December 19, 2017

Re: Draft Guidance on Sucralfate Oral Suspension, October 2017 (Refer to Docket ID FDA-2007-D-0369, FDA Register Number: 2017-22736, posted on October 20, 2017, Section III. Drug Products for Which Revised Draft Product-Specific Guidances Are Available, Table 2, Product: Sucralfate)

To Whom It May Concern:

Based on information available from the product label, clinical data, and literature references, we are of the opinion that the draft product-specific guidance for sucralfate oral suspension, while providing a well-rounded approach for characterization of the complex API and the suspension formulation, does not fully represent, via bioassays, the primary product-controlled multi-factorial mechanisms that elicit both the early and extended *in vivo* actions of sucralfate and is, therefore, inadequate to determine equivalence of test and reference formulations.

Based on its prescribing information, sucralfate suspension accelerates healing of duodenal ulcers and is known to exert its effect through a local, rather than systemic, action. Also according to the label for Carafate® oral suspension (1), the following observations (delineated below) from clinical and *in vitro* data suggest that sucralfate forms a comprehensive protective barrier (2) that covers the ulcer site and protects it against further attack by noxious substances such as acid, pepsin, and bile salts.

1. Studies in human subjects and with animal models of ulcer disease have shown that sucralfate forms an ulcer-adherent complex with proteinaceous exudate at the ulcer site (Product label and supported by clinical data from Ref. 3).

2. *In vitro*, a sucralfate-albumin film provides a barrier to diffusion of hydrogen ions (Product label and supported by *in vitro* data from Ref. 4).

3. In human subjects, sucralfate given in doses recommended for ulcer therapy inhibits pepsin activity in gastric juice by 32% (Product label and supported by clinical data from Ref. 4).

4. *In vitro*, sucralfate adsorbs bile salts (Product label and supported by clinical data from Ref. 5).

The bioassays recommended in the FDA product-specific guidance for sucralfate suspension (October 2017) do not adequately represent this complex cascade of events that result in the accelerated healing of the duodenal ulcers for the reasons detailed below:

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1. FDA Recommended Bioassay #1 (Product-Specific Draft Guidance on Sucralfate, Section III. 1) : *In vitro* equilibrium binding study with human serum albumin (HSA) or bovine serum albumin (BSA)

   Absorption Systems feedback: FDA recommends performing protein binding assays based on the Guidance for Cholestyramine oral powder. However, determination of the binding constant to a single protein (HSA or BSA) is not sufficient to characterize sucralfate's formation of an ulcer-adherent complex, or the "sucralfate-albumin film" that provides a protective barrier, prolonging the therapeutic actions of the drug. In other words, binding affinity/capacity alone is not indicative of barrier formation, which is sucralfate's primary proposed defensive mechanism of action (6) for an uninterrupted healing process between doses.

   - The negatively charged polyanions of sucralfate (available SO_3^-, after release of aluminum) only bind to the positive charges on albumin at acidic pH below 2.5. At pH conditions consistent with the duodenal region (approx. pH 4.5 to pH 6), binding of sucralfate to albumin becomes less efficient and is poorly manifested when performed *in vitro*. Therefore, albumin binding cannot be tested *in vitro* at a pH high enough to be relevant to *in vivo* physiological conditions at the site of action as indicated in the product-specific guidance. An additional protein such as human fibrinogen would be more representative of the proteinaceous exudate at the ulcerated site of action and a more appropriate choice to study sucralfate-protein interaction at the pH condition of the duodenum.

   - Protein binding is only one of several postulated precursor steps that lead to the overall action of sucralfate, and there appears to be no direct correlation between binding and formation of an adherent protective barrier against acid and pepsin diffusion (1) in the gastroduodenal environment (6, 7).

   - In addition, binding is non-discriminatory, so while individual components (e.g., sucrose octasulfate or the API) may exhibit the same binding affinity/capacity as sucralfate suspension, they do not result in formation of a barrier comparable to the formulated product (7). Critical and quantifiable barrier properties when filling in a mucosal defect, such as its uniformity, adhesiveness, selective retention on ulcerated tissue, and ability to restore the transmural (mucosal-to-serosal) potential difference, are needed to adequately discriminate between test and reference formulations with regard to the formulation-dependent barrier formation.

2. FDA Recommended Bioassay #2 (Product-Specific Draft Guidance on Sucralfate, Section III. 2): *In vitro* equilibrium binding study with bile salts

   Absorption Systems feedback: While the product label for Carafate® indicates that sucralfate adsorbs bile salts *in vitro*, it is yet to be determined whether the clinical

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efficacy of sucralfate is a result of bile salt adsorption/depletion (by sucralfate that has not yet formed a barrier) or barrier formation by sucralfate that results in a delay of bile salt migration to the damaged mucosa. Post-ingestion, most of the sucralfate binds to the walls of the gastrointestinal tract and a small amount dissolves (4). This strongly suggests that "adsorption" may occur via a multiplicity of actions (5) and that evaluation of binding alone per the methodologies suggested in the product-specific guidance is not sufficiently predictive of sucralfate's *in viv*o interaction with bile salts.

3. FDA Recommended Bioassay #3 (Product-Specific Draft Guidance on Sucralfate, Section III. 3): *In vitro* kinetic binding study with bile salts

   See #2 above.

   Additionally, it has been shown that bile salts are rapidly adsorbed by sucralfate (e.g., adsorption complete within 7 ± 2 minutes for taurodeoxycholate (8)); and thus evaluation of kinetic binding over a brief time interval is not informative of the formulation's ability to act as a barrier to the action of bile salts for an extended duration.

4. FDA Recommended Bioassay #4 (Product-Specific Draft Guidance on Sucralfate, Section III. 4): *In vitro* enzyme (pepsin) activity study

   Absorption Systems feedback: We agree that the interaction of sucralfate with pepsin is one of the fundamental characteristics of the product and, therefore, equivalence with respect to the percent decrease in pepsin activity should be based on quantitative measures and not just a qualitative comparison.

In conclusion, while the bioassays recommended by FDA place selective and less than comprehensive emphasis on the early actions of sucralfate, they provide very limited insights into the barrier properties governed by the formulation, which is the primary basis for the product's uninterrupted protective and healing properties between doses. As the physicochemical properties of the formulation that translate into the product's viscous adhesiveness are poorly understood, and not directly correlated to the early actions of the product, it is imperative that methodologies be developed to evaluate formation of the barrier *in vitro*, under relevant physiological conditions, so that its critical properties (e.g., uniformity, retention, and elevation of potential difference) can be quantified and compared to demonstrate equivalence between reference and test formulations. Furthermore, using effective orthogonal bioassays for key processes related to the *in vivo* performance of sucralfate will reduce the uncertainty in any formulation differences, as these product-specific, multiple meaningful measurements, may also be able justify potential Q2 differences and thereby augment the overall confidence in the bioequivalence of the test product.

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