A Survey on Recommendation of Food Conditions in Bioequivalence Studies with Pharmacokinetic Endpoints for Generic Oral Antineoplastic Drug Development

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BACKGROUND:

- Product-specific guidances (PSGs) for oral antineoplastics generally recommend patients as the study population in pharmacokinetic (PK) bioequivalence (BE) studies. These PSGs typically recommend one BE study in patients following the current standard of care and recommendations in reference listed drug (RLD) labeling.
- This project aimed to explore the actual practice regarding food conditions in PK BE studies and identify gaps among the conducted BE studies and the recommendations in the RLD labeling and their PSGs.

METHODS:

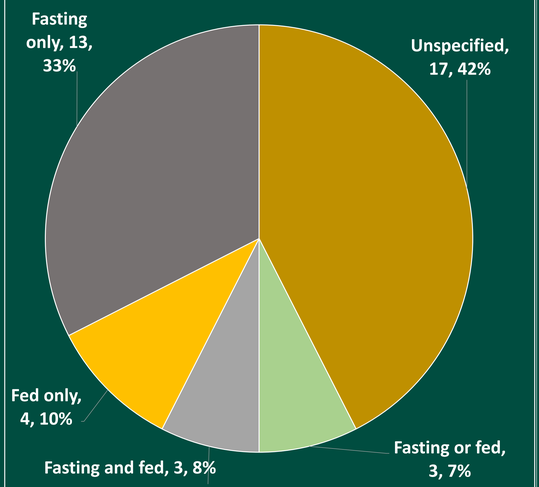
- PSGs for oral antineoplastics recommending PK BE studies in patients were identified using FDA databases.
- Food instructions from the labeling and recommendations for food conditions (i.e., fasting only, fed only, etc.) and subject population described in the PSG were collected for each RLD.
- BE study reports (i.e., study design, meal type, and subject population) in support of abbreviated new drug applications (ANDAs) of the drugs selected for the current survey (submitted between 2013 and 2023) were reviewed.

RESULTS:

- Forty PSGs (40 RLDs; 37 active pharmaceutical ingredients) were identified to recommend PK BE study in patients, of which 13 recommend under only fasting, 4 under only fed, 3 under both fasting and fed (two studies), and 3 under fasting or fed (one study). Seventeen PSGs do not specify food condition (Figure 1).
- The food conditions described in 6 PSGs appear to be discordant from their labeling by recommending BE stud(ies) under the condition not specified or unknown in the labeling (Figure 2).

The food condition of PK BE studies conducted in patients were generally consistent with the recommendation in the PSGs. For PSGs with unspecified food condition, four ANDAs conducted BE studies under fasting state in patients, and three ANDAs conducted BE studies under fed state in patients (Figure 3).

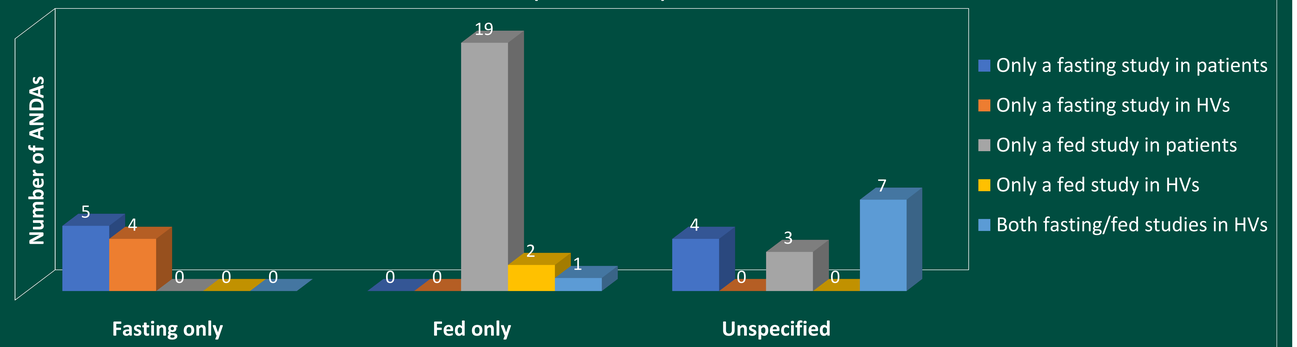
Figure 1: Current PSG recommendations on food condition (i.e., type of study) for PK BE studies in patients (N=40 PSGs)*



*37 PSGs recommend one PK BE study in patients; 3 PSGs recommend two PK BE studies (fasting/fed) in patients;

Figure 2: Comparison of food condition recommendations between PSG and RLD Labeling (N=40)

Figure 3: Food conditions in PK BE studies that were conducted in patients or healthy volunteers for an ANDA (N=46 ANDAs)**



**1 ANDA conducted a fasting study in HVs and a fed study in patients

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RESULTS (cont.):

- Out of 40 RLDs, 13 had 82 ANDAs (from 2013 to 2023), of which 27 ANDAs were submitted with biopharmaceutics classification system biowaiver, and 9 ANDAs could not be retrieved due to inaccessibility of electronic documents.
- Forty-six ANDAs for 11 RLDs conducted in vivo PK BE studies. Thirty-one of the 46 ANDAs were conducted in patients, and the food condition in the studies was generally consistent with the recommendation in the PSG. Of note, when the PSG carries no specific food conditions, the BE studies were conducted under the only one condition that the sponsor chose or justified (Figure 3).
- Fifteen of the 46 ANDAs enrolled health volunteers (HVs) for their BE studies. Majority of those ANDAs conducted a single BE study with the PSG-specified food condition despite of the use of study population that is different from the recommendation in the PSG (Figure 3).

DISCUSSION AND CONCLUSION:

- This survey identified some discordances in food condition selection among PSGs, RLD labeling, and PK BE studies in ANDAs for oral antineoplastics.
- Further investigation is ongoing to evaluate how food condition selection process has been performed for non-antineoplastic drugs when their BE studies were conducted in patients and identify their justifications for the selection of food condition.
- The collected information would be utilized to create a decision framework to provide robust recommendation on food conditions when recommending PK BE studies in patients for generic drug development.

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