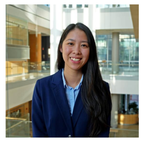
Utilization of Pharmacogenomic Information in Bioequivalence Studies for Generic Drug Development



PRESENTER:
Karen Li

BACKGROUND

- Given the impact of pharmacogenomics (PGx) on drug safety and pharmacokinetics, consideration of PGx information as part of bioequivalence (BE) study design for product-specific guidance (PSG) development is warranted for subject safety and data quality.
- This study aimed to explore the role of PGx information in PSGs to further enhance subject safety and BE study data quality.

METHODS

- PGx information from the FDA published PSGs were retrieved using the following key word search terms: deficiency, genetic, enzyme, and cytochrome P450 (CYP).[1]
- PSGs of solid oral dosage forms (capsule and tablet) were initially surveyed.
- We collected BE study recommendations (e.g., exclusion criteria) intended to improve subject safety or formulate an effective study design due to inherited enzyme deficiencies or polymorphic CYP enzymes from these PSGs.

RESULTS

- Eleven PSGs of solid oral drug products recommended use of PGx information for subject recruitment in their BE studies.
- These drugs are associated with inherited enzyme deficiencies or polymorphic CYP enzymes with PGx-related information in their product labeling.
- PGx information is incorporated in these PSGs to either prevent serious adverse events (AEs) (n=9), ensure balanced groups in parallel study (n=1), or a combination of both factors (n=1).

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Eleven Product-Specific Guidances (PSGs) of solid oral drug products recommended consideration of PGx information to prevent serious AEs and (or) to formulate an effective BE study design. In PSG development, consideration of PGx for other drugs associated with polymorphic enzymes in their product labeling is warranted to further improve subject safety and study efficiency.

Enzymes	Drugs	Labeling information in relation to PGx (Labeling Section)	Key consideration for PGx recommendation
Thiopurine methyltransferase (TPMT)	Mercaptopurine	Dose adjustment and safety warning with TPMT or nucleotide diphosphatase (NUDT15) deficiency (Sections 2, 5 & 12)	Safety (i.e., prevent serious AEs)
	Azathioprine	Dose adjustment and safety warning with TPMT or nucleotide diphosphatase (NUDT15) deficiency (Sections 2, 5 & 12)	Safety
Glucose-6-phosphate dehydrogenase (G6PD)	Primaquine phosphate	Contraindication with severe G6PD deficiency (Section 4)	Safety
	Quinine sulfate	Safety warning with G6PD deficiency (Section 5)	Safety
	Tafenoquine succinate**	Contraindication with G6PD deficiency or unknown G6PD status (Section 4)	Safety
	Dabrafenib mesylate	Safety warning with G6PD deficiency (Section 5)	Safety
Dihydropyrimidine dehydrogenase (DPD)	Capecitabine	Safety warning with low or absent DPD activity (Section 5)	Safety
CYP2C9	Siponimod fumaric acid	Contraindication with CYP2C9*3/*3 genotype (Section 4)	Safety
	Amlodipine besylate/celecoxib	Not recommended in known or suspected poor CYP2C9 metabolizers (PMs) (Section 8)	BE study design (i.e., ensure balanced groups in parallel study)
CYP2D6	Aripiprazole	Dosage adjustment in CYP2D6 PMs (Section 2 & 8)	Both safety and BE study design

**There are two PSGs for tafenoquine succinate oral tablets with different NDA numbers.

SUMMARY AND DISCUSSION

- From our survey results of PSGs, recommendations on subject recruitment based on PGx information in BE studies for generic drug development are limited.
- PGx information currently incorporated in the PSGs mainly intends to ensure subjects' safety with two recently published PSGs incorporate PGx information to facilitate a robust study design.
- Further investigation is ongoing to explore the utility of PGx information for other drugs associated with polymorphic enzymes to help determine when PGx information to identify subjects vulnerable to serious AEs, minimize carryover effects in a crossover study, and ensure balanced groups in a parallel study may be considered in developing PSGs.

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Disclaimer: The poster reflects the views of the authors and should not be construed to represent FDA's views or policies.

[1] Database for Product-Specific Guidances for Generic Drug Development. Available at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

Karen Li[1,2], Jihong Shon[2], Heather Boyce[2], Sue-Chih Lee[2], Mitchell Frost[2], and Myong-Jin Kim[2]

[1]Oak Ridge Institute for Science and Education

[2]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration (FDA)