Session 3: Therapeutic Equivalence Evaluation and Standards

"FDA Research Update"

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FY2018 Generic Drug Research
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Scope of the Panel

- General bioequivalence (BE) issues for systemically acting drugs
- Biowaivers and predictive dissolution methods for solid oral products
- Equivalence of modified release (MR) products including abuse deterrent formulations (ADFs)

Abuse Deterrence (AD) of Opioid Drugs

- Draft guidance on evaluating AD of generic solid oral opioid products (March 2016)
  - Opened the door for generic competition

- As of April 2017, 9 marketed brand-name products but no approved ANDA for generic AD products
  - Multi-billion market and high public health impact

- Final guidance expected by Nov 2017

- Research still needed to make generics available

ANDA: abbreviated new drug application

Research Objectives for Generic ADFs

- Identify optimal in vitro and in vivo methods for evaluating generic AD opioid products at the levels of:
  - Formulation
  - Physical and chemical manipulations
  - PK
  - PD

- Standardize in vivo evaluation of AD properties:
  - Nasal PK studies
  - Oral (chewed and/or crushed) PK studies
  - Nasal PD studies (i.e., clinical abuse potential) for AD products containing aversive agents

- Standardize in vitro evaluation of AD properties:
  - Extraction studies
  - Syringeability studies
  - Sublimation studies

PK: pharmacokinetic, PD: pharmacodynamic

Current Research Projects

Grants/Contracts:

- FY13 contract – Evaluation of drug product formulation in vitro performance characteristics related to AD for solid oral dosage forms of opioid
- FY15 contract – PK study of AD opioid drug products following insufflation of milled drug products

Internal Collaboration:

- In vivo predictive method for determining opioid availability following chewing of solid oral opioids
- Regional deposition fraction quantification and dissolution testing of nasally insufflated OxyContin using an *in vitro* method

Modeling and Simulation:

- IVIVC development of chewed vs whole Hysingla tablets using in vitro drug release based on the simulated chewing method
- PBPK modeling and simulation of nasal insufflation of AD OxyContin
- PBPK and PKPD modeling of hydrocodone for intranasal and oral routes

IVIVC: in vivo in vitro correlation, PBPK: physiologically-based pharmacokinetic

Future Research Considerations

- **Human Insufflation PK Studies:**
  - All current AD RLDs have AD labeling related to abuse by insufflation in the nasal route
  - Since nasal powders for systemic drug delivery are not a common dosage form, no in vivo-predictive in vitro method is established
  - Draft guidance recommends in vivo PK studies for the nasal route
  - Research is needed to understand the critical attributes (e.g. particle size and role of polymeric excipients) as well as manipulation methods to prepare T and R products for insufflation

- **AD Products Containing Aversive Agents:**
  - Aversive agents are not generally listed as active ingredients and thus legally can differ in a generic
  - Draft guidance recommends a comparative PD (i.e. drug liking) study if T product contains a different aversive agent or a lesser amount of the same aversive agent
  - Are there any alternative approaches that could evaluate a generic ADF with a different aversive agent from R?

RLDs: reference listed drugs, T: test, R: reference

Current Issues in BE for Solid Oral Dosage Forms

- When is PK profile similarity needed for BE?
  - Addition of pAUC or similarity in Tmax
- When are tighter BE limits needed?
  - Does this product have a narrow therapeutic index?
- Is in vitro dissolution reliable for regulatory decision making about BE?
- As labels expand to include more informational about specific populations, methods of administration, or DDIs with PPI are more in vitro or in vivo BE data needed?

pAUC: partial area under the curve, Tmax: time to maximum plasma concentration, DDIs: drug drug interactions, PPI: proton-pump inhibitor

Reason for Use of pAUC as BE Evidence

- PK/PD relationship that shows clinically significant sensitivity to PK differences

- Early pAUC for quick onset of effect
  - Methylphenidate ER tablets – $pAUC_{0\text{-}3hr}$

- Later pAUC for sustained drug release
  - Naltrexone injectable (ER suspension) - $pAUC_{10\text{-}28day}$

- Evaluate similarity of drug release throughout GI tract
  - Mesalamine DR tablets - $AUC_{8\text{-}48hr}$

ER: extended release, GI: gastrointestinal

Narrow Therapeutic Index Drugs

- Narrow therapeutic index (NTI) drugs have a small exposure window where they are both safe and effective

- BE standards should be risk-based and therefore should allow less variation for NTI drugs
  - Four period fully replicate design
  - Must pass both the reference scaled limits and the unscaled average BE limits of 80.00-125.00%
  - Upper limit of the 90% CI of the ratio of the within-subject standard deviation of T to R product is less than or equal to 2.5

Evaluation of Dissolution Differences

- MR products with formulation design differences

- Post-approval product quality investigations that note dissolution differences

Labeled Instructions for Use

- RLD product can be administered via a feeding tube

- RLD label describes interactions with proton-pump inhibitors

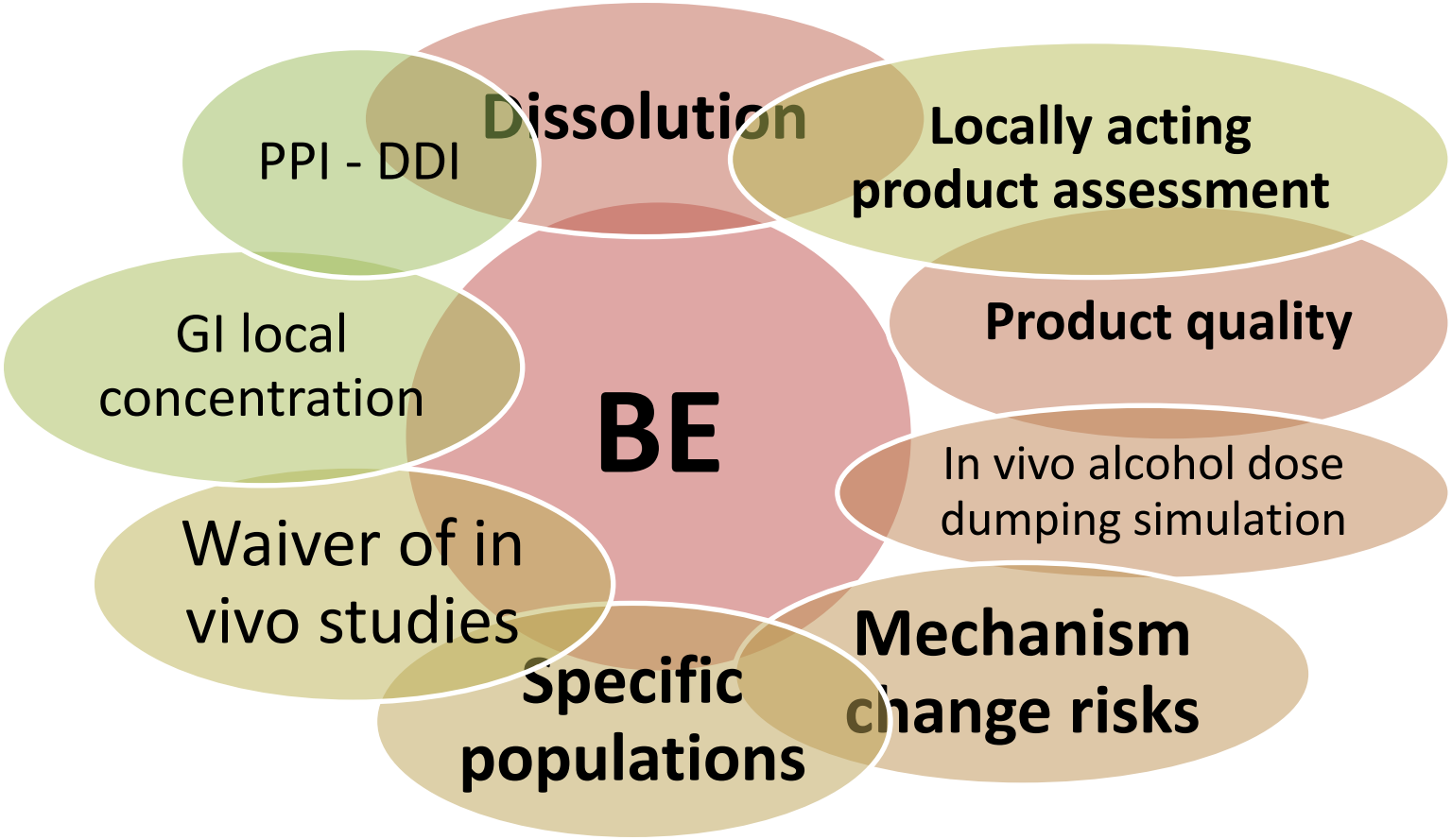
Modeling and Simulation: Decision Accelerators

- FDA: Uses M&S and virtual BE ~~studies~~ simulations to examine each of these cases to guide regulatory standards
  - Focus can be PBPK, PK/PD or formulation/dissolution depending on the case

- Industry: Use virtual BE ~~studies~~ simulations to support situations where you disagree with FDA BE recommendations and propose alternative BE approaches

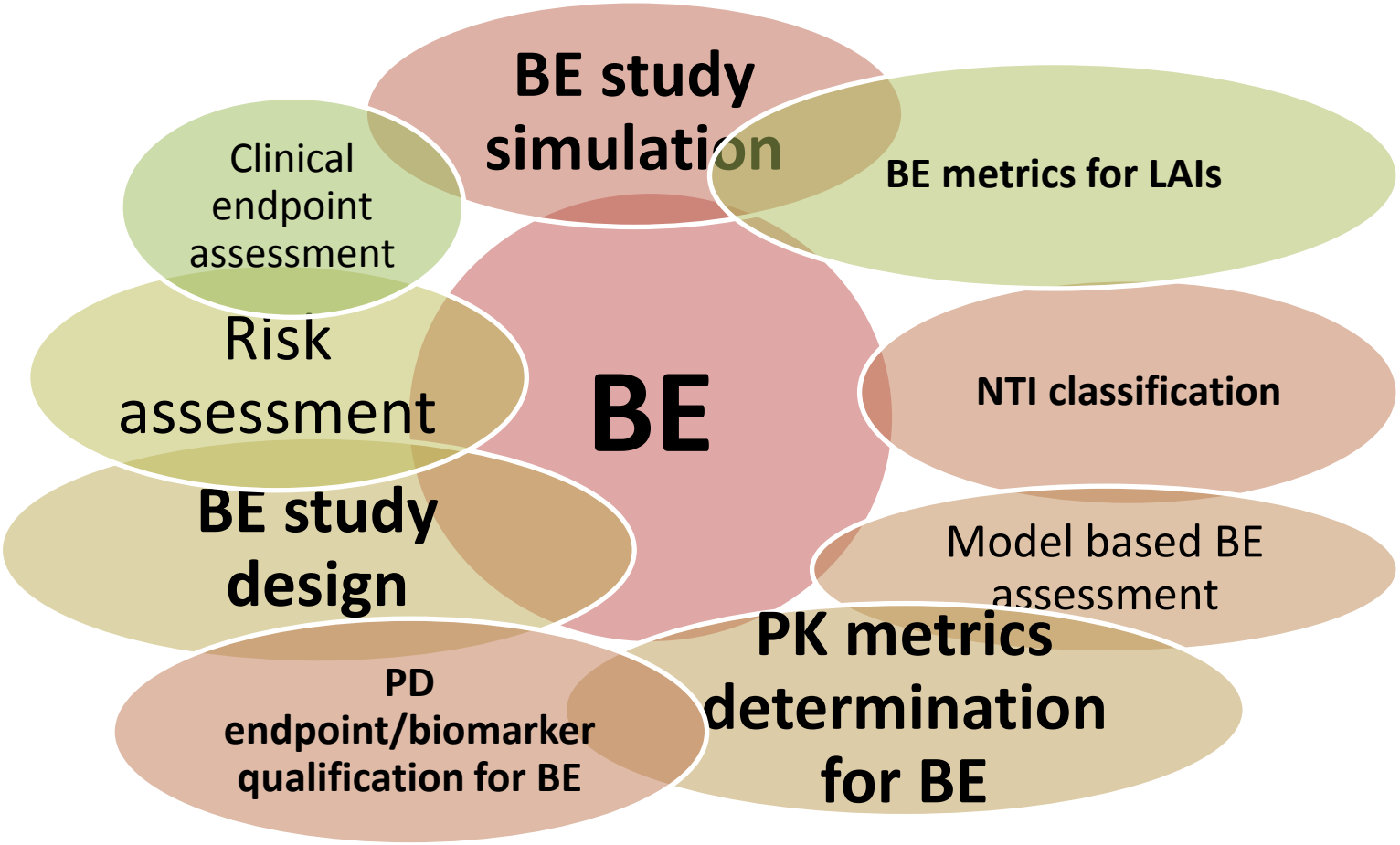
M&S: modeling and simulation

PBPK Model Applications for Generic Products



Increasing use of PBPK models to support regulatory decision making for generic drugs

QCP Model Applications for Generic Products



Pharmacometric models used to support regulatory decision making for generic drugs

QCP: quantitative clinical pharmacology, LAIs: long-acting injectables

Current Research Projects

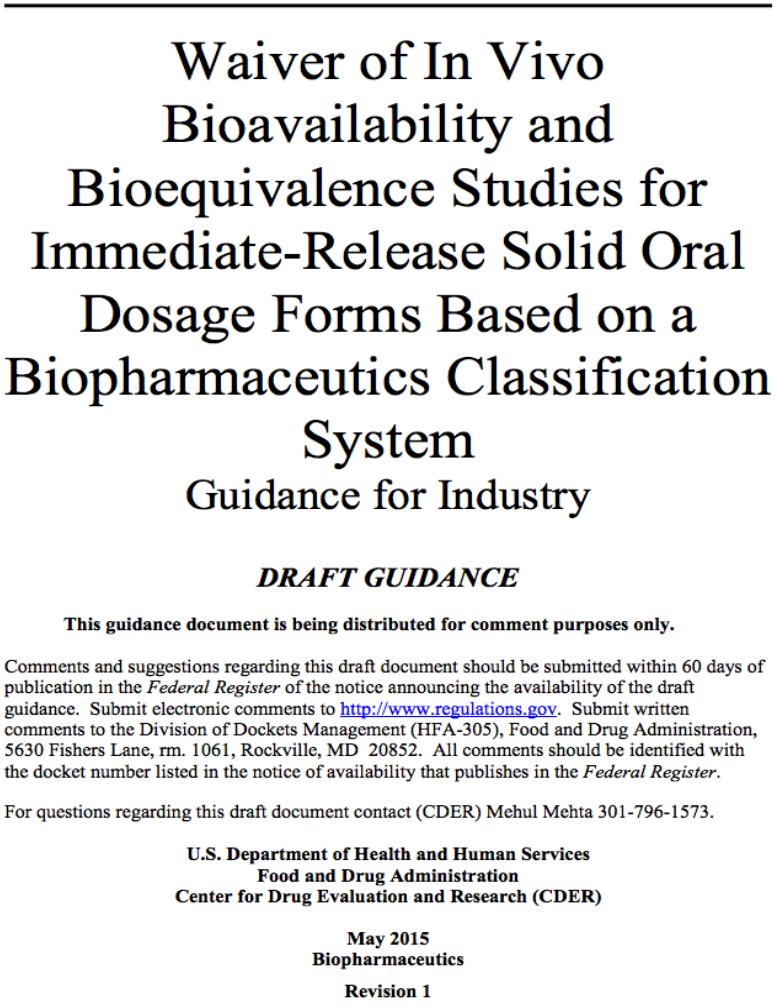
Population PK/PD, dose-toxicity modeling and simulation for NTI drugs
Clinical practice data to aid NTI drug classification
Pharmacometric M&S for a generic drug substitutability evaluation and post marketing risk assessment
A model- and systems-based approach to efficacy and safety questions related to generic substitution
Pharmacometric modeling of immunosuppressants for evaluation of BE criteria
Pharmacometric modeling of long-acting injectable products
Therapeutic index evaluation for tacrolimus and levetiracetam
Design, development, implementation and validation of a mechanistic PBPK framework for prediction of in vivo behavior of supersaturating drug products
Enhancing the reliability, efficiency, and usability of Bayesian population PBPK modeling
PBPK M&S for non-oral product including ocular, dermal and topical products

Future Research

- Goal: Integrate predictive dissolution, PBPK and PK/PD models for decision making about generic drug BE standards

- What will help to reach this goal?
  - Close scientific gaps and improve predictability
  - Virtual BE study best practices

Biopharmaceutics Classification System (BCS)



Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written 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 (CDER) Mehul Mehta 301-796-1573.

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

May 2015
Biopharmaceutics

Revision 1

BCS Class 3 Drugs:

Low Permeability/High Solubility

Examples:

Acyclovir, Cimetidine, Fexofenadine, Metformin

BCS based Biowaivers

- BCS class 1 (high solubility, high permeability)
  - Waivers when the drug product (test and reference) is rapidly dissolving

- BCS class 3 (high solubility, low permeability)
  - Waivers when the drug product (T and R) is very rapidly dissolving
  - Product formulations are qualitatively the same and quantitatively very similar
    - Based on a concern that excipients might affect bioequivalence

Biopharmaceutics Classification System 2015 Draft Guidance
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf

BCS Class 3 Waiver Expansion

- Guidance for BCS class 3 biowaivers was a GDUFA I commitment letter deliverable

- Current BCS guidance on class 3 waivers is not very useful to the generic drug industry
  - Most generic solid oral products use different excipients than the RLD

- Research path forward
  - Quantify excipient interactions with transporters
  - Integrate into PBPK models of oral absorption
  - Combine with FDA data warehouse of successful BE studies on products with different excipients
  - Test via prospective in vivo studies

Priorities for the Panel

- In vitro alternative to in vivo nasal studies for abuse deterrence of solid oral opioid products

- Integrate predictive dissolution, PBPK and PK/PD models for decision making about generic drug bioequivalence standards

- Expand BCS class 3 waivers to non-Q2 formulations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