# Common Deficiencies and Case Studies of In-Vitro Binding Bioequivalence (BE) Studies

## - Sucralfate Suspension and Tablets

***SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval***

*Day 2, Session 5: In Vitro Binding Study for Locally Acting GI Drug Products*

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# Learning Objectives

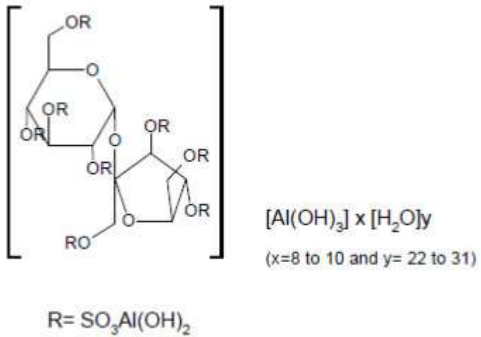
- Outline common deficiencies identified in *in vitro* binding BE studies
- Describe ways to reduce review cycles for abbreviated new drug applications (ANDAs) containing *in vitro* binding studies
- Describe the alternative approaches and comprehensive scientific justifications for BE establishment

# Outline

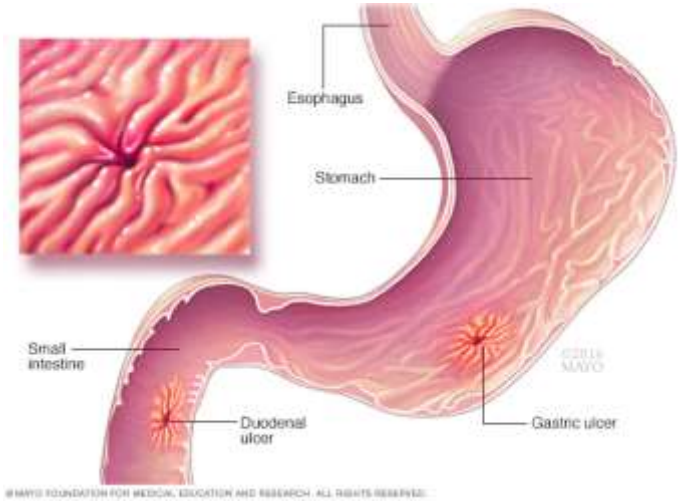
- Introduction
  - Products with in vitro binding studies recommended
  - Sucralfate (suspension and tablets)
- Common Deficiencies on In Vitro Binding Studies
- Case Studies
- Summary

# Drug Products with In Vitro Binding Study Recommended

| Control of serum phosphorus | Control of serum cholesterol | Treatment of active duodenal ulcer |
|---|---|---|
| • Calcium acetate<br>• Lanthanum carbonate<br>• Sevelamer carbonate<br>• Sevelamer hydrochloride | • Colesevelam hydrochloride<br>• Colestipol hydrochloride<br>• Cholestyramine | • Sucralfate |



# Sucralfate Mechanism of Action




- Minimally absorbed from the gastrointestinal tract
- Locally acting rather than systemically
- Ulcer-adherent complex with proteinaceous exudate at the ulcer site
- A sucralfate-albumin film provides a barrier to diffusion of hydrogen ions
- Inhibits pepsin activity in gastric juice by 32%
- Sucralfate adsorbs bile salts

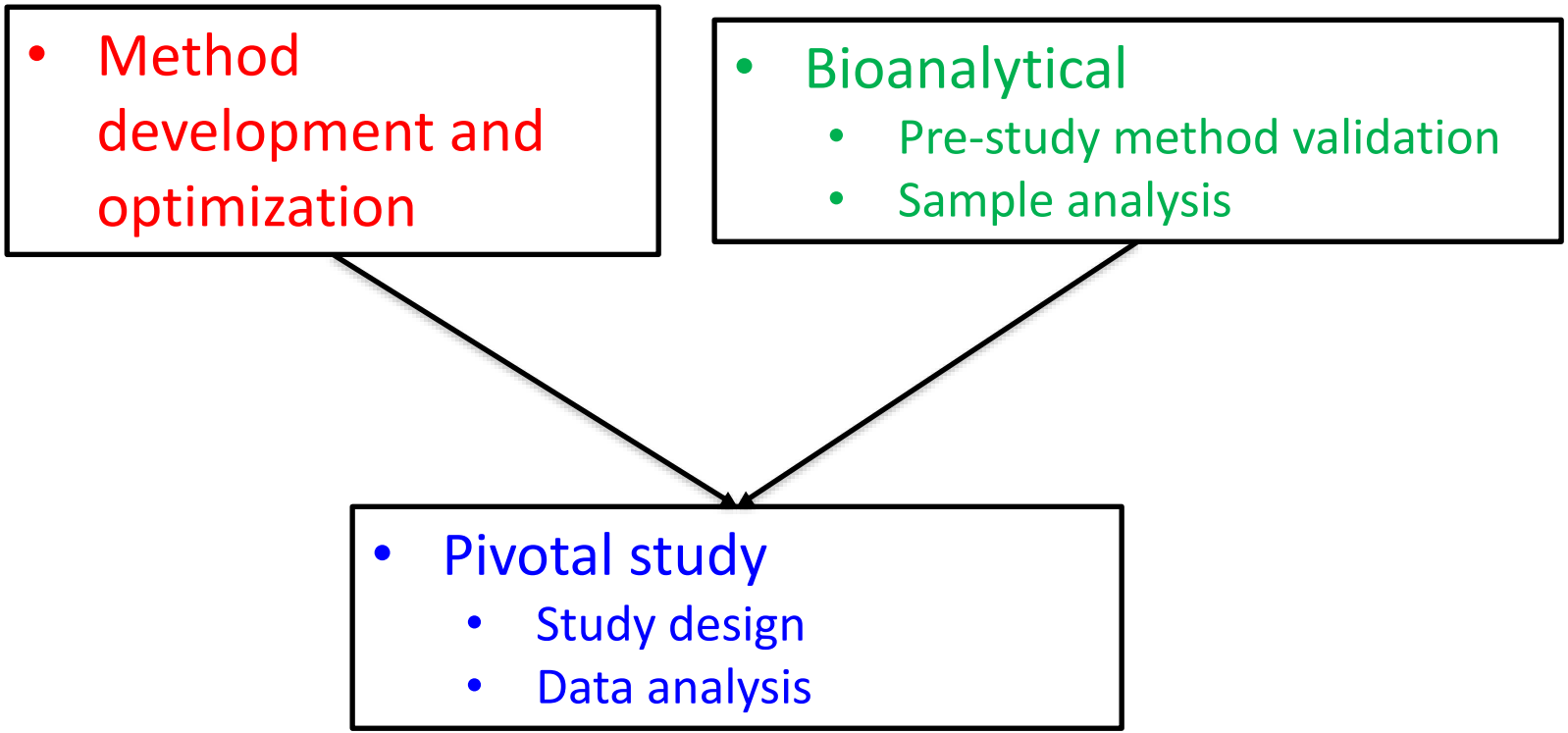
# Product-Specific Guidance (PSG) on Sucralfate Suspension and Tablets*

| In Vitro Option | |
|---|---|
| Formulations & Physicochemical Characterizations | Bioassays |
| • Active pharmaceutical ingredient (API) sameness<br>• Qualitatively (Q1) and quantitatively (Q2) the same except the flavor/color<br>• Acceptable comparative physicochemical characterizations<br>• Disintegration time (Tablets) | • In vitro equilibrium binding – Human or Bovine Serum Albumin (HSA/BSA)<br>• In vitro equilibrium and kinetic binding - Bile Salts<br>• In vitro enzyme activity – Pepsin |

* Suspension PSG: https://www.accessdata.fda.gov/drugsatfda_docs/psg/Sucralfate_oral%20suspension_NDA%20019183_RV08-17.pdf

Tablets PSG: https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_018333.pdf

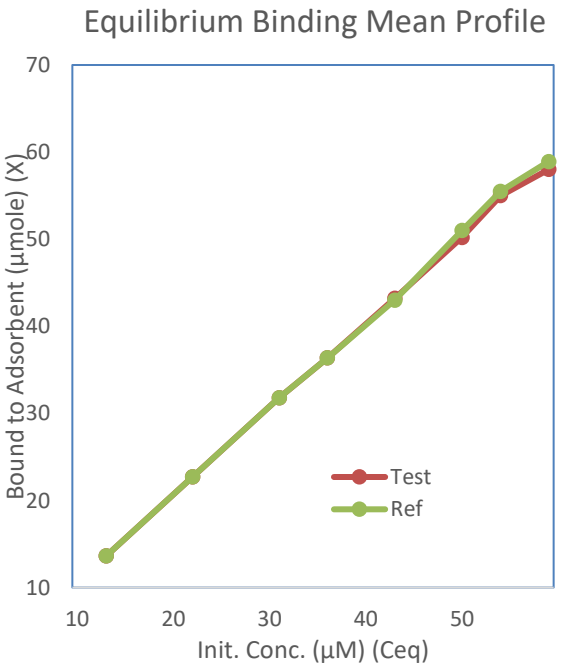
# In Vitro Binding Study Deficiencies



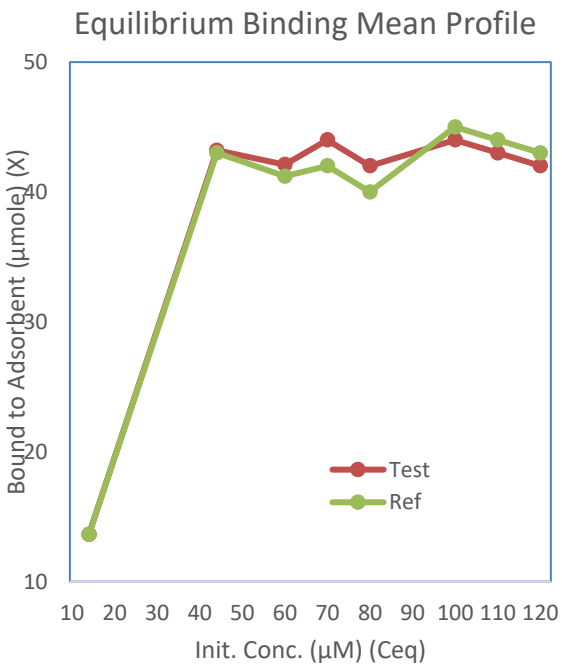
# Common Deficiencies – Method Development and Optimization

- Missing method development and optimization in one or more of the following parameters
  - e.g., incubation media, pH, volume, amounts, and duration
- Insufficient method development and optimization
  - e.g., lack of supporting data with experimental details and no rationale for the parameter selection
- Non-optimal adsorbent/adsorbate concentration and range selection
  - did not clearly demonstrate the rising portion of the binding curve and the maximum binding region (plateau region)

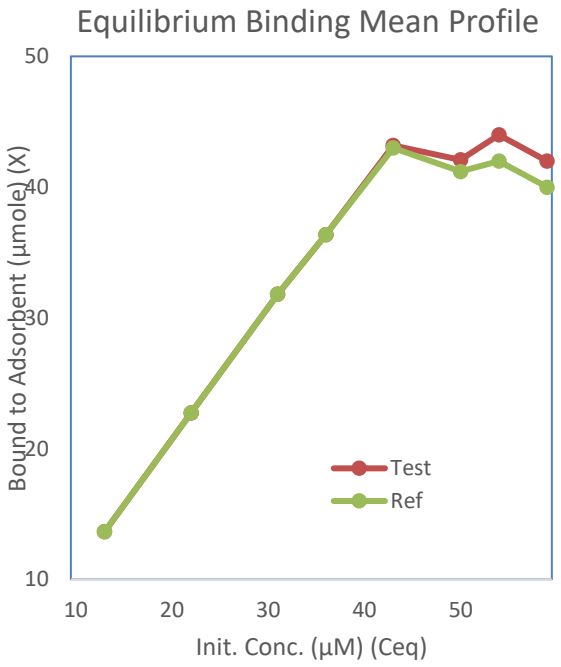
# What is an Acceptable Binding Profile?




No Plateau




No Rising Portion




Acceptable

# Common Deficiencies - Bioanalytical

- Incomplete analytical method validation or data submission
  - Incomplete stability data
  - Incomplete dilution integrity data
  - Incomplete individual bile salt and total bile salt data
  - Missing 100% analytical raw data and/or 20% chromatogram submission for pivotal study

# Common Deficiencies – Pivotal study

- Pivotal study
  - Study design based on inadequate method development
- Data analysis
  - Incorrect units in the data file and analysis
  - Langmuir constants $K_1$ and $K_2$ calculated from the mean of twelve replicates
  - Incorrect 90% CI acceptance range on $K_2$
    - untransformed data: 80.00%-120.00%

# Case Studies in ANDAs for Sucralfate Suspension/Tablets

- Formulation
- Serum albumin binding
- Bile salt binding

# Case Study #1: Proposed Test Formulation Deviated from Recommendation in PSG

- Q1 the same but not Q2 the same as reference listed drug
  - There is no regulatory requirement on Q2 for oral suspension
  - Q2 the same is recommended for in vitro BE option
  - Impact on in vitro BE assessment:
    - Scientific justification

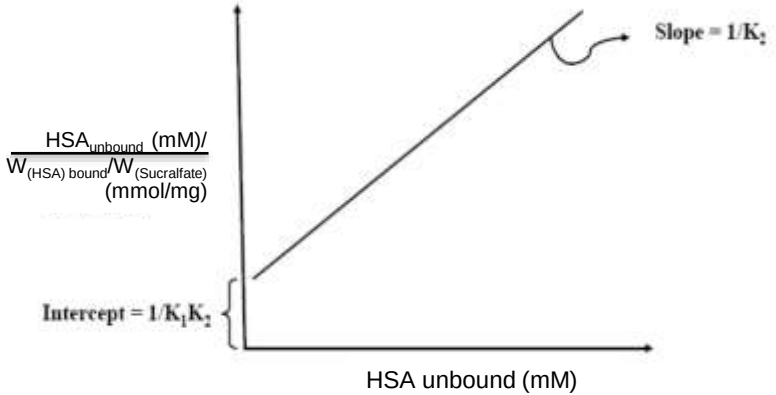
# Case Study #1: Proposed Test Formulation Deviated from Recommendation in PSG

- Additional bioassays were conducted to demonstrate the comparable results of the following
  - Total sucralfate adhered to stomach:
    - Mucoadhesion (stomach) assay
  - Barrier to diffusion of hydrogen ions:
    - Delay in acid diffusion assay
  - Barrier to diffusion of bile salts:
    - Delay in bile salt (taurodeoxycholic acid, TDC) diffusion assay

# Case Study #2: Study Design on HSA Binding

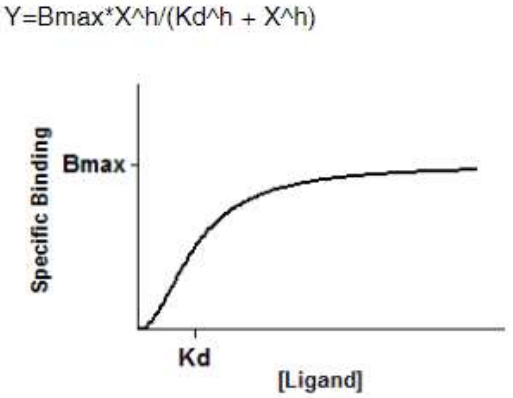
## Fixed amount of sucralfate (PSG)

Langmuir constants $k_1$ and $k_2$ values calculated using Langmuir equation




## Fixed amount of HSA

$K_d$ values calculated using the Hill equation



# Case Study #2: Study Design on HSA Binding

- Rationale behind the method selection
- Method sensitivity concern: is $K_d$ sufficient for BE determination?
- Alternative approaches should be scientifically justified with comprehensive supporting data and explanation

# Case Study #3: Bile Salt Binding

- Selection of bile salt(s):
  - TDC was selected as the bile salt for binding study
  - The decision was made based on literature information alone
  - No experimental data support as there were no development and optimization studies conducted
  - The justification is insufficient

# Case Study #3: Bile Salt Binding

- Method development and optimization study on bile salt selection was conducted
  - Sucralfate binding with different bile salts, including single salt and mixture of salts, was studied
  - The binding profiles and capacities were analyzed
  - Optimal salt(s) was selected

# Summary

- Avoid Common Deficiencies to Reduce Review Cycles
  - Method development and optimization are critical
  - Deficiencies on missing documents/study data should be minimized
- Alternative BE approach should be scientifically justified with comprehensive data and explanation
- Early communication with the Agency is encouraged for proposed alternative approaches

# Challenge Question #1

**Which of the following is true?**

A. 90% CI acceptance range on $K_2$ is 80.00%-125.00%.

B. An acceptable equilibrium binding profile should clearly demonstrate both a rising portion and a maximum binding region.

# Challenge Question #2

**Which of the following statements is NOT true?**

A. Alternative BE approaches are only recommended in these locally acting GI drug products.

B. Both controlled correspondence and pre-ANDA product development meeting provide communication channels to discuss with the Agency for alternative BE approaches.

C. The draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.

D. Physiologically relevant conditions should be taken into consideration in designing and conducting the in vitro binding studies.

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