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COMMENTARY

Toward the harmonization of bioequivalence guidelines in Europe: Commentary on the state of the art and future priorities under ICH M13A for immediate-release oral forms

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[Correction added on 14 January 2026, after first online publication: The copyright has been changed.]

1 | STATE OF THE ART

Bioequivalence (BE) studies are designed to compare two medicinal products or different formulations of the same active substance to verify that their relative bioavailability (BA) (rate and extent of drug absorption) after administration in the same molar dose lies within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, that is, similarity in terms of safety and efficacy.[1] These studies are regulated by guidelines issued by major Health Authorities, which define the requirements for manufacturing and marketing authorization of pharmaceutical products. In 2010, the European Medicines Agency (EMA) finalized the guideline on the investigation of BE, commonly referred to as 1401/98 Rev.1. In force across the European Union since then, this guideline represented a major regulatory milestone, prompting generic drug manufacturers to comply with the new framework to gain market access and maintain competitiveness.

In recent years, generic medicinal products have accounted for more than 50% of the total pharmaceutical market in countries that are members or observers of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). Specifically, generics represent approximately 89% of the pharmaceutical market in the United States, 56% in Europe, and 60% in Japan, with even higher percentages in low- and middle-income countries.[2]

In Italy, more than 80% of the annual applications for new marketing authorizations whether national, decentralized, or via mutual recognition procedures concern generic medicinal products.

In an increasingly globalized economic and regulatory environment, harmonizing evaluation criteria and quality standards in BE studies has become essential. To advance global harmonization efforts, the Network on Bioavailability and Biopharmaceutics (BABP) of the European Federation for Pharmaceutical Sciences (EUFEPS) initiated in 2015 the Global Bioequivalence Harmonization Initiative (GBHI). These international conferences provided—over the course of the six editions—a platform for scientists from academia, industry, and regulatory authorities to discuss key bioequivalence issues and work toward shared and harmonized positions.

In fact, based on the discussion and efforts advanced through the GBHI meetings, the ICH initiated the development of a new series of guidelines in 2019—known as the M13 series—aimed at harmonizing regulatory and methodological aspects of BE studies for immediate-release solid oral dosage forms, designed to deliver drugs to the systemic circulation. This includes tablets, capsules and other non-modified release oral formulations such as orodispersible tablets, chewable tablets, and granules/powders for oral suspensions.

The aim of these ICH guidelines is to harmonize current regional guidelines; reduce the need to conduct multiple BE studies across different jurisdictions and support a more streamlined approach to global

drug development. As a result, these new guidelines seek to minimize assessor–sponsor back-and-forth and to shorten time-to-decision by stating, up front, what must be justified in protocols and statistical analysis plans (SAPs). It also includes additional recommendations, such as guidance on the use of multiple comparator products and alternative formulations.

The first guideline in the series, M13A, came into effect on 25 January 2025. Subsequently, on 13 March 2025, the final draft of guideline M13B was published. This document introduces regulatory considerations for granting biowaivers for one or more additional strengths, if BE has been demonstrated for at least one strength of the product. Furthermore, it should be specified that in February 2025, the development of the third guideline in the series, M13C, was initiated. This guideline will address data analysis and BE evaluation for highly variable drugs (HVDs) and narrow therapeutic index drugs (NTIDs) and will include methodological considerations related to complex study designs, for example, adaptive BE study design.[3]

ICH Guideline M13A superseded applicable parts of EMA guideline 1401/98 Rev.1 related to bioequivalence study considerations and data analysis for a non-replicate study design. Any specific topics not addressed in ICH M13A will continue to apply until they are replaced by new ICH guidance. Because M13A is an ICH harmonization text, its provisions are intended to align expectations across the EU, US and Japan; here we use EMA 2010 as the practical baseline for EU practice. Thus, this commentary appraises the shift in European BE requirements for immediate-release oral dosage forms from EMA guideline 1401/98 Rev.1 (2010) to the new ICH M13A guideline (in force since January 2025), focusing on regulatory, methodological and operational implications for the design, conduct and assessment of BE studies.[4,5]

2 | WHAT CHANGES UNDER ICH M13A *VS.* EMA CPMP/EWP/QWP/1401/98 REV.1, 2010

Specifically, the ICH M13A guideline introduces new definitions, implements procedural requirements related to study design and the medicinal products to be compared and clarifies statistical aspects, in comparison with significant differences from 1401/98 Rev.1. A summary of these differences is presented in Table 1.

Regarding the study design, the ICH M13 introduces the term '*comparator product*' defined as a '*drug product accepted by regulatory agencies that an applicant can use to compare against the test product in conducting a BE study*' replacing the traditional term '*reference product*'. A major difference is that the ICH guideline also permits BE studies involving multiple comparator products to streamline the BE demonstration reducing the burden of multiple clinical trials against local comparator products without prejudice to regional legal requirements, or multiple test products with different formulations within the same trial.

Another regulatory innovation is the concept of 'high-risk' medicinal products in the context of fed and fasting BE studies. High-risk products are those for which formulation complexity, excipient

TABLE 1 Overview on differences between 1401/98 rev.1 guideline (2010) and the new ICH M13A guideline (2025).

Topic	CPMP/EWP/QWP/1401/98 rev. 1	EMA/CHMP/ICH/953493/2022 - ICH M13A
Terminology	Uses the term *reference product*	Introduces the term *comparator product*
Number of comparators/test products	Not addressed	Allows inclusion of multiple comparators in the same study; multiple test products with different formulations also permitted
Study conduct: Fasting and fed study conditions	Based on the SmPC of the reference or on anticipated adverse events	Introduces the concept of 'high-risk' products → mandatory bioequivalence studies under both fasted and fed conditions
Dose or strength to be studied	Based on pharmacokinetics linearity	Considers solubility in addition; in case of non-linearity, requires extended analysis (AUC + Cmax); restricts the use of multiple units of the highest strength
Multi-group design	Not addressed	Introduced: statistical models must account for multi-group design; assessment of potential heterogeneity across groups required
Multiple test products	Not addressed	Alpha adjustment required for multiple test formulations; not required for comparators from different regions
Early exposure	It does not specify a formal early exposure endpoint. Standard parameters: Cmax, AUC(0–t)	Introduces pAUC or Tmax where clinically relevant (e.g., rapid onset of action)
Study population: Reason for exclusion	For the reference product only: exception for subjects with non-measurable or very low concentrations, defined as those with an AUC below 5% of the geometric mean.	The exception is applicable to the test product as well, involving both arms of the study.
Gastric pH interactions	Not addressed	Additional bioequivalence assessments with gastric pH-modifying agents (e.g., with proton pump inhibitors) introduced

Abbreviations: AUC, area under the curve; pAUC, partial AUC; Tmax, time of maximal concentration; SmPC, summary of product characteristics.

properties, or manufacturing processes result in a high probability that gastrointestinal conditions may influence in vivo performance. Consequently, for these products, BE studies under both fed and fasting conditions are mandatory. Selection of the type of BE study (fasting or fed and meal type in terms of food composition) depends on the instructions for the administration of the comparator product, the properties of drug substance and the properties of the products being compared ('non-high risk' or 'high risk'). In contrast, 1401/98 Rev.1 determined study conditions based on the Summary of Product Characteristics (SmPC) of the reference drug or serious adverse event are anticipated under fed/fasting conditions.[1,6] While the recommendation to conduct two BE studies reflects the need for caution in evaluating high-risk products, some stakeholders argue that adhering to the SmPC conditions would be more appropriate. Moreover, requiring studies in both conditions may increase development costs and timelines. A more sustainable approach, already partially adopted, involves the development of product-specific guidelines that define study requirements on a case-by-case basis, based on the active substance and formulation characteristics.[3] These assessments were discussed extensively during different GHBI conferences,[7] where it was emphasized that certain excipients and formulation characteristics may make the in vivo performance of immediate-release products sensitive to nutritional status. ICH M13A formalized this concept by introducing the category of 'high-risk' products.

Regarding the selection of dose(s) and strength(s) to be studied, the ICH guideline M13A introduces the 'solubility' of the drug substance as parameter to be considered in addition to linearity of pharmacokinetics. Furthermore, it specifies that, in the presence of nonlinear pharmacokinetics, dose proportionality must be confirmed through extended analysis compared to the previous guideline, including Cmax in addition to AUC. Furthermore, although the recommendations on dose selection in the case of non-proportionality remain consistent with the current European guideline, the use of multiple units of the highest strength, in cases of bioanalytical sensitivity limitations, is now restricted to higher total doses within the labelled dosage range.[1,3]

Regarding statistical analysis, multi-group design studies have been introduced by ICH M13A in order to fill in the gap in case where it is needed to dose the subjects in more than one group in a single BE study (e.g., lack of space in the clinical site). As BE study should be designed to minimize the group effect in the study, now it is clarified that the statistical model should take into account the multi-group nature of the BE study. Moreover, even if BE should be determined based on the overall treatment effect in the whole study population, the Applicant is called to evaluate potential for heterogeneity of treatment effect across groups and discuss its potential impact on the study data.[1]

A noteworthy aspect is also the multiplicity correction by the alpha adjustment in case of multiple test products (e.g., two different pharmaceutical formulations during drug development). It is needed when the BE has to be shown for each of the tested formulations.

Furthermore, in case of multiple comparator products from different regions, no alpha adjustment is required, as the comparators are considered independent and region-specific.[1]

Regarding Data Analysis, an additional change introduced by ICH M13A pertains to the section on early exposure. For immediate-release oral products, BE is generally evaluated using the parameters Cmax and AUC(0–t), which indicate the rate and extent of absorption, respectively. However, in cases where the onset of therapeutic action is clinically significant, these parameters might not be adequate. In such cases, additional pharmacokinetic parameters may be employed, such as the time of maximal concentration (tmax) or a partial AUC (pAUC) calculated between administration and a predefined time interval, chosen based on a clinically relevant pharmacodynamic endpoint (such as reduction in blood pressure, pain relief, or lowering of blood glucose).[1] The same assessments emerged during the sixth GHBI conference.[8]

As an additional difference, ICH M13A extends the exclusion criteria for subjects with very low plasma concentrations. Under 1401/98 Rev.1, subjects with plasma concentrations below 5% of the geometric mean AUC could be excluded only for the reference product. M13A now permits exclusion from both test and reference arms, provided specified criteria are met and exclusions are justified according to the study protocol.[1,6] This extension likely facilitates the management of rare outliers and simplifies final data analysis.

ICH M13A also introduces provisions for additional BE assessments involving gastric pH-modifying agents (e.g., proton pump inhibitors), as formulation differences between comparator and test products may impact bioavailability.[1]

The pharmaceutical industry has called for greater clarity and flexibility, suggesting the use of physiologically based pharmacokinetic modelling; however, to date, experience with these innovative approaches remains limited, and is not yet sufficient to support a definitive comparative assessment of the products based solely on simulation studies.

The regulatory innovations introduced by ICH M13A have been implemented at the European level by the work of Product-Specific Bioequivalence Guideline's drafting group (PSBGL-DG), operating under the leadership of EMA's Methodology Working Party (MWP). These documents have contributed to a more transparent, predictable and scientifically robust evaluation process. Although some of these PSBGLs have been updated according to ICH M13A guideline, others already had some features of the above-mentioned guideline before it came into force.

Relevant examples are listed below and include medicinal products for which the PSBGL has been released before and after the ICH M13A with the aim to highlight the consistency and robustness of scientific knowledge:

Updated according to ICH M13A:

- Tadalafil (EMA/CHMP/315234/2014 Rev.3*): classified as a high-risk product, it requires bioequivalence studies under both fasted and fed conditions. Additionally, partial AUC or Tmax are introduced as a key pharmacokinetic parameter for the assessment of bioequivalence, given the need for a rapid onset of action in the treatment of erectile dysfunction.[9]

- Tolvaptan (EMA/CHMP/254395/2024): also considered high-risk, requiring BE studies under both fasting and fed conditions.[9]

Pre-ICH M13A:

- Dasatinib (EMA/CHMP/675838/2014/Rev.1): high-risk product. Some subjects may randomly exhibit low plasma concentrations of dasatanib when administered under fasting conditions. The incidence of these low-liers has been observed to depend on the formulation. Therefore, dasatinib medicinal products are considered to have specific formulation characteristics requiring BE studies under both fasted and fed conditions.[9]
- Dabigatran (EMA/151692/2025 Rev. 1*): pH-dependency. Solubility of dabigatran etexilate is pH-dependent and bioequivalence studies are required both under fasting conditions and following pre-treatment with a proton pump inhibitor (PPI). Note: this PSBGL introduced in May 2025 the possibility to request a waiver for this PPI study if it can be demonstrated that the test, reference products are manufactured using the same technology, and that excipients potentially affecting gastric pH are qualitatively identical and quantitatively similar.[9]

3 | WHAT STILL NEEDS TO BE DONE (NEAR-TERM PRIORITIES)

Efforts to achieve regulatory harmonization in BE assessment require the development of updated guidelines and operational recommendations that are aligned with the most recent scientific progress and digital innovations. The following priorities warrant careful consideration:

- *development of new guidelines (for the PBPK and silico systems)*;

The use of computational methods such as physiologically based pharmacokinetic (PBPK) modelling and in silico systems is becoming increasingly relevant. A systematic review published in 2024[10] highlighted that these approaches significantly improve the prediction of pharmacokinetic profiles, optimize dosing regimens, and reduce the need for large-scale clinical trials. Regulatory agencies such as the FDA and EMA have recognized the value of these tools and are working to develop frameworks that support the integration of in silico methods into drug regulatory assessments. However, several challenges remain, including study heterogeneity and publication bias, which limit generalizability. The sixth GHBI conference emphasized that PBPK models are not yet sufficiently mature to support waivers of in vivo bioequivalence studies, particularly under fed conditions for high-risk oral products. This position is reflected in ICH M13A. However, their future potential is acknowledged, and further research and development are encouraged.

- *M13B and M13C readiness* and *enhancement of specific product guidelines*;

The implementation of ICH M13A has replaced only specific sections of EMA guideline 1401/98 Rev.1; consequently, a fully harmonized regulatory framework has yet to be established. Completing and finalizing the entire M13 guideline series will be crucial to creating a comprehensive and consistent regulatory foundation. A structured dialogue among industry representatives, regulatory authorities, and research institutions is necessary in this context to tackle current challenges introduced by ICH M13A—such as defining high-risk products and improving the development of product-specific guidance.

4 | CONCLUSION

The implementation of the ICH M13 guideline series marks a significant step toward the global harmonization of BE standards. It changes day-to-day BE practice by moving from broad principles to prespecified, auditable rules and potentially can shorten assessments while preserving scientific rigour. While challenges remain—particularly in defining risk categories and integrating modelling tools—the transition from EMA 1401/98 Rev.1 to ICH M13A is a pivotal development in aligning regulatory approaches across regions.

CONFLICT OF INTEREST STATEMENT

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organizations with which the authors is/are employed/affiliated.

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