these circumstances, sponsors should consult with review Divisions.

B. Immediate-Release Products of Weak-Acid Drugs

There is less experience with the evaluation of the impact of pH-dependent DDIs for weak-acid drugs compared to weak-base drugs. It is possible that co-administration with a PPI or a H_2 blocker could result in a higher rate or extent (maximum concentration (C_{max}) 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 data from currently approved weak-acid drugs, the magnitude of pH-dependent DDIs for weak-acid drugs is generally small. Whether to conduct a clinical study depends on the safety profile or dose/exposure-safety relationship of a weak-acid 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 clinical pH-dependent DDI evaluation for these modified-release products. Sponsors should consult the appropriate review division for drugs that have a modified-release profile that could have a pH-dependent DDI liability.

III. DESIGN AND CONDUCT OF CLINICAL DDI STUDIES

- **Study population:** Generally, dedicated 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) in which case these studies should be performed in patients for whom the investigational drug is being developed. The number 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 to reduce inter-subject variability. A parallel study design can be considered if a drug has a long half-life.

- **Choice of ARAs:** Selection of ARAs and associated dosing regimens for DDI studies depends on the purpose (e.g., characterization of a worst-case scenario or identification of an appropriate mitigation strategy such as staggered administration). Among the currently approved ARAs, PPIs result in prolonged effects on gastric pH; therefore, it is recommended that the study be conducted with or include a PPI. Effects of other classes

of ARAs can be evaluated as alternatives as needed. Some considerations are discussed in detail below.

- **PPIs:** Pre-treatment with PPIs for several days (e.g., 4 to 7 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 effect of PPIs on gastric pH (e.g., mean pH over 24 hours, percentage of the time when the pH ≥4 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.[16,17]

- **H_2 blockers:** In general, administration of single or multiple doses of H_2 blockers ahead of the investigational drug (e.g., 2 hours) can maximize the pH-elevating effect.[18,19] 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). Such a strategy should be confirmed with a clinical study.

- **Antacids:** Concomitant administration of a single dose of an antacid could be used due to their direct gastric acid neutralizing effect.

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

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[16] 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.

[17] 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.

[18] Hedenström H, C Alm, M Kraft, A Grahnén, 1997, Intragastric pH After Oral Administration of Single Doses of Ranitidine Effervescent Tablets, Omeprazole Capsules and Famotidine Fast-Dissolving Tablets to Fasting Healthy Volunteers, Aliment Pharmacol Ther, 11(6):1137-41.

[19] Miner Jr, PB, LD Allgood, JM Grender, 2007, Comparison of Gastric pH with Omeprazole Magnesium 20.6 mg (Prilosec OTC) o.m. Famotidine 10 mg (Pepcid AC) b.d. and Famotidine 20 mg b.d. Over 14 Days of Treatment, Aliment Pharmacol Ther, 25(1):103-9.

- **Dose:** To characterize the worst-case scenario, sponsors should select the highest dose of an ARA in the DDI study that is commonly used in clinical practice (e.g., 40 mg esomeprazole, 40 mg omeprazole, 40 mg pantoprazole). The maximum recommended dose of an investigational drug that is intended for therapeutic use is recommended since it is more susceptible to pH-dependent DDI effects. Sponsors should provide a justification if an alternative dose or dosing regimen is proposed.

- **Formulation:** The pH-dependent DDI effect can be formulation dependent. Thus, a dedicated study is recommended with the to-be-marketed formulation of an investigational drug. It is recognized that such a formulation might not be available during early drug development. If a study is performed with an early formulation, the sponsor should provide a rationale that justifies why the pH-dependent DDI effect can be extrapolated to the to-be-marketed formulation.

- **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 late-phase clinical trials. Administration of a drug with a high-fat meal could underestimate the pH-dependent DDI effect of ARAs compared to other types of food, since high-fat meals elevate the baseline gastric pH more than other meals and stimulate more secretion of bile acids which help solubilize drugs.

- **Pharmacokinetic sampling and data collection:** Pharmacokinetic (PK) sampling times should be sufficient to adequately characterize the $AUC_{0\text{-}INF}$ (or steady-state $AUC_{0\text{-}TAU}$ for multiple-dose studies), the C_{max}, the time to reach C_{max} (T_{max}), and if clinically relevant, the minimal concentration (C_{min}) or partial AUC of an investigational drug administered alone and when co-administered with an ARA. Sponsors 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 analysis:** DDIs with ARAs can be evaluated within clinical trials using population pharmacokinetic analyses. General design considerations

for such analyses can be found in the FDA guidance for industry entitled *Population Pharmacokinetics* (February 2022). Some considerations specific to ARAs are discussed below.

- **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 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 (PBPK) simulations:** In conjunction with the assessment framework outlined in Figure 1, 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 applications of PBPK are still evolving and are continuously being evaluated by the FDA. Therefore, sponsors are encouraged to consult the appropriate review division if they pursue a PBPK simulation approach to evaluate pH-dependent DDIs. General considerations for using PBPK approaches in drug development can be found in the FDA guidance for industry entitled *Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry* (August 2018).[20]

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).

[20] Also see the FDA draft guidance entitled *The Use of Physiologically Based Pharmacokinetic Analyses - Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls* (September 2020). When final, this guidance will represent the Agency's current thinking on this topic.

- Extrapolation of the findings with an ARA to other in-class ARAs may 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 for extrapolating results from a dedicated study to develop labeling recommendations. The framework depicts the example of a weak-base, immediate-release investigational drug product evaluated with a PPI (Figure 2). Sponsors should consult the appropriate review division if they pursue alternative strategies to evaluate pH-dependent DDIs.

- In general, 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 or safety) relationship of an investigational drug. Refer to the FDA guidance for industry entitled *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) for recommendations regarding interpreting the results of the DDI studies.

- If the study of the investigational drug with a PPI demonstrates a clinically significant change in the exposure of an investigational drug, the FDA has the following recommendations regarding mitigation strategies and for conducting additional studies with the investigational drug to optimize DDI mitigation:

    - **PPIs:** 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.

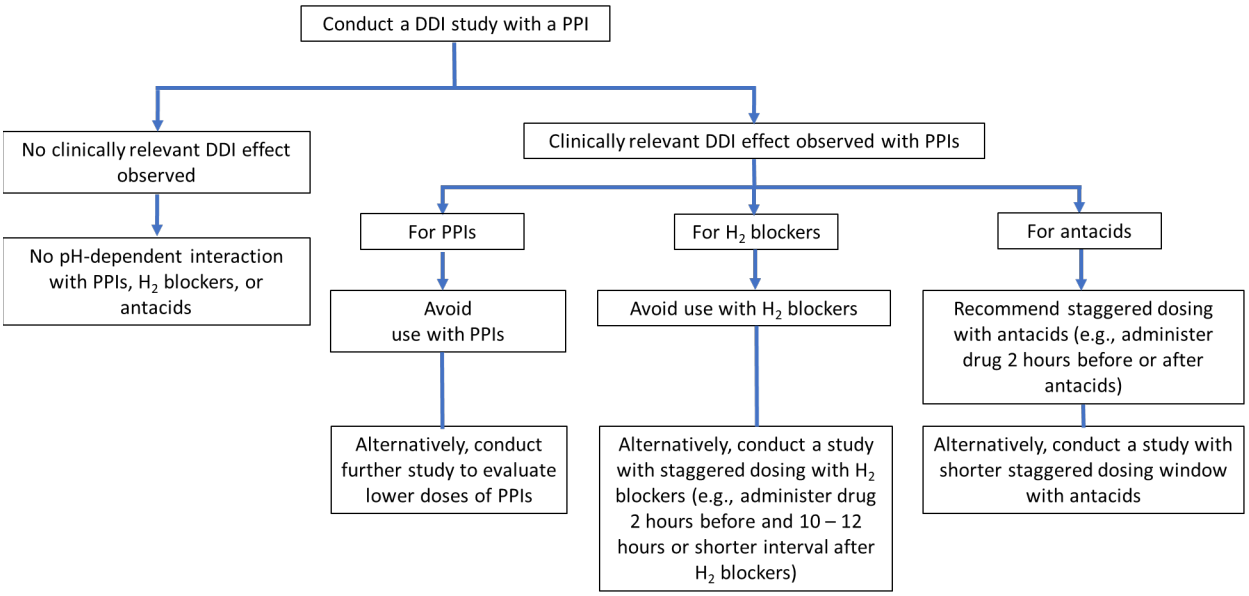
    - **H_2 blockers:** Avoid the use of the drug with H_2 blockers. Alternatively, the sponsor can conduct an additional study with the investigational drug to evaluate one or more staggered dosing schedules to identify a clinically practical dosing regimen to mitigate the risk of pH-dependent DDIs.

    - **Antacids:** Drug dosing can be staggered with antacids (e.g., administer the drug 2 hours before or 2 hours after antacid use) because the antacid effect is short-term.[21] If needed, the sponsor can conduct a study to evaluate a shorter period of staggered dosing of the investigational drug with antacids.

    Such mitigation strategies should be appropriately communicated in labeling.

[21] Lin, MS, P Sun, HY Yu, 1998, Evaluation of Buffering Capacity and Acid Neutralizing-pH Time Profile of Antacids, J Formos Med Assoc, 97(10):704-10.

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



VI. LABELING RECOMMENDATIONS

The Prescribing Information must contain a summary of essential scientific information needed for the safe and effective use of the drug by the healthcare provider.[22] For specific requirements and recommendations regarding how to incorporate DDI information in labeling, refer to 21 CFR 201.57 and the following FDA guidances:[23,24]

- *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for 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)*

[22] 21 CFR 201.56(a)(1).

[23] For additional human prescription drug labeling guidance documents, see the FDA's Labeling Resources for Human Prescription Drugs website (available at https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs).

[24] Also see the FDA draft guidance entitled *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023). When final, this guidance will represent the Agency's current thinking on this topic.

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