Evaluation of Subject Populations Enrolled in Bioequivalence Studies for Generic Drug Development

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Background

Per the Agency's current draft guidance on bioequivalence (BE) studies for drugs submitted under an abbreviated new drug application (ANDA), healthy subjects (non-smoking adults without existing medical conditions or required medications that exert physiological effects) are generally recommended for pharmacokinetic (PK) BE studies.[1] However, the general population (adults who may or may not have stable, chronic medical conditions and may or may not be treated with therapeutic drugs that will not interfere with the study) may be permitted under certain circumstances. Enrolling the general population in PK BE studies may be beneficial to generic drug developers by allowing flexibility in subject enrollment and increasing generalizability of BE data. However, PK BE studies should exclude subjects who have predisposing conditions or co-medications that can potentially increase safety risks in the general population.

Such exclusion could impact a large percentage of the general population and may be difficult for investigators to properly assess subjects for their enrollment. Thus, selecting healthy subjects for PK BE studies would be more appropriate and practical. These circumstances may raise questions regarding the feasibility of enrolling the general population for PK BE studies. There is a need to assess the appropriateness of including "general population" as a study population option and to explore how generic drug developers define "healthy subjects" and "general population" in their PK BE studies.

Purpose

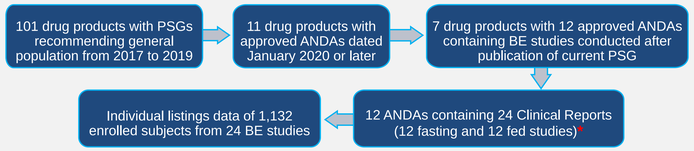
To assess the necessity of "general population" as a study population option, we analyze the eligibility criteria used in BE studies submitted for approved ANDAs of drug products with product-specific guidances (PSGs) that recommend "general population" and explore potential factors that generic drug developers considered when selecting a study population.

Methods

Various FDA internal databases were used to generate a list of oral drug products with PSGs published between 2017 and 2019 that recommend enrollment of "general population" in PK BE studies. The drug products were further filtered to finalize the list of ANDAs for evaluation with the following criteria: **a)** actively developed for generic drugs (e.g., five or more ANDAs), with **b)** approved ANDAs dated January 2020 or later, and **c)** BE studies for ANDAs were conducted after publication of its corresponding PSG. Eligible ANDAs were selected for evaluation of eligibility criteria, individual subject listings data, and safety assessments from clinical study reports and case report forms. The following subject data from the eligible ANDAs were collected and analyzed: screening data (e.g., smoking status), safety monitoring data (e.g., blood pressure [BP] and liver function tests [LFT]), and reported adverse reactions.

Results

Figure 1: Schematic Diagram of Drug Product and ANDA Selection for the Current Investigation



- **All 12 ANDAs were found to enroll "healthy subjects" (as defined by the study sponsor)***
- **This investigation demonstrated that ANDA studies used different enrollment criteria for healthy subjects (e.g., with regard to smoking status, BP, and LFT)**

Table 1: Potential Safety Risks of Drug Products for the Current Investigation (12 ANDAs)

Drug	# of ANDA	Hepatotoxicity or Hypertension Risk from Current Labeling
#1	1	Reported adverse reactions include abnormal liver function, cholestatic jaundice, hepatic insufficiency, and fulminant hepatic necrosis.
#2	1	Reports of elevated LFT, hepatitis, hyperbilirubinemia, and jaundice.
#3	1	Increased ALT commonly reported in pediatric patients.
#4	4	*No reported safety risks of interest*
#5	1	Liver failure has been reported in patients. Rare cases of hypertension have been reported in patients.
#6	3	*No reported safety risks of interest*
#7	1	*No reported safety risks of interest*

Results (cont.)

1. Smoking Status as eligibility criterion in 12 ANDAs

- Smoking status as eligibility criteria for the enrollment of healthy subjects varied among the 12 ANDAs included in the current investigation (**Table 2**).
- All study protocols included smoking status in the subject selection except for one ANDA that did not specify smoking status for enrollment.
- Based on the exclusion criteria from the study protocols, two ANDAs excluded smokers and nine ANDAs allowed enrollment of current smokers as healthy subjects. However, most of the nine studies excluded subjects who smoked greater than a given limit per day (e.g., ≥ 10 cigarettes per day) and required subjects to abstain from smoking during the study (**Table 2**).
- The majority of enrolled subjects were non-smokers. Out of 1,132 evaluated subjects from 12 ANDAs, 74 (7%) and 70 (6%) subjects were identified as current smokers or former smokers, respectively.

2. Blood Pressure (BP) as eligibility criterion in 12 ANDAs

- Seven out of 12 ANDAs did not specify numerical cut-offs of blood pressure (BP) in the eligibility criteria (**Table 3**). Four out of five BE studies that provided BP reference ranges used cut-offs proposed by the American Heart Association (AHA) and American College of Cardiology (ACC) as Stage 1 hypertension (HTN), defined as systolic blood pressure (SBP) between 130-139 mmHg or diastolic blood pressure (DBP) between 80-89 mmHg.[2]
- Out of 1,132 evaluated subjects, 290 (26%) enrolled in healthy subject BE studies reported pre-dose BP readings that exceeded the 2017 AHA/ACC cut-offs of SBP > 129 mmHg and/or DBP > 79 mmHg. Of these 290 subjects, 20 subjects were enrolled in BE studies of a drug product with potential HTN risk. All 20 subjects were found to have experienced elevated BP at multiple timepoints during the study (**Figure 2**).
- Seven subjects enrolled in two ANDA studies were found to have BP abnormalities at screening that were on the border or exceeded the upper limits defined in each study protocol (**Table 4**).

Table 3: BP Criteria for Exclusion in 12 ANDAs of 7 drugs

# of ANDA	Exclusion criteria for enrollment
7	*No numerical BP cutoffs provided in eligibility criteria.*
3	Systolic > 140 mm Hg or < 90 mm Hg Diastolic < 60 mm Hg or > 90 mm Hg
1	Systolic > 140 mm Hg or < 110 mm Hg Diastolic < 70 mm Hg or > 90 mm Hg
1	BP < 100/60 and > 129/79 mm Hg

Table 2: Smoking Status Criteria for Exclusion in 12 ANDAs of 7 drugs

# of ANDA	Exclusion criteria for enrollment
1	Subjects who smoke 10+ cigarettes per day or 20+ bidis per day, or who cannot refrain from smoking during the study period.
1	Subjects who smoke >10 cigarettes/bidis/pipes per day, or who cannot abstain from tobacco products at least 72 hours prior to dosing and throughout sampling points.
2	Subjects with a history of significant chronic smoking (10+ units per day of cigarettes, bidis, cigars, etc.) or consumption of tobacco products.
3	Subjects who smoke or use tobacco products within 48 hours prior to dosing until after the last blood sample collection in each study period.
1	Subjects who smoke 9+ cigarettes per day or are unable to abstain 48 hours prior to and during the study.
1	Subjects with a tobacco habit (9+ cigarettes, bidis, cigars, etc. per day).
1	Smoking status not included in eligibility criteria.
2	Subjects who are current or former smokers are excluded.

Figure 2: Pre-dose BP Status of 1,132 Subjects from 12 ANDAs

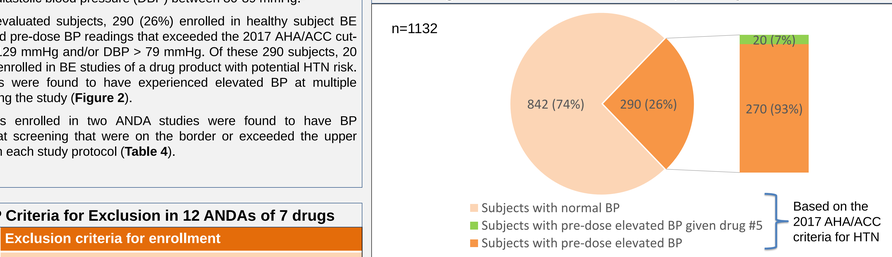


Table 4: Enrolled Subjects with Borderline/Out-Of-Range BP in 12 ANDAs

Drug	# of ANDA	# of Subjects	Pre-dose Border/OOR BP	Post-dose Border/OOR BP
#2	1	96	1 subject	None
#3	1	96	6 subjects	None

3. Liver Function Tests (LFT) Assessment

- The applied reference ranges for LFT varied among ANDAs, with upper limit cut-offs ranging from 40 to 108 U/L for ALT and 35 to 96 U/L for AST. The 12 evaluated ANDAs did not specify acceptable LFT ranges in the eligibility criteria, and all reference ranges were found in the case report forms.
- Out of 1,132 evaluated subjects, 81 (7%) subjects were found to have AST and/or ALT abnormalities at screening that exceeded the upper limits defined in each study but were deemed clinically not significant and enrolled into the study. Of these 81 subjects, 53 subjects also showed abnormal ALT and/or AST values at post-dose measurement and 11 subjects were reported to have post-dose hepatic adverse events (AEs) that are possibly related to the study drug based on the study reports (**Table 5**).

Table 5: Enrolled Subjects with Out-Of-Range AST and/or ALT in 12 ANDAs

Drug	# of Subjects	Pre-dose OOR LFT	Both Pre- & Post-dose OOR LFT	Reported hepatic AE	Relationship of AE to drug product
#1	80	3 subjects (4%)	2 subjects (3%)	1 subject (1%)	Possible (1; 1%)
#2	96	*None*			
#3	96	1 subject (1%)	*None*	*None*	*N/A*
#4	392	61 subjects (16%)	43 subjects (11%)	8 subjects (2%)	Possible (8; 2%)
#5	58	*None*			
#6	318	10 subjects (3%)	6 subjects (2%)	2 subjects (<1%)	Possible (2; <1%)
#7	92	6 subjects (7%)	2 subjects (2%)	*None*	*N/A*

Conclusions

The current investigation demonstrated that the BE studies for 12 approved ANDAs enrolled "healthy subjects" based on the study sponsors' determination, whereas the corresponding PSGs recommend "general population".

However, the eligibility criteria (e.g., smoking status) and measured screening values (e.g., BP or LFT) appeared to be discrepant from the definition of "healthy subjects" in the Agency's guidance[1], with several subjects exhibiting abnormal baseline LFT values reporting hepatic AEs post-dose. Most of the studies did not specify acceptable BP ranges in their eligibility criteria and several studies that provided BP ranges included values that are considered abnormal by the 2017 AHA/ACC guidelines. Varying smoking statuses were also considered.

Due to the limited number of BE studies and drug products that were reviewed in this current investigation, further evaluation with additional considerations is needed to adequately reassess the value of "general population" as a study population option in PK BE studies.

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References: (1) U. S. Food and Drug Administration. Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA: Guidance for Industry (DRAFT GUIDANCE). Published 2021. **(2)** Whelton, P. K et al. (2018). 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension (Dallas, Tex. : 1979), 71(6), e13–e115. https://doi.org/10.1161/HYP.0000000000000065

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