

# 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

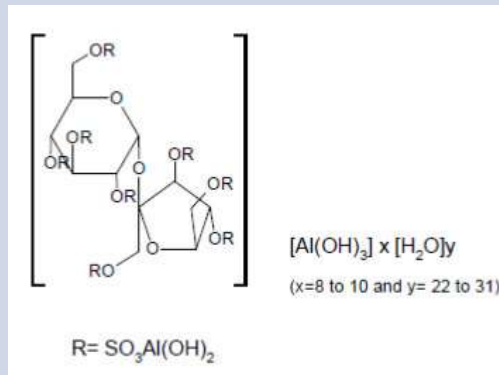
- Calcium acetate
- Lanthanum carbonate
- Sevelamer carbonate
- Sevelamer hydrochloride

## Control of serum cholesterol

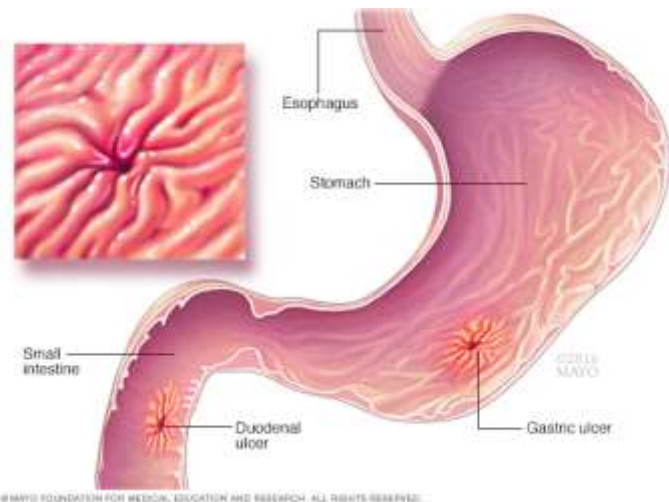
- Colesevelam hydrochloride
- Colestipol hydrochloride
- Cholestyramine

## Treatment of active duodenal ulcer

- 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

- Active pharmaceutical ingredient (API) sameness
- Qualitatively (Q1) and quantitatively (Q2) the same except the flavor/color
- Acceptable comparative physicochemical characterizations
- Disintegration time (Tablets)

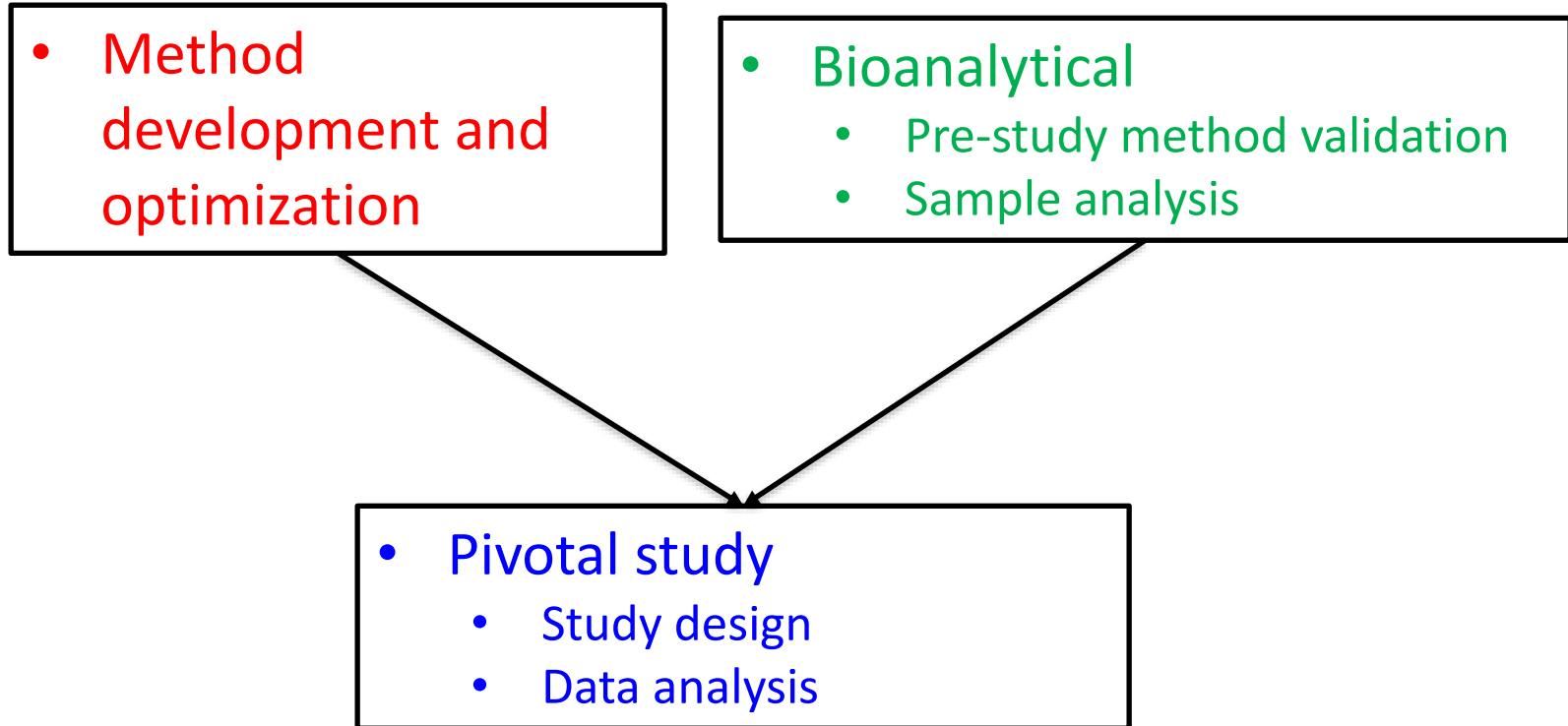
### Bioassays

- In vitro equilibrium binding – Human or Bovine Serum Albumin (HSA/BSA)
- In vitro equilibrium and kinetic binding - Bile Salts
- In vitro enzyme activity – Pepsin

\* Suspension PSG: [https://www.accessdata.fda.gov/drugsatfda\\_docs/psg/Sucralfate\\_oral%20suspension\\_NDA%20019183\\_RV08-17.pdf](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](https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_018333.pdf)

# In Vitro Binding Study Deficiencies



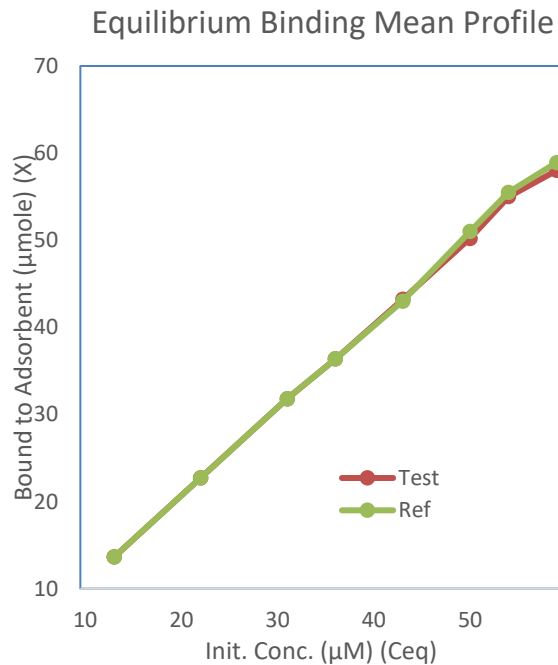
# Common Deficiencies – Method Development and Optimization



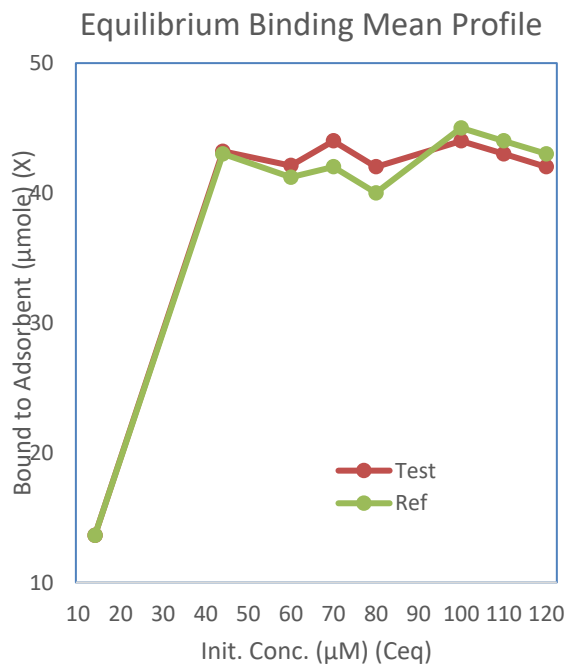
- Missing method development and optimization in one or more of the following parameters
  - e.g., incubation media, pH, volume, amounts, and duration
- Insufficient method development and optimization
  - e.g., lack of supporting data with experimental details and no rationale for the parameter selection
- 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



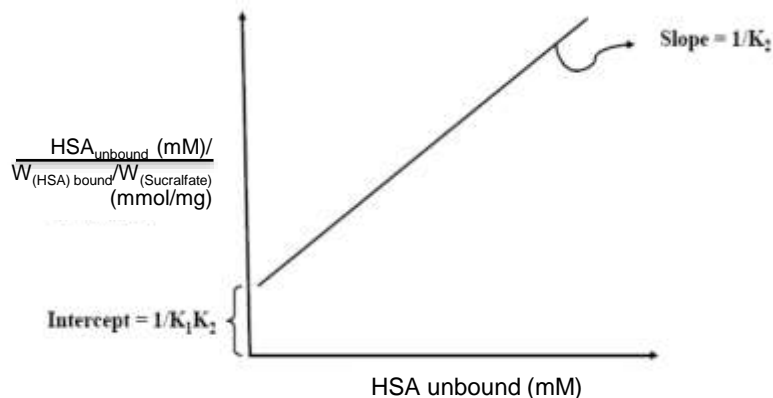
- Additional bioassays were conducted to demonstrate the comparable results of the following
  - Total sucralfate adhered to stomach:
    - Mucoadhesion (stomach) assay
  - Barrier to diffusion of hydrogen ions:
    - Delay in acid diffusion assay
  - Barrier to diffusion of bile salts:
    - Delay in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

# Case Study #2: Study Design on HSA Binding



## Fixed amount of sucralfate (PSG)

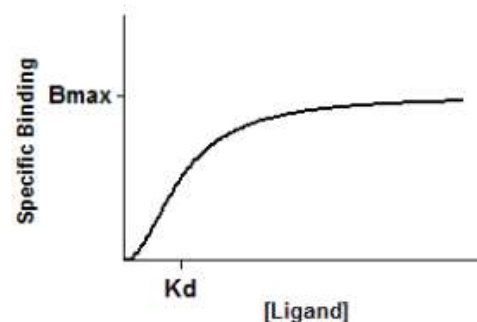
Langmuir constants  $k_1$  and  $k_2$  values calculated using Langmuir equation



## Fixed amount of HSA

$K_d$  values calculated using the Hill equation

$$Y = B_{max} * X^h / (K_d^h + X^h)$$



## 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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