U.S. FOOD & DRUG ADMINISTRATION

Guidance Snapshot for Industry

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

Final Guidance for Industry

What is recommended in this guidance?

This final guidance provides current FDA recommendations on evaluating pH-dependent drug-drug interactions (DDIs) during drug development, including:

- When clinical studies are needed to assess pH-dependent DDIs
- Design and interpretation of clinical DDI studies to assess pH-dependent DDIs
- Management of pH-dependent DDIs via labeling recommendations

Why is this guidance important?

A DDI can occur when two or more drugs are co-administered. Acid-Reducing Agents (ARAs) are widely used drugs that can treat a number of disorders, including heartburn. ARAs can elevate gastric pH, which could alter the bioavailability of concomitantly administered drugs, potentially resulting in loss of efficacy or increased toxicity.

What are Acid-Reducing Agents (ARAs)?

- ARAs are among the most commonly used drugs in the U.S.
- Common ARAs include antacids, histamine H2-receptor antagonists (H2 blockers), and proton pump inhibitors (PPIs)
- Many ARAs are available over the counter
- ARAs work by reducing acid in the stomach and are used for a number of disorders, including heartburn

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about the evaluation of gastric pH-dependent drug interactions with acid-reducing agents, read the guidance.

Assessment of pH-Dependent DDI Potential

Why:	When:	How:
Drug developers should assess the potential for pH-dependent DDIs during development of an investigational new drug because ARAs are among the most commonly used drugs in the U.S. and pH-dependent DDIs can result in a loss of efficacy or increased toxicity for concomitantly administered drugs.	It is important to assess the susceptibility of investigational drugs to DDIs mediated by changes in gastric pH early in drug development.	This guidance describes approaches for: ✓ Assessment of DDI risk with an ARA based on the physicochemical properties of the investigational drug substance and dissolution profiles of the drug product ✓ Characterization of DDI effects, including clinical investigations when appropriate ✓ Communication of relevant findings in drug product labeling

Drug Development Timeline

* Apply the Guidance Recommendations Early in Drug Development

BASIC RESEARCH

PROTOTYPE DESIGN OR DISCOVERY

PRECLINICAL DEVELOPMENT*

Sponsors should perform an assessment of DDI risk with an ARA based on the physicochemical properties of the investigational drug.

CLINICAL DEVELOPMENT*

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 or provide a rationale justifying the lack of a pH-dependent DDI based on in vitro, in silico, or clinical information.

FDA FILING & APPROVAL

POSTMARKET OR POSTAPPROVAL STUDIES

Guidance Recap Podcast

Hear highlights from FDA staff

Speaker(s): Xinning Yang, PhD, and Anuradha Ramamoorthy, PhD

Click here to listen

Click here to read transcript

Guidance Snapshots are a communication tool and are not a substitute for the guidance document.

To learn more about the evaluation of gastric pH-dependent drug interactions with acid-reducing agents, **read the guidance**.

To see additional Guidance Snapshots, **check out the pilot program**.