Consideration Factors on Study Population Selection for Bioequivalence Studies with Pharmacokinetic Endpoints

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April 25, 2024

CDER Small Business and Industry Assistance

Disclaimer

- This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Purpose

- To highlight consideration factors for the selection of pharmacokinetic (PK) bioequivalence (BE) study population.
- To present the current regulatory practice on each consideration factor for the selection of study population when developing or revising product-specific guidances (PSGs).

Background-1

❖ **Guidance for industry: BE Studies With PK Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (ANDA)** *(Draft-2021)**

III. ESTABLISHING BIOEQUIVALENCE

A. Pharmacokinetic Studies

5. Study Population

In general, unless otherwise recommended in a PSG, healthy subjects or other populations as appropriate are recruited. Any restrictions on admission into a study are primarily based on safety considerations. Sometimes, safety considerations preclude the use of either healthy subjects or the general population.

* *https://www.fda.gov/media/87219/download*

Background-2

❖ **Recommendation on study population in published PSGs**

- To warrant safety and acceptable tolerability in study subjects enrolled in BE studies from clinical and ethical perspectives
- When developing or revising each PSG, clinical safety assessment is conducted to support the recommendation on study population.
- The clinical safety assessment focuses on addressing potential safety concerns under the circumstance of BE studies (e.g., healthy subjects at single administration of an intended dose to be studied).

Consideration factors for study population selection

Toxicology profile

- Nonclinical toxicology data and -associated risk assessment

Safety profile in patients

- Safety issues of interest in patients: drug-specific and class effects
- Nature of adverse events (severity, reversibility, and clinical course and management)

Safety data from healthy subjects

- Availability of healthy subject studies
- Safety data in healthy subjects (NDA, ANDA and literature)

Drug exposure in BE study

- Drug exposure in healthy subjects at the dose to be studied

✓ Study population is generally determined on a case-by-case basis.

✓ Implementing assessment frameworks for study population selection.

1.1 Nonclinical toxicology

❖ Cytotoxicity

- Cytotoxic agents generally warrant BE studies in patients.
- Some cytotoxic agents (e.g., amphotericin B, nifurtimox, and venetoclax) still recommend healthy subjects.
- Requirements of "Investigational New Drug Application" (21 CFR 320.31(a))* for cytotoxic agents.

*https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.31

1.1 Nonclinical toxicology (cont.)

❖ **Genotoxicity and carcinogenicity**

- Genotoxicity tests: bacterial mutation and mammalian cell tests
- Carcinogenicity: carcinogenic potential at short-/long-term exposure
- Safety margin compared to human recommended dose and an intended dose in BE studies.

1.2 Nonclinical **toxicology** (cont.)

❖ **Reproductive toxicity**

Reproductive toxicity findings in animals

- Embryo-fetal development (EFD) toxicity
- Infertility potential in females or males

Recommendations in PSGs

- Exclusion of females or males of reproductive potentials
- Additional comments on contraception requirement

1.2 Nonclinical **toxicology** (cont.)

❖ **Reproductive toxicity**

→ **Considerations for exclusion of females of reproductive potentials**

Factors	Main review points	Review checkpoints
EFD toxicity potential	• Toxicity potential at clinical dose • Embryofetal mortality in animals	- Safety margin (NOAEL*) - Fetal lethality
Contraception	• Recommended contraception duration	>1 month
Concurrent risk potential	• Genotoxicity • Fertility impairment in females/males	- Mechanism, potency - Reversibility, potency
Healthy subject studies	• Recruitment of subjects of reproductive potential	Enrollment in healthy subject studies

*NOAEL: No-observed-adverse-effect-level

1.3 Study population selection in relation to reproductive toxicity:

Examples

Drug	PSG recommendation	Rationale
Belumosudil Rho-associated coiled-coil kinase (ROCK) inhibitor	Healthy males and heathy females not of reproductive potential*	Females • Mechanism of action (ROCK inhibitor) • EFD toxicities (e.g., fetal losses) in animals < the exposure at the recommended dose • The recent Phase 1 studies excluded females of reproductive potential.
Cabozantinib Broad-target tyrosine kinase inhibitor	Healthy males not of reproductive potential (i.e., surgically sterile) and healthy females not of reproductive potential**	Males • Cabozantinib-associated possible irreversible damages on male reproductive function in animals • No sufficient safety margin at BE dose Females • Significant adverse reactions including embryo-fetal lethality in animal studies • Contraception in females > 4-month

*https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_214783.pdf

**https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_208692.pdf

2.1 Safety profile specific to a drug or its class

❖ **Safety issues that are commonly discussed for study population selection during the development of PSGs**

- Hepatotoxicity
- Adverse effects on heart rhythm (e.g., QT interval prolongation potential and –associated safety events)
- Hypersensitivity (e.g., severe skin reactions)
- Blood dyscrasia (e.g., infection or hemorrhage events)

2.2 Clinical assessment of drug-specific safety profile

❖ **Clinical assessment of each safety risk for study population selection**

Key questions for assessment

- How likely does a single-dose administration of the highest strength cause clinically relevant events?
- Are any alternative options considered?

Recommendations in PSGs

- Patients
- Healthy subjects
  - Selection of study dose (e.g., a lower dose)
  - Additional safety comments

2.3 Study population selection via review of safety profile

❖ **What information supports study population selection:**

- Significant safety findings in patients
  - ✓ Clinical manifestation of each major safety issue in patients
- Safety data in healthy subjects
  - ✓ NDA and ANDA programs
  - ✓ Literature reports and clinical trial registry
- Pharmacological plausibility: mechanistic understanding and dose-response relationship
- Relevant safety profile of other drugs in the same class
- Previous regulatory history
- Pharmacovigilance databases

2.3 Study population selection via review of safety profile (cont.)

❖ **Recommendations in PSGs based on clinical safety assessment**

Recommendation	Examples	Key safety issues	Ref.
Selection of patients	Pazopanib	Hepatic enzyme abnormalities in healthy subjects	www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022465.pdf
Use of a lower dose	Aripiprazole	Acute laryngeal dystonia potential	www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021729.pdf
	Vandetanib	QT interval prolongation potential	www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021729.pdf
	Mavacamten	Reduction in heart function	www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_214998.pdf
Exclusion criteria for study (predisposing factors)	Many drugs	Risk potential on adverse events following single dose ➢ "Exclude subjects with abnormal liver function tests." ➢ "Exclude subjects with risk factors for prolonged QTc interval and Torsades de Pointes."	

Summary

- PSGs describe the Agency's current thinking on the most appropriate options (e.g., study population and dose to be studied) for PK BE studies.
- Safety assessment for the selection of BE study population is performed based on nonclinical toxicology findings, safety data from patients and healthy subjects, and plausibility of each safety risk at a dose to be studied.
- Up-to-date safety information and communications with generic drug developers have been leveraged to develop robust decision frameworks for the selection of study population.

Acknowledgement

- Clinical Safety and Human Subject Research Team, Division of Therapeutic Performance II
  - Karen Li and Duyen Nguyen
  - Tony Tran, Jihyun Bae (Nancy) and Cynthia Tsui
- Leadership in Office of Research and Standards (ORS), OGD
  - Myong-Jin Kim and Silvana Borges
  - Robert Lionberger and Lei Zhang
- All collaborators within OGD
  - Generic Drug Development Safety Committee
  - Division of Clinical Review
  - Division of Pharmacology-Toxicology Review