



Mathematical and regulatory limitations of the similarity factor f_2 under incomplete dissolution: analysis of the ICH M13B guideline and applicability of alternative metrics

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Abstract

Introduction. The similarity factor f_2 (Moore & Flanner, 1996) remains the gold standard for assessing dissolution profile equivalence in pharmaceutical development, biowaiver procedures, and the justification of post-approval changes. However, the mathematical framework of this metric was conceived in the late 1990s strictly for routine quality control under complete dissolution conditions ($Q > 85\%$). The international guideline ICH M13B establishes a threshold rule: dissolution profiles with less than 10 % release are deemed comparable without mathematical evaluation, whereas profiles exceeding 10 % release require calculation of f_2 (or Bootstrap f_2). Under non-sink conditions, typical for Biopharmaceutics Classification System (BCS) Class II and IV active substances in physiological media lacking surfactants, the f_2 metric loses sensitivity to relative kinetic discrepancies.

Aim. To analyze the mathematical limitations of the similarity factor f_2 under incomplete dissolution, to perform a comparative evaluation of f_2 , the difference factor f_1 , and the Two One-Sided Tests (TOST) procedure, and to provide recommendations for statistical evaluation of comparative in vitro dissolution test (CIDT) data within the framework of EAEU regulations and the ICH M13B guideline.

Materials and methods. Using a critical model CIDT scenario for a poorly soluble compound with mean dissolution profiles of the test product $T = (6.0\%; 10.0\%; 13.0\%; 18.0\%)$; and the reference product $R = (11.0\%; 18.0\%; 22.0\%; 30.0\%)$; parallel calculations of f_2 and f_1 were performed in accordance with Annex 5 to the EEC Council Decision No. 85 dated November 3, 2016, along with an equivalence assessment on a relative logarithmic scale (TOST approach).

Results and discussion. For the analyzed dataset, the f_2 metric was 52.49, formally satisfying the similarity criterion ($f_2 \geq 50$), despite the reference product releasing 1.7–1.9 times faster and more completely than the test product. Conversely, calculation of the difference factor f_1 yielded 41.98 %, which is nearly three times higher than the regulatory threshold for acceptable difference ($f_1 \leq 15\%$). The mean dissolution ratio T/R ranged between 54.55 % and 60.00 %, falling well outside the bioequivalence acceptance interval (80.00–125.00 %). This paradox arises from the absolute dimensionality of the Moore and Flanner metric, which is anchored to a 0–100 % scale and remains indifferent to substantial relative discrepancies at low analyte concentrations.

Conclusion. Relying on f_2 within the range of incomplete dissolution (from 10 % to 30–40 %) introduces substantial regulatory and technical risks of concluding pseudo-equivalence between batches. When conducting CIDT for poorly soluble BCS Class II and IV compounds in physiological media without surfactants, a comprehensive statistical evaluation is required, including mandatory calculation of f_1 , application of TOST on a relative scale, and physiologically based pharmacokinetic (PBPK) modeling.

Keywords: comparative in vitro dissolution testing, CIDT, similarity factor f_2 , difference factor f_1 , biowaiver, ICH M13B, EEC Council Decision No. 85, incomplete dissolution, BCS Class II, PBPK, TOST

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Математические и регуляторные ограничения фактора подобия f_2 при неполном растворении: анализ руководства ICH M13B и применимость альтернативных метрик

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Резюме

Введение. Фактор подобия f_2 (Moore & Flanner, 1996) остается золотым стандартом оценки подобия профилей растворения при фармацевтической разработке, процедурах биоэквивалентности и обосновании пострегистрационных изменений. Однако математическая структура метрики проектировалась во второй половине 1990-х годов исключительно для рутинного контроля качества в условиях полного растворения ($Q > 85\%$). В международном руководстве ICH M13B (утверждено в августе 2026 г., вступит в силу в марте 2027 года) заложено пороговое правило: профили с высвобождением менее 10 % признаются сопоставимыми без математической оценки, а для профилей со степенью растворения более 10 % требуется расчет f_2 (или Bootstrap f_2). В условиях отсутствия предельного растворения (sink conditions), характерных для действующих веществ II и IV классов биофармацевтической классификационной системы (БКС) в физиологических средах без поверхностно-активных веществ, метрика f_2 теряет чувствительность к относительным кинетическим различиям.

Цель. Анализ математических ограничений фактора подобия f_2 при неполном растворении, сопоставительная оценка метрик f_2 , фактора различия f_1 и процедуры двух односторонних тестов (TOST), а также выработка рекомендаций по статистической оценке данных теста сравнительной кинетики растворения (ТСКР) в контексте требований правил ЕАЭС и руководства ICH M13B.

Материалы и методы. На основе критического модельного сценария ТСКР для малорастворимого соединения со средними профилями растворения исследуемого препарата $T = (6,0\%; 10,0\%; 13,0\%; 18,0\%)$ и референтного препарата $R = (11,0\%; 18,0\%; 22,0\%; 30,0\%)$ проведен параллельный расчет метрик f_2 и f_1 в соответствии с Приложением № 5 к Решению Совета ЕЭК от 03.11.2016 № 85, а также оценка эквивалентности с применением подходов TOST.

Результаты и обсуждение. Установлено, что для анализируемого набора данных метрика f_2 составляет 52,49, что формально удовлетворяет критерию подобия ($f_2 \geq 50$), несмотря на то что референтный препарат высвобождается в 1,7—1,9 раза полнее и быстрее исследуемого. Напротив, расчет фактора различия f_1 дал значение 41,98 %, что почти в 3 раза превышает нормативный порог допустимого различия ($f_1 \leq 15\%$). Отношение средних степеней растворения T/R составило 54,55—60,00 %, что заведомо выходит за стандартные границы эквивалентности (80,00—125,00 %). Выявленный парадокс обусловлен абсолютной размерностью метрики Мура — Фланнера, привязанной к 100-процентной шкале и индифферентной к кратным относительным расхождениям при низких концентрациях аналита.

Заключение. Использование фактора f_2 в интервале неполного растворения (от 10 % до 85 %) создает серьезный регуляторный и технологический риск признания псевдоэквивалентности серий. При проведении ТСКР для труднорастворимых соединений классов II и IV по БКС в средах без добавления ПАВ необходима комплексная статистическая оценка с обязательным расчетом фактора f_1 , применением TOST в относительной шкале, а также физиологически обоснованного фармакокинетического моделирования (PBPK).

Ключевые слова: тест сравнительной кинетики растворения, ТСКР, фактор подобия f_2 , фактор различия f_1 , биоэквивалентность, ICH M13B, Решение Совета ЕЭК № 85, неполное растворение, БКС класс II, PBPK, TOST

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INTRODUCTION

In vitro comparative dissolution testing (CIDT) has undergone fundamental evolution over the past three decades: from a specialized tool for industrial quality control (QC) of finished products to a primary surrogate marker of *in vivo* therapeutic equivalence and bioavailability. In modern regulatory practice across the Eurasian Economic Union (EAEU)¹, the European Medicines Agency (EMA)², the US Food and Drug Administration (FDA)³, and the International Council for Harmonisation (ICH)^{4,5} CIDT outcomes serve as the foundation for:

1. Selecting biobatches prior to conducting bioequivalence studies and verifying pharmaceutical development decisions;
2. Granting biowaivers of *in vivo* bioequivalence studies based on the Biopharmaceutics Classification System (BCS-based biowaiver) for Class I and Class III active substances;
3. Justifying additional strength biowaivers for proportionally formulated product lines (including BCS Class II and IV substances);
4. Demonstrating the consistency of biopharmaceutical performance during scale-up, manufacturing site transfers, and post-approval modifications (the SUPAC concept)⁶.

¹ EEC Council Decision No. 85 dated November 3, 2016 (amended on April 12, 2024). "On Approval of the Rules for Conducting Bioequivalence Studies of Medicinal Products within the Framework of the Eurasian Economic Union". Available at: <https://docs.eaeunion.org/> Accessed: 01.10.2026. (In Russ.)

² European Medicines Agency. Guideline on the Investigation of Bioequivalence. CPMP/EWP/QWP/1401/98 Rev. 1/Corr**. London: EMA; 2010. 27 p. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf Accessed: 01.10.2026.

³ US Food and Drug Administration. Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. Rockville: FDA; 1997. 17 p. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dissolution-testing-immediate-release-solid-oral-dosage-forms> Accessed: 01.10.2026.

⁴ International Council for Harmonisation. ICH Harmonised Guideline: Biopharmaceutics Classification System-Based Biowaivers M9. Geneva: ICH; 2019. 16 p. Available at: https://database.ich.org/sites/default/files/M9_Guideline_Step4_2019_1116.pdf Accessed: 01.10.2026.

⁵ International Council for Harmonisation. ICH Harmonised Guideline: Bioequivalence for Immediate-Release Solid Oral Dosage Forms: Additional Strengths Biowaiver M13B). Geneva: ICH; 2026. 18 p. Available at: https://database.ich.org/sites/default/files/M13B_Draft%20Guideline_Step2_2025_0212_0.pdf Accessed: 01.10.2026.

⁶ US Food and Drug Administration. Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. Rockville: FDA; 1997. 17 p. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dissolution-testing-immediate-release-solid-oral-dosage-forms> Accessed: 01.10.2026.

The universally recognized criterion for comparing dissolution kinetic profiles across regulatory frameworks is the similarity factor f_2 , proposed by James W. Moore and Henry H. Flanner in 1996 [1]. According to current regulatory standards, two profiles are considered equivalent if the calculated f_2 value falls between 50 and 100^{7,8}.

At the same time, the mathematical framework of the Moore and Flanner equation and its underlying premises were established in 1996–1997 under vastly different analytical circumstances. During that period, CIDT was performed almost exclusively in QC release specification media. For poorly soluble compounds, these media were routinely modified by adding surfactants (such as sodium lauryl sulfate or polysorbates) or by selecting extreme pH values to maintain sink conditions (where the medium volume exceeds the drug saturation solubility by at least threefold) and achieve complete dissolution ($Q > 85\%$) [2].

This paradigm changed substantially following the introduction of multi-media CIDT requirements across three aqueous physiological buffer media at pH 1.2, 4.5, and 6.8 **without surfactants** (surfactant addition is strictly prohibited for BCS-based biowaivers and permitted only with specialized justification for strength biowaivers)^{9,10}. When testing low-solubility substances (BCS Class II and IV) — such as weak acids under low pH or weak bases in the weakly alkaline small intestine — dissolution is restricted by the thermodynamic solubility of the active pharmaceutical ingredient (API). As a result, the dissolution profiles of both compared formulations reach an artificial plateau at $Q \ll 85\%$.

This issue is underscored by the harmonized international guideline **ICH M13B** (*Bioequivalence for Immedi-*

⁷ US Food and Drug Administration. Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. Rockville: FDA; 1997. 17 p. Available at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dissolution-testing-immediate-release-solid-oral-dosage-forms> Accessed: 01.10.2026.

⁸ International Council for Harmonisation. ICH Harmonised Guideline: Biopharmaceutics Classification System-Based Biowaivers M9. Geneva: ICH; 2019. 16 p. Available at: https://database.ich.org/sites/default/files/M9_Guideline_Step4_2019_1116.pdf Accessed: 01.10.2026.

⁹ EEC Council Decision No. 85 dated November 3, 2016 (amended on April 12, 2024). "On Approval of the Rules for Conducting Bioequivalence Studies of Medicinal Products within the Framework of the Eurasian Economic Union". Available at: <https://docs.eaeunion.org/> Accessed: 01.10.2026. (In Russ.)

¹⁰ International Council for Harmonisation. ICH Harmonised Guideline: Bioequivalence for Immediate-Release Solid Oral Dosage Forms: Additional Strengths Biowaiver M13B). Geneva: ICH; 2026. 18 p. Available at: https://database.ich.org/sites/default/files/M13B_Draft%20Guideline_Step2_2025_0212_0.pdf Accessed: 01.10.2026.

ate-Release Solid Oral Dosage Forms: Additional Strengths Biowaiver)¹. The guideline establishes a formal threshold rule: if drug release across all media is below 10 %, profiles are considered similar automatically without mathematical evaluation. If release exceeds 10 %, calculation of f_2 (or Bootstrap f_2 under high variability) is mandatory.

The objective of this study was to analyze the mathematical limitations of the similarity factor f_2 within the incomplete dissolution region ($Q > 10$ %, but $Q < 85$ %), demonstrate false equivalence using a model dataset, compare f_2 with alternative metrics (difference factor f_1 , TOST criteria), and establish recommendations for sponsors and regulatory assessors during CDT dossier review within the EAEU.

MATHEMATICAL BASIS AND GENESIS OF THE MOORE AND FLANNER EQUATION

The similarity factor f_2 represents a logarithmic transformation of the sum of squared discrepancies between two profiles:

$$f_2 = 50 \cdot \log_{10} \left[\frac{100}{1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2} \right] = 50 \cdot \log_{10} \left[\left(1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right)^{-0.5} \cdot 100 \right], \quad (1)$$

where n is the number of standardized sampling time points; R_t and T_t are the mean percentages of drug dissolved from the reference (R) and test (T) products at time point t relative to the nominal content.

The regulatory acceptance threshold $f_2 \geq 50$ is derived from an empirical consensus: profiles are considered similar if the mean absolute difference across all observation points does not exceed 10 % [1, 3]. If $|R_t - T_t| = 10$ %, at all points, the mean squared error (MSE) is:

$$MSE = \frac{1}{n} \sum_{t=1}^n (10)^2 = 100.$$

Substituting $MSE = 100$ into equation (1) yields:

$$f_2 = 50 \cdot \lg[(1 + 100)^{-0.5} \cdot 100] = 50 \cdot \lg\left(\frac{100}{\sqrt{101}}\right) \approx 50 \cdot \lg(9.95) \approx 49.99 \approx 50.0.$$

¹ International Council for Harmonisation. ICH Harmonised Guideline: Bioequivalence for Immediate-Release Solid Oral Dosage Forms: Additional Strengths Biowaiver M13B). Geneva: ICH; 2026. 18 p. Available at: https://database.ich.org/sites/default/files/M13B_Draft%20Guideline_Step2_2025_0212_0.pdf Accessed: 01.10.2026.

The underlying mathematical paradox lies in the fact that equation (1) operates on an **absolute 0—100 % scale**. The metric calculates Euclidean distance in absolute percentage space and remains indifferent to the baseline concentration against which the deviation occurs:

- Under complete dissolution, when reference drug release is $R_t = 100$ %, and test drug release is $T_t = 90$ %, an absolute difference of 10 % corresponds to a relative difference of:

$$\frac{|100 - 90|}{100} \cdot 100 \% = 10.0 \%.$$

This difference is minor and typically translates to clinical bioequivalence for $C_{\max}$ and AUC within the standard 80.00–125.00 % boundaries.

- Under incomplete dissolution, when reference product release reaches an equilibrium plateau at $R_t = 11.0$ % and test product release is $T_t = 6.0$ %, the absolute difference is only $\Delta = 5.0$ %. Equation (1) calculates $(R_t - T_t)^2 = 25$ and yields a passing similarity outcome ($f_2 > 50$). In relative terms, however, the test product releases:

$$\frac{6.0}{11.0} = 100 \% = 54.5 \%.$$

Thus, the test product dissolves at **almost half the rate and extent of the reference product** ($T/R \approx 0.55$).

Under EAEU regulations (Annex 5 to EEC Council Decision No. 85)², in contrast to FDA guidance and ICH M13B, calculation of the difference factor f_1 remains mandatory:

$$f_1 = \left[\frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \right] \cdot 100. \quad (2)$$

Equation (2) incorporates the cumulative sum of reference values $\sum R_t$ in the denominator, scaling the absolute difference against the total extent of dissolution as a weighted relative parameter. The criterion for profile equivalence according to EEC Council Decision No. 85 is an f_1 value between 0 and 15 %.

² EEC Council Decision No. 85 dated November 3, 2016 (amended on April 12, 2024). "On Approval of the Rules for Conducting Bioequivalence Studies of Medicinal Products within the Framework of the Eurasian Economic Union". Available at: <https://docs.eaeunion.org/> Accessed: 01.10.2026. (In Russ.)

MATERIALS AND METHODS

To illustrate this issue and mathematically compare these metrics, a typical CIDD scenario for BCS Class II and IV compounds in a solubility-limited medium was simulated (e.g., a weak base in pH 6.8 phosphate buffer without surfactants).

Model experiment conditions.

1. Number of sampling time points: $n = 4$ ($t = 10, 15, 20, 30$ min);
2. Test product profile (T): (6.0 %; 10.0 %; 13.0 %; 18.0 %);
3. Reference product profile (R): (11.0 %; 18.0 %; 22.0 %; 30.0 %);
4. Differences between profiles: $R_t - T_t > 0$, across all points, with absolute deviations of 5.0 %, 8.0 %, 9.0 % and 12.0 %.

This dataset meets all qualifying criteria of ICH M13B:

1. Drug release for both products exceeds the 10 % threshold (at the final sampling point), precluding automated declaration of similarity without calculation;
2. Neither profile exhibits an asymptote above 85 %, requiring inclusion of all four points in statistical calculations^{1,2};
3. Coefficients of variation (CV) conform to regulatory requirements (<20 % for the early 10-minute point and <10 % for remaining points), permitting direct evaluation using mean profiles.

Calculations of f_2 and f_1 were performed using equations (1) and (2). Equivalence was additionally evaluated using Two One-Sided Tests (TOST) on a multiplicative (logarithmic) scale — standardly applied in evaluating *in vivo* bioavailability parameters ($C_{\max}$, AUC) [4] — with acceptance boundaries of 80.00–125.00% (to simplify demonstration, comparisons were performed on mean values without incorporating variability at each sampling point).

¹ EEC Council Decision No. 85 dated November 3, 2016 (amended on April 12, 2024). "On Approval of the Rules for Conducting Bioequivalence Studies of Medicinal Products within the Framework of the Eurasian Economic Union". Available at: <https://docs.eaeunion.org/> Accessed: 01.10.2026. (In Russ.)

² International Council for Harmonisation. ICH Harmonised Guideline: Bioequivalence for Immediate-Release Solid Oral Dosage Forms: Additional Strengths Biowaiver M13B). Geneva: ICH; 2026. 18 p. Available at: https://database.ich.org/sites/default/files/M13B_Draft%20Guideline_Step2_2025_0212_0.pdf Accessed: 01.10.2026.

RESULTS AND DISCUSSION

Calculated statistical metrics for the model dissolution profiles are summarized in Table 1.

Stepwise evaluation of the similarity factor f_2 :

1. Sum of squared differences:

$$\frac{1}{n} \sum (R_t - T_t)^2 = \frac{314}{4} = 78.5.$$

2. Radical expression:

$$1 + 78.5 = 79.5.$$

3. Root and reciprocal:

$$\sqrt{79.5} = 8.9163 \Rightarrow \frac{100}{8.9163} = 11.2154.$$

4. Logarithm and result:

$$\log_{10}(11.2154) = 1.04982$$

$$f_2 = 50 \cdot 1.04982 = 52.49$$

Because $f_2 \geq 50$ ($f_2 = 52.49$), a sponsor operating under ICH M13B or FDA guidance could claim *in vitro* dissolution profile similarity. For an additional strength biowaiver, a regulatory authority relying exclusively on f_2 would approve the application without *in vivo* clinical verification.

Stepwise evaluation of the difference factor f_1 demonstrates a conflicting result:

1. Sum of absolute differences:

$$\sum_{t=1}^4 |R_t - T_t| = 5.0 + 8.0 + 9.0 + 12.0 = 34.0 \text{ \%}.$$

2. Sum of reference values:

$$\sum_{t=1}^4 R_t = 11.0 + 18.0 + 22.0 + 30.0 = 81.0 \text{ \%}.$$

3. Final difference factor:

$$f_1 = \frac{34.0}{81.0} \cdot 100 \% = 41.98 \text{ \%}.$$

An f_1 value of 41.98 % exceeds the regulatory threshold ($f_1 \leq 15$ %) almost threefold. Ratios of dissolved substance between products T and R across time points are:

- Point 10 min: $6.0/11.0 = 54.55$ %;
- Point 15 min: $10.0/18.0 = 55.56$ %;
- Point 20 min: $13.0/22.0 = 59.09$ %;
- Point 30 min: $18.0/30.0 = 60.00$ %.

Table 1. Comparative evaluation of dissolution profile equivalence metrics under incomplete dissolution

Таблица 1. Сравнительная оценка метрик эквивалентности профилей растворения при неполном высвобождении

Analyzed parameter / Metric Анализируемый параметр / Метрика	Calculated value Расчетное значение	Regulatory acceptance criterion Регуляторный критерий приемлемости	Statistical outcome Статистическое заключение	Biopharmaceutical interpretation Биофармацевтическая интерпретация
Similarity factor f_2 (Moore & Flanner) Фактор подобия f_2 (Moore & Flanner)	52,49	$50 \leq f_2 \leq 100$	Pass (Equivalent) Эквивалентны (Pass)	Metric insensitivity to relative discrepancy due to absolute delta scaling «Слепота» метрики к относительному расхождению за счет фиксации абсолютной дельты
Difference factor f_1 (EAEU Decision No. 85) Фактор различия f_1 (Решение № 85)	41,98 %	$0 \leq f_1 \leq 15 \%$	Fail (Non-equivalent) Неэквивалентны (Fail)	Normalization to release scale ΣR_t reveals unacceptable 42 % deviation Нормировка на масштаб высвобождения ΣR_t выявляет недопустимое 42%-е расхождение
Dissolution extent ratio (T/R) Отношение степеней растворения (T/R)	54,55—60,00 %	80,00—125,00 %	Fail (Non-equivalent) Неэквивалентны (Fail)	Test product releases API almost twice as slow and incompletely as reference Исследуемый препарат высвобождает АФС почти в 2 раза медленнее и хуже оригинатора

Таблица предоставлена авторами
The table was provided by the authors

The mean dissolution ratio of the test product relative to the reference product is 58.02 %. Biopharmaceutically, if this behavior persists *in vivo* within the proximal intestine (dissolution limitation under non-sink conditions), the test product would provide systemic exposure ($C_{\max}$ and early AUC), roughly half that of the reference product, leading to failed bioequivalence *in vivo* [4, 5].

Applying non-parametric bootstrap analysis (Bootstrap f_2) [6, 7] does not resolve this issue. Bootstrapping estimates confidence intervals around f_2 based on observed variance. Given low intra-batch variability, the 90 % confidence interval remains centered near 52.49 (e.g., 50.4—54.2), and the lower boundary continues to exceed 50.0, reinforcing a false-positive conclusion.

This indicates a methodological vulnerability in the **ICH M13B** guideline¹:

¹ International Council for Harmonisation. ICH Harmonised Guideline: Bioequivalence for Immediate-Release Solid Oral Dosage Forms: Additional Strengths Biowaiver M13B). Geneva: ICH; 2026. 18 p. Available at: https://database.ich.org/sites/default/files/M13B_Draft%20Guideline_Step2_2025_0212_0.pdf Accessed: 01.10.2026.

- The 10 % cutoff is arbitrary. Products with 9 % dissolution are accepted without mathematical testing, while products with 11 % and 18 % dissolution are assessed via f_2 , which yields false similarity due to 100 % scale compression.
 - The f_2 metric functions reliably only when profiles plateau above 85 % (complete dissolution), where a 10 % absolute deviation corresponds to an acceptable 10—12 % relative difference.
 - In regions of incomplete dissolution (10 % to 85 %), f_2 displays systemic overestimation of profile similarity.
- In this context, EAEU regulations (Annex 5 to Decision No. 85)² provide an advantage by retaining f_1 . Because f_1 normalizes by cumulative reference release, it maintains sensitivity across low concentration ranges.

² EEC Council Decision No. 85 dated November 3, 2016 (amended on April 12, 2024). "On Approval of the Rules for Conducting Bioequivalence Studies of Medicinal Products within the Framework of the Eurasian Economic Union". Available at: <https://docs.eaeunion.org/> Accessed: 01.10.2026. (In Russ.)

To address these limitations when evaluating poorly soluble compounds (BCS Class II and IV), a stepwise statistical strategy should be implemented:

1. Under incomplete dissolution ($Q < 85\%$), f_2 should not serve as the sole criterion for equivalence;
2. Calculation of f_1 should be required (with acceptance criterion $f_1 \leq 15\%$) when dissolution is incomplete and variability criteria are satisfied;
3. In cases of incomplete dissolution accompanied by high release variability, point-by-point equivalence should be evaluated on a relative scale using 90 % confidence intervals for T/R ratios (modified TOST with 80.00—125.00 % boundaries), or alternative acceptable statistical approaches should be used [1, 8];
4. In critical cases, the biopharmaceutical relevance of *in vitro* differences should be evaluated using physiologically based pharmacokinetic (PBPK/PBBM) modeling (e.g., PK-Sim or GastroPlus) [9, 10] to translate dissolution profiles into simulated human plasma concentration curves and assess virtual bioequivalence.

CONCLUSION

1. The similarity factor f_2 has an inherent mathematical limitation: because it operates on an absolute percentage scale (0—100 %), it loses sensitivity to relative profile differences under incomplete dissolution ($Q > 10\%$, but $Q < 85\%$).
2. In the evaluated model dataset with profiles $T = (6.0\%; 10.0\%; 13.0\%; 18.0\%)$ and $R = (11.0\%; 18.0\%; 22.0\%; 30.0\%)$, f_2 yields a passing result ($f_2 = 52.49 \geq 50$), concealing an approximate twofold deficit in release rate and extent ($T/R \approx 58\%$).
3. The international guideline ICH M13B contains a methodological vulnerability by relying exclusively on f_2 (or Bootstrap f_2) for profiles exhibiting dissolution above 10 %.
4. The regulatory framework of the EAEU (Annex 5 to Decision No. 85), which permits parallel use of f_1 , provides a more discriminating standard: in the evaluated scenario, f_1 was 41.98 %, rejecting false equivalence.
5. For BCS Class II and IV substances in media without surfactants, relying solely on f_2 should be replaced by comprehensive statistical assessment, including f_1 , relative TOST analysis, and predictive PBPK modeling.

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