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

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PURPOSE

- Product-specific guidances (PSGs) outline the Agency's current thinking and expectations on the most appropriate methods for establishing therapeutic equivalence between test generic drug products and their reference listed drug (RLD) products.
- The selection of study population for bioequivalence (BE) studies with pharmacokinetic (PK) endpoints is based on safety considerations, including reproductive toxicity.
- Exclusion of males of reproductive potential (MRP) has been recommended in PSGs for drugs associated with male fertility impairment.
- Currently, the recommendation to exclude MRP 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 research retrospectively analyzed the toxicological data on male fertility impairment, genotoxicity, and carcinogenicity along with the restrictions on healthy subject recruitment imposed by RLD programs.

METHODS

- A list of oral drug product PSGs recommending the exclusion of all males or MRP in PK BE studies were identified with keywords such as birth control, condom, contraception, fertility, reproductive, sterile, and surgical.
- PSGs for RLDs indicated for use in female only were excluded. PSGs recommend excluding a specific subset of males (i.e., males with pregnant female sexual partners, males wishing to father a child, or males planning to donate sperm) or only requiring effective contraception in males were also excluded.
- Nonclinical toxicology profiles (i.e., male fertility impairment, genotoxicity, and carcinogenicity), United States Pharmacopeia (USP) Therapeutic Categories, contraception requirement for male patients, and enrollment of healthy subjects in RLD programs were collected and analyzed.

RESULTS

- Thirteen oral drug product PSGs (11 active pharmaceutical ingredients) recommended the exclusion of all males or MRP (as of June 2023) **[Figure 1]**.
- Out of five RLDs with genotoxicity potential **[Figure 4]**, three RLDs showed potentials for clastogenicity (in vitro), and two RLDs showed potentials for clastogenicity (in vitro and in vivo) and mutagenicity.
- Chronic exposure for all RLDs in animal studies negatively impacted spermatogenesis with eight having irreversible effects. Four RLDs had reversible effects after 4-22 weeks after the last dose. One RLD did not have information on reversibility **[Figure 5]**.
- All RLDs resulted in degeneration of the male reproductive organs.

RESULTS, CONT.

Figure 1: Steps in identifying a list of oral drug product PSGs recommending the exclusion of males or MRPs

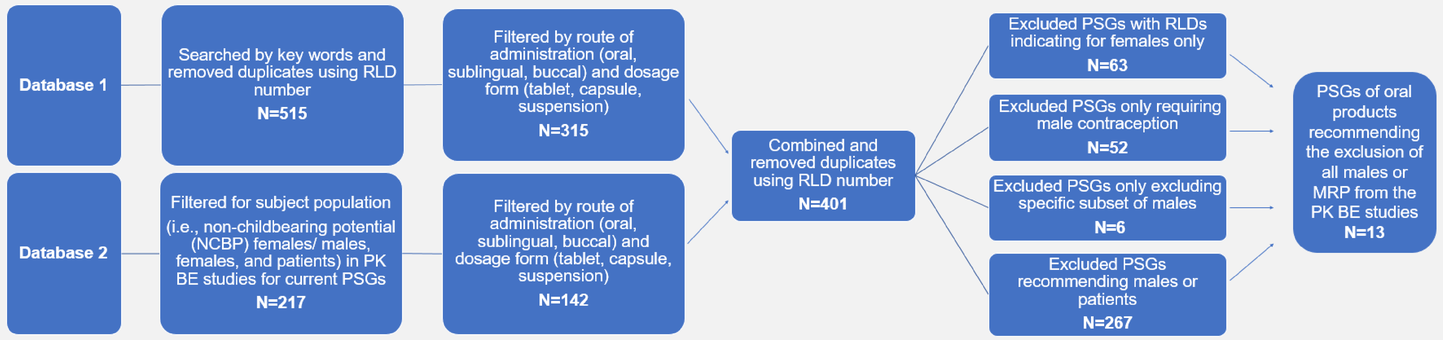


Figure 2: USP Therapeutic Categories for RLDs with PSGs recommending the exclusion of MRP (N=13)

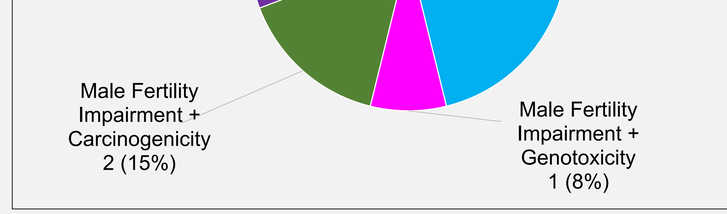
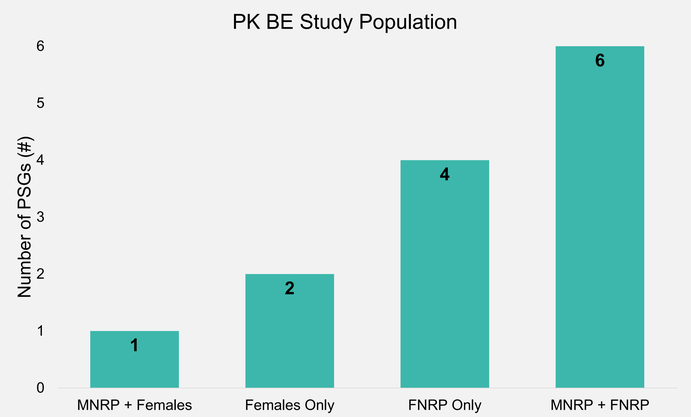


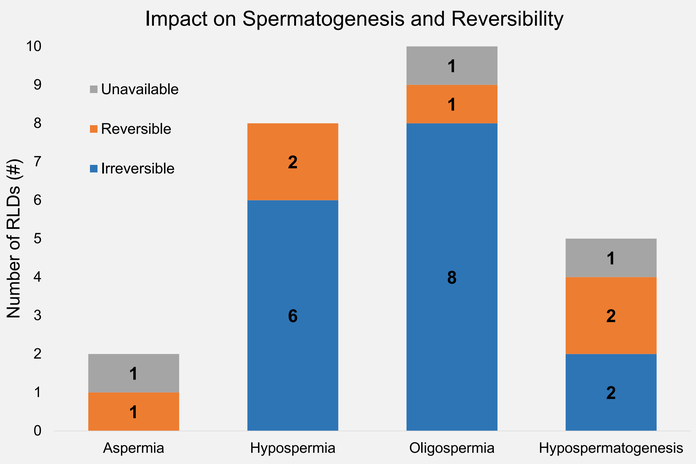
Figure 3: The recommended PK BE study population in PSGs (N=13)



* MNRP = males not of reproductive potential
* FNRP = females not of reproductive potential
* Females only = females of reproductive potential and FNRP

Figure 4: Potentials for male fertility impairment, genotoxicity, and carcinogenicity in RLD labeling (N=13)

Figure 5: Impact on spermatogenesis and reversibility



* Each category is out of 13 RLDs (e.g., two out of 13 RLDs resulted in aspermia)

RESULTS, CONT.

- Male fertility impairment was observed in repeat-dose toxicity and/or dedicated fertility studies in animals dosed for a duration as short as 14 days.
- Eleven RLDs resulted in male fertility impairment with no-observed-adverse-effect level (NOAEL) ≤ maximum recommended human dose (MRHD), one with MRHD < NOAEL < 10x MRHD, and one without NOAEL identified (lowest-observed-adverse-effect level < MRHD).
- The labeling for four RLDs recommended contraception for male patients during treatment and for 1 week to 4 months after the last dose.
- All 13 RLD programs included healthy subjects.
- Among these RLD programs, 11 included healthy male subjects, 1 excluded all males, and 1 did not have demographic information. Of these 11 RLD programs, 1 allowed MNRPs, 8 allowed MNRPs and MRPs, and 2 did not have information on reproductive potential of male subjects.
- Male fertility impairment was highlighted in the RLD labeling with four listed in Warnings and Precautions while other RLDs were only listed in Specific Populations.

IMPLICATIONS

- The current analysis provided insights into the risk factors (male fertility impairment, genotoxicity, and carcinogenicity) supporting the exclusion of MRP from PK BE study population in current PSGs.
- Ultimately, this collective information will be utilized to develop a standardized decision framework to inform recommendations for PK BE study population in PSG development and to ensure subject safety in PK BE studies.
- Such decision framework could further improve consistency of the PSG development process and ensure subject safety in PK BE studies for oral generic drug development.
- Furthermore, the current analysis could be utilized to re-evaluate PSGs that share the same mechanism of action as 13 RLDs to consider the exclusion of MRPs.

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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.