GDUFA Regulatory Science Initiatives:
Public Workshop for 2019 Generic Drug Research

May 24, 2018
FDA White Oak Campus,
Silver Spring, MD

Individual Physiology, Biology, Anatomy and Their Interplay with Formulation:
Impossible Permutations of Conditions to be Studied for Bioequivalence

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BE & Me: Going Long way Back!

Sensitivity of Indirect Metrics for Assessing “Rate” in Bioequivalence Studies—Moving the “Goalposts” or Changing the “Game”

Amin Rostami-Hodjegan, Peter R. Jackson, and Geoffrey T. Tucker

• Discussing the ambiguities related to assurance of pharmaceutical quality vs clinical safety and efficacy

• Advocating for indirect measures of safety and efficacy

Main goals of the workshop:

• To identify research that will be relevant to the generic industry as they attempt to develop “substitutable generic products” by the choice or the most informative BE studies

• To provide ideas on alternatives to in vivo studies that are not informative

• To offer approaches in assessing and identifying potential problems with substitution that may occur in different patient groups
BE & Me: Going Forward!

Past, Present and Future of Bioequivalence: Improving the Assessment and Extrapolation of Therapeutic Equivalence

RODRIGO CRISTOFOLETTI, MALCOLM ROWLAND, LAWRENCE J LESKO, HENNING BLUME, AMIN ROSTAMI-HODJEGAN, JENNIFER B DRESSMAN

J Pharm Sci 2019 (Under Review)

• Systems approach has created a paradigm shift such that instead of relying extensively on end product testing and one-size-fits-all regulatory criteria, focus is on building quality into the product by design as well as fostering product specific clinically relevant specifications.

• Evolution of bioequivalence regulations shows a trajectory towards applying a Bayesian-like approach, and considering all relevant prior knowledge, to guide decisions in a patient-centric environment.
The first US legal definitions of BA and BE were stated in the Code of Federal Regulation 21CFR320.1. For systemically acting drugs,

BA was defined in the Act as

“the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action”

... and BE as

“the 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 administered at the same molar dose under similar conditions in an appropriately designed study”
Open Questions – Possible Answers

1. Can BE for two formulations be established in healthy volunteers and yet there is no BE in patient populations?
   YES IT CAN BE THE CASE

2. Do we need to conduct BE in the patient populations?
   NOT NECESSARILY

3. How do we refute the likelihood of difference in BE status between healthy volunteers and patients?
   VIA VIRTUAL CLINICAL STUDIES

4. How reliable – qualified are these Virtual Studies?
   ALL DEPENDS ON DATA THAT INFORMS THE POPULATION AND VERIFICATION OF PREVIOUS CASES
Interpretation of interaction studies should focus not only on mean effect but also the observed and theoretically conceivable extremes.
Efficacy-Safety Evidence Gap Over Time: Even for New Drugs

(Courtesy of Dr Bob Powel)

Real People Are Made of “INTERACTING COVARIATES”

**Intrinsic Factors**
- Hepatic Impairment
- Renal Impairment
- Bariatric Surgery & Obesity
- Pregnancy
- Ethnicity & Genetics
- Pediatrics
- Cancer

**Extrinsic Factors**
- Smoking
- Alcohol
- Diet
- Polypharmacy/Drug-drug Interactions
Sub-Models within PBPK and Link to QSP

The Task is Not Just About Models:

- Obtaining reliable POPULATION DATA for biological, patho-physiological and anatomical attributes is essential.
Impossible Task of Investigating the Multiple Factors Which May Affect BE

- **Food / Drinks**
  - Arm 1: *without* food
  - Arm 2: *with* food

- **Formulation**
  - Arm 1: *Reference* formulation
  - Arm 2: *Enabling* formulation

- **DDI**
  - Arm 1: *without* perpetrator
  - Arm 2: *with* perpetrator

- **Enzyme Transporter**
  - Arm 1: *without* inhibitor
  - Arm 2: *with* Inhibitor

Number of arms = Levels^{effects}

Even in the simplest case of two level (High and Low) = 16
Fed state Fasted State with hypochlorhydria (PPI) 

Fasted State (using pH0;)
Fasted State (using gastric bulk pH)

Formulation-Dependent Dissolution in Stomach:

- Might not be important for BE of one drug but may affect another.
- BE in healthy volunteers might be the same but not in patient groups taking PPI
Virtual bioequivalence for achlorhydric subjects: The use of PBPK modelling to assess the formulation-dependent effect of achlorhydria

Kosuke Doki\textsuperscript{a,b,\*}, Adam S. Darwich\textsuperscript{a}, Nikunjkumar Patel\textsuperscript{c}, Amin Rostami-Hodjegan\textsuperscript{a,c}

Formulation-Dependent Dissolution in Stomach:

- BE in healthy young Caucasian volunteers might be the same but not in patient groups belonging to older age in a different ethnic group
<table>
<thead>
<tr>
<th>Victim (CYP3A substrate)</th>
<th>Posaconazole Change (formulation effect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus (Trough conc./dose ratio)</td>
<td>2.7 fold (400 mg bid/200 mg tid)</td>
</tr>
<tr>
<td>Sirolimus (AUC ratio)</td>
<td>8.3-fold (400 mg bid)</td>
</tr>
<tr>
<td>Midazolam, po (AUC ratio)</td>
<td>4.4-fold (200 mg bid) 4.8-fold (400 mg bid)</td>
</tr>
</tbody>
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BIOPHARMACEUTICS & DRUG DISPOSITION
PUBLISHED ONLINE 14 FEBRUARY 2017 IN WILEY ONLINE LIBRARY (WILEYONLINELIBRARY.COM) DOI: 10.1002/bdd.2058

The absorption kinetics of ketoconazole plays a major role in explaining the reported variability in the level of interaction with midazolam: Interplay between formulation and inhibition of gut wall and liver metabolism.

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Takanobu Matsuzuki et al (under preparation)
What is the Clinical Relevance of BE in the Relevant Population

Original Investigation

Results of ASERTAA, a Randomized Prospective Crossover Pharmacogenetic Study of Immediate-Release Versus Extended-Release Tacrolimus in African American Kidney Transplant Recipients

Jennifer Trofe-Clark, Daniel C. Brennan, Patricia West-Thielke, Michael C. Milone, Mary Ann Lim, Robin Neubauer, Vincenza Nigro, and Roy D. Bloom

• There were no significant differences in AUC$_{0-24}$ or C$_{\text{min}}$ between CYP3A5 expressers and nonexpressers during administration of either IR- or CR.

• With IR, tacrolimus C$_{\text{max}}$ was 33% higher in CYP3A5 expressers compared with nonexpressers (P = 0.04) ; With CR, this difference was only 11% (P = 0.4).

• Achieving therapeutic tacrolimus trough concentrations with IR in most African Americans results in significantly higher peak concentrations, potentially magnifying the risk for toxicity and adverse outcomes. This PGx effect is attenuated by delayed tacrolimus absorption with CR.
The effects of CYP3A5 on conventional twice-daily tacrolimus (IR) and extended-release once-daily tacrolimus (ER) formulations in terms of exposure, dose requirements, and dose conversion ratios are well established in whites.

A randomized prospective study in which most participants were white demonstrated no clinical benefit of CYP3A5 genotype–based IR dosing in de novo kidney transplantation.

The bioavailability of the different tacrolimus formulations has not been formally evaluated in African American kidney transplant recipients.

Trofe-Clark et al showed in a prospective randomized comparative crossover pharmacokinetic study (ASERTAA [A Study of Extended Release Tacrolimus in African Americans]) that achieving therapeutic trough concentrations with IR in CYP3A5-expressing African American patients was accompanied by significantly higher peak concentrations (Cmax), an effect that was attenuated when using the CR formulation.
Could have we predicted this? Possibly yes!
Filling the Gaps: Systems Information vs Drug LCMS/MS Proteomics of Relevant Tissues in Relevant Patient Populations

Trypsin → fractionation / LC-ms-ms
Discussions & Debate