

# NAVIGATING FOOD EFFECTS FOR IMMEDIATE-RELEASE PRODUCTS UNDER ICH M13A

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## ABSTRACT

*Regulatory expectations for food-effect assessment in immediate-release (IR) products have long diverged: historically, the US FDA broadly expected a fed bioequivalence (BE) study using a high-fat, high-calorie meal, whereas the EMA approach was more variable—often fasting BE unless a meaningful food effect was anticipated, with fed conditions not uniformly specified. Beyond policy, real-world diets differ: in much of Europe and other regions (ex. Japan which is also a ICH adhering country, customary breakfasts are lower in calories and fat than typical US/UK “test meals,” complicating global programs and sometimes prompting duplicative studies. ICH M13A provides a pragmatic middle ground. It harmonizes when fed studies are needed for IR products and standardizes the fed condition using explicit caloric/macronutrient targets. M13A also aligns key BE elements (design, endpoints, sampling, analysis), reducing variability due to regional practice. The result is a single, globally acceptable strategy for evaluating food effects that preserves scientific rigor, respects dietary realities, and streamlines development, bridging prior FDA–EMA and other countries differences and enabling efficient worldwide submissions.*

## INTRODUCTION

For immediate-release (IR) drug products, the impact of food on bioavailability has long been a regulatory flashpoint. Sponsors planning global programs frequently encountered divergent expectations: in the United States, FDA practice consistently centered on conducting a fed bioequivalence (BE) study with a standardized high-fat, high-calorie meal; in Europe, EMA requirements were more context-dependent—often fasting BE by default, with fed assessments triggered when a meaningful food effect was anticipated. The result was an uneven landscape that invited parallel studies, inconsistent meal specifications, and prolonged timelines.

Beyond policy, culture and diet complicated matters. The “test meal” historically used in the US and UK resembles a calorically dense, fat-rich breakfast that is not representative of routine breakfasts across much of continental Europe, Asia, or Latin America. In these regions, customary morning meals are lighter and leaner, raising practical questions about feasibility, tolerability, and clinical relevance. Developers were left to reconcile scientific rigor with regional dietary norms, sometimes at the cost of added complexity or duplicative trials.

ICH M13A changes this equation. As the foundational module in the M13 series on bioequivalence, it offers a harmonized framework for IR products that clarifies **when** a fed study is warranted and **how** the fed condition should be implemented. Instead of prescribing a single, culturally specific menu, M13A defines target caloric and macronutrient characteristics and allows regionally appropriate meals that meet those targets. This “middle-ground” approach preserves the sensitivity of a challenging fed condition while acknowledging legitimate differences in dietary patterns and clinical practice around the world.

Equally important, M13A aligns core BE elements—study design (typically crossover), primary PK endpoints (AUC and C<sub>max</sub>), sampling windows, and statistical analysis—so that a single well-designed program can satisfy authorities in the US, EU, and other ICH regions. The guidance reduces ambiguity around meal composition, minimizes avoidable repetition, and provides a common lexicon for regulators, ethics committees, and clinical sites.

This article explains the prior FDA–EMA differences that shaped food-effect strategy for IR products, why regional dietary realities made a one-size-fits-all menu impractical, and how ICH M13A offers a pragmatic solution. We highlight the implications for protocol design, operational execution, and global submissions, and we propose practical tips for implementing M13A’s fed condition across diverse settings—without compromising scientific rigor or patient safety.

## EMA REQUIREMENTS EXISTENT PRIOR TO ICH M13A

Before ICH M13A, EMA’s core reference was the **Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr)**, effective 1 August 2010. For immediate-release (IR) products with systemic action, the **default** expectation was a **single-dose BE study under fasting conditions**, because fasting was considered the most sensitive state to detect formulation differences. If the reference product’s SmPC directed intake **only with food**, the BE study was to be run **under fed conditions**. For IR products with specific formulation characteristics (e.g., **microemulsions, solid dispersions**), EMA generally expected **both fasted and fed studies**, unless the product was to be used exclusively in one state. Sponsors could run **two separate two-way crossover studies** or a **single four-way crossover** to cover both states.

When a **fed** study was required but the originator SmPC did **not** specify a meal, EMA recommended a **standard high-fat, high-calorie meal: ~800–1000 kcal with ~50% of calories from fat** (approx. **150 kcal protein, 250 kcal carbohydrate, 500–600 kcal fat**). Timing was also standardized: **start the meal 30 minutes prior to dosing and consume it within 30 minutes**. The meal’s macronutrient composition had to be documented (grams and kcal).

Operationally, EMA provided additional conduct details: follow the originator SmPC for meal timing if specified; otherwise apply the **30-minute pre-dose start** rule above; standardize posture and activity; and restrict foods/drinks that affect GI/hepatic/renal function (e.g., alcohol, grapefruit). Sampling needed to capture early absorption and ensure **AUC(0–t) ≥ 80% of AUC(0–∞)**; **AUC(0–72 h)** was acceptable for IR forms when appropriate.

Clarifications and case examples were issued via the **PKWP Q&A** document. Notably, EMA reaffirmed that **fasting** is the general rule **even when later data suggest a food effect**, if the originator SmPC permits dosing “with or without food.” Conversely, for products like **cyclosporine** (an NTID), EMA required BE **in both fasting and fed states** and applied **narrowed acceptance ranges** in both. These positions underscored EMA’s SmPC-anchored approach and risk-based triggers for fed assessments prior to harmonization.

In summary, pre-M13A EMA policy centered on: **fasting by default; fed if the SmPC required it or the formulation warranted it; standardized high-fat/high-calorie meals when fed state was needed; and clear operational rules for meal timing and study conduct**. This framework differed in emphasis from FDA practice and set the stage for the harmonized, globally implementable fed-study specifications later codified in **ICH M13A**.

## US-FDA REQUIREMENTS EXISTENT PRIOR TO ICH M13A

Prior to ICH M13A, the FDA’s expectations for immediate-release (IR) products were anchored in three guidance pillars: (1) **Food-Effect Bioavailability and Fed Bioequivalence Studies** (2002), (2) **Bioavailability and Bioequivalence—General Considerations** (2003; updated draft 2020), and (3) **BE Studies With PK Endpoints for ANDAs** (most recently revised 2021). Collectively, these documents drove a consistent practice: **evaluate BE under fasting conditions and, for most IR generics, also perform a fed BE study using a standardized high-fat, high-calorie meal—unless labeling or product-specific guidance clearly indicated otherwise**.

**Standard fed test meal and timing**. FDA specified a challenging fed condition to maximize the likelihood of detecting food effects on rate/extent of absorption. The recommended meal was **high-fat (~50% of total calories) and high-calorie (~800–1000 kcal; often expressed as ~150 kcal protein, ~250 kcal carbohydrate, remainder from fat)**. Subjects began the meal **30 minutes before dosing**, finished it **within 30 minutes**, and the dose was

administered **30 minutes after the meal started** (i.e., immediately upon completion). These specifics were reiterated widely in FDA documents and the clinical literature implementing the guidance.

**When to do fed vs fasting.** For IR products, the **fasting single-dose, 2×2 crossover study in healthy adults** was the baseline. A **fed BE study** was commonly expected in addition, particularly when product-specific guidance called for it or when food could plausibly alter GI physiology/biopharmaceutics (e.g., low-solubility drugs, bile-dependent dissolution). FDA's ANDA BE guidance framed design/analysis expectations, while product-specific guidances operationalized the need for fed studies.

**Design and analysis basics.** FDA emphasized **PK endpoints** (AUC, C<sub>max</sub>) as the preferred, most sensitive measures for BA/BE when systemic exposure can be characterized, reserving PD or clinical endpoints only when PK is not feasible. BE was assessed using **log-transformed PK, 90% CIs, 80.00–125.00%** acceptance limits. Sampling had to capture early absorption and sufficient terminal data; study conduct (meals/fluids, activity, concomitants) was to be standardized across periods.

#### **Operational details frequently applied pre-M13A.**

- **Population:** healthy adults of both sexes, unless safety/ethical concerns dictated otherwise.
- **Meals:** composition documented in grams and calories; standardized menus/site SOPs to ensure compliance with the high-fat specification.
- **Labeling linkage:** Food-effect findings informed **Dosage and Administration** and **Clinical Pharmacology** sections; the 2019 FDA food-effect labeling guidance provided templates to translate exposure changes into clear instructions.

In practice, the FDA's codified **high-fat, high-calorie meal** and routine expectation for **fed BE alongside fasting BE** produced a robust, reproducible framework—but it sometimes clashed with regional dietary norms and EMA's more conditional fed-study triggers. These differences were a key driver for the subsequent **ICH M13A** effort to align *when* to study food effects and *how* to specify the fed condition across regions.

#### **UK REQUIREMENTS BEFORE ICH M13A**

**Regulatory basis.** Prior to ICH M13A, the UK (MHRA) applied the **EMA Guideline on the Investigation of Bioequivalence** (CPMP/EWP/QWP/1401/98 Rev.1/Corr) for immediate-release (IR) products. MHRA documents and FOI responses routinely pointed applicants to this EMA guideline (and its biowaiver appendices) as the UK standard.

**Fasted vs fed—when a fed study was required.** In line with EMA, the UK default was a **single-dose fasting BE study** for IR products with systemic action. A **fed BE study** was required if (i) the innovator SmPC mandated dosing with food, or (ii) a **clinically relevant food effect** was anticipated (e.g., formulation/biopharmaceutic considerations). Thus, the trigger for fed studies was **conditional**, not automatic.

**Fed-meal specification.** When a fed study was needed and the SmPC did not define the meal, the UK followed EMA's **high-fat, high-calorie** test meal: **~800–1000 kcal** with **~50% of calories from fat** (≈150 kcal protein, 250 kcal carbohydrate, 500–600 kcal fat), with dosing **30 minutes after the meal starts** and the meal consumed within ~30 minutes. Sites were expected to document macronutrients and timing.

#### **How this differed from the US FDA (pre-M13A).**

- **Triggering a fed study:** The **FDA commonly expected both fasting and fed BE** for IR generics, using the same high-fat/high-calorie meal as a sensitive condition; the UK/EMA approach **did not require fed by default**, anchoring the decision to the SmPC and risk of a food effect.
- **Meal composition: Not materially different.** Both jurisdictions used a similar **high-fat (~50%), 800–1000 kcal** meal when a fed study was performed. Differences lay in **policy triggers**, not in breakfast composition.

**Why the “UK breakfast” didn’t change the rulebook.** Although a traditional UK cooked breakfast resembles the caloric/fat profile of the US standard test meal, **UK regulatory practice tracked EMA policy**, not national eating habits. Sponsors ran fed studies **only when justified/required**, but when they did, the **meal matched the EMA high-fat test condition**, effectively mirroring the FDA meal specification.

In the UK, sponsors often submitted **fasting-only BE** unless the SmPC or science mandated a fed arm; in the US, sponsors typically planned **both fasting and fed BE**. This procedural gap—**conditional (UK/EMA) vs routine (FDA) fed studies**—was a recurring source of duplicative designs and regional divergence that **ICH M13A** later set out to harmonize.

## JAPAN REQUIREMENTS BEFORE ICH M13A

**Regulatory basis.** Before ICH M13A, Japan applied the *Guideline for Bioequivalence Studies of Generic Products* issued by MHLW (English translation, 2012) plus an official Q&A (2020). For IR, single-dose, crossover BE in **healthy adults** was the default; fed evaluation was added when labeling or biopharmaceutics indicated a clinically relevant food effect. The core PK framework (AUC, C<sub>max</sub>; 90% CI within 80.00–125.00%) paralleled other regions.

**When fed studies were run.** As in the EU, fed BE was **not automatic** for IR generics; it was triggered by SmPC/Japanese labeling or a plausible food effect based on formulation or BCS/biopharmaceutics considerations. (Japan’s guidance also contains unique provisions—for example, enrolling **achlorhydric** subjects when dissolution differences around pH 6.8 suggest sensitivity to gastric acidity.)

**Meal composition and timing.** When a fed study was required, Japan accepted the standard **high-fat, high-calorie test meal (~800–1000 kcal; ~50% of calories from fat)** and aligned dosing relative to the meal. These specifics appear consistently in PMDA review reports of food-effect/BE studies submitted in Japan.

**Operational nuances (timing rules).** The 2020 Q&A clarified dosing offsets: products administered **10 minutes after a high-fat meal** (to create a sensitive fed condition); where fasting studies were difficult to conduct, **administration 30 minutes after a low-fat meal** could be used to *minimize* meal effects (primarily discussed in the context of modified-release, but widely referenced operationally).

**Convergence with global practice.** Comparative surveys before M13 noted Japan among jurisdictions that **define caloric and macronutrient targets** for fed studies—i.e., the same “high-fat/high-calorie” challenge condition used by FDA/EMA—while differing mainly in **when** fed BE was expected (conditional in Japan/EU vs commonly routine in the US for IR).

### Summary (pre-M13A).

- **Default:** single-dose, fasting BE in healthy adults for IR generics.
- **Fed BE:** required when labeling or science indicated a meaningful food effect (not by default).
- **Meal:** high-fat/high-calorie (~800–1000 kcal; ~50% fat) with defined dosing offsets; documentation of menu/macros expected.
- **Special cases:** provisions for subjects with altered gastric acidity when dissolution signals warranted.

This landscape—largely aligned with EMA on **triggers** but harmonized with FDA/EMA on **meal specs**—set the stage for ICH M13A to codify a single, globally consistent approach to food-effect and fed BE for immediate-release products.

## ICH M13A IN CONTEXT: WHO ICH IS, WHEN M13A TOOK EFFECT, AND WHAT IT CHANGES FOR FOOD-EFFECT STUDIE

The International Council for Harmonisation (ICH) is a global forum that brings **regulators and industry together** to align technical requirements for pharmaceutical development and registration—so a single development program can satisfy multiple authorities. Founding regulators were the **EU (EC/EMA), US (FDA), and Japan (MHLW/PMDA)**; today, the Assembly also includes other regulatory members such as **Health Canada, Swissmedic, MHRA (UK), NMPA (China), ANVISA (Brazil), MFDS (Korea), HSA (Singapore), TFDA (Chinese Taipei), CDSCO (India)** and more, plus industry associations (EFPIA, JPMA, PhRMA, IGBA, etc.).

### The guideline and timing

The full title is “**M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms.**” It reached **Step 4 (adoption by the ICH Assembly) on July 23, 2024**. Regional “in-force” dates vary; in the **EU it came into effect on January 25, 2025**, superseding relevant parts of the EMA BE guideline. FDA has posted its implementation page and finalised adoption of M13A in 2024.

### Food-effect (fed/fasted) requirements under ICH M13A

M13A harmonises *when* to run fed vs. fasted BE for immediate-release (IR) products and *how* to standardise the meal:

- **General principle:** Single-dose **fasting BE** usually offers the most discrimination; for **many non-high-risk IR products, one fasting study is sufficient**.
- **Label-driven cases (non-high-risk):**
  - If the comparator is labelled “**only with food**” for PK reasons, do a **single fed BE** study.
  - If it is “**only with food**” for tolerability (non-PK) reasons, a **single study under either fasting or fed** conditions is acceptable.
- **High-risk products** (e.g., low-solubility actives in **solid dispersions, lipid-based, nano/micro-emulsion** or other specialised technologies): conduct **both fasting and fed BE** regardless of label, if safety permits.
- **Meal standardisation (fed studies):**
  - Start the meal **30 minutes before dosing** and finish it within **30 minutes**.
  - For studies requiring both states (e.g., high-risk), use a **high-fat/high-calorie meal: ~900–1000 kcal, ~50% fat (≈150 kcal protein, 250 kcal carbohydrate, 500–600 kcal fat)**.
  - For a **single fed study** with non-high-risk products, either the above **high-fat** meal or a **low-fat/low-calorie** meal (e.g., **~500 kcal, ~25% fat**) may be used—**unless** the comparator’s labelling specifies a meal, in which case follow that. Document the meal’s macros (grams/kcal/%).

Together, these provisions give a **globally consistent, diet-agnostic** framework—preserving a sensitive fed challenge where needed, while allowing regionally appropriate menus that **meet defined caloric/macronutrient targets**.

### CONCLUSIONS

With **ICH M13A** now in force, a food-effect study designed and conducted in line with this guideline can be submitted **across ICH member regions** once implemented locally, eliminating the need to tailor separate protocols to divergent regional expectations. This is a **major advance**: it reduces duplicative development, lowers operational costs, and—most importantly—**saves healthy volunteers and patients** from enrollment in redundant studies that add burden without adding scientific value.

Harmonisation also clarifies an important nuance: **no prior regional approach was “wrong.”** Rather, each reflected local practice and dietary habits that were not universally shared. M13A provides a **clear, globally applicable framework**—standardizing when fed studies are needed and how meals should be composed—while still allowing regionally appropriate menus that meet defined caloric and macronutrient targets.

The result is an **ethically stronger and scientifically consistent** pathway for assessing food effects in immediate-release products. Sponsors can now plan a single, well-designed program that **navigates differences in dietary patterns and regulatory expectations** without sacrificing sensitivity or rigor. In short, M13A delivers what global development has long needed: **clarity, efficiency, and ethical prudence** in the design of food-effect studies.

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