# **Title:** Exploring the Relationship of Drug BCS Classification, Food-Effect, and Gastric pH-Mediated Drug Interactions



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### **BACKGROUND:**

Food-effect (FE) and gastric pH-mediated drug-drug interactions (DDIs) are absorption-related. Here, we evaluated if the Biopharmaceutical Classification System (BCS) may be correlated with FE or pH-mediated DDI observed.

#### **METHODS:**

Trends in FE data were investigated for **170 drugs** with clinical FE studies from the literature and new drug applications (2013-2019) (UW Drug Interaction Database & Drugs@FDA search).

FE studies were defined as:

- No effect (AUC ratio [AUCR] Fed/Fasting, 0.80-1.25),
- Positive (AUCR  $\geq$  1.25), or
- Negative (AUCR ≤0.8)

<u>DIDB data query</u>: PK of object in food-effect Other routes of administration N = 0• • • • • • studies ------------\_\_\_\_\_ Modified-release Oral dosage forms dosage forms ••••• N = 359 Immediate-release Fixed-dose combinations dosage forms **|**•••••**|**●| N = 18 N = 332 Other meal types Single agent drugs (or not specified) N = 314 N = 72 \_\_\_\_\_ Evaluated with a nvestigational drugs high-fat meal N = 72 N = 242 Not evaluated in a pH-mediated U.S. FDA approved drugs DDI with a proton pump inhibitor N = 170 FE DATASET Also evaluated for pH-mediated DDI with a proton pump inhibito N = 38FE + DDI DATASET

A subset of 38 drugs was also evaluated to determine whether FE results can inform the need for a gastric pH-mediated DDI study.

#### **RESULTS:**

- Overall, drugs with significantly positive FE (AUCR  $\geq 2.0$ ; N=14) were BCS Class 2 or 4, while drugs with significantly negative FE (AUCR  $\leq 0.5$ ; N=2) were BCS Class 1 or 3 (Table 1 & Figure 2).
- Lack of FE was aligned with the lack of a pH-mediated DDI for all seven BCS Class 1 or 3 drugs (azacitidine, baricitinib, cobimetinib, eliglustat, isavuconazonium (isavuconazole), osimertinib, and ponatinib) but not for BCS Class 2 or 4 drugs in this dataset (Figure 1).
- For the 12 BCS Class 2 or 4 weak base drugs (WBDs) with a **positive FE**, only 6 had a pH-mediated DDI (AUCR ≤0.8) (Figure 1).
- Among the 13 BCS Class 2 or 4 WBDs with **no FE**, 6 had a pHmediated DDI (AUCR  $\leq 0.8$ ): acalabrutinib, dacomitinib, entrectinib, palbociclib, riociguat, and velpatasvir (Figure 1).

# The lack of a food-effect aligned with the lack of a pH-mediated DDI for BCS Class 1 or 3 drugs, but not for BCS Class 2 or 4 drugs.



## FE change in exposure

Figure 1. Change in drug exposure (AUC and C<sub>max</sub> ratios) of weak base drugs during evaluation of FE and gastric pH-mediated DDI, by BCS class; AUC and C<sub>max</sub> ratios within 0.8–1.25; --- AUC and C<sub>max</sub> ratios within 0.5–2.0 (drugs are weak bases, unless otherwise specified).





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#### **Table 1.** Overall summary of FE dataset by BCS class based on AUCR; N (%)

**BCS Clas BCS** Clas **BCS** Clas **BCS Clas** BCS Class



and Lei Zhang<sup>2</sup>

	N drugs	No FE	Positive FE	Negative FE
		(AUCR 0.8-1.25)	(AUCR ≥1.25)	(AUCR ≤0.8)
is 1	25	24 (96)	0 (0)	1 (4)
s 2	69	39 (57)	26 (38)	4 (6)
s 3	26	16 (62)	3 (12)	7 (27)
s 4	26	19 (73)	6 (23)	1 (4)
s not specified $*$	24	12 (50)	8 (33)	4 (17)

\*Including BCS Class 1/3 (N=6), BCS Class 2/4 (N=17), and BCS Class 3/4 (N=1).

**Figure 2.** AUC and C<sub>max</sub> ratios for all drugs with FE studies, by BCS class:  $\triangle$  amphoteric or neutral;  $\bigcirc$  weak base;  $\square$  weak acid; - AUC and C<sub>max</sub> ratios within 0.8–1.25; --- AUC and  $C_{max}$  ratios within 0.5–2.0.

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