Provisional Translation (as of June 2026)*

Points to Consider for the Evaluation of the Effects of Food on the Pharmacokinetics of Oral Drug Products
(Early Consideration)

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Center for Product Evaluation
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1. Introduction

The absorption of drugs from the gastrointestinal tract may be affected by the presence or composition of food. In the development of oral drug products, it is important to clarify the effects of food on gastrointestinal absorption in order to understand the pharmacokinetic profile of the drug and to appropriately determine the dosage regimen.

In Japan, the notification regarding basic principles of clinical pharmacokinetic studies necessary for the submission of a new drug application (NDA) states that, for orally administered drugs, the effects of food on gastrointestinal absorption should be evaluated using the "final formulation," which is defined as a formulation that has the same composition as the marketed product and is manufactured using the same process at a scale of not less than one-tenth of the actual commercial production lot. [1)]

The U.S. Food and Drug Administration (FDA) guidance indicates that a food-effect clinical study (FE study) may be waived for immediate-release drug products containing drug substances classified as Biopharmaceutics Classification System (BCS) Class I (high solubility and high permeability) when the drug product has a bioavailability of 85% or higher. Also, the European Medicines Agency (EMA) guideline indicates that, if the formulation is modified during clinical development or if a new pharmaceutical form is developed, the possibility of an altered food effect should be considered, and an additional FE study may be needed; thus, a FE study using the final formulation is not necessarily required.

In recent years, there have also been instances in Japan where FE studies have been conducted using formulations other than the final formulation; however, no document has explicitly described the underlying considerations for such approaches.

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* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Based on this background, this document aims to present the points to consider for evaluating the effects of food on pharmacokinetics using FE studies conducted with formulations other than the final formulation. Please note that these points to consider were developed based on currently available knowledge, and that they may change in the future due to newly obtained knowledge.

2. Points to consider for the evaluation of food effects on oral drug products

2.1 Points to consider based on bioequivalence between formulations

When bioequivalence has been demonstrated between different formulations, differences in the magnitude of the effects of food on gastrointestinal absorption are considered to be limited. Therefore, if a FE study is conducted using a formulation under development and it can be adequately explained that the formulation used in the study is bioequivalent to the final formulation, it is generally considered unnecessary to conduct an additional FE study using the final formulation.

2.2 Points to consider based on drug substance solubility and permeability in immediate-release drug products

Based on surveys using information from previously approved products in Japan, no effects of food on the area under the concentration–time curve (AUC) have been observed for immediate-release drug products containing drug substances with high solubility and high permeability.[4)5) Note1] Accordingly, if a FE study conducted using an immediate-release drug product containing a drug substance with high solubility and high permeability (absorption) (e.g. the products have an absolute bioavailability of 85% or greater) under development indicates that no effects of food on AUC are observed, it can be inferred that no effects of food on AUC will also be observed for the final formulation.

On the other hand, based on one of the surveys described above, it has been reported that effects of food on the maximum concentration (C_{max}) have been observed for multiple products, even for immediate-release drug products containing drug substances with high solubility and high permeability.[4)] This suggests that the effects of food on C_{max} may differ between the formulation used during development and the final formulation. Therefore, for drugs for which C_{max} is considered important for efficacy and safety, it is necessary to carefully evaluate the effects of food on the final

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NOTE1: The definitions of high solubility and high permeability in Reference 4) are as follows.

High solubility was designated for drugs. The highest single therapeutic dose was completely soluble in aqueous media of 250 mL or less at a pH value around 1.2, 4.5, and 6.8 regardless of aqueous medium temperature.

High permeability was designated if the absolute bioavailability was ≥ 0.85 or if ≥ 0.85 of the administered dose was recovered in the urine as unchanged (parent drug) or as the sum of the parent drug plus phase 1 oxidative and phase 2 conjugative metabolites. Regarding metabolites in feces, only oxidative and conjugative metabolites were considered. In Reference 5), high solubility and high permeability were determined with reference to the Biopharmaceutics Classification System (BCS) classification (Pharm Res. 1995; 12: 413–20).

formulation.

Based on the above considerations, if all of the following conditions are met, it may be determined that conducting an additional FE study using the final formulation is unnecessary:

- The product is an immediate-release drug product containing a drug substance with high solubility and high permeability.
- It can be justified that C_{max} is not critical for the efficacy and safety of the drug.
- No effects of food on AUC are observed in the FE study conducted using the formulation under development.

To confirm the appropriateness of such evaluations, sponsors are encouraged to utilize PMDA's consultation services as appropriate.

3. References

1) Clinical Pharmacokinetic Studies of Pharmaceuticals (PAB/ELD Notification No. 796 dated June 1, 2001) <https://www.pmda.go.jp/files/000206738.pdf>
2) US Food and Drug Administration. Assessing the Effects of Food on Drugs in INDs and NDAs －Clinical Pharmacology Considerations. Guidance for Industry. (2022) < https://www.fda.gov/media/121313/download >.
3) European Medicines Agency. Guideline on the investigation of drug interactions. (2015) <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf >.
4) Honma, N., Yamagishi, K., Ideno, Y., Takaoka, R.,& Ishiguro, A. Regulatory Perspective Based on Survey of Relationship Between Biopharmaceutical Characteristics and Food Effects on Systemic Pharmacokinetics. *Clin Pharmacol Ther* 2025; 118: 29-32 < doi:10.1002/cpt.3622>
5) Nishida, C., Okada, A. & Nagai, N. Food-effect Studies in New Drug Development: Considerations on Study Designs Based on an Analysis of Recent New Drug Applications in Japan. *RSMP* 2022; 12: 125–41 < doi:10.14982/rsmp.12.125 >