Exploration of Food Conditions and Study Population in Bioequivalence Studies with Pharmacokinetic Endpoints for Oral Antineoplastic Drugs in Generic Drug Development

Jihyun Bae[1,2], Tony Tran[1,2], Jihong Shon[2], Myong-Jin Kim[2], and Karen Li[2]

[1]Oak Ridge Institute for Science and Education
[2]Division of Therapeutic Performance II, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. FDA

Background and Purpose

- Product-specific guidances (PSGs) describe FDA's current thinking on the approaches recommended to demonstrate the bioequivalence (BE) between the test and reference listed drug (RLD) products. Fed BE studies are generally recommended in addition to fasting BE studies in healthy subjects, except when the RLD labeling states that the product should be taken on an empty stomach or serious adverse events are anticipated under fed conditions. For BE studies with PK endpoints in patients, the current practice is to follow standard of care.[1]
- BE studies with PK endpoints are recommended in patients when the risks preclude the enrollment of healthy subjects. Challenges with PK BE studies in patients include recruitment, high cost/duration, difficulties to control meals, etc. PSGs for oral antineoplastics recommending PK BE studies in patients are of interest as revisions based on actual practice in current PK BE studies can help improve the challenges and promote consistency across labeling and guidances. The project aims to explore the common factors as well as potential differences among recommendations for PK BE studies in relation to actual practice and RLD labeling and to identify potential opportunities for PSG revisions of oral antineoplastic agents in generic drug development.

Methods

- A list of oral drug product PSGs recommending PK BE studies in patients was filtered by USP Therapeutic Categories to include only antineoplastics.
- FDA PSG recommendation (i.e., type of study [in vivo or Biopharmaceutics Classification System (BCS)-based biowaiver], design, subjects, additional comments) and food instructions from labeling were collected for each RLD. In general, RLD labeling and PSGs do not specifically recommend the specific fat content of a meal, the meal types (the caloric and content breakdown) reported in the PK BE studies were evaluated for consistency using the general FDA guidance definitions of test meals.
- The criteria for ANDAs to be included in the analysis were the followings: submitted between 2013 and 2023 and having statuses of approved, pending, complete response (CR), or tentative approval.
- Key components from the available corresponding EMA product–specific BE guidances for the RLDs were collected: food condition and study population.

Results

- Forty-one PSGs (38 active pharmaceutical ingredients) for oral antineoplastic drug products recommended patients in PK BE studies (as of May 2023).
- Eleven out of 41 PSGs did not reflect food instructions from the RLD labeling. Most of the PSGs recommended fasting, but labeling was either silent or recommended intake with or without food (Figure 3).
- Sixteen PSGs with 81 corresponding ANDAs met the specified criteria, among which 45 ANDAs conducted 56 in vivo PK BE studies Six PSGs with 17 corresponding ANDAs conducted PK BE studies in healthy subjects. Three out of the 17 ANDAs (from 2 different PSGs) were submitted prior to their initial PSG publication (Figures 4 and 5).
- Majority of the PK BE studies were conducted under fasting condition (N=22) or with a high-fat meal (N=19). The specifications for low-fat meals were heterogenous and overlapped with moderate-fat meals, with fat content from 20-40% and total calories from 250-600 kilocalories.[2]
- Food administration in all but 3 ANDAs that conducted in vivo PK BE studies in healthy subjects were consistent with food recommendations specified in PSGs (Table 1).
- For three PSGs with BCS biowaiver option, 50-78% of ANDAs opted for the alternative approach (23 ANDAs). Four ANDAs (from 3 different PSGs) opted for BCS waiver although their PSGs did not indicate the option.
- Only eight of the 41 RLDs had product-specific bioequivalence guidances available from EMA. All specified a food recommendation, but 5 of which recommended a different food administration compared to FDA PSGs. Five of 8 EMA BE guidances recommended healthy subjects, instead of patients, for PK BE studies.

Results, cont.

1) RLD Labeling and PSG Recommendations Regarding Food Administration

Figure 1: Food Instructions in the RLD Labeling (N=41 RLDs)

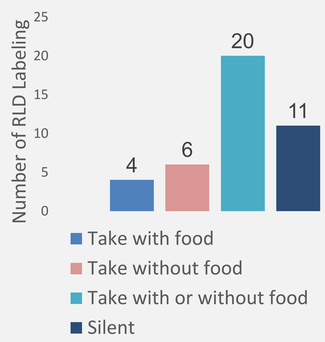
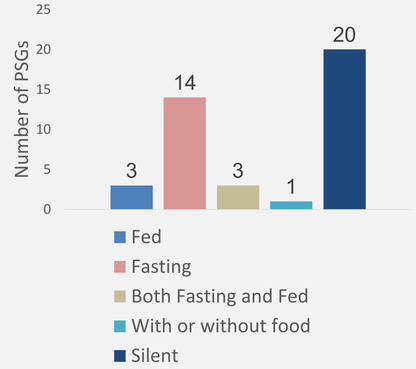
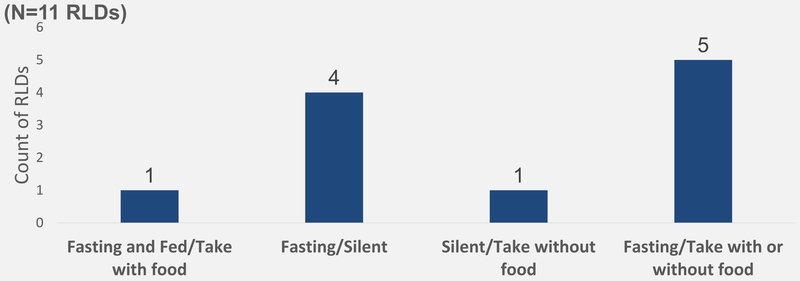


Figure 2: PSG Recommendation Regarding Food (N=41 PSGs)*



***38 PSGs recommended one in vivo PK BE study in patients; 3 PSGs recommended two in vivo PK BE studies (both fasting/fed) in patients.**

Figure 3: Differences in Food Recommendation Between PSG vs. RLD Labeling (N=11 RLDs)



2) Food Conditions and Study Population for 56 In Vivo PK BE Studies

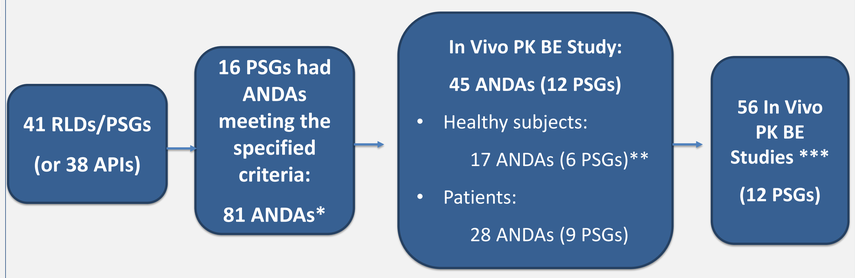


Figure 4: Flowchart for ANDA Studies Search

***27 ANDAs opted for BCS biowaiver; 9 ANDAs did not have available study reports**

****3 of 6 PSGs had ANDAs with 19 PK BE studies in healthy subjects and ANDAs with 18 PK BE studies in patients**

*****9 ANDAs conducted 1 fasting / 1 fed PK BE studies, 1 ANDA conducted 2 fasting studies, and 1 ANDA conducted 2 fed studies**

Figure 5: Study Population in In Vivo PK BE Studies (N=56 PK BE Studies)

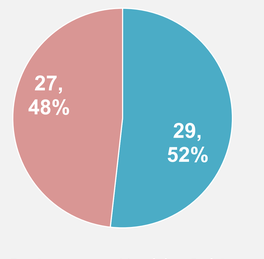


Table 1: Food conditions in ANDAs that conducted in vivo PK BE studies in healthy subjects (N= 17 ANDAs)

PSG Recommendation	Labeling – Food Administration	Food condition in ANDAs (N = # ANDAs)
Fasting in patients (3 RLDs/PSGs)	Take with or without food (RLD 1) Take without food (RLD 2, 3)	RLD 1: Only fasting study **(N=1)** → **Deviation** (Status: Pending) RLD 2, RLD 3: Only fasting studies **(N=5)**
Fed in patients (1 RLD/PSG)	Take with food (RLD 4)	RLD 4: • Only fed study **(N=2)** • Both fasting/fed studies **(N=1)** → **Deviation** (Status: Approved)
Silent on Food administration & in patients (2 RLDs/PSGs)	Take with or without food (RLD 5, 6)	RLD 5: • Both fasting/fed studies **(N=5)** • Fasting study in healthy, fed study in patients **(N=1)** → **Deviation** (Status: CR) RLD 6: • Both fasting/fed studies **(N=2)**

Table 2: Food administration in ANDAs that conducted in vivo PK BE studies in patients (N= 28 ANDAs)

PSG Recommendation	Food administration in ANDAs (N= # ANDAs)
Fasting in patients (3 RLDs/PSGs)	Only fasting studies (N=3)
Fed in patients (3 RLDs/PSGs)	Only fed studies (N=20)
Silent on food recommendations & in patients (3 RLDs/PSGs)*	Only fasting studies (N=3) Only fed studies (N=2)**

***No food restriction required in labeling; **Non-high-fat/high-calorie meal**

Conclusion

The exploratory analysis provided insights into differences of study population and food conditions for 41 oral antineoplastics among their RLD labeling, in vivo PK BE studies in ANDAs, FDA PSGs, and product-specific BE guidances from EMA. Food instructions in RLD labeling for oral antineoplastics, actual practice for in vivo PK BE studies, as well as product-specific BE guidances from EMA are found to be generally in agreement with recommendations from current FDA PSGs with some deviations. Further analyses and revisions of those PSGs may be warranted to promote consistency on food conditions and study population for oral antineoplastic agents in generic drug development.

Acknowledgements

Drs. Bae and Tran were supported in part by an appointment to the Research Participation Program at the U.S. Food and Drug Administration (FDA) administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the U.S. Food and Drug Administration.

Special thanks to Drs. Robert Lionberger and Lei Zhang.

References

1. U.S. FDA Draft Guidance for Industry (2021). *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted under an ANDA.*
2. U.S. FDA Guidance for Industry (2022). *Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations.*

Disclaimer

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.