ASSESSMENT OF MALE INFERTILITY RISKS TO SUPPORT PRODUCT-SPECIFIC GUIDANCE DEVELOPMENT FOR GENERIC ORAL PRODUCTS

PRESENTER:

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BACKGROUND:

- Product-specific guidances (PSGs) describe the U.S. Food and Drug Administration (FDA)'s current thinking on the most appropriate method for establishing therapeutic equivalence between generic drugs and their reference listed drugs (RLDs).
- Exclusion of males of reproductive potential (MRPs) in pharmacokinetic (PK) bioequivalence (BE) studies has been recommended in PSGs on a case-by-case basis to avoid male infertility risks.
- This project aimed to retrospectively analyze the nonclinical toxicology and other factors (e.g., contraception recommended for male patients) supporting this recommendation in currently published oral drug PSGs to develop a standard decision framework for potentially excluding MRPs in PSG-recommended PK BE studies.

METHODS:

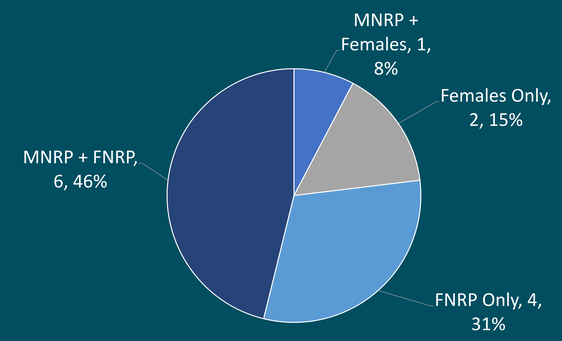
A list of oral drug PSGs recommending exclusion of MRPs or all males in PK BE studies was compiled using an internal FDA search engine with keywords (e.g., fertility, sterile, surgical). PSGs for RLDs with approved indications only in females were excluded. Nonclinical toxicology profiles (i.e., male fertility impairment, genotoxicity), United States Pharmacopeia (USP) Therapeutic Categories, and contraception requirements for male patients in the RLD labeling were collected and analyzed.

RESULTS:

- Thirteen oral drug PSGs (13 RLDs; 11 unique active pharmaceutical ingredients) recommended the exclusion of MRPs or all males (as of August 2023). These included PSGs recommending the conduct of PK BE studies in males and females both not of reproductive potential (n=6), in females not of reproductive potential only (n=4), in females only (n=2), and in males not of reproductive potential and females (n=1) [Figure 1].
- The most common USP Therapeutic Category was antineoplastics (n=5) [Table 1].
- All RLDs carried potential for male infertility, as reflected in both decreased sperm count/production and decreased organ weight. These findings were observed in repeat-dose toxicity and/or dedicated fertility studies [Table 2] in animals dosed for a duration as short as 14 days.

Thirteen oral drug product-specific guidances recommended the exclusion of males of reproductive potential or all males in PK BE studies. All reference listed drugs carry potential for male infertility, with most reference listed drugs (n=11) having no-observed-adverse-effect-levels within the maximum recommended human dose in animal studies.

Figure 1: 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

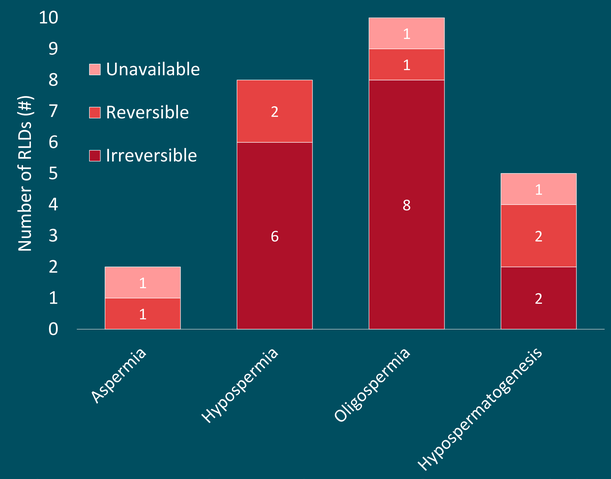
Table 1: USP Therapeutic Category of the RLDs (N=13)

RLD USP Therapeutic Category	Number of PSGs n (%)
Antineoplastics	5 (38.4%)
Antiparasitics	2 (15.4%)
Genetic, Enzyme, or Protein Disorder: Replacement, Modifiers, Treatment	2 (15.4%)
Uncategorized	2 (15.4%)
Antimycobacterials	1 (7.7%)
Antivirals	1 (7.7%)

Table 2: Type of study and NOAELs in animal studies where male fertility impairment was observed (N=13)

	NOAELs Compared to MRHD n (%)		
Type of Study	≤ MRHD	> MRHD	Not reached
Repeat-Dose Toxicity + Male Fertility	5 (38.4%)	1 (7.7%)	0 (0%)
Repeat-Dose Toxicity	3 (23.1%)	0 (0%)	1 (7.7%)
Male Fertility	2 (15.4%)	0 (0%)	0 (0%)
Male Fertility + Testicular Morphology	1 (7.7%)	0 (0%)	0 (0%)

Figure 3: Impact on sperm count/production and reversibility in animal studies



Each category is out of 13 RLDs (e.g., 2 out of 13 RLDs resulted in aspermia)

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RESULTS (cont.):

- 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 with NOAEL not reached (lowest-observed-adverse-effect level < MRHD) [Table 2].
- Impact on sperm count/production was irreversible for eight RLDs. Four RLDs showed reversibility after 4-22 weeks recovery. The remaining one RLD did not have information on reversibility available [Figure 3].
- Male fertility impairment risk was communicated in Section 8 (Use in Specific Populations) of the labeling for all RLDs. For four RLDs, this risk was also highlighted in Warnings and Precautions.
- Five RLDs also carry potential for genotoxicity. Out of these five RLDs, three RLDs tested positive for clastogenicity in in vitro assays only, while two RLDs tested positive for clastogenicity both in in vitro and in vivo assays.
- The labeling for four RLDs recommended contraception for male patients, with durations of during treatment and for 1 week (n=1), 3 months (n=1), and 4 months (n=2) after the last dose.

DISCUSSION AND CONCLUSION:

- The current analysis identified factors (e.g., potentials for male fertility impairment and genotoxicity, contraception duration) supporting the exclusion of MRPs from PK BE studies in currently published PSGs.
- These findings will be leveraged to develop a standard decision framework for potentially excluding MRPs in PSG-recommended PK BE studies, thereby improving PSG consistency while ensuring subject safety in PK BE studies for generic drug development.
- Furthermore, the current analysis could be utilized to re-evaluate PSGs of drug products of the same API but different dosage forms or of those that share the same mechanism of action to consider for 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.

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