Recommended In Vitro Studies

SBIA 2022: An in-depth look at the April 2022 Final FDA Guidance: Bioavailability studies submitted in NDAs or INDs – General Considerations
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DISCLAIMER

The views expressed in this presentation are those of the Speaker and do not necessarily represent the views or policies of the FDA.
A quality product of any kind consistently meets the expectations of the user – drugs are no different.

Patients expect safe and effective medicine with every dose they take.

Pharmaceutical quality is assuring every dose is safe and effective, free of contamination and defects.

It is what gives patients confidence in their next dose of medicine.
IN VITRO APPROACHES FOR BA

1. Batch release test - Dissolution

2. BA Prediction – IVIVC for ER dosage forms
OUTLINE

- Biowaivers
- In vitro studies – IR products
- In vitro studies – MR products
- In vitro studies – Other MR products
- Alcohol dose dumping – MR products
- Summary
BIOWAIVERS

• 21 CFR 320.22(a)

• Biowaiver requirements
  - no additional BA/BE studies
  - in vitro data; in vivo data requirement waived
  - Linear PK for higher strengths
BIOWAIVERS

Multiple strengths

• proportional similarity
• high potency drugs; composition < 5%
• Bilayer tablets
BIOWAIVERS

Multiple strengths

• Different strengths not proportionally similar
• Fixed combination products
BIOWAIVERS

Multiple strengths

- Different strengths not proportionally similar
- Fixed combination products
In Vitro Studies Conducted in Support of BA 21 CFR 320.24
IMMEDIATE RELEASE PRODUCTS

• In vitro dissolution data needed
  - BA of capsules, tablets, suspensions
  - strength or pH independent drug release
  - 3 media; pH 1.2, 4.5, 6.8

• Appropriate test statistic for similarity – $f_2 (>50)$
IMMEDIATE RELEASE PRODUCTS

• Over-encapsulation for blinding
  - No new excipients; otherwise, in vivo study
  - Comparable dissolution @ pH 1.2, 4.5, 6.8
  - No impact on drug release
  - Enzymes could be added to medium
IMMEDIATE RELEASE PRODUCTS

SUPAC-IR (Scale-up & post-approval changes)

• Formulation or manufacturing changes
• Levels of change: 1, 2, & 3
• Impact on drug release
• Dissolution data as measure of BA

MODIFIED RELEASE PRODUCTS

• SUPAC-MR (Scale-up & post-approval changes)
  - Dissolution data support changes

MODIFIED RELEASE PRODUCTS

Beaded Capsules

• Strengths differ only in fill weight
• Proportional similarity is evident
• Biowaiver – up; new higher strength (Linear PK)
• Regulatory dissolution method
• Putative dissolution method – pH 1.2, 4.5, & 6.8
MODIFIED RELEASE PRODUCTS

Other MR dosage forms

• In vivo BA study on highest strength
• Lower strength(s) BA – similar comparative dissolution data
  – The same dosage form
  – Proportionally similar
  – The same mechanism of drug release
  – Linear PK
MODIFIED RELEASE PRODUCTS

Other MR dosage forms

Strengths not proportionally similar

• BA data on highest and lowest strengths
• Biowaiver for Intervening strength(s)
  – Similar multimedia dissolution profiles
  – Similarity factor, $f_2 > 50$
  – Dissolution safe space via IVIVC or IVIVR; virtual BE
Alcohol –Induced Dose Dumping
MODIFIED RELEASE PRODUCTS

Alcohol Dose Dumping

• Alcoholic beverages & drug PD effects

• MR products - alcohol may cause dose dumping
  – altered systemic exposure
  – Undesired pharmacologic effects
MODIFIED RELEASE PRODUCTS
Alcohol Dose Dumping

- Risk mitigation – in vitro studies
- Studies on highest & lowest strengths
  - Optimum dissolution method
  - Alcohol concentrations: 0, 5, 20, & 40 %
  - n = 12
  - Multiple time points for full profiles
MODIFIED RELEASE PRODUCTS
Alcohol Dose Dumping

• Dissolution medium: 0.1 N HCl (pH 1.2)
• Different media – 0.1 N HCl + proposed method
  – the MR characteristics maintained?
  – estimate $f_2$ for each alcohol conc. Vs. the control (0% alcohol)
  – data: individual, plots, descriptive stats, etc
MODIFIED RELEASE PRODUCTS

Alcohol Dose Dumping

• Results: dose dumping or no dose dumping

• Dose dumping
  – in vivo BA study?
  – Labeling?
  – Other risk mitigation strategy?
SUMMARY

• Assess BA and BE with in vitro studies
• In vitro data can be surrogates for BA and BE
• Product lifecycle: pre- and post-approval
• Type of dosage form: IR & MR
SUMMARY

• Multiple dosage strengths
• Alcohol can impact drug release & absorption from MR products
• Absence of dose dumping – no action
• Dose dumping – contact FDA before filing
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