

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

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, $f_2 > 50$
 - 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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