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General Commentary

Reply to "On the Effect of Common Excipients on the Oral Absorption of Class 3 Drugs"

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ABSTRACT

We previously concluded that 12 common excipients need not be qualitatively the same and quantitatively very similar to reference for Biopharmaceutics Classification System–based biowaivers. This conclusion for regulatory relief is based upon a series of bioequivalence studies in humans involving cimetidine and acyclovir. Limitations were also discussed. We understand the major concern of García-Arieta et al. is that "results obtained by Vaithianathan et al. should not be extrapolated to other drugs." We understand that individuals conducting their own risk/benefit analysis may reach that conclusion, and we reply to the concerns of García-Arieta et al. We continue to conclude that the 12 common excipients need not be qualitatively the same nor quantitatively very similar to reference, but rather, simply be not more than the quantities studied in our manuscript for cimetidine and acyclovir, and potentially other class 3 drugs with similar properties.

We previously published "Effect of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs Cimetidine and Acyclovir" that concluded "Overall, 12 common excipients were found in large amounts to not impact Biopharmaceutics Classification System (BCS) class 3 drug absorption in humans, such that these excipients need not be qualitatively the same nor quantitatively very similar to reference, but rather simply be not more than the quantities studied here. Meanwhile, for each HPMC and microcrystalline cellulose, BCS class 3 biowaivers require these two excipients to be qualitatively the same and quantitatively very similar to the reference."[1] This conclusion for regulatory relief is based on a series of bioequivalence (BE) studies in humans involving cimetidine and acyclovir. Table 8 summarizes overall conclusions. For each of 12 common excipients that we conclude are eligible in a biowaiver even if not qualitatively and quantitatively the same (i.e., even if not Q1/Q2), Table 8 lists the maximum amount of excipients that we believe BCS class 3 biowaivers can accommodate. These excipients are sodium lauryl sulfate (SLS), corn starch, sodium starch glycolate, colloidal silicon dioxide, dibasic calcium phosphate, crospovidone, lactose, povidone, stearic acid, pregelatinized starch, croscarmellose sodium, and magnesium stearate (i.e., "the 12 common excipients"). We also discuss limitations. "A limitation of these studies is that only two drugs were evaluated, cimetidine and acyclovir. It is possible that other BCS class 3 drugs have properties that differ from cimetidine and acyclovir to render those drugs susceptible to other excipient influences that cause modified drug absorption."[1] We have read the commentary by García-Arieta et al. and have no edits to our article. They comment that some of the text mentioned previously is contradictory, but we disagree as we are aware of, and have pointed out, the limitations of the study. We understand that they have no issues about our methods or data.

Abbreviations used: BCS, biopharmaceutics classification system; BE, bioequivalence; HPMC, hydroxypropyl methylcellulose; IR, immediate-release; SLS, sodium lauryl sulfate.

The views expressed in this article are those of the authors (Sam H. Haidar, Xinyuan Zhang, and Wenlei Jiang) and not necessarily those of the Food and Drug Administration (FDA).

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We understand the major concern of García-Arieta et al. is that "results obtained by Vaithianathan et al. should not be extrapolated to other drugs."[2] We understand that a risk/benefit analysis of our article may lead one to that conclusion. Currently, FDA and EMA recommend BCS class 3 biowaivers based on immediate-release (IR) formulations to be qualitatively the same and quantitatively very similar, as well as very rapidly dissolving. Some emerging data (e.g., our recent publication and biowaiver monographs) provide evidence to suggest the use of a more permissive approach for certain drugs. For example, we do not think that the 12 common excipients in Table 8 would impact the absorption of ranitidine hydrochloride, atenolol, or acetaminophen based on the physiochemical and biopharmaceutic properties of these drugs.[3-5] Of note, the atenolol BCS biowaiver monograph lists excipients that are not expected to affect the rate and extent of atenolol absorption if used in amounts that are normally used in IR tablet formulations, and 11 excipients in that list are in Table 8 of our article.[4] Similarly, 7 and 10 excipients that are not expected to affect absorption of ranitidine hydrochloride and acetaminophen, respectively, are listed in Table 8.[3,5]

García-Arieta et al. comment about SLS. As noted in our article, we included SLS because it is a common excipient and because many laboratories, including ours,[6] have observed that SLS increases drug permeability *in vitro*. In fact, in study 1, 3 formulations included SLS, reflecting our highest interest in this excipient. Nevertheless, we found that SLS did not impact cimetidine or acyclovir BE. García-Arieta et al. indicate "…it has already been reported in the literature[2] that SLS can increase 5-6 fold the bioavailability of alendronate, another class 3 drug with much lower oral bioavailability than these two drugs, in contrast to the lack of effect observed by Vaithianathan et al.[1]" References 1 and 2 of García-Arieta et al. are references 1 and 7 here, respectively.[1,7] We have read the review article by García-Arieta.[7] We do not agree that the evidence provided in the review article is sufficient to change our conclusions that 0-50 mg of SLS will generally not impact *in vivo* BE of class 3 drugs in IR formulations with very rapid dissolution in all BCS media. However, we continue to believe that it is possible that other BCS class 3 drugs have properties that differ from cimetidine and acyclovir so that those drugs susceptible to other excipient influences that cause modified drug absorption. For example, "the greatest concern would appear to be a drug that depends on an uptake transporter that an excipient inhibits by virtue of the excipient having molecular structure similarity to the transporter's pharmacophore or recognition site."[1]

It is well appreciated that alendronate is a very unusual orally administered drug, with one of the lowest intestinal permeabilities and one of the lowest fraction doses absorbed due to low permeability.[8,9] García-Arieta et al. believe that "results obtained by Vaithianathan et al. should not be extrapolated to other drugs" because the presence of 4 mg of SLS apparently increased 5-6 fold the bioavailability of an alendronate tablet.[7] We question this report, which is unpublished, because it uses urine rather than plasma samples for pharmacokinetic comparison (FDA guidance on alendronate recommends plasma samples for BE studies),[10] and urine sampling for the *in vivo* BE study stopped early. In addition, it is unclear whether alendronate tablets were very rapidly dissolving. Alendronate is a highly variable drug[11] and typically requires large numbers of subjects or replicated studies to demonstrate *in vivo* BE. For example, the package insert indicates "In healthy subjects, oral prednisone (20 mg three times daily for five days) did not produce a clinically meaningful change in oral bioavailability of alendronic acid (a mean increase ranging from 20% to 44%)."[12,13] "Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%." We question whether the presence of 4 mg of SLS or aledronate's high variability underpins the perceived increase in bioavailability. Furthermore, if we understand García-Arieta correctly, the Mylan product showed this apparent 5-6 fold bioavailability increase but then was later shown to be BE, resulting in an approved package insert with SLS.[7,13,14]

Regarding the García-Arieta et al. comment about sorbitol, sorbitol was not a major focus of our study. It was not included in any of our test capsules, not present in Table 8, and is clearly outside the scope of our conclusions.

Regarding the García-Arieta et al. comment about magnesium stearate, the use of 40 mg/capsule of magnesium stearate and the Turbula mixer in our study 1B caused over-lubrication, slower dissolution (59.6%-75.6% dissolved at 15 min in Table 1), and reduced AUC and Cmax. We disagree with García-Arieta et al. that "… it is not clear if this [magnesium stearate and Turbula mixer] effect can be detected by the required in vitro dissolution testing of BCS-based biowaiver." In fact, the test formulation did not show very rapid dissolution. Very rapid dissolution requires at least 85% dissolution in 15 min or less in all three BCS media.[15,16]

Similarly, in paragraph 5, García-Arieta et al. inaccurately define and misinterpret very rapid dissolution and *in vivo* BE. These misinterpretations affect the expected concordance of dissolution and *in vivo* BE. In examining formulation CimTest-1 and CimTest-2 in study 1A, García-Arieta et al. indicate "Therefore, in this case, in vitro dissolution was not as discriminative as expected." In fact, in cimetidine study 1A, formulation CimTest-1 was in vivo BE to CimTest-2, although CimTest-1 was not very rapidly dissolving while CimTest-2 was very rapidly dissolving.

In paragraph 5, García-Arieta et al. performed 2 calculations concerning Cmax, because of the high Cmax of CimTest-A, which includes 2 excipients that we conclude need to be qualitatively the same and quantitatively very similar to the reference. One calculation compares Cmax of CimTest-A versus CimTest B. Their approximation of Cmax ratio being 115.4% is accurate. However, our article concludes that hydroxypropyl methylcellulose (HPMC) and microcrystalline cellulose should be qualitatively the same and quantitatively very similar to the reference, so their point is not clear. If the point is that Cmax is not always the best approach to assess BE, we would agree. Limitations of Cmax as a BE metric are well known.[17-20] AUC point estimate was 106.7% for CimTest-A versus CimTest B.

A second Cmax calculation in paragraph 5 concerns CimTest-1 in study 1A versus CimTest-A from study 2, by comparison of the commercial cimetidine solution that was included in both studies. In comparing CimTest-1 versus CimTest A, García-Arieta et al. conclude that increasing HPMC from 20 mg to 45 mg reduced Cmax to about 85.74%. (We agree with García-Arieta et al. that the terminal calculation of a Cmax ratio of approximately 85.7% for CimTest-1 versus CimTest A. Regarding an intermediate calculation, the Cmax ratio of CimTest-A versus the sorbitol-containing commercial solution is not 1.4535, but 1.405, from Table 7.) Hence, García-Arieta et al. conclude "Then, it could be hypothesised that even if we require the same qualitative composition of excipients for class 3 drugs, a >10% difference in Cmax caused by small quantitative difference in HPMC might not be detected by in vitro dissolution testing." This statement overlooks the fact that CimTest-1 was not very rapidly dissolving and that our conclusion does not allow for a large quantitative difference in HPMC, such as "… a difference of 25 mg of HPMC …". In addition, although we clearly indicate HPMC can slow or decrease drug absorption, a view of comments by García-Arieta et al. should recognize the AUC point estimate was 100.0% for CimTest-1 versus CimTest A from Tables 4 and 7, such that others may view our conclusion about HPMC (and microcrystalline cellulose) as conservative.

Although limitations of Cmax as a BE metric are well known,[17-20] García-Arieta et al. remind us all to consider possible scenarios where BCS biowaivers may not assure BE, and of the benefits of surveys of non-BE results for class 1 and 3 drugs.[21] In a survey of BE studies in Brazil, 12 of 115 studies of class 3 drug products provided a non-BE results, with 5 of those being bioinequivalent (i.e., point estimate outside of 80%-125%).[22] Interestingly, the relative risks of non-BE and of bioinequivalence for class 3 drug products was the same as for class 1 drug products. For each BCS 1, 2, and 3 studies that did not show BE, Cmax was of course the metric that usually did not pass.

In summary, we appreciate the interest by García-Arieta et al. and acknowledge that individuals conducting their own risk/benefit analysis may reach differing conclusions about regulatory relief.[14] We continue to conclude that the 12 common excipients need not be qualitatively the same nor quantitatively very similar to reference, but rather, simply be not more than the quantities studied in our article for cimetidine and acyclovir, and potentially other class 3 drugs with similar properties.

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