Establishing Bioequivalence for Generic Oral Modified-Release Products: Regulatory Considerations and Utility of In Vivo Predictive Dissolution

Sue-Chih Lee, Ph.D.

Division of Quantitative Methods and Modeling (DQMM)
Office of Research and Standards (ORS)
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)

March 9, 2018

ODD iPD-FPD Workshop, Lake Tahoe, NV, March 4-9, 2018

Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies."

Outline

- Background
- Challenges and issues to be addressed in establishing bioequivalence (BE) for generic oral modified-release (MR) products
    - Generic MR products can have a different drug-release controlling mechanism and formulation design from those of the reference listed drug (RLD)
    - Clinical implications of dissolution profile differences (pre-approval) and dissolution failures (post-approval)
    - BE for intended patient population
        - Effects of disease state, concomitant medications and polymorphism of drug metabolizing enzymes
    - Excipient effects on drug uptake/efflux transporters
- Regulatory research
- Summary

Generic Drugs

- **Substitutability**
  - A generic drug product is expected to have similar safety and efficacy profiles as the brand name product so that it can substitute the latter in the intended patient population

- **Pharmaceutically equivalent**
  - Same active ingredient(s); dosage form; route of administration; strength

- **Bioequivalent to its RLD**
  - Differences between a generic drug and the RLD is due to the formulation differences
  - Oral systemic generic drug products: No significant differences in the rate and extent of absorption compared to its RLD

- **21 CFR §314.3 - Bioequivalence**

"…[T]he absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administrated at the same molar dose under similar conditions in an appropriately designed study…"

Factors affecting oral absorption

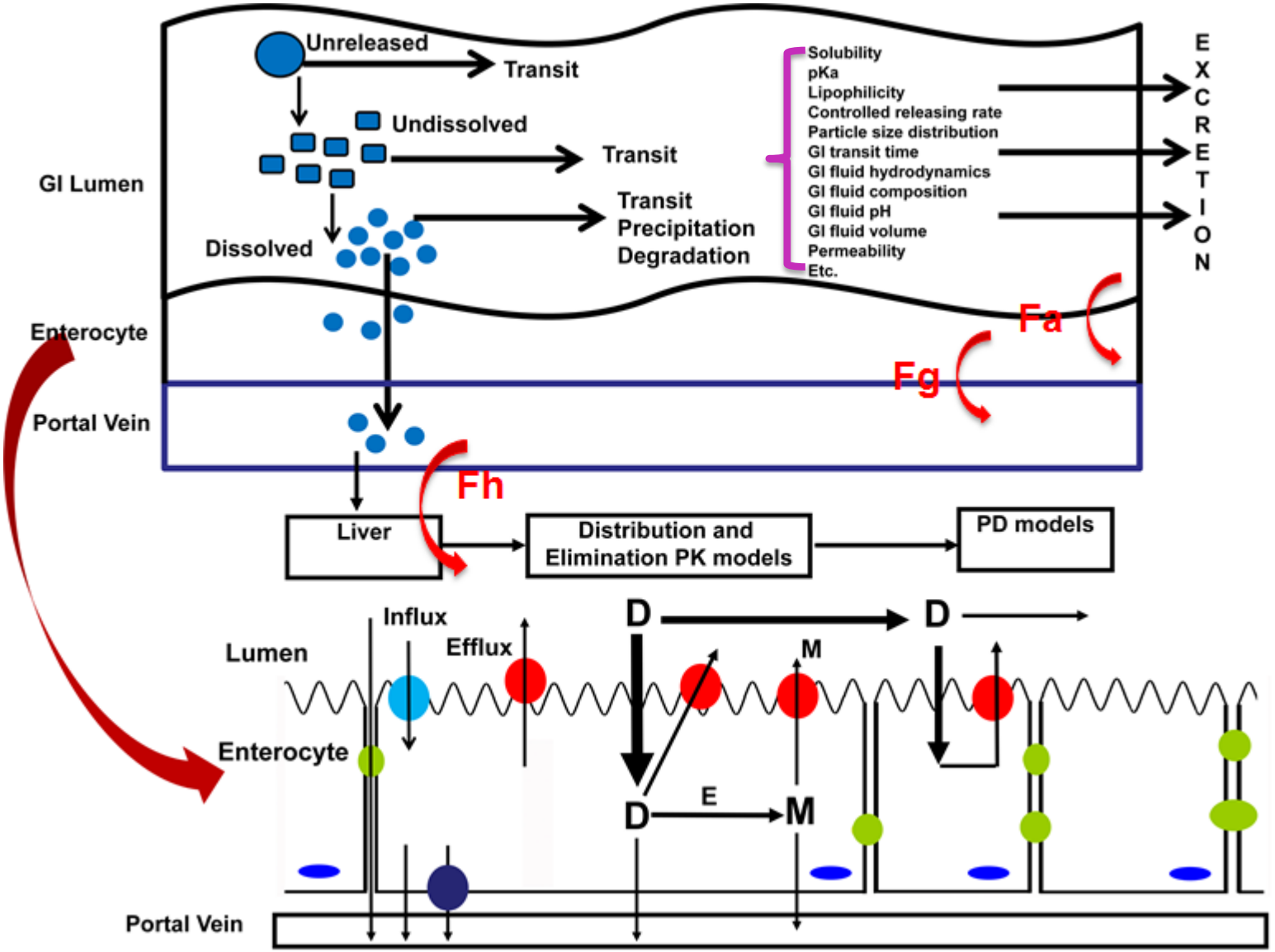
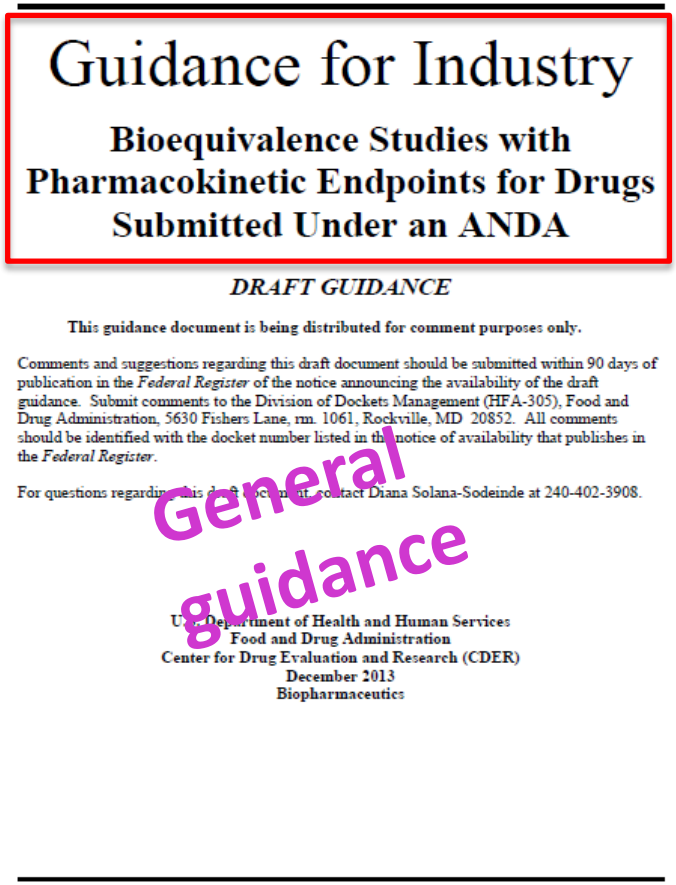


Figure Adapted from Dr. Xinyuan (Susie) Zhang

Demonstrating BE for generic drugs: FDA Guidances



Guidance for Industry

Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

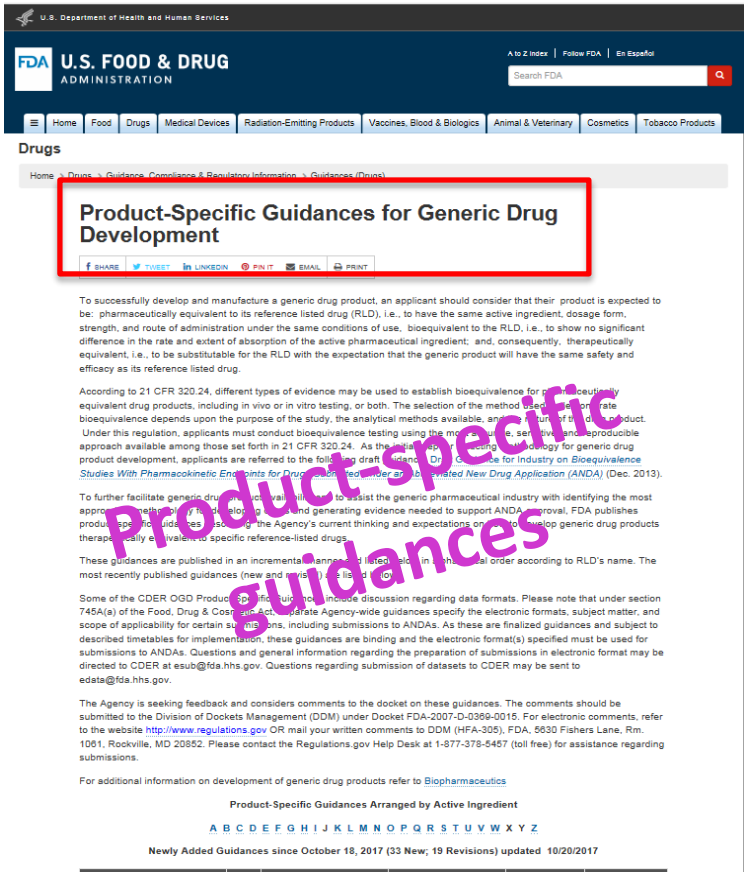
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact Diana Solana-Sodeinde at 240-402-3908.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 2013
Biopharmaceutics

General guidance

https://www.fda.gov/downloads/drugs/guidances/ucm377465.pdf



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Product-Specific Guidances for Generic Drug Development

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To successfully develop and manufacture a generic drug product, an applicant should consider that their product is expected to be: pharmaceutically equivalent to its reference listed drug (RLD), i.e., to have the same active ingredient, dosage form, strength, and route of administration under the same conditions of use, bioequivalent to the RLD, i.e., to show no significant difference in the rate and extent of absorption of the active pharmaceutical ingredient; and, consequently, therapeutically equivalent, i.e., to be substitutable for the RLD with the expectation that the generic product will have the same safety and efficacy as its reference listed drug.

According to 21 CFR 320.24, different types of evidence may be used to establish bioequivalence for pharmaceutically equivalent drug products, including in vivo or in vitro testing, or both. The selection of the method used to demonstrate bioequivalence depends upon the purpose of the study, the analytical methods available, and the nature of the product. Under this regulation, applicants must conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24. As the preferred testing methodology for generic drug product development, applicants are referred to the following draft guidance: Draft Guidance for Industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (ANDA)* (Dec. 2013).

To further facilitate generic drug development, FDA is to assist the generic pharmaceutical industry with identifying the most appropriate method to use in developing and generating evidence needed to support ANDA approval, FDA publishes product-specific guidances reflecting the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference-listed drugs.

These guidances are published in an incremental annotated listing in chronological order according to RLD's name. The most recently published guidances (new and revised) are listed below.

Some of the CDER OGD Product-Specific Guidances include discussion regarding data formats. Please note that under section 745A(a) of the Food, Drug & Cosmetic Act, appropriate Agency-wide guidances specify the electronic formats, subject matter, and scope of applicability for certain submissions, including submissions to ANDAs. As these are finalized guidances and subject to described timetables for implementation, these guidances are binding and the electronic format(s) specified must be used for submissions to ANDAs. Questions and general information regarding the preparation of submissions in electronic format may be directed to CDER at esub@fda.hhs.gov. Questions regarding submission of datasets to CDER may be sent to edata@fda.hhs.gov.

The Agency is seeking feedback and considers comments to the docket on these guidances. The comments should be submitted to the Division of Dockets Management (DDM) under Docket FDA-2007-D-0369-0015. For electronic comments, refer to the website http://www.regulations.gov OR mail your written comments to DDM (HFA-305), FDA, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Please contact the Regulations.gov Help Desk at 1-877-378-5457 (toll free) for assistance regarding submissions.

For additional information on development of generic drug products refer to Biopharmaceutics

Product-Specific Guidances Arranged by Active Ingredient

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Newly Added Guidances since October 18, 2017 (33 New; 19 Revisions) updated 10/20/2017

Product-specific guidances

https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm

Product-specific guidance (PSG)

Contains Nonbinding Recommendations

Draft Guidance on Paliperidone

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

1. *Drug name and dosage form*
2. *In vivo BE studies: fasting & fed*
3. *Multiple strength "waiver"*
4. *In vitro testing*

Active Ingredient: Paliperidone **1**

Form/Route: Extended-release tablets; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 6 mg
   Subjects: Healthy males and nonpregnant females, general population

2. Type of study: Fed **2**
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 6 mg
   Subjects: Healthy males and nonpregnant females, general population

Analytes to measure (in appropriate biological fluid): Paliperidone in plasma

Bioequivalence based on (90% CI): Paliperidone

Waiver request of in vivo testing: 1.5 mg, 3 mg, and 9 mg based on (i) acceptable bioequivalence (BE) studies on the 6 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths **3**

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA). **4**

In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of the test and reference products generated using U.S. Pharmacopoeia (USP) Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, 6.8 buffer, and water) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Methodology should include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the FDA currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing conditions: 900 mL, 0.1 N HCl, USP apparatus 2 (paddle) @ 50 rpm, with or without alcohol **4 -cont'd**

Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5 % (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Both test and Reference Listed Drug (RLD) products must be tested accordingly, and data must be provided on individual unit, means, range, and %CV on all strengths.

Recommended Nov 2007; Revised Mar 2012; Mar 2015

How to ensure a generic MR product bioequivalent to the RLD? (1)

- **Generic MR products can differ from the reference listed drug in**
  - **Release-controlling mechanism**
  - **Release-controlling excipients**
  - **Formulation design**

- **Are there particular risks of bioinequivalence due to the product design features?**

Regulatory BE assessment for generic oral MR products

- **In vivo BE studies**
  - Fasting; fed; sprinkle (as applicable)
  - PK measures
    - $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and Cmax (single dose studies); $AUC_{0\text{-}tau}$ and CmaxSS (steady state studies)
    - Partial exposure (partial AUCs) as applicable
    - Report Tmax, Kel and t1/2 (single dose studies); CminSS, CavSS, degree of fluctuation, swing and Tmax (steady state studies)
- **Comparative in vitro dissolution testing**
  - Compendial or FDA recommended dissolution method (see Dissolution Methods Database), and firm's own method as applicable
  - Dissolution in at least 3 media (e.g., pH 1.2, 4.5 & 6.8 buffers)
  - Alcohol dose dumping assessment (0.1N HCl with 0%, 5%, 20% & 40% alcohol)

Guidance for Industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA https://www.fda.gov/downloads/drugs/guidances/ucm377465.pdf

Multiple strength "biowaiver" for generic MR products

- In vivo BE studies are generally conducted on one strength
- BE for other strengths may be demonstrated through
  - Acceptable BE study on the designated strength
  - Acceptable in vitro dissolution testing of all the strengths
  - Proportional similarity of the formulations across all strengths

- **Proportional similarity across strengths**
  - All active and inactive ingredients are in similar proportion between different strengths
  - For high-potency drug substances (where the amount of active drug substance in the dosage form is relatively low)
  - Active and inactive ingredients that are not in similar proportion between different strengths can be considered proportionally similar with adequate justification
  - For MR products, compositional proportionality may fail to show similar performance. Product design and comparative in vitro dissolution in multiple media could be revealing on product performance.

Modified Release products

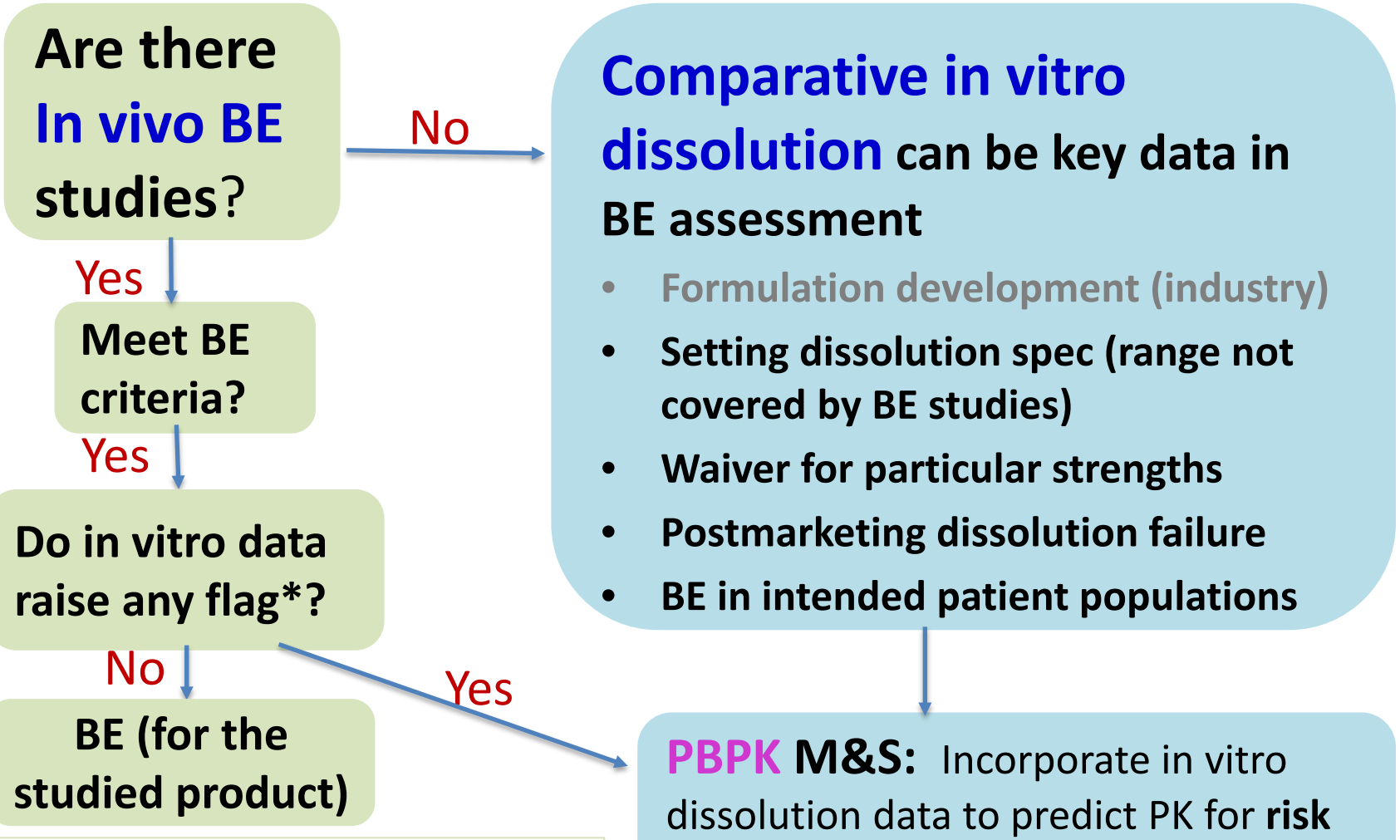
- *In addition to waiver of an in vivo BE requirement under 21 CFR 320.22, there are certain circumstances in which BE can be evaluated using in vitro approaches under 21 CFR 320.24(b)(6). In such circumstances, an in vivo data requirement is not waived, but rather, FDA has determined that in vitro data is the most accurate, sensitive, and reproducible for a product, as required under 21 CFR 320.24(a). Nonetheless, for ease of the audience, in this presentation we will refer to accept in vitro BE data in accordance with 21 CFR 320.24(a) as a "biowaiver."

Challenges in establishing BE for Generic oral MR products

- **Setting in vitro dissolution test specifications**

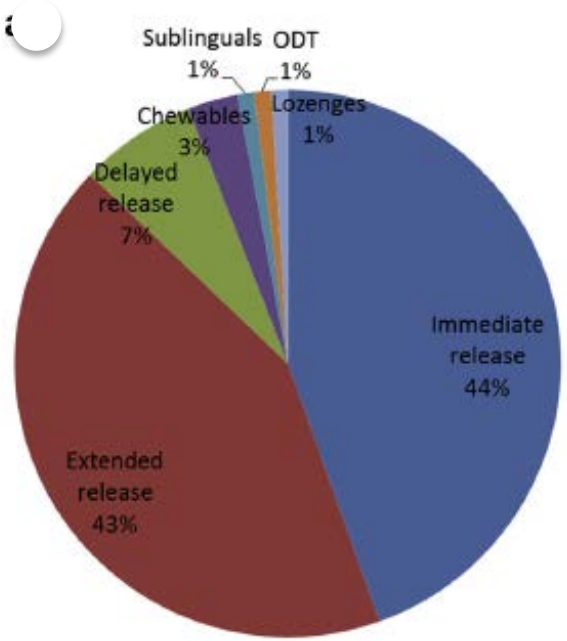
- **BE assurance (generic substitution) in patient populations**
  - Potential bioinequivalence risk due to product design (venlafaxine)
  - Waiver for particular strengths (bupropion)
  - Postmarketing dissolution failures (field report)
  - Untested populations (poor metabolizers - metoprolol ER; pediatrics; disease states)
  - Drug interactions with acid reducing agents (nifedipine ER)
  - Potential impact of differences in excipients or composition of excipients

How to ensure a generic MR product bioequivalent to the RLD? (2)



Dissolution failures: what are the clinical implications?

Dissolution Failure of Solid Oral Drug Products in Field Alert Reports



D Sun, et al, J Pharm Sci 2017;106(5):1302-1309

Dissolution failures for solid oral drug products during 2005-2014:

- 370 reported; brand (48%) vs. generics (52%). Note that generics had a higher share than brand in retail prescriptions with a 74.5% share in 2009.
- Overall, MR products failed dissolution as frequently as IR products.
- MR products appear to fail dissolution at a higher rate than their IR counterparts. (In 2016, 13% of the ~2100 approved solid oral drug products were MR products.)
- In vivo predictive dissolution coupled with PBPK modeling and simulation can aid in risk-based assessment of dissolution failures

Utilizing in vitro dissolution profiles to address bioinequivalence risk via PBPK modeling

PBPK Model Development

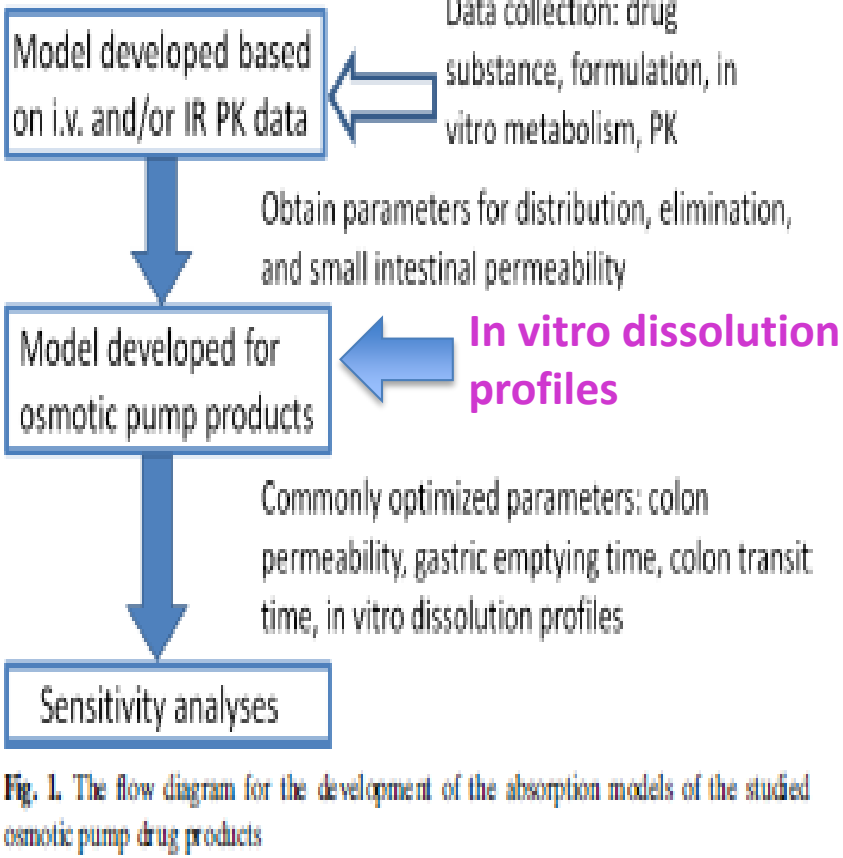
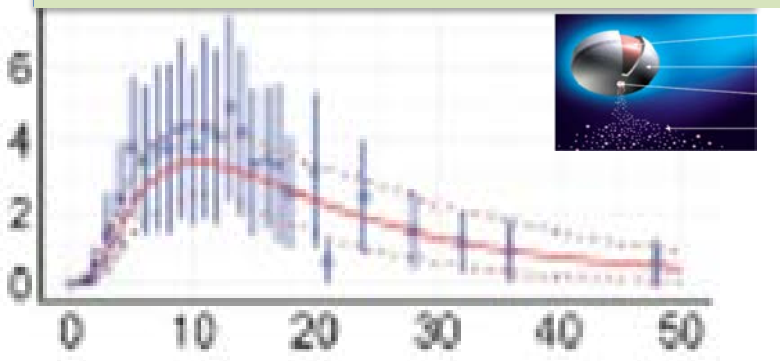


Fig. 1. The flow diagram for the development of the absorption models of the studied osmotic pump drug products

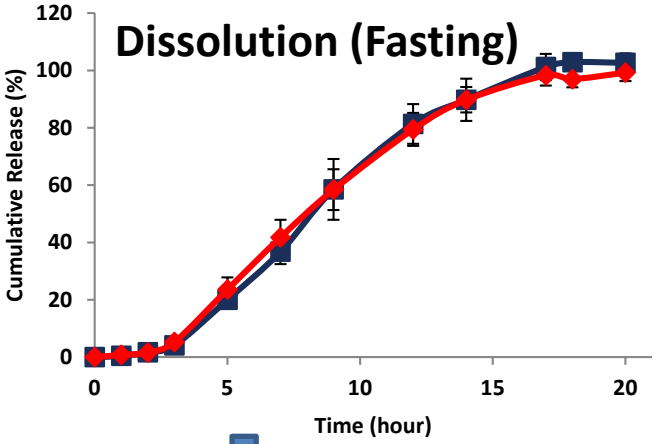
Z Ni, et al, AAPSJ 19:4 1045-1053 (2017)

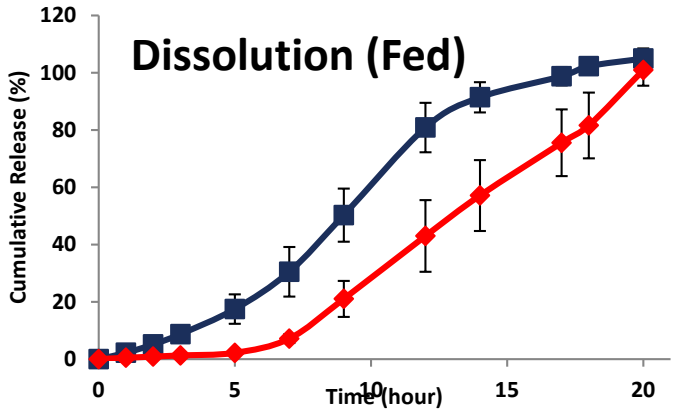
Oxybutynin PK profile (pred vs. obs)

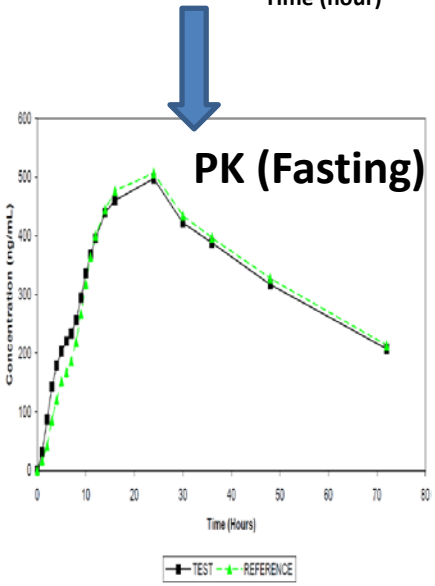


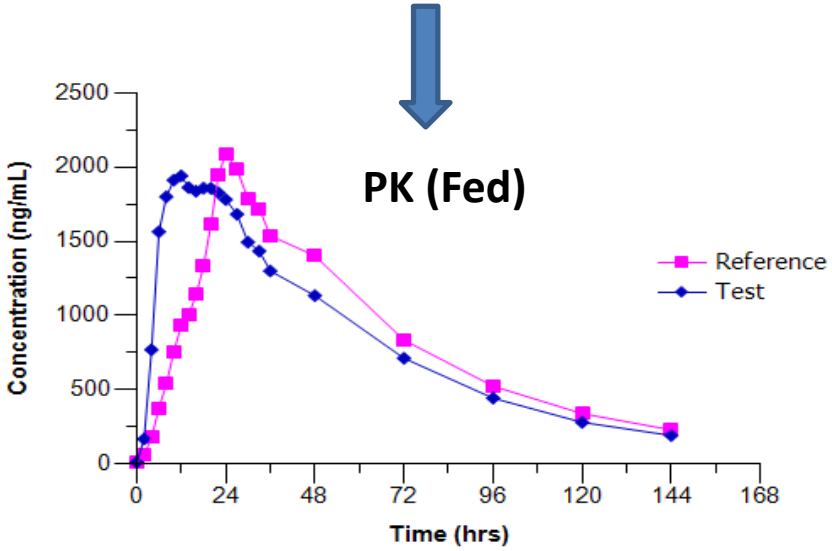
- Eight osmotic pump products investigated
- Optimized model parameters: GI physiology, dissolution profiles
- **Oxybutynin**: Using dissolution data from a 2-stage dissolution testing **underpredicted** the oxybutynin PK. (Note that there are 5 USP dissolution methods for this product.)

Waiver of a higher strength: Did dissolution differences under fed conditions result in BE failure? - Drug A

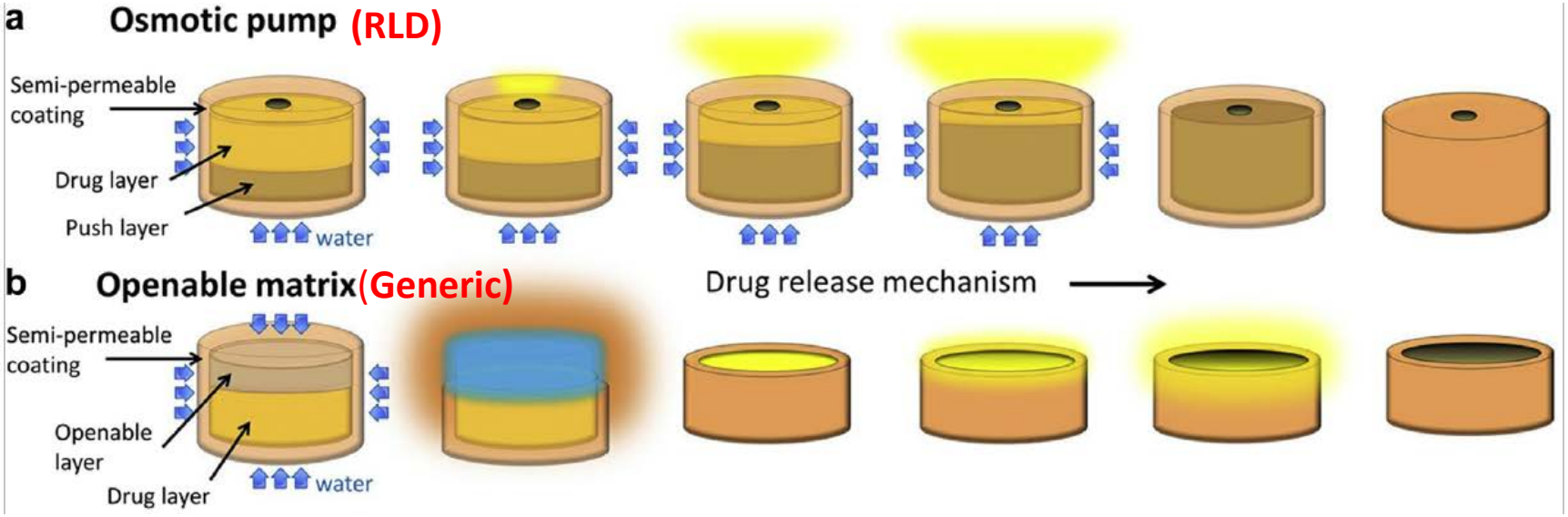








Assessing the risk of bioinequivalence due to product design features



Journal of Pharmaceutical Sciences 105 (2016) 3088-3096

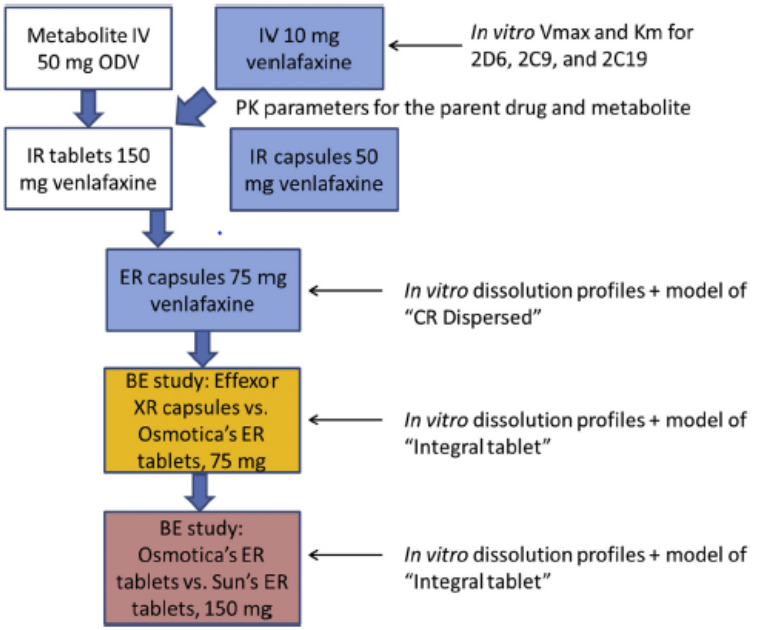
Physiologically Based Pharmacokinetic Modeling for Substitutability Analysis of Venlafaxine Hydrochloride Extended-Release Formulations Using Different Release Mechanisms: Osmotic Pump Versus Openable Matrix

Ho-Pi Lin, Dajun Sun, Xinyuan Zhang*, Hong Wen*

Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland 20993

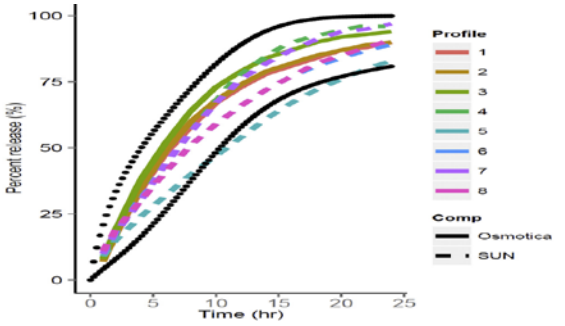
(time lag in the bursting of openable matrix)

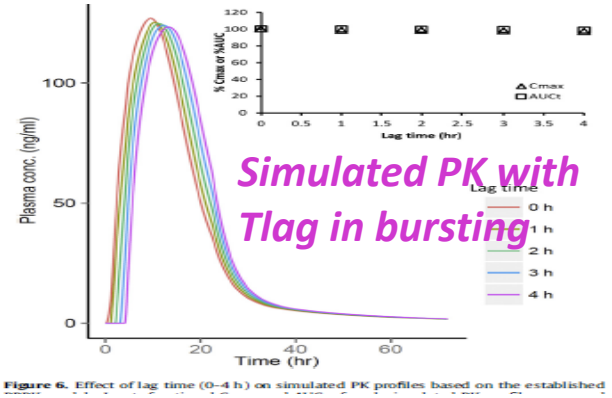
Time lag in the bursting of openable layer poses a low risk for bioinequivalence



H-P Lin et al, J Pharm Sci. 105 (2016) 3088-3096

Dissolution at various pH's





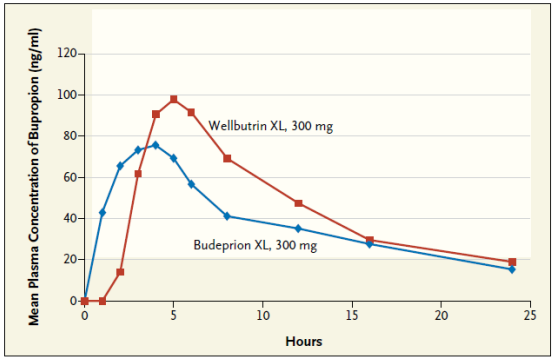
Simulated PK with Tlag in bursting

Figure 6. Effect of lag time (0–4 h) on simulated PK profiles based on the established

- ***Tlag tested***: 0-4 h
- ***Dissolution profiles***: obtained under various dissolution conditions
- ***Results***: Cmax and AUCt within the BE limits of 80%-125%
- ***Conclusion***: Risk of bioinequivalence is minimal (BE metrics do not include partial AUCs)

Bupropion ER Tablets

- **Indication**: major depressive disorder and smoking cessation
- **RLD**: Wellbutrin XL tablets 150 mg /300 mg
- **Budeprion XL tablets** (generic)
  - 150 mg strength: BE compared to the RLD
  - 300 mg strength: Approved through a waiver approach (i.e, BE for the 150 mg strength and acceptable dissolution and formulation similarity between 150 mg and 300 mg strengths)
  - Subsequent in vivo BE study showed bioinequivalence of the 300 mg strength; the product was withdrawn from the market.



Mean Plasma Concentration of Bupropion (Budeprion XL and Wellbutrin XL) as a Function of Time in 24 Fasting Healthy Volunteers.

Woodcock J, N Engl J Med 367:26,2463-2465 (2012)

Absorption modeling can be used to evaluate the totality of the evidence for BE waivers

- An absorption modeling framework can account for the PK differences observed with the proposed generic product (vs. RLD) in the BE study and the differences in dissolution between strengths of the generic product to identify high risk cases where these differences are synergistic

In vitro dissolution at multiple pHs for generic MR products

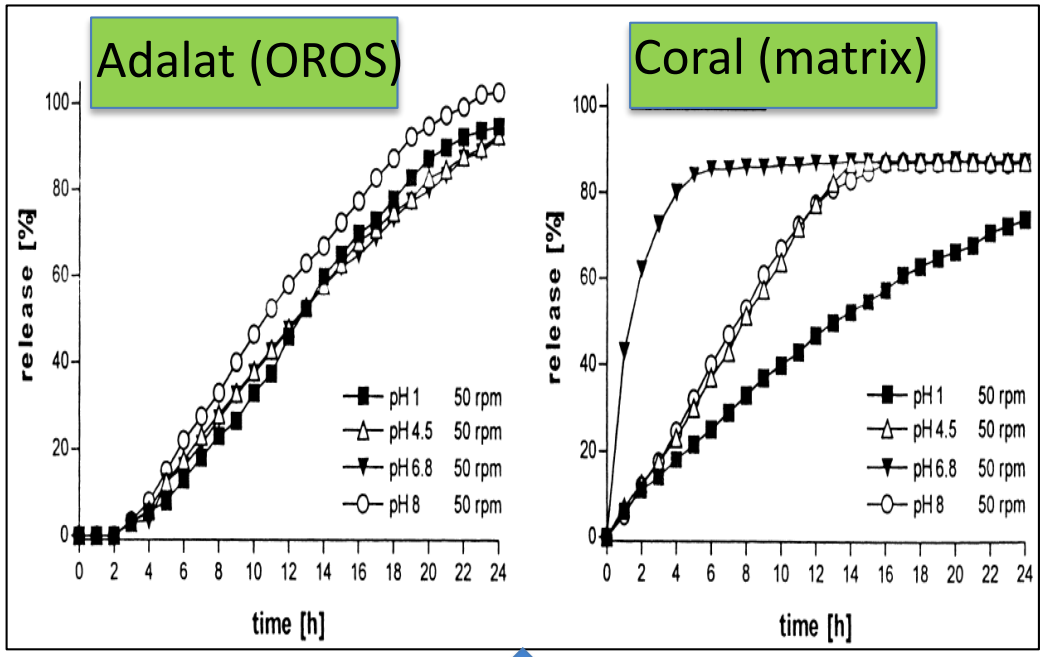
- ***In vivo studies***: Fasting (90 mg & 60 mg) and Fed BE (90 mg) studies
- **Waiver**: 30 mg (conditioned on acceptable BE, dissolution profiles and proportional similarity)
- ***In vitro dissolution***
  - Water (50 mL), Apparatus 7, 15-30 cycles/min (rod), 4/8/12/16/20/24 h
  - Multiple pH (1.2, 4.5 & 6.8) dissolution, Apparatus I or II
  - Alcohol dose dumping studies

Dissolution test method and sampling times:
Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

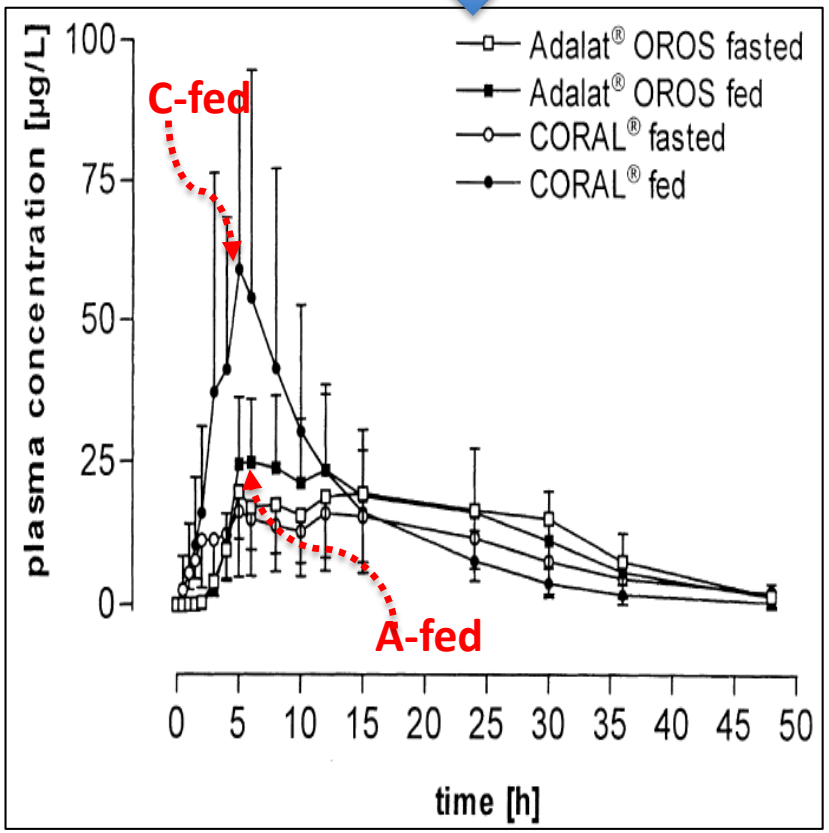
In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased

Nifedipine ER tablets: 2 formulations

Differences in dissolution (at various pH's) and food effect



- *Similar fasting PK*
- *Different food effect*
  - **Adalat OROS vs. CORAL**



In vitro dissolution (pH: 1, 4.5, 6.8, 8)

- **Adalat OROS 60 mg** (osmotic pump)
- **CORAL 60 mg** (an erosive tablet/generic in Europe)

Schug BS et al, Eur J Pharm Sci 15(3):279-85, 2002

Can drug interactions with acid reducing agents differ between a generic drug and its RLD?

NIH U.S. National Library of Medicine

ClinicalTrials.gov

- **Drug Interaction With Proton Pump Inhibitors for Nifedipine ER Tablets** (NCT03100838)
  - A single-dose, open-label, randomized, XO, DDI study of nifedipine ER tablets with or without multiple-dose administration of omeprazole/sodium bicarbonate in healthy volunteers
- Contract #HHSF223201610004I
- ***Contract research ongoing***

- Linear PK over 30-180 mg; T1/2 ~ 2 h
- Procardia: Food increases Cmax but not AUC

- ***R***: Procardia XL tablets, 60 mg
- ***T***: Nifedipine ER tablets, 60 mg
- **Acid reducing agent (with and c/o)**
  - Omeprazole/sod. Bicarbonate (40 mg/1100 mg)
- PK sampling for BE assessment (Cmax & AUC)
- pH in the GI tract: measured using Smart Pill (an ingestible pH and pressure capsule)

Metoprolol ER tablets: Can differences in drug release rate result in non-BE in poor metabolizers?

- **Pharmacological Class**: a beta1-selective adrenoceptor blocking agent
- **Metabolism**: CYP2D6, a polymorphic enzyme
- **Poor metabolizers of CYP2D6**: ~7% (Caucasian); 2% (Asians)
- **PK**: Nonlinear due to saturable metabolism

- **Research**: An open-label PK-PD study (NCT00642096); study ongoing
  - Compare the **pharmacokinetics and cardiovascular effects** of brand name and generic metoprolol ER products in patients with hypertension
  - Determine the impact of **gastric pH variation** on the concentration-response relationship with different metoprolol ER products
  - Examine the **effect of *CYP2D6* genotype on the pharmacokinetics of different metoprolol ER products**

Can excipients impact oral drug absorption by modulating transporters?

- **Grant awarded to UCSF-Stanford CERSI: Interactions of Excipients with Intestinal Transporters**
- Excipients such as mannitol and sorbitol have long been considered as having an impact on oral drug absorption
- Efforts are ongoing to evaluate the potential for various excipients to modulate drug transporters in the GI tract and liver, thus modulating the drug absorption

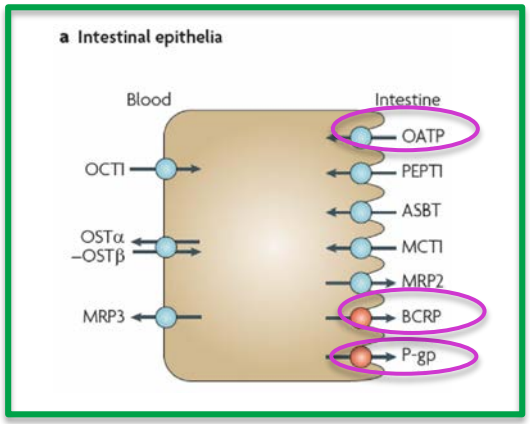
Clin Pharmacol Ther. 2017;101(3):320-323.

A Molecular Basis for Innovation in Drug Excipients

JJ Irwin[1], J Pottel[1], L Zou[2], H Wen[3], S Zuk[3], X Zhang[3], T Sterling[1], BK Shoichet[1], R Lionberger[3] and KM Giacomini[2]

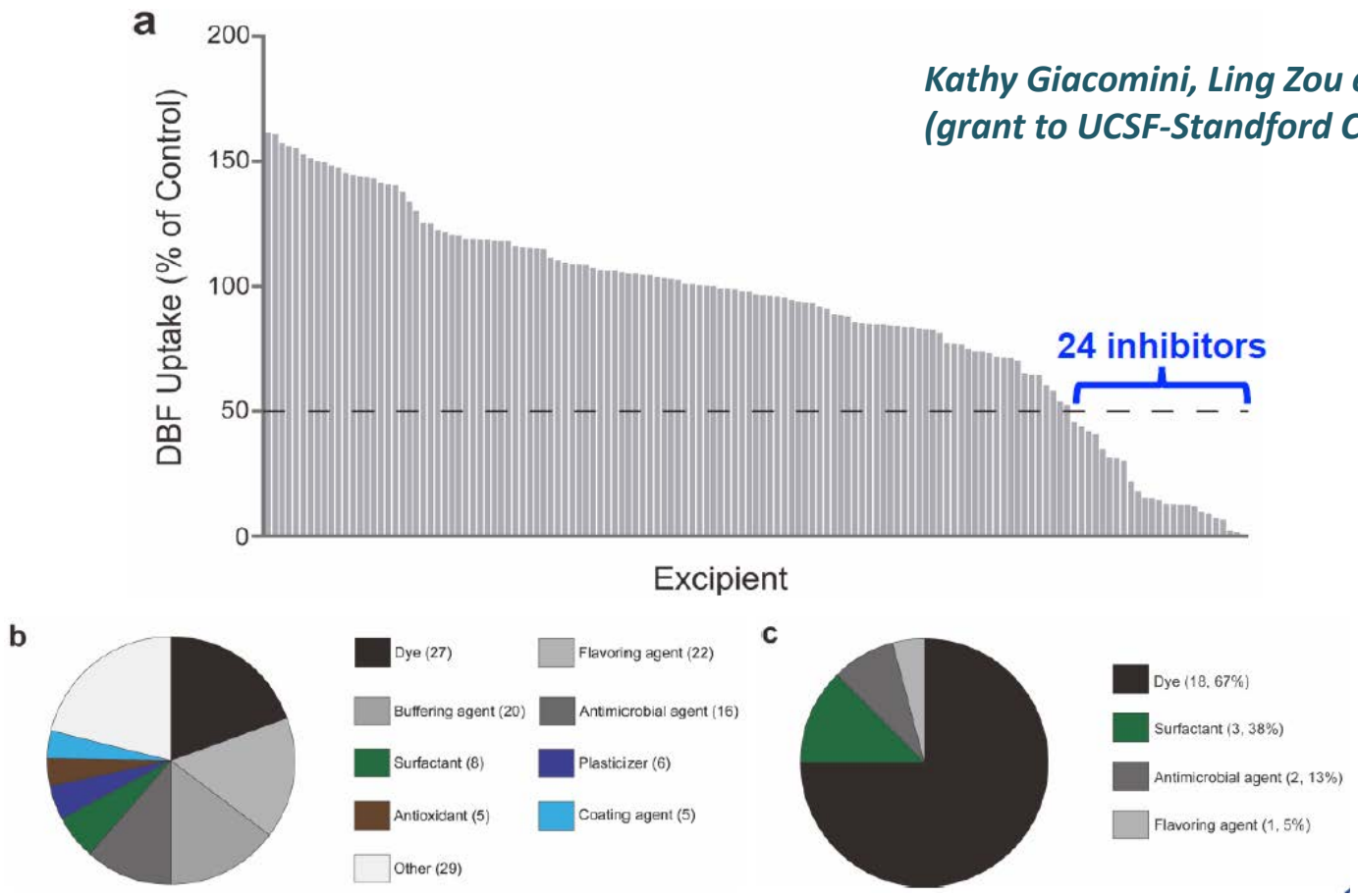
Excipients are ubiquitous in drug formulation, ensuring that active ingredient drugs are properly released on dosing, retain their properties over time, and are palatable, among other roles. Despite their crucial roles, surprisingly little is known about their systemic availability and activities on molecular targets. Here we review key excipient properties, introduce a public-accessible database that enumerates and categorizes them, and sketch a strategy for exploring their possible direct actions on molecular targets.

Transporters in the Intestine



Giacomini KM. et al, Nat Rev Drug Discov. 2010; 9(3): 215–236.

Twenty four excipients were identified as inhibitors of OATP2B1



Kathy Giacomini, Ling Zou et al (grant to UCSF-Standford CERSI)

- **Further studies are needed to evaluate the in vivo significance**

Summary

- Generic MR products can differ from its RLD in product design, which add to the complexity in BE assessment.

- OGD strives to issue product-specific BE guidances on MR products that take into consideration various factors with the goal of ensuring BE under untested conditions. For one, criteria for granting waiver when multiple strengths exist continue to undergo evaluations.

- In vivo predictive dissolution coupled with PBPK can greatly enhance assessment of bioinequivalence risk. Advancement in both dissolution methodology and GI physiological parameters is highly desirable.

Acknowledgments

- FDA/OGD/ORS
  - Robert Lionberger, Ph.D.
  - Lei Zhang, Ph.D.
  - Liang Zhao, Ph.D.
  - Myong-Jin Kim, Pharm.D.
  - Zhanglin Ni, Ph.D.
  - Eleftheria Tsakalozou, Ph.D.
  - Zhichuan (Matt) Li, Ph.D.
  - Jianghong Fan, Ph.D.
- Collaborators within and outside FDA on many research projects

THANK YOU!

Characterization of OATP2B1-mediated dibromofluorescein (DBF) uptake