FINAL GUIDANCE:

Evaluation of Gastric pH-DDIs With ARAs: Study Design, Data Analysis, & Clinical Implications

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SBIA Webinar

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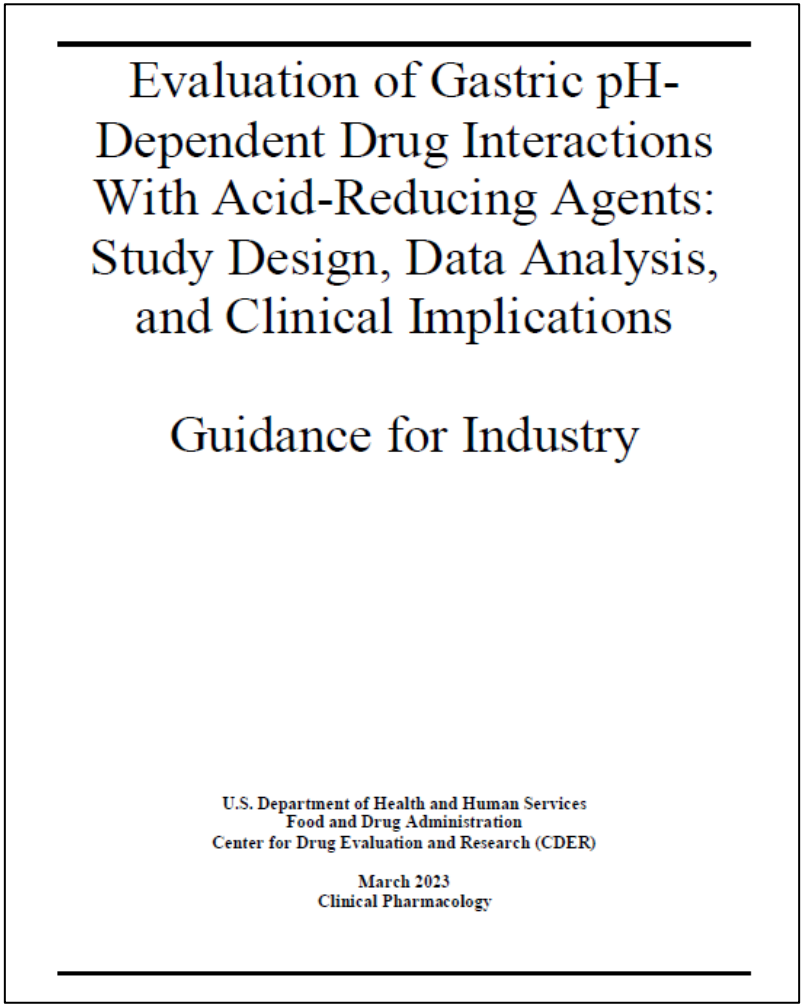


Guidance link

Guidance Recommendations

FDA's recommendation regarding:


When clinical DDI studies with ARAs are needed


Design of clinical DDI studies


Interpretation of study results


Communication of findings in the labeling

Guidance Recommendations

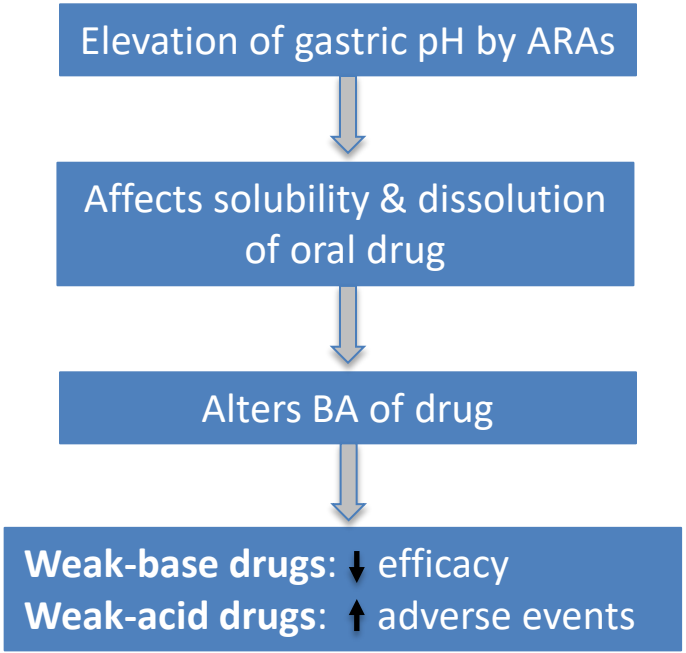
Why is it Important to Assess Gastric pH-Dependent DDIs?

Acid Reducing Agents (ARAs)

- **Antacids**
  Example: Aluminum hydroxide, Magnesium hydroxide, Magnesium trisilicate, Calcium carbonate

- **Histamine receptor antagonists** (H2 blockers)
  Example: Famotidine, Ranitidine, Nizatidine, Cimetidine

- **Proton pump inhibitors** (PPIs)
  Example: Omeprazole, Esomeprazole, Lansoprazole, Dexlansoprazole, Pantoprazole, Rabeprazole, Vonoprazan



Guidance Recommendations

When Should DDI Risk Assessment be Conducted?

- **Early in development** to inform subsequent decisions
  - Especially for indications where a significant proportion of patients are likely to be taking ARAs

- If pH-dependent DDI potential is identified, a **clinical study** to characterize the effect of ARAs on investigational drug PK

- Alternatively, provide rationale to justify the lack of concern

Products Considered

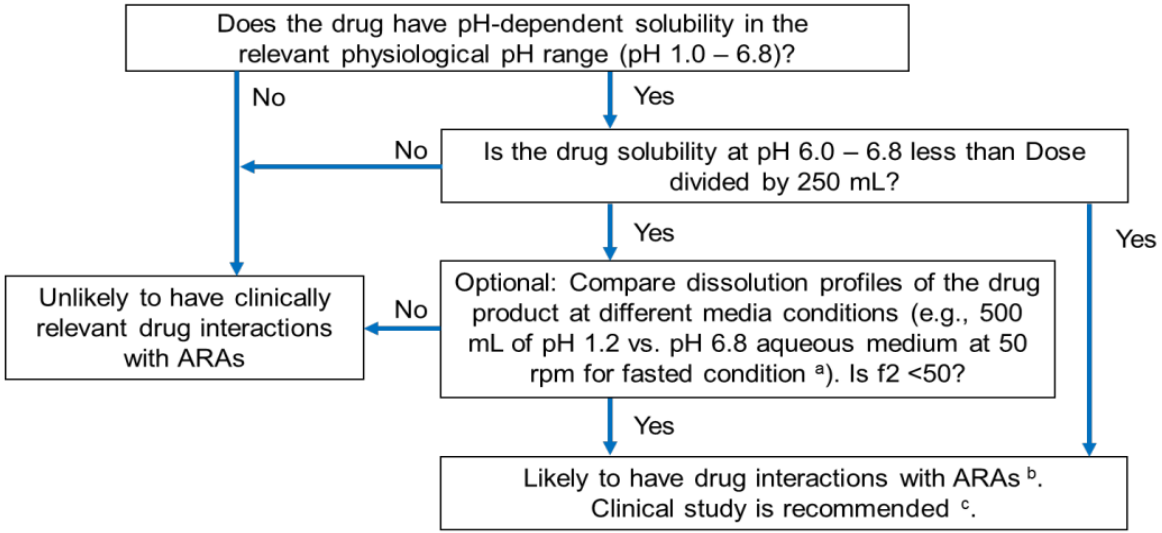
Immediate-release products of weak-base drugs

Immediate-release products of weak-acid drugs

Modified-release products

Framework to Assess Clinical DDI Risk for ARAs

Immediate-Release Products of Weak-Base Drugs



rpm – revolutions per minute

f2 – similarity factor[6]

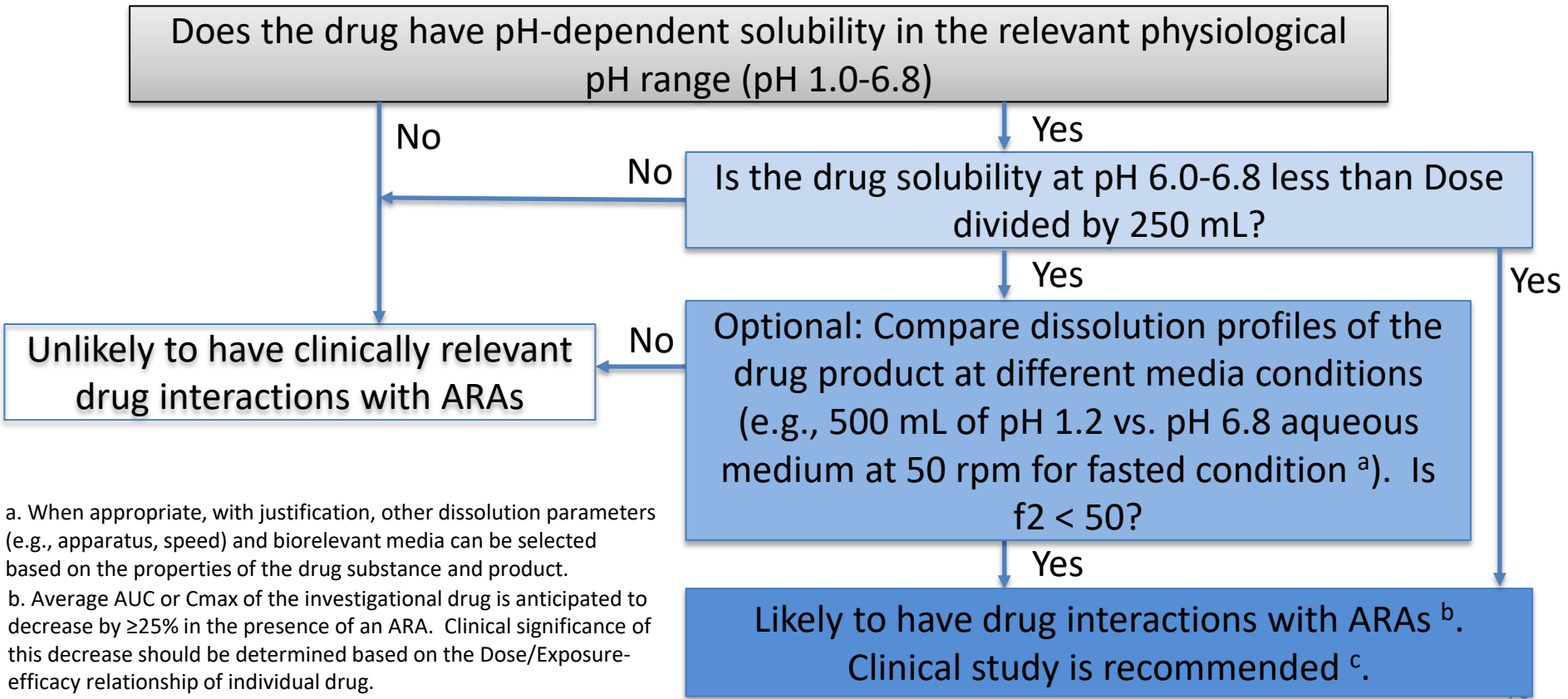
a. When appropriate, with justification, other dissolution parameters (e.g., apparatus, speed) and biorelevant media can be selected based on the properties of the drug substance and product.

b. Average AUC or Cmax of the investigational drug is anticipated to decrease by ≥25% in the presence of an ARA. Clinical significance of this decrease should be determined based on the Dose/Exposure-efficacy relationship of individual drug.

c. Alternative approaches (e.g., popPK or PBPK) can be considered.

Framework to Assess Clinical DDI Risk for ARAs

Immediate-Release Products of Weak-Base Drugs



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Additional Considerations

Solubility

- Physiologically relevant range
- Maximum therapeutic dose intended to be marketed

Formulation & dose

- Initial formulation
- Final formulation related considerations

Effect of food

- Drugs intended to be taken under fed condition
- Assess impact of gastric-pH changes because of food
- Consult with FDA

Guidance Recommendations

Design and Conduct of Clinical DDI Studies

- **Study population and design**
  - Generally conducted in healthy subjects
  - Cross-over study design often used

- **Choice of ARAs**
  - PPIs
    - PPIs are preferred (longer PD effect)
    - Pre-treatment of PPIs needed to reach steady-state of PD
  - H2 blocker
    - Staggered dosing with H2 blockers may be studied as a strategy to mitigate pH-DDI
  - Antacids
  - Avoid ARAs affecting other mechanisms that are involved (e.g., inhibition of CYPs or transporters)

- **Formulation**
  - pH-dependent DDI effect can be formulation dependent
  - To-be-marketed formulation of an investigational drug is recommended for the clinical DDI study
  - If a study is performed with an early formulation, justification should be provided for the relevance of the results to the to-be-marketed formulation

Design and Conduct of Clinical DDI Studies

- **Dose**
  - Investigational drug (highest intended therapeutic dose)
  - ARAs (commonly used highest recommended dose)

- **Food intake**
  - For drugs that can be taken regardless with food, study should be done under fasting condition
  - For drugs to be taken with food, study should be conducted under the fed condition that are consistent with late-phase clinical trials.

- **PK sampling and data collection**
  - 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), Cmax, Tmax, and if clinically relevant, Cmin or partial AUC
  - Active metabolite concentrations if the metabolites substantially contribute to efficacy or safety

Guidance Recommendations

Alternative Approaches

- Population PK (popPK)
  - Record of the dosing information (investigational drug, ARAs, food intake)
  - PK sampling (try to include samples during absorption phase)
  - Data analysis (not simply lump all patients receiving ARAs together)

- Physiologically based PK (PBPK)
  - Evolving
  - Early communication with FDA encouraged

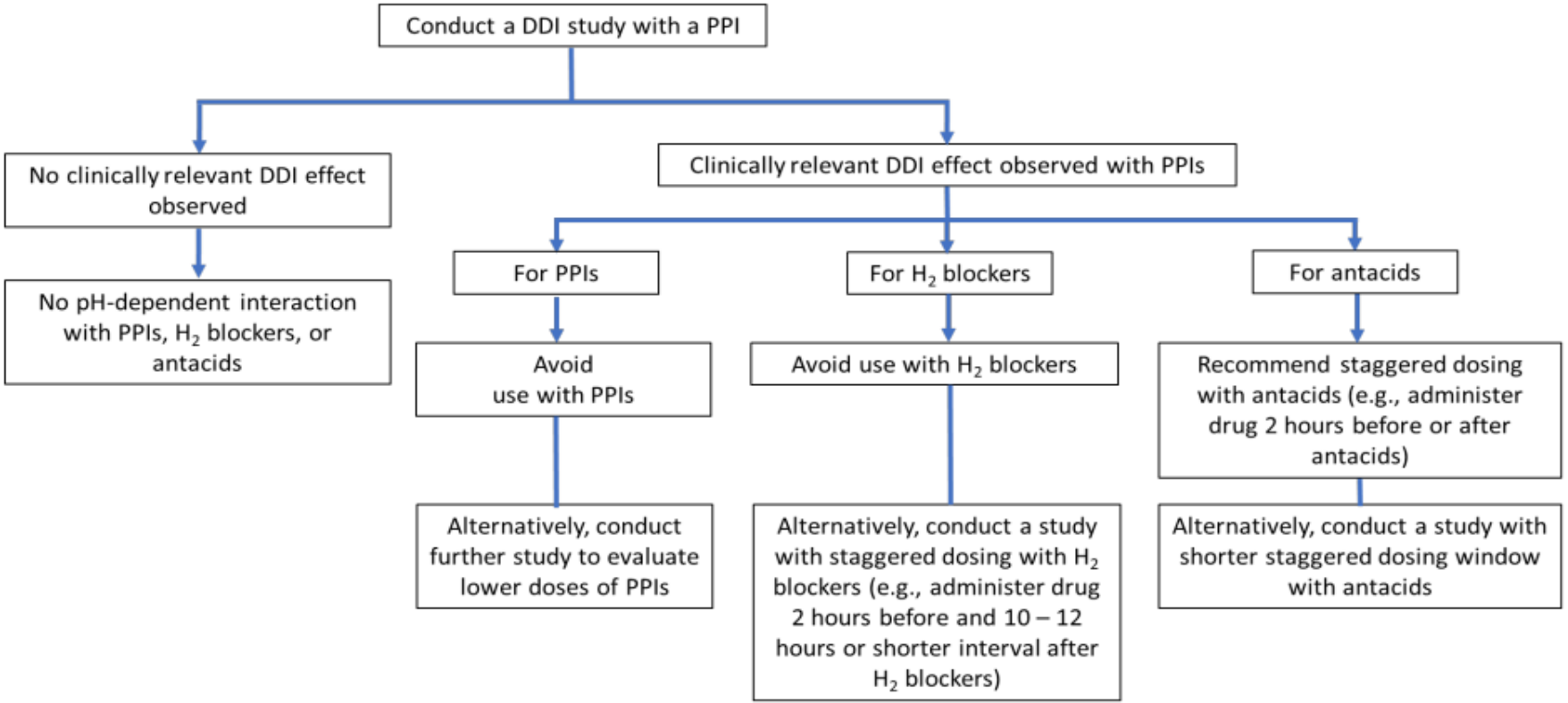
Guidance Recommendations

Extrapolation

- Generally clinical study results with an ARA can be extrapolated to other ARAs within the same class (e.g., 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 may be confounded when a dedicated DDI study is conducted with an ARA that has multiple interacting mechanisms besides a change in gastric pH.

Extrapolating Clinical DDI Study Results and Implications



CE Question

Concomitant administration of a drug with an acid reducing agent (ARA) could alter the bioavailability of the drug, potentially resulting in a loss of efficacy or increased adverse events. Common classes of ARAs of concern include:

a) Antacids
b) Histamine H2-receptor antagonists (H2 blockers),
c) Proton pump inhibitors (PPIs)
d) All of the above

Questions?

Panelists:

- Insook Kim, OCP
- Anuradha (Anu) Ramamoorthy, OCP
- Fang Wu, OGD
- Xinning Yang, OCP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