Updates and Current Landscape for Study Population Selection and Additional Mitigation Strategies in Bioequivalence Studies

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Purpose

To provide updates on specific considerations pertaining to subject safety in pharmacokinetic (PK) bioequivalence (BE) studies, specifically on:

- Re-assessment of patient-based product-specific guidances (PSGs)
- Additional features to ensure subject safety in healthy subject-based studies:
  - Pharmacogenetics (PGx) considerations, and
  - Use of concomitant medications (e.g., antiemetics)

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Re-assessment of Patient-Based PSGs

Background

Guidance for Industry: M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (Oct 2024)

"…To reduce variability not related to differences between drug products, the studies should normally be performed in healthy subjects unless the drug carries safety concerns that make this approach unethical... If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy subjects, the study may instead be conducted in a targeted patient population under suitable precautions and supervision."

"If the highest strength of a drug product cannot be administered to healthy subjects for safety and/or tolerability reasons, a single-dose study in healthy subjects using a lower strength may be acceptable."

Clinical Assessment Factors for Study Population Selection in PSG Development

- Nonclinical toxicology profile
- Safety data in patients and healthy subjects (if available) from NDA, ANDA, post-marketing data, and public reports (e.g., literature)
- Drug exposure at the dose intended for BE studies
- Relevant safety profiles of other drugs within the same class
- Pharmacological plausibility

NDA - new drug application; ANDA - abbreviated new drug application

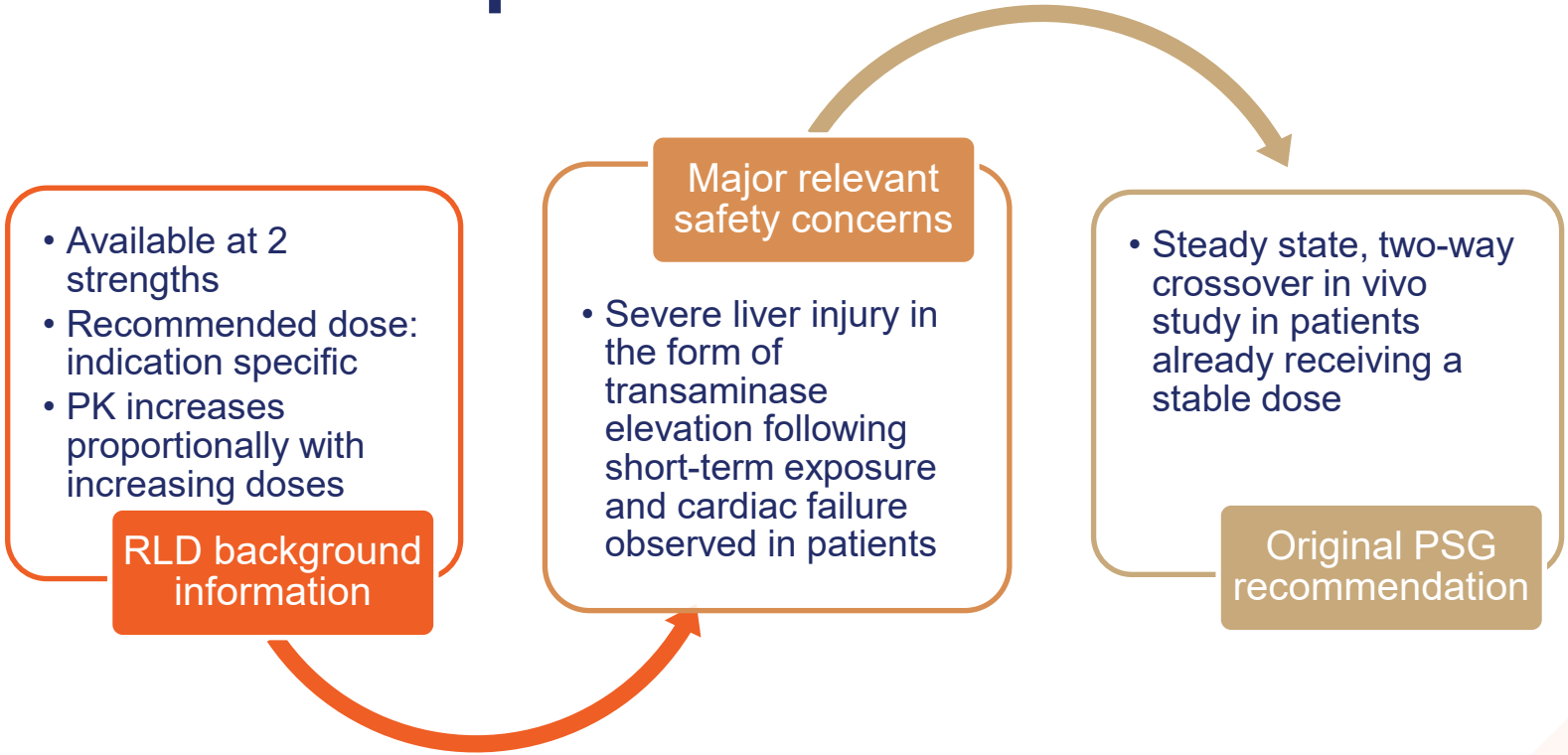
Core and Common Safety Criteria to Guide Study Population Selection for PK BE Studies

- Cytotoxicity (direct cellular damage)
- Genotoxicity and carcinogenicity (potential for primary malignancy)
- Reproductive toxicity (embryo-fetal toxicity and fertility impairment)
- Hepatotoxicity
- Cardiac related (arrythmias including QT prolongation)
- Hypersensitivity (severe skin reactions)
- Blood dyscrasia (immune function and bleeding risk)
- Effects on central nervous system (cognitive impairment)

Mitigation Strategies Adopted in PSGs to Enhance Subject Safety for Healthy Subject-Based Studies

Strategy	Examples
Reduce exposure to healthy subjects	Lower strength for BE studies, parallel study design
Exclusion criteria	Exclude subjects with abnormal liver function tests or with risk factors for prolonged QTc interval and Torsades de pointes
Targeted monitoring	Monitor liver function tests
Subpopulations	Males or females not of reproductive potential, exclude geriatric subjects
PGx factor (if appropriate)	Exclude certain subjects due to safety or PK reasons
Concomitant medications	Use of antiemetics

Re-assessment of Patient-Based PSGs: Example 1



Re-assessment of Patient-Based PSGs: Example 1 (cont.)

Cumulative data in healthy subjects from NDA and ANDA programs

- Additional safety data in healthy subjects received since the original PSG publication supported healthy subject enrollment
- Majority of adverse events (AEs) were mild to moderate in severity and generally manageable

Drug-exposure response relationship for safety risks

- The incidence and severity of hepatic and cardiac abnormalities in healthy subjects were higher at highest strength compared to the lower strength

Potential risk of carcinogenicity

- Malignancy cases observed in post-marketing surveillance lacked causal relationship and lacked information on lifestyle, concomitant diseases, or medications

Re-assessment of Patient-Based PSGs: Example 2

- Available at 3 strengths
- Recommended dose: middle strength once daily x 7 days, then highest strength once daily
- PK is dose proportional in a range covering middle and highest strength

RLD background information

Major relevant safety concern

- Specific toxicity with early onset:
  - In patients requiring dose titration
  - In healthy subjects including serious adverse events

- Steady state, crossover in vivo study in patients already receiving a stable dose at highest strength

Original PSG recommendation

Re-assessment of Patient-Based PSGs: Example 2 (cont.)

Pre-approval data in patients

- Incidence was dose-related and occurred within 7 days of initiation

Pre-approval data in healthy subjects

- 4-fold higher number of AEs of potential toxicity subjects receiving single doses of highest strength vs. middle strength of similar sample sizes
- All AEs of potential toxicity in subjects receiving single doses of middle strength were mild and manageable with non-pharmacological modalities

Post-approval data in patients

- No cases were reported in real-world setting (i.e., following approved titration regimen)

Additional Features to Ensure Subject Safety in BE Studies: PGx Considerations

"Phenotyping and/or genotyping of subjects may be considered for safety or PK reason." - *Guidance for Industry: M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (Oct 2024)*

Why PGx Considerations Matter in PK BE Studies

- Exclude subjects at higher risk for AEs related to genetic variations in drug metabolism
- Mitigate exposure-dependent or severe AEs
- Optimize crossover study design for drugs with long elimination half-life (e.g., adequate washout period, intersubject variability)
- Ensure balanced group allocation in parallel study designs

Current Implementation of PGx in PK BE Studies

- Over 390 drugs [counted per active pharmaceutical ingredient] contain PGx information in FDA labeling*
- 17 published PSGs include PGx recommendations
- Common enzymes involved:
  - CYP enzymes (n=9): CYP2D6, CYP2C19, CYP2C9
  - Non-CYP enzymes (n=8): G6PD, DPD, TPMT, NUDT15

CYP – cytochrome P450; G6PD – glucose-6-phosphate dehydrogenase; DPD – dihydropyrimidine dehydrogenase; TPMT – thiopurine methyltransferase; NUDT15 – nudix hydrolase 15

*Table of Pharmacogenomic Biomarkers in Drug Labeling. Available at https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling

Key Considerations for Integrating PGx into PSGs

- *Effect of polymorphic enzymes on drug PK (PK variability based on genotype)*
- *Effect of genetic variation on drug safety across genotypic subgroups*
- *Labeling contraindication or requirement for testing of polymorphic enzymes prior to the treatment initiation*
- *Clinical/PK implications of PGx in healthy subjects for PK BE studies (e.g., safety or study design related)*

Example: PGx-Based Subject Exclusion Due to Labeling Contraindications and Dosage Adjustments in Specific Genotypes

- Siponimod, a sphingosine 1-phosphate receptor modulator, is indicated for treatment of relapsing forms of multiple sclerosis
- Siponimod is available as 0.25 mg, 1 mg, and 2 mg tablets
- The labeling recommends
  - Test patients to determine CYP2C9 genotype before treatment initiation
  - Avoid use in patients with a CYP2C9*3/*3 genotype [contraindication]
  - Reduced maintenance dose in patients with a CYP2C9*1/*3 or *2/*3 genotype
- Siponimod AUC was approximately 61%, 91%, and 285% higher in CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3 subjects
- Mean half-life is prolonged in CYP2C9*2/*3, and CYP2C9*3/*3 subjects

Example: PGx-Based Subject Exclusion Due to Labeling Contraindications and Dosage Adjustments in Specific Genotypes (cont.)

- **Current PSG recommendation**
  - *"Exclude subjects with CYP2C9*3 allele, such as CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3"*

Rationale for PGx comment	• 2- to 4-fold higher exposures in CYP2C9*3 allele carriers • Contraindicated in CYP2C9*3/*3 genotypes and recommends dosage adjustment for CYP2C9*1/*3 and *2/*3 genotypes • Minimize carryover effect following a crossover study • Ensure balanced groups of subjects in a parallel study

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Additional Features to Ensure Subject Safety in BE Studies: Concomitant Antiemetics

Why Concomitant Antiemetics Matter in BE Studies

- Gastrointestinal (GI) events such as nausea and vomiting are among the most commonly reported adverse reactions in BE studies conducted in healthy subjects and significantly affect their tolerability and compliance.
- Vomiting within a specific timeframe can impact absorption of oral drug products and increase the variability in PKs, potentially requiring removal of subjects from PK analysis to avoid confounding the BE conclusions.
- Mitigation strategies for vomiting in BE studies for high-emetogenic drugs may be crucial to subject retention and sample size estimation. Although concomitant medication is generally prohibited in BE studies in healthy subjects, concomitant antiemetics may be considered provided that its use does not compromise study integrity or affect BE outcomes.

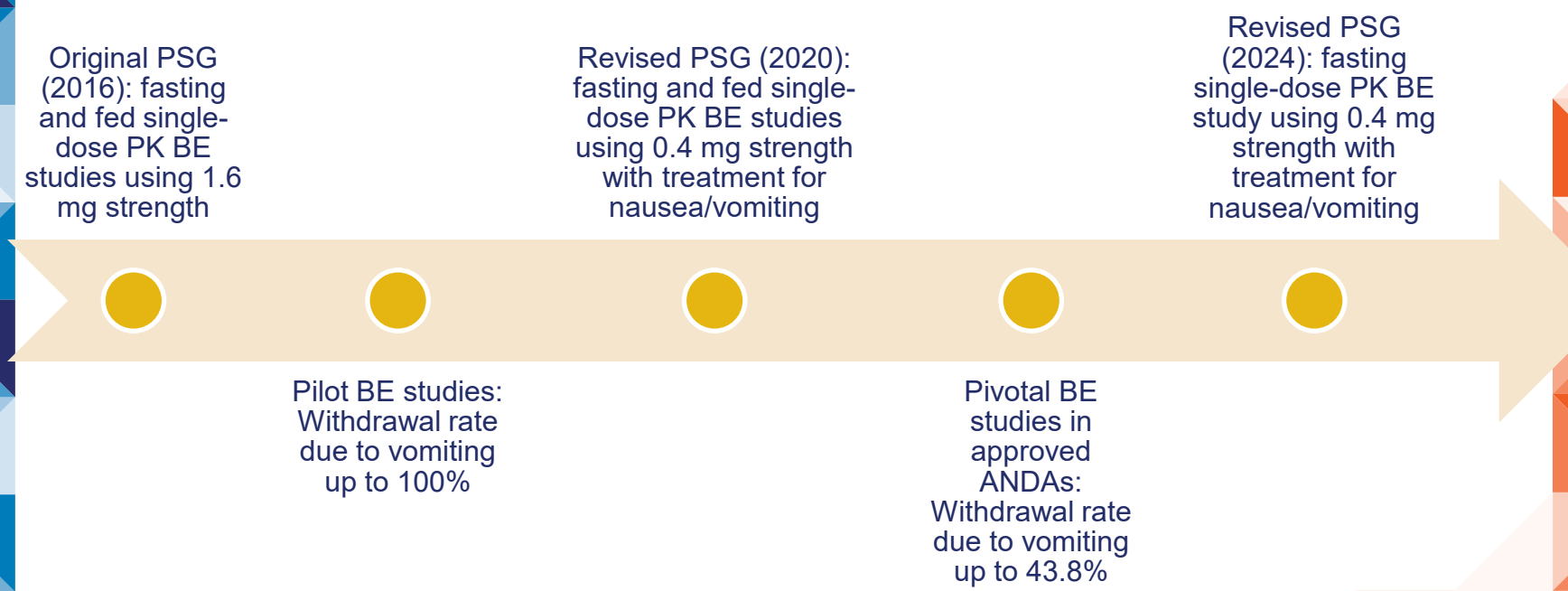
Current State and Considerations for Use of Antiemetics in PK BE Studies

- 5 published PSGs (3 active pharmaceutical ingredients) include antiemetic recommendations. Most corresponding BE studies incorporated antiemetics as recommended
- Considerations for use of antiemetics in BE studies:
  - Low risk of PK interactions with study drug (e.g., via absorption, elimination, GI motility)
  - Non-oral routes of administration (e.g., intramuscular, intravenous, transdermal)
  - Rationales for specific antiemetic and administration method should be provided in the protocol

Example: PSG Revision to Reduce Dose and Addition of Antiemetics

Drug Name, Dosage Form	Selexipag oral tablet
Strengths	0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1 mg, 1.2 mg, 1.4 mg, and 1.6 mg
Indication	A prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH
Dosage and Administration	• The recommended starting dosage of UPTRAVI tablets is 0.2 mg given twice daily. • Increase the dose in increments of 0.2 mg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1.6 mg twice daily. If a patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous tolerated dose.

Example: PSG Revision to Reduce Dose and Addition of Antiemetics (cont.)



Summary

- Clinical assessment for the selection of BE study population and dose is based on nonclinical toxicology data, safety data from NDAs/ANDAs/post-marketing data/literature, drug exposure profiles, and pharmacological plausibility.
- Patient-based PSGs undergo re-evaluation based on accumulated safety data and evolving regulatory experience with specific drug products.
- The development of new PSGs and revision of existing PSGs incorporate emerging safety mitigation strategies for healthy subjects, including PGx factors, use of non-highest strength, and concomitant antiemetic therapy.
- Strategic study designs incorporating appropriate safety measures may be implemented to ensure subject safety without compromising regulatory decision-making.

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