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Brand-to-generic therapeutic equivalence analysis of modified-release (MR) oral drug products

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PURPOSE

- Among the top 200 prescription drugs in the US, approximately one-third are MR oral drug products (e.g. ER, DR) which provide unique clinical benefits compared to their IR counterparts. The complicated formulation designs and manufacturing processes of MR oral dosage forms have posed regulatory challenges for the evaluation of ANDAs.
- The **Office of Generic Drugs (OGD)** has proactively initiated a series of internal/external research projects to confirm therapeutic equivalence between generic MR oral drug products and their reference counterparts. The process and scientific findings from these projects will advance generic drug development and regulatory review (e.g. BE guidance development and optimization of the review process) of MR oral drug products.

METHODS

- OGD performed a comprehensive and systematic analysis on generic MR oral drug products in different therapeutic classes based on in-house data on formulation, drug exposure, clinical performance and post-market surveillance as shown in Fig 1.

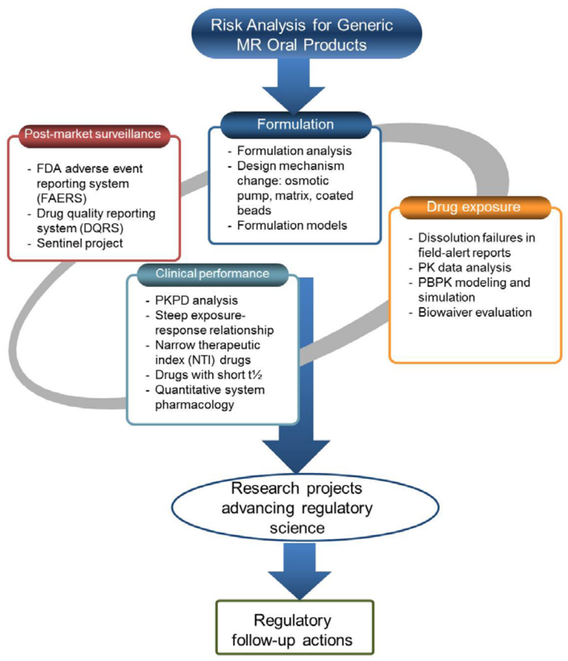

Fig 1: Scheme of risk analysis approach for generic MR oral products

Specific risk analyses include:

(1) We analyzed the brand and generic product formulation designs and release mechanisms coupled with the physicochemical and biopharmaceutical properties of drug substances based on submitted ANDA information.

(2) Physiologically based pharmacokinetic (**PBPK**) and pharmacokinetic-pharmacodynamic (**PK-PD**) models were used to predict the impact of different formulation design and in vitro performance on their resulting PK profiles at simulated physiological conditions (e.g. fasting or fed, co-medication) and corresponding therapeutic performance.

(3) For approved products, we also monitor FDA Adverse Event Reporting System (**FAERS**) and Drug Quality Reporting System (**DQRS**) to explore any potential substitutability issue.

RESULTS

- The formulations of 15 osmotic pump, 28 cardiovascular, and 29 neurological MR oral drug products and all their approved and pending generic counterparts were identified and analyzed for potential failure modes related to bioequivalence based on the developed model of potential failure modes for MR oral products (Fig 2).

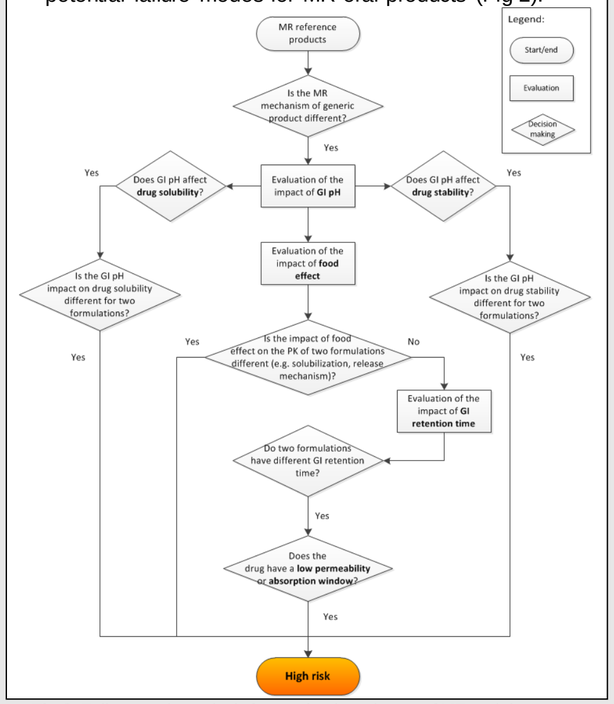

Fig 2: Failure mode analysis for mechanism change of MR oral drug products

- Specifically, PBPK modeling was used to predict the impact of dissolution variations of carbamazepine, metoprolol succinate, venlafaxine HCl (lag time of drug release), and nifedipine (pH-dependent dissolution behavior) MR oral drug products on the resulting PK profiles. These simulation studies help identify the range of release curve alterations within which the BE of generic products can be maintained and also help suggest potential *in vivo* predictive dissolution conditions. Examples are provided below (Fig 3-4).

Eg 1. Carbamazepine

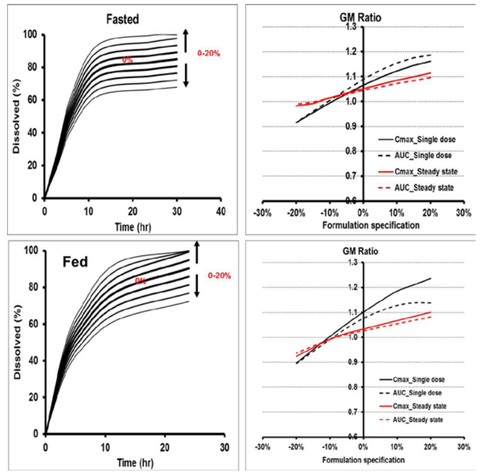

Fig 3. Effect of dissolution variation on the resulting PK metrics for carbamazepine ER tablets under fed and fasting conditions

Eg 2. Venlafaxine HCl

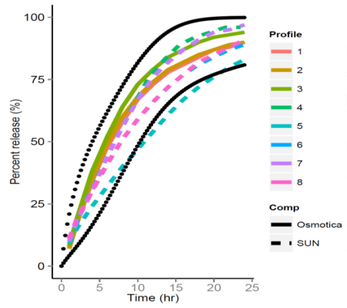

Fig 4. Effect of dissolution variation on the resulting Cmax for venlafaxine ER tablets. 2 dissolution profiles plotted in black dots represent the lower and upper limits of 80% and 125% Cmax compared with that of venlafaxine HCl ER tablets using dissolution profile number 4.

- In addition, the PBPK absorption models for lamotrigine, quetiapine fumarate, and oxybutynin chloride were used to confirm bioequivalence at strengths which a biowaiver was granted. Moreover, the sensitivity of using pAUC metrics to evaluate bioequivalence of oxybutynin chloride and quetiapine fumarate was investigated in a quantitative PK-PD model.

- Several clinical studies have been proposed and initiated to complement the above risk assessment and help explore alternative BE study design and BE metrics (Table 1).

(1) OGD has been conducting fully replicate BE studies on lamotrigine and methylphenidate ER tablets to investigate whether fully replicate BE studies can provide additional information for the MR drug products with different formulation designs.

(2) To evaluate whether bioequivalence evaluation may be influenced by a drug-drug interaction with proton pump inhibitors (PPIs), a BE study has been proposed to evaluate nifedipine ER tablets with different formulation designs (*i.e.* osmotic pump versus matrix) with and without PPI co-administration.

(3) There are studies about metoprolol ER tablets in hypertensive patients and methylphenidate ER tablets in pediatric attention-deficit/hyperactivity disorder (ADHD) patients to further understand PK-PD relationships for MR oral drug products.

Table 1. GDUFA research studies on MR oral drug products

FY	Study title	Awardees
13	Investigation of Inequivalence of Bupropion Hydrochloride Extended Release Tablets: In Vitro Metabolism Quantification Awarded to the (HHSF223201310183C)	University of Michigan
13	Pharmacokinetic Study of Bupropion Hydrochloride Products with Different Release Patterns (HHSF223201310164C)	University of Michigan
13	Bioequivalence of Generic Bupropion (4U01FD004899-03)	Washington University
14	Pharmacokinetic/Pharmacodynamic Studies of Methylphenidate Extended Release Products in Pediatric Attention Deficit Hyperactivity Disorder Patients (5U01FD005240-02)	Massachusetts General Hospital
14	Bioequivalence and Characterization of Generic Drugs (methylphenidate, warfarin) (#HHSF223201210030I, #HHSF22301001T)	Vince & Associates Research, Inc.
15	Bioequivalence Study of Lamotrigine Extended-Release Tablets in Healthy Subjects (#HHSF223201210030I)	Vince & Associates Research, Inc.
16	Evaluation of formulation dependence of drug-drug interaction with proton pump inhibitors (PPIs) for oral extended-release drug products (#HHSF 22320160004I)	Biopharma Services Inc

- Considering the limitation of passive surveillance systems such as FDA Adverse Event Reporting System (FAERS), we are also collaborating with Office of Surveillance and Epidemiology (OSE) to develop a tool in the Sentinel Initiative to evaluate utilization and brand-to-generic switching and switchback patterns of MR oral drug products.

CONCLUSION

Given the above data analyses, the risk of brand-to-generic therapeutic inequivalence is considered minimal. OGD continues its research efforts to conduct regulatory science projects which support product-specific guidance development, ANDA review, and post-approval product safety and efficacy as part of the overall GDUFA commitment. With this in mind, we hope to actively communicate the ongoing projects and current thinking of generic drug evaluation related to MR oral drug products with the pharmaceutical and healthcare communities.

REFERENCE, ACKNOWLEDGEMENT, AND DISCLAIMER

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