Exploration for Exclusion of Females of Reproductive Potential as a Bioequivalence Study Population in Product-Specific Guidances for Generic Drug Development

PRESENTER:

Duyen Nguyen

BACKGROUND:

- Product-specific guidances (PSGs) for generic drug development generally recommend the inclusion of female subjects for pharmacokinetic (PK) bioequivalence (BE) studies if such drug product is intended for use in females. One major safety consideration for including females of reproductive potential (FRP) in PK BE studies is the potential for reproductive toxicity. Currently, the recommendation to exclude FRP for PK BE studies in PSGs is determined on a case-by-case basis in consideration of various factors, and no standardized approaches have been established for the assessment.
- This project aimed to retrospectively analyze the toxicological evidence and any additional factors supporting the exclusion of FRP for PK BE studies in currently published PSGs of oral drug products intended for use in females.

METHODS:

- Internal FDA PSG databases were utilized to collect PSGs for oral drug products recommending the exclusion of FRP in PK BE studies using variations of the following search terms: reproductive potential/postmenopausal/ sterile/childbearing, embryofetal toxicity, and teratogenicity. The databases were also filtered to retrieve PSGs recommending PK BE studies in male subjects only (e.g., excluding all females).
- The labeling of the reference listed drugs (RLDs) were reviewed to exclude PSGs for drug products indicated for use in postmenopausal females only or in males only.
- The following information on the RLDs' labeling was collected and analyzed: nonclinical toxicology profiles (i.e., genotoxicity, embryofetal developmental (EFD) toxicity, female fertility impairment), and contraception recommendation for female patients.

RESULTS:

- Fifty-nine PSGs (50 unique active pharmaceutical ingredients) for oral drug products recommended the exclusion of FRP in PK BE studies (as of October 2022). These included PSGs recommending the conduct of PK BE studies in males only (n=28, 47.5%), in females not of reproductive potential only (n=5, 8.5%), and in males + females not of reproductive potential (n=26, 44.0%).
- The most common therapeutic categories among the RLDs were antineoplastics (n=24, 40.7%), anticonvulsants (n=6, 10.2%), antivirals (n=6, 10.2%), and respiratory tract agents (n=6, 10.2%) [Table 1].

Fifty-nine PSGs for oral drug products recommended the exclusion of females of reproductive potential in PK BE studies. The RLD labeling for 53 of these PSGs (89.8%) contained a contraindication, boxed warning, or warning/precaution on embryofetal developmental toxicity.

Table 1: Therapeutic category of the RLDs for PSGs recommending the exclusion of FRP (N=59)

RLD Therapeutic Category	Number of PSGs n (%)
Antineoplastics	24 (40.7%)
Anticonvulsants	6 (10.2%)
Antivirals	6 (10.2%)
Respiratory Tract Agents	6 (10.2%)
Immunological Agents	5 (8.4%)
Cardiovascular Agents	4 (6.8%)
Dermatological Agents	3 (5.0%)
Hormonal Agents	2 (3.4%)
Anti-Obesity Agents	1 (1.7%)
Central Nervous System Agents	1 (1.7%)
Gastrointestinal Agents	1 (1.7%)

Figure 1: Potentials for EFD toxicity, genotoxicity, and female fertility impairment in RLD labeling for PSGs recommending the exclusion of FRP (N=59)

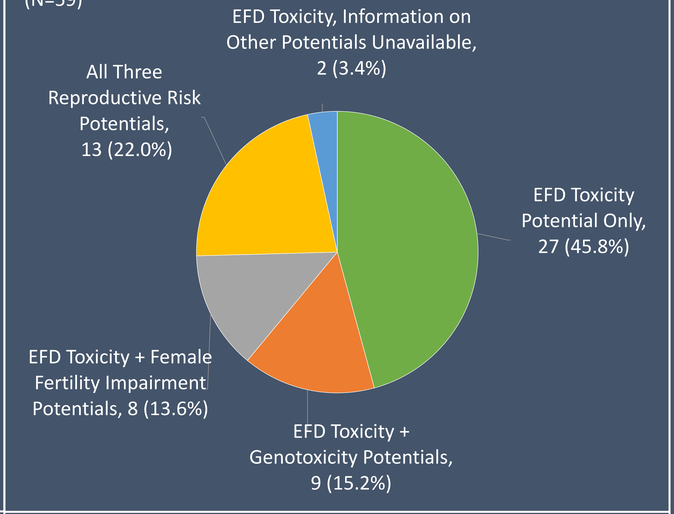


Figure 2: Level of EFD toxicity in RLD labeling for PSGs recommending the exclusion of FRP (N=59)

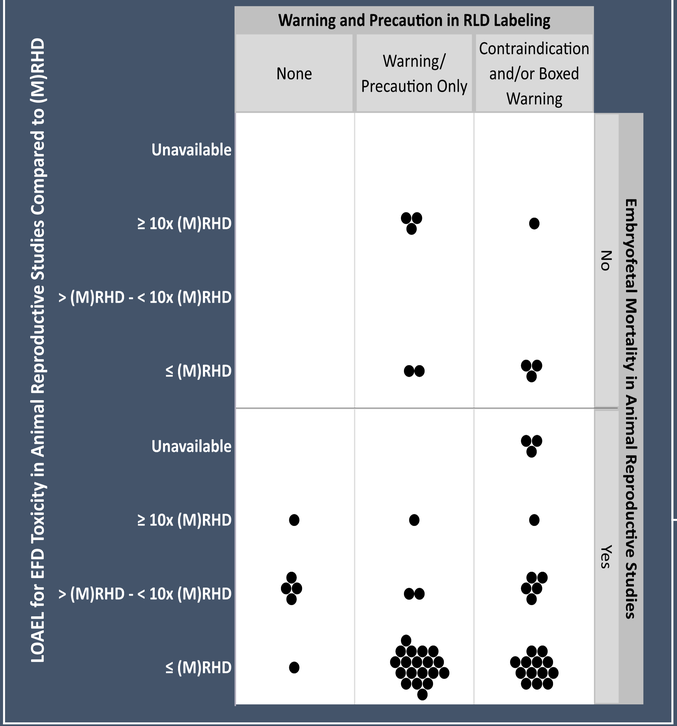
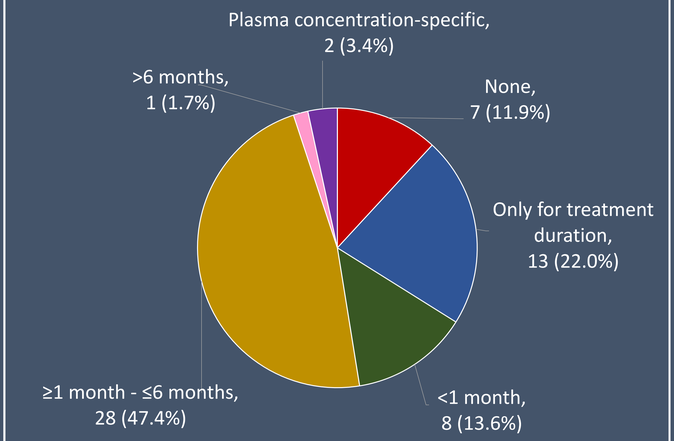


Figure 3: Recommended contraception duration for female patients in RLD labeling for PSGs recommending the exclusion of FRP (N=59)



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RESULTS (cont.):

- The RLDs for all 59 PSGs were associated with EFD toxicity potential. For 30 PSGs (50.8%), the RLDs were also reported to carry potentials for genotoxicity and/or female fertility impairment [Figure 1].
- The RLD labeling for 53 PSGs (89.8%) contained either a contraindication, boxed warning, or warning/precaution on EFD toxicity. Embryofetal mortality was reported in animal reproductive toxicity studies for the RLDs of 50 PSGs (84.7%). The lowest-observed-adverse-effect-levels (LOAEL) for EFD toxicity were less than 10x the (maximum) recommended human dose ((M)RHD) for the RLDs of 49 PSGs (83.1%) [Figure 2].
- Contraception was recommended for female patients during treatment with the RLDs of most PSGs (n=52, 88.1%). The RLD labeling for 39 PSGs (66.1%) recommended to continue practicing adequate contraception after discontinuation from 1 week to up to longer than 1 year [Figure 3].

DISCUSSION AND CONCLUSION:

- The current analysis provided insights into the factors supporting the exclusion of FRP as a PK BE study population in current PSGs. Major common factors among most of these 59 PSGs included the following:
  - Level of EFD toxicity (toxicity at exposures within human exposure, embryofetal mortality reported in animal reproductive toxicity studies),
  - Contraception recommended for female patients after treatment discontinuation, and
  - Additional reproductive risk potentials (i.e., genotoxicity, female fertility impairment).
- The collective information will be utilized to develop a standardized decision framework for the selection of PK BE study population to improve consistency and efficiency of the PSG development process and ensure subject safety in PK BE studies for generic drug development.

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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.

Christian Grace Paleracio*[,1,2], **Duyen Nguyen***[,1,2], Karen Li[2], Cynthia Tsui[1,2], Mitchell Frost[2], Myong-Jin Kim[2], and Jihong Shon[2]

[1]Oak Ridge Institute for Science and Education

[2]Division of Therapeutic Performance II, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. FDA