Safety Considerations of Subject Population Selection in Bioequivalence Studies for Generic Drug Development

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BACKGROUND:

- Healthy volunteers (HV) are generally recommended for pharmacokinetic (PK) bioequivalence (BE) studies in the product-specific guidances (PSGs) for generic drug development. If safety considerations preclude the use of HVs, patients for whom the drug is intended to treat are recommended. However, conducting PK BE studies in patients may pose some potential challenges (e.g., recruitment, cost, duration, intrinsic variability).
- This project aimed to retrospectively analyze the nonclinical toxicology and clinical safety profiles to understand the rationale for study population selection in PSGs developed by the U.S. Food and Drug Administration (FDA).

METHODS:

- FDA's PSG database was utilized to compile a list of oral drug product PSGs recommending PK BE studies in patients. PSGs recommending comparative clinical endpoint BE studies in patients were excluded. PSGs with a revision of study population from patients to HV or vice versa were identified.
- The United States Pharmacopeia (USP) drug classification and the reference listed drug (RLD) labeling were used to identify therapeutic categories and pertinent safety related elements.
- The New Drug Application (NDA) program for each drug product was reviewed to collect drug exposure data in healthy subjects.
- Available corresponding product-specific BE guidances (hereinafter referred to as PSGs) from the European Medicines Agency (EMA) were reviewed for comparative information.

RESULTS:

- Fifty-seven PSGs (55 RLDs; 49 active pharmaceutical ingredients) for oral drug products recommending PK BE studies in patients were identified (as of May 2023).

Fifty-seven product-specific guidances (PSGs) recommend patients for PK BE studies. Most drugs had risks for more than one toxicity in nonclinical toxicology profile (genotoxicity, cytotoxicity, and carcinogenicity) [Figure 1] and (or) safety risks (e.g., hepatoxicity and cardiotoxicity) reported in clinical trials.

Table 1: USP Therapeutic Category of the RLDS for PSGs Recommending Patients for PK BE Studies (N=57)

RLD Therapeutic Category	Number of PSGs n (%)
Antineoplastics	40 (70.2%)
Anticonvulsants	3 (5.3%)
Antipsychotics	3 (5.3%)
Immunological Agents	3 (5.3%)
Genetic, Enzyme, or Protein Disorder: Replacement, Modifiers, Treatment	2 (3.5%)
Hormonal Agents	2 (3.5%)
Antiparasitics	1 (1.8%)
Antivirals	1 (1.8%)
Central Nervous System Agents	1 (1.8%)
Antiemetics	2 (1.8%)

Figure 1: RLDs with Nonclinical Toxicities Identified in Labeling (N=55)

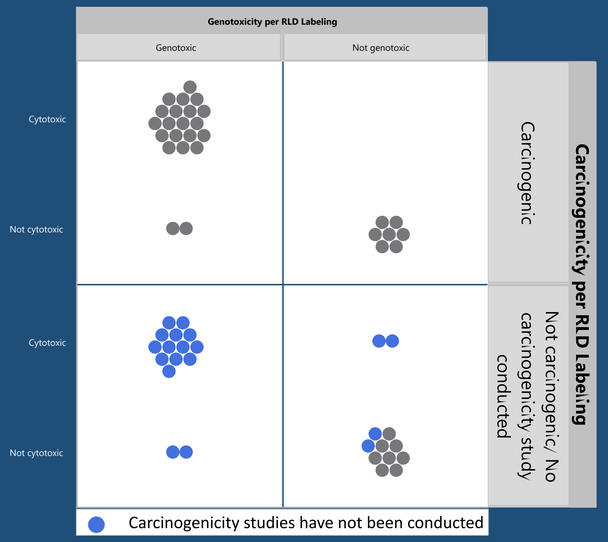


Figure 2: PSG Recommendations Updated from Patients to Healthy Volunteers and Vice Versa

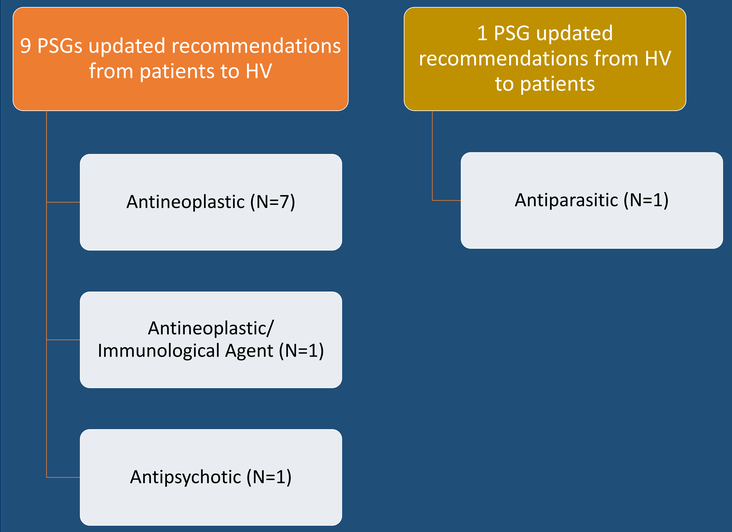
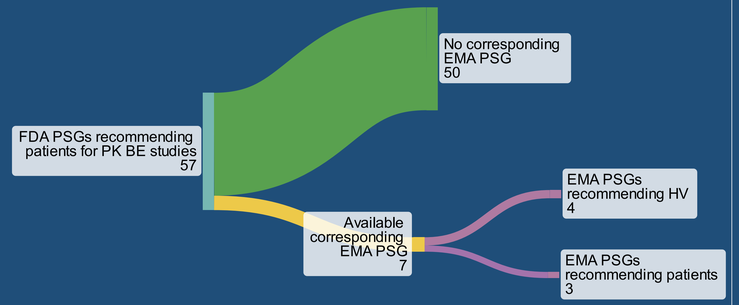


Figure 3: Comparison Between FDA PSG and EMA PSG (N=57)



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RESULTS (cont.):

- The common therapeutic category identified was antineoplastics.
- Of 55 RLDs, risks for genotoxicity (N=37), cytotoxicity (N=34), carcinogenicity (N=28), hepatotoxicity (N=19), and cardiotoxicity (N=16) were commonly identified.
- The majority (61%) carried more than one toxicity of carcinogenicity, genotoxicity, or cytotoxicity. Safety risks (e.g., hepatoxicity and cardiotoxicity) reported in patients and (or) healthy subjects also served as key factors for study population selection in some PSGs.
- Nine PSGs were revised from patients to HV, and one PSG was from HV to patients, supported by the re-evaluation of existing and newly collected safety data in BE studies for Abbreviated New Drug Application (ANDA) or from public domain.
- Seven PSGs published by EMA recommended either HV (N=4) or patients (N=3) [Figure 3].

CONCLUSION:

- Nonclinical toxicology and clinical safety profile (genotoxicity, cytotoxicity, carcinogenicity, hepatotoxicity, and cardiotoxicity) were the major consideration factors when PSGs recommend PK BE studies in patients.
- The collected findings would provide a basis for developing a decision framework for proper selection of study population for PK BE studies.
- Analysis of updated safety data for each drug may be warranted to reassure study population selection for its BE studies.

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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.

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