How Research Can Help Us Rethink Lifecycle Management and Post-Approval Changes: Oral Products

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Perspective

• The societal promotion of generic products has contributed to the interest in more definitive and scientific public standards for “sameness” in the bioequivalence area.

• However, “innovator” products are frequently evaluated for equivalent quality and/or bioequivalence, in the pre- and post-approval time frames.
Topics

• “Switching” and the Easter Bunny
• When are in vitro studies (i.e. equivalent quality) better than in vivo BE?
• ER, design space, and scale-up
  – MR of anti-epileptic drugs (AEDs)
• Current issues with in vitro dissolution and Need for a second in vitro dissolution method
• IVIVC, IVIVR, and biopharmaceutic risk
• Excipient material properties that impact performance
Clinical sensitivity to switching

Tablet quality

↓

Quality control (QC) specs (in vitro)

↓

Every manufactured batch

Safety and efficacy standard

↓

Bioequivalence window (in vivo)

↓

NDAs, sNDA, 505(b)(2)’s, ANDAs, and major post-approval changes
“Switching” and the Easter Bunny

• Brand to generic (and generic to brand)
• Generic to generic
• Old product to new product after a SUPAC change?
• Initial dosing of a drug-naïve patient of brand formulation (of a non-NTI, not precisely titrated drug) that is not phase 3 clinical trial material?
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Ongoing product quality and Importance of the bioequivalence standard

Concordance and Discordance between Vitro and In Vivo Results

- Truly not BE
  - Both correctly conclude not BE
  - In vitro wrong
  - In vivo wrong

- Truly BE
  - Both correctly conclude BE
  - Both wrong

Oval – in vitro concludes BE
Diamond – in vivo concludes BE
Yes, in vitro are studies sometimes better than conventional human BE studies in assessing equivalence. Why?

• 1. Reduce costs
  – Reduce the cost of “no brainers”
  – Reduce the cost of type II errors

• 2. More directly assess product performance
  – In vitro studies allow for focus on product performance, which is dissolution and absorption.
  – Conventional BE testing suffers from complications (e.g. HVD) due to its indirect approach.

• 3. Offer benefits in terms of ethical considerations
  – Better embraces “No unnecessary human testing should be performed”
  – Can result in faster development

• 4. Potentially better gain physician confidence and understanding
Can result in faster development

*Generally 3-6 clinical bioequivalence tests are conducted in a NDA

Ref: Ajaz Hussain, FDA’s ACPS Meeting, 1997
When are in vitro studies better?

- Class I with rapid dissolution
- Class III with very rapid dissolution
- HVD with rapid dissolution and that are not bio(equivalence)problem drugs
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Lack of BE

Graph showing the mean plasma concentration of bupropion over time for Wellbutrin XL, 300 mg and Budeprion XL, 300 mg.
Factors impacting ER performance

• Drug substance and dose(s)
• Formulation and mechanism of release
• In vivo environment

• In vitro predictive tools
  – Methods
  – Specification setting approaches
Design space

- Because design space is potentially scale- and equipment-dependent, the design space determined at the laboratory scale may not be relevant to the process at the commercial scale.

MR of Anti-epileptic Drugs (AEDs)

- Carbatrol and Equetro (carbamazepine ER cap)
- Tegretol XR (carbamazepine ER tab)
- Depakote ER (divalproex sodium ER tab)
- Keppra XR (levetiracetam ER tab)
- Lamictal (lamotrigine ER tab)
- Oxtellar XR (oxcarbazepine ER tab)
- Trokendi XR and Qudexy XR (topiramate ER cap)
- Qsymia (phenterimine/topiramate ER cap)
- Dilantin (extended phenytoin sodium)

IVIVCs from 2009-2012

- 32 NDAs vs 4 INDs
- n=25 oral solid dosage forms

N=36
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Two of the Most Common Complaints about In Vitro Dissolution

• Too sensitive (i.e. over discrimination)
• Not sensitive enough (i.e. not discriminating enough)

• Opportunities
  – Regulatory relief
  – Methods development/validation/standardization of more challenging dissolution problems (e.g. BCS class 2)
Complications

• Attaining complete dissolution and sink conditions
  – Enhanced drug solubility (e.g. via additional surfactant) tends to reduce dissolution test sensitivity.

• Same EVERYTHING across dose strengths
  – Historical tendency to prefer the same test methods and same specs, even though different doses can result in a fundamental change in the dissolution problem.

• A higher dose may dissolve slower or to a lesser extent, than lower dose.
Roles of In Vitro Dissolution

• Product development tool
• QC test
• Clinically relevant assessment tool [a/k/a in vivo performance test]
  – Meaning?
• A measure of in vivo dissolution
  – As assessed by deconvolution of PK profile when absorption is dissolution-limited?
Need for a Second In Vitro Dissolution Method

• QC test
  – Use: current application in batch-to-batch consistency

• Clinically relevant assessment tool [a/k/a in vivo performance test]
  – Meaning?
  – Use: Product development tool; SUPAC-type situations
Meaning of “In Vivo Performance”

- In vivo dissolution (profile)
- In vivo absorption (profile)
- In vivo pharmacokinetic profile
- Sensitive to efficacy or safety

- Sure, all related, but lack of clarity is a barrier.
- Do we want in vitro dissolution to predict first-pass metabolism?
- We have to be careful about what we expect of in vitro dissolution. Lack of clarity detracts from reliable utility of in vitro dissolution.
- IVIVR – in vitro dissolution – in vivo absorption relationship
  - Absorption = dissolution + permeation
Beyond In Vitro Dissolution Science: Status Quo and the Confidence Game

• Organizations will often not pursue approaches that lack utility in drug development or lack high regulatory certainty.

• Status quo
  – Stakeholder know current strength/limitations of in vitro dissolution
  – Budget
    • No requirement for “biostudies with several formulations”

• Uncertain elements
  – Budget
  – Acceptable role of modeling and simulation
Novel In Vitro Dissolution Methods

• Two major elements
  – Apparatus and operating conditions
  – Media

• Apparati
  – Compendial
  – Two or more “lumen” compartments (e.g. stomach and duodenum per ASD model)
  – Systems with “absorption compartment” (e.g. biphasic systems to mimic absorption during dissolution for low solubility drugs to avoid “too much” surfactant)
Continuous dissolution/Caco-2 system

- Mark J. Ginski, Rajneesh Taneja, and James E. Polli. Prediction of Dissolution-Absorption Relationships from a Continuous Dissolution/Caco-2 System. AAPS PharmSci 1999; 1 (3) article 3

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Biopharmaceutic Risk

• Is an IVIVC/IVIVR possible or even likely for a BCS 1 IR tablet?
• ... a BCS 2 IR tablet?
• ... a BCS 3 IR tablet?
• ... a BCS 4 IR tablet?

• Is it possible to understand how dissolution contributes to the absorption kinetics?
Biopharmaceutic Risk

• What type of drug product would you be most comfortable developing if you could only rely on in vitro dissolution as the key pharmacokinetic/biopharmaceutic test (i.e. not rely on in vivo pharmacokinetic testing)?
Biopharmaceutic Risk

• For a SUPAC change, a IR tablet of a BCS Class 2 drug demonstrates rapid in vitro dissolution (including being in spec). Is a biowaiver possible?

• For a SUPAC change, a ER tablet of a BCS Class 2 drug demonstrates in vitro dissolution in spec. Is a biowaiver possible?
Biopharmaceutic Risk

• For an IR product, in what way is it desirable that in vivo dissolution be the rate-limiting step for drug absorption?
• For an IR product, is there any advantage for in vivo dissolution to not be the rate-limiting step for drug absorption?
• If in vivo dissolution is not-limiting for drug absorption, and in vitro dissolution exactly measures in vivo dissolution, what would be the relationship between dissolution and absorption?
Biopharmaceutic Risk

32 NDAs vs 4 INDs
n=25 oral solid dosage forms

Categories of IVIVC/IVIVR

- Convolution (FDA Level A) AAA
- Deconvolution AA
- Deconvolution (but only linear) A
  - USP Level A
- Summary parameters B
- Point estimates C
- Rank order D

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Excipient material properties that impact performance

• Excipients often
  – Multi-source
  – Critical to product performance

• Process properties more studies than material properties
  – Assumes that excipient composition not critical and covered by CoA and NF, particularly since not the API