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 October 26, 2022.

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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

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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

SUPAC IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (October 1997)

MODIFIED RELEASE PRODUCTS

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

SUPAC-MR: Modified-Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (October 1997)

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, f2 > 50
  - Dissolution safe space via IVIVC or IVIVR; virtual BE

U.S. FOOD & DRUG ADMINISTRATION

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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