Office of the IQ Secretariat:
1500 K Street, NW, Suite 1100
Washington, DC 20005
Telephone: +1 202.230.5621
Email: info@iqconsortium.org
Website: https://iqconsortium.org

23-July-2018

IQ Consortium Comments to FDA Docket "Framework for Assessing pH-Dependent Drug-Drug Interactions"[1]

These comments are being submitted in response to the FDA request for public comment to the docket[2] "Framework for Assessing pH-Dependent Drug-Drug Interactions"[1]. These comments were prepared by the Drug Metabolism and Clinical Pharmacology Leadership Groups (DMLG and CPLG) of the International Consortium for Innovation and Quality in Pharmaceutical Development ("IQ Consortium", www.iqconsortium.org).

The IQ Consortium is a not-for-profit, technically-focused organization of pharmaceutical and biotechnology companies[3] with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader research and development community. The IQ DMLG and CPLG welcome the opportunity to provide the following comments, which are structured around the specific questions posed by the FDA[1]:

> FDA is particularly interested in responses to the following overarching questions:
>
> 1. What are the characteristics of drugs that are susceptible to pH-dependent DDIs? Can a stepwise approach be applied to evaluate the interaction potential? Please provide the rationale for your suggestions.
>
> 2. When conducting pH-dependent DDI assessments:
>
> a. What are the utilities and limitations of different approaches to evaluating DDIs (*e.g.*, in silico, in vitro, and dedicated clinical studies, as well as population pharmacokinetic analyses)?
>
> b. What are the study design considerations (*e.g.*, study population, choice of ARAs, dosing regimen and administration, and pharmacokinetic sampling) for the in vivo assessments discussed in 2a above? Please describe the rationale for any design considerations proposed.
>
> c. Can we extrapolate the findings from a clinical DDI study with one ARA drug (a PPI, H_2 blocker, or antacid) to anticipate the DDI potential for other ARAs in the same class or in a different class? Please provide the rationale for your proposal.

IQ Consortium is committed to addressing scientific issues in a collaborative fashion, and is willing to discuss with the agency these topics further, as appropriate.

[1] Federal Register Notice. Establishment of a Public Docket; Request for Comments https://www.federalregister.gov/documents/2018/05/22/2018-10927/framework-for-assessing-ph-dependent-drug-drug-interactions-establishment-of-a-public-docket-request

[2] FDA Docket https://www.regulations.gov/docket?D=FDA-2018-N-1820

[3] The list of IQ member companies and further information are available at https://iqconsortium.org/about/current-members/

1. What are the characteristics of drugs that are susceptible to pH-dependent DDIs? Can a stepwise approach be applied to evaluate the interaction potential? Please provide the rationale for your suggestions.

Drug characteristics that can affect absorption due to modulation of gastric pH often make a drug susceptible to pH-dependent DDIs. Such properties include pH-dependent dissolution, solubility, metabolic stability or permeability. In particular, weakly basic drugs with relatively low intrinsic solubility can be sensitive to changes in gastric pH when co-administered with ARAs.

While it is reasonable to use a stepwise approach in progressing from in vitro studies to in vivo studies, it is difficult to establish a simplified process that can be broadly applied to structurally diverse compounds to evaluate the ARA interaction potential, as multiple factors need to be considered. For example, in Zhang et. al.[4], a decision tree was presented to provide direction in selecting in vitro assessments to evaluate potential DDIs in a stepwise manner. However, those guidelines did not adequately consider the impact of factors such as the type of ARA (i.e., antacid, H2-receptor antagonist or PPI), temporal impact and magnitude of change in gastric pH, intra- and inter-subject variability in gastric pH, efflux transporter, first pass effect, etc. The effects of these and other factors on changes in absorption due to changes in pH contribute to the challenges of translating in vitro results to predict in vivo behavior, and should not be ignored.

Drugs that are susceptible to pH-dependent DDIs typically show pH-dependent solubility and/or permeability. These agents are typically weakly basic agents, have relatively good solubility at the regular gastric acidic environment, e.g., pH 1-2, but have reduced solubility, and thus, absorption and bioavailability at higher pH conditions (this an increase in pH may be likely to occur due to co-administration of acid reduction agents, disease, aging, or other conditions). These agents typically exhibit exponentially decreasing solubility in the pH range 1–4 and at the maximum dose strength. These agents are typically not soluble in 250 ml of water at higher pH (close to 7).

It is recommended that an integrated approach to assessing DDI potential is needed to better understand the interplay between the multiple physicochemical, material, formulation and physiological factors. A combination of in vitro data (e.g., pH solubility, dissolution across broad range of pH, precipitation kinetics, permeability) and in vivo data (e.g., absolute bioavailability, estimate of oral absorption, effect of food, and in vivo precipitation) is recommended for determining drug characteristics that may contribute to the interaction potential. Additionally, clinical assessment of a pH-dependent DDI may also need to consider the therapeutically relevant dose of the victim drug instead of a lesser dose, as the "loss" of stomach solubilization due to PPI can be compensated by solubilization in the small intestine when the dose is low. These studies could be arranged in a step-wise fashion, e.g., in vitro solubility/dissolution studies, in vitro permeability test for passive permeability and active transport, plus optional PBPK modelling or optional animal (pre-clinical) testing, concluding with in vivo studies if needed.

In the first (in vitro) step, the sponsor could determine if a signal for pH-dependent solubility/dissolution is present (e.g., carbonate buffer with lower buffer capacity may be used). In the case that an in vitro signal is seen and exceeds a certain threshold, such as a certain dose number

[4] Zhang L, Wu F, Lee SC, Zhao H and Zang L. pH dependent drug-drug interactions for weak base drugs: Potential implications for new drug development. Clin Pharmacol Ther. 2014;96(2):266-277.

(dose/250 mL not soluble at pH close to 7, e.g., 6.8), the PBPK (in silico) modelling and/or animal studies may be used to determine if a pH-dependent interaction is likely to be seen in humans, to determine if a clinical study is necessary. In the case that the PBPK or animal models suggest that a pH-dependent DDI may be likely, in vivo studies in humans may be recommended.

2. When conducting pH-dependent DDI assessments:

a. What are the utilities and limitations of different approaches to evaluating DDIs (*e.g.,* in silico, in vitro, and dedicated clinical studies, as well as population pharmacokinetic analyses)?

Study Type	Utilities	Limitations
In silico evaluation and PBPK modeling	PBPK model that incorporates the effect of pH on permeability, dissolution, solubility, and metabolic stability would be more appropriate for simulation. PBPK modeling provides a dynamic model to integrate information from multiple sources, and can be used to simulate multiple scenarios to guide DDI study design, can be used to simulate in vivo studies if the model is validated and may be used to aid in the development of dosing adjustment recommendations. Early identification of potential interactions as part of the risk assessment. Interaction with PPI which are pH mediated can be readily predicted using PBPK Models provided a qualified model is available. PBPK models provide valuable platform to integrate physicochemical, in vitro and in vivo data into a mechanistic framework which can yield a broader understanding of pH dependent DDIs (Kesisoglou et. al.[5], Chung et. al.[6])	So far, the published cases/models were mainly focused on using the dissolution and solubility data to simulate the in vivo DDIs and, therefore, more research is needed to improve the accuracy of the prediction. Examples for weak acids are less common. For weak bases, there is lack of understanding of in vivo precipitation, which is a key determinant of pH-dependent DDI. Bottom-up modeling approach assumes i) that all relevant factors are captured in the model; and ii) that in vitro to in vivo translation is accurate. Therefore, verification of PBPK simulations with clinical data is recommended before application to predict untested situations.

[5] Kesisoglou F, Vertzoni M, Reppas C. Physiologically Based Absorption Modeling of Salts of Weak Bases Based on Data in Hypochlorhydric and Achlorhydric Biorelevant Media. AAPS PharmSciTech. 2018. doi: 10.1208/s12249-018-1059-3

[6] Chung J, Alvarez-Nunez F, Chow V, Daurio D, Davis J, Dodds M, et al. Utilizing Physiologically Based Pharmacokinetic Modeling to Inform Formulation and Clinical Development for a Compound with pH-Dependent Solubility. Journal of Pharmaceutical Sciences. 2015;104(4):1522-32. doi: 10.1002/jps.24339

Study Type	Utilities	Limitations
In vitro	In vitro studies can be used for screening purposes and they provide the initial assessment of pH-dependent solubility and dissolution, and permeability for both passive permeability and active transport. The results of the in vitro assessment may be used to identify the pH for optimal absorption and trigger further examination of pH-dependent DDI potential. In vitro studies are fast and provide data to enable early understanding of drug properties such as permeability, solubility, dissolution and precipitation and the effect of pH on these characteristics. Provide insight regarding pH-dependent PK.	In vitro studies are unable to provide the information about the magnitude of the in vivo DDIs and are not able to provide guidance for a dosing adjustment if it is needed. In vitro to in vivo extrapolation (IVIVE) is not established. In vitro studies only provide insight into isolated processes and need to be integrated to deliver a fuller assessment of in vivo effects.
Non-clinical in vivo studies	Non-clinical studies can be used to determine the translatability of the in vitro pH-dependent solubility findings. Mechanistic studies are possible non-clinically that are not possible in the clinic, e.g., pre-treatment with pentagastrin.	Non-clinical findings don't necessarily translate to the clinic due to physiological differences such as gastric pH.
Dedicated clinical studies	Clinical studies are the gold standard to evaluate pH-dependent DDIs, which can be used to investigate the in vivo effects of ARAs on the investigational drugs, and thus, to provide information, e.g., about if dosing adjustment is needed for co-administration. They are key to verifying understanding of a drug's susceptibility to pH-dependent DDIs.	Study design and conditions typically do not fully reflect the situation for the patient. Taken alone, clinical studies provide only limited insight into mechanisms driving pH-dependent DDIs. It is not realistic to perform clinical studies which cover all ARAs and under all possible scenarios. As dedicated studies are typically run in healthy volunteers instead of the target population, they may not always represent the clinical situation (e.g., due to poly-pharmacy, concomitant diseases, demographic effects such as in the elderly & Japanese patients, who have higher gastric pH). Furthermore, the requirement to conduct a clinical study may result in unnecessarily exposing of healthy volunteers to the test substance.

Study Type	Utilities	Limitations
		Such studies should therefore be considered only if other methods are unable to adequately answer the question regarding pH-dependent DDIs.
Population PK Analyses	DDIs can be evaluated in the target population and can be used for detecting unexpected DDIs or for confirming an expected DDI interaction of ARAs in a real life situation (e.g., often via simultaneous administration), thereby giving information about potential clinical relevance. DDI results from a popPK analysis of phase 2/3 data can be used for the support of drug labels if a data quality standard has been met.	DDI results could be confounded due to inaccurate dosing and sampling recordings, co-medications which inhibit or induce metabolic pathways, and/or bias caused by study design (e.g., patients with higher exposure tend to drop out). PK results are less sensitive compared to dedicated DDIs (might cause false negatives, although may also better reflect the clinical situation) due to higher inter-individual variability in patients. A false positive is also possible as described in Bonate et.al.[7], which discusses assessing DDI using popPK approaches with data from phase 2/3 studies.

b. What are the study design considerations (*e.g.,* study population, choice of ARAs, dosing regimen and administration, and pharmacokinetic sampling) for the in vivo assessments discussed in 2a above? Please describe the rationale for any design considerations proposed.

- Expected use of the ARA in the patient population (e.g., in many oncology indications, patients frequently take acid-reducing agents for sustained periods).
- PK/PD profile of the ARA selected, PK/PD profile & physicochemical properties of the victim drug.
    - Propose PBPK simulations to guide the study design appropriately and allow exploration of different scenarios (e.g., staggering of dosing with regard to the two interacting drugs).
- Study population:
    - In most situations, dedicated clinical pH-dependent DDI studies can be performed in healthy volunteers (exception: e.g., cytotoxic drugs), and the results can be extrapolated and applied to the targeted patient population. For oncology drugs, studies may have to be conducted in patients to avoid toxicities.
- Selection of ARAs:

[7] Bonate PL, et al. Methods and strategies for assessing uncontrolled drug–drug interactions in population pharmacokinetic analyses: results from the International Society of Pharmacometrics (ISOP) Working Group. Journal of Pharmacokinetics and Pharmacodynamics, 2016; 43: 123.

  - ARAs may cause DDIs by mechanisms other than their pH-effect, such as metabolic interaction and interaction with transporters. Thus, the ARAs with no confounding effects are to be selected for the clinical/in vivo DDI studies. For example, of the available PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, and dexlansoprazole), esomeprazole and omeprazole are time-dependent inhibitors of CYP2C19 while the other PPIs are competitive inhibitors of CYP2C19. Among the commonly prescribed H2 blockers (ranitidine, famotidine, cimetidine, and nizatidine), many are inhibitors of multiple transporters and metabolism enzymes (CYPs).
  - Because PPIs generally have a longer duration of suppression on gastric acid secretion than do H2 blockers and antacids, and are expected to interfere with the intestinal absorption of pH-dependent victim drugs to a greater extent, the use of a PPI may be considered a worst-case scenario in the in vivo evaluation of the pH effect.
- Study-design:
  - The crossover study design is preferred as it can reduce variability. Multiple dosing with the highest therapeutic dose is preferred as it would be expected to exert a maximal effect.
    - A few days pre-treatment is typically needed to reach maximum (steady-state) effects for both PPIs and H2-blockers; thus, multiple-dosing studies should generally be used in DDI studies with ARAs.
    - ARAs should be administered in a dose that is relevant to their clinical use.
    - Both PPIs and H2 blockers have been shown to exhibit dose-related suppression of gastric acid secretion; thus, the approved highest dose with an appropriate time-lag between PPI and victim drug administration may be considered in the study to achieve maximal effects (i.e., the worst-case scenario).
    - For antacids, a single-dose study may be acceptable as the mechanism of action is to directly neutralize gastric acid effect.
  - Types of crossover study design that could be considered:
    - Single-sequence crossover design (for PPIs, considering the potential for their carryover acid-reducing effects).
    - Randomized crossover design (for H2 blockers and antacids).
  - In some cases, parallel designs (rather than fixed-sequence or crossover designs) may be warranted, such as when clinical ARA DDI assessment need to be conducted in cancer patients (i.e., if ARA administration in the population cannot be interrupted).
- Considerations for the selection of dose and dosing regimen:
  - Preferably use the approved clinical dose and appropriate dosing regimen of ARAs.
  - PPIs and H2 blockers exhibit dose-related suppression of gastric acid secretion.
  - Single or multiple dose administration of ARA (e.g., to achieve steady-state pH elevation, pretreatment with PPIs for several days is needed prior to co-administration with victim drug).
  - Single- or multiple-dose administration of pH-dependent victim drug.
  - Timing of dosing between the victim drug and an ARA is important:

- For PPIs, it is acceptable to dose concomitantly with the victim drug because separation of doses between the drug and the PPI may not eliminate the interaction due to the sustained gastric acid–suppression effect of PPIs.
- Investigate for H2 blockers and antacids, consider strategies to potentially mitigate the interactions with alternative dosing regimens (e.g., staggered dosing). Make use of PBPK simulations to address this. However, it should be noted that currently there are no best practices to include such time effects in PBPK models, nor are there generally agreed-upon media to measure a solubility time-course that could be used for this.
- Timing of administration of both victim and ARA should be considered ,for more accurate assessment of potential interaction (which is critical to assess for use of popPK).

o For investigational anticancer agents that display pH-dependent solubility, determination of the impact of concomitant acid-reducing therapy should be done early in drug development.

c. Can we extrapolate the findings from a clinical DDI study with one ARA drug (a PPI, H_2 blocker, or antacid) to anticipate the DDI potential for other ARAs in the same class or in a different class? Please provide the rationale for your proposal.

Due to distinct mechanisms of action for these three classes of ARAs, it is generally considered that findings from one class of ARA drug may not be fully extrapolated to another class of ARAs. Extrapolation can be done to some degree, given these all reduce pH and absorption, although there are limitations. PPIs are considered worst-case scenarios, as discussed above. If no DDIs were observed with PPIs, one would not expect DDIs with other ARA classes, such as P-CAB, H2 blocker and/or antacids. For ARAs in the same class, some numeric difference in magnitude of DDI may exist; however, the findings from a DDI study with one ARA can generally be extrapolated to another ARA in the same class.

We propose the use of PBPK modelling to extrapolate effects from one ARA to another. The PBPK model can capture the drug-specific properties and their use for translation between ARA relies upon appropriate representation of the physiological changes caused by the different ARAs. However, PBPK models for antacid-weak acid interaction would not be straightforward because the required in vitro measurements are quite complex. One may also consider complex formation between API and Al/Mg salts in antacids (as observed with, e.g., tetracyclines) as an aspect where the DDI risk could still be captured with PBPK modelling in combination with a detailed physicochemical characterization of the compound.

More work is needed to define the physiological changes caused by ARAs. Some relevant data and some verification for specific drugs have already been published. After more verification of the utility of PBPK, we also propose the use of PBPK as the optimal way to extrapolate effects from one formulation to another, e.g., as when a dedicated PPI study was conducted with a non-final market formulation[8].

[8] Sieger P, Cui Y, Scheuerer S. pH-dependent solubility and permeability profiles: A useful tool for prediction of oral bioavailability. Eur J Pharm Sci. 2017 Jul 15;105:82-90. doi: 10.1016/j.ejps.2017.04.016. Epub 2017 May 3. PubMed PMID: 28478135.