# Dissolution Testing and Bioequivalence: f2 Similarity, Biowaivers

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## Executive Summary

Dissolution testing and bioequivalence (BE) evaluation form the analytical backbone of generic drug approval and post-approval manufacturing change control worldwide. At the center of this system sits the **f2 similarity factor**, a model-independent statistic that compares two dissolution profiles on a 0 to 100 scale. When the applicable conditions are met, an f2 value of **50 or greater** indicates similar dissolution profiles; f2 alone does not establish bioequivalence or product interchangeability (Source: www.fda.gov) (Source: www.ema.europa.eu). The formula, first validated statistically in Pharmaceutical Research in 1998 and quickly adopted into regulatory practice, requires a minimum of three post-zero time points and typically **12 dosage units** per product, though peer-reviewed statistical work has since shown the estimate itself is "a biased and conservative estimate" whose confidence interval cannot be derived analytically (Source: pubmed.ncbi.nlm.nih.gov).

Dissolution testing commonly uses the four apparatuses described in USP <711>—basket, paddle, reciprocating cylinder, and flow-through cell—while USP also provides specialized drug-release apparatuses for products such as transdermal systems. The paddle method (Apparatus 2) accounts for roughly **70 percent** of methods used across U.S. Food and Drug Administration (FDA) approved commercial products (Source: pmc.ncbi.nlm.nih.gov). Media selection, ranging from simple pH 1.2 hydrochloric acid to biorelevant fasted and fed state simulated intestinal fluids (FaSSIF and FeSSIF), is calibrated to physiologically realistic gastrointestinal conditions and to maintaining **sink conditions**, generally defined as a dissolution medium holding at least three times the saturated solubility of the active pharmaceutical ingredient (Source: pmc.ncbi.nlm.nih.gov). The European Medicines Agency (EMA) applies parallel method-development conventions, recommending paddle-apparatus development begin at **50 rpm** (Source: www.ema.europa.eu).

Biowaivers, which allow a sponsor to substitute in vitro dissolution data for a costly in vivo BE study, are governed by the **Biopharmaceutics Classification System (BCS)**, proposed by Gordon Amidon and colleagues in 1995 (Source: pubmed.ncbi.nlm.nih.gov), which sorts drug substances into four classes by solubility and intestinal permeability. Under the harmonized **ICH M9** guideline, adopted by the International Council for

Harmonisation on **20 November 2019** and made legally effective in the European Union on **30 July 2020**, BCS-based biowaivers are available to Class 1 (high solubility, high permeability) and, under stricter excipient and dissolution-rate conditions, Class 3 (high solubility, low permeability) drug products, but the pathway remains restricted to immediate-release, solid, orally administered dosage forms (Source: database.ich.org) (Source: www.gabionline.net). FDA finalized its M9-aligned guidance in May 2021 (Source: www.federalregister.gov). WHO issued a separate updated BCS-based biowaiver guideline in 2024 that states it was revised to align with ICH M9 (Source: cdn.who.int). Japan's Pharmaceuticals and Medical Devices Agency (PMDA) and Health Canada maintain broadly consistent, though separately documented, frameworks (Source: www.pmda.go.jp).

For generic drugs that cannot qualify for a biowaiver, pharmacokinetic bioequivalence studies are commonly used. A two-way crossover study is the usual design for many oral products, although scientifically justified alternatives, including parallel designs when crossover is impractical, may be appropriate. For unscaled average bioequivalence, the 90 percent confidence interval for the test-to-reference ratio of both area under the curve (AUC) and maximum concentration (Cmax) is generally evaluated against **80.00 percent to 125.00 percent** (Source: www.fda.gov) (Source: www.who.int). FDA issued final guidances in May 2026 on statistical approaches to establishing bioequivalence and on pharmacokinetic-endpoint BE studies for ANDAs (Source: www.fda.gov) (Source: www.fda.gov). This infrastructure underpins a generics market that filled **90 percent** of all U.S. prescriptions in 2024 while accounting for only **12 percent** of prescription drug spending, saving the U.S. healthcare system an estimated **$467 billion** that year according to the Association for Accessible Medicines (AAM) and the IQVIA Institute (Source: accessiblemeds.org) (Source: accessiblemeds.org).

The system is not infallible, and not always in the direction critics assume. This report examines FDA's 2012 determination that generic **Budeprion XL 300 mg** was not bioequivalent to Wellbutrin XL, the agency's 2014 to 2016 action against generic **Concerta**, and a peer-reviewed 2011 finding that a WHO/FIP biowaiver procedure applied to two already clinically bioequivalent **ibuprofen** products declared them "in vitro inequivalent," suggesting biowaiver criteria can sometimes be more stringent than clinical necessity requires (Source: pmc.ncbi.nlm.nih.gov) (Source: web.archive.org). It also surveys the GDUFA III fee schedule, under which a standard ANDA filing fee for fiscal year 2025 is **$321,920** (Source: www.federalregister.gov), and explains how in vitro in vivo correlation (IVIVC) models, particularly Level A correlations, can extend biowaiver logic to justify post-approval manufacturing changes without new clinical studies (Source: www.fda.gov). For life-sciences organizations, the throughline is that dissolution testing, f2 analysis, BCS classification, and IVIVC are not independent technical exercises but a single, tightly regulated evidentiary chain connecting a formulation change in a manufacturing suite to a clinical assurance of interchangeability at the pharmacy counter.

## Introduction and Background

Every generic drug approved in the United States, the European Union, and most other regulated markets must demonstrate that it performs in the human body the same way as the branded reference product it is designed to replace. Directly measuring that performance in every patient population, for every manufacturing batch, and after every formulation tweak would be prohibitively expensive and slow. Regulators have therefore built an elaborate substitute system: **in vitro dissolution testing**, standardized apparatus and media that simulate how a tablet or capsule releases its active pharmaceutical ingredient (API) under controlled laboratory conditions, paired with statistical tools like the **f2 similarity factor** that translate a dissolution curve comparison into a single, regulator-recognized pass or fail criterion.

This system matters because it sits at the intersection of pharmaceutical science, cost containment, and patient safety. Dissolution or, where appropriately justified, disintegration testing is commonly included in Chemistry, Manufacturing, and Controls (CMC) release specifications for solid oral dosage forms. ICH Q6A states that a drug product specification includes a test to measure release of drug substance, but permits disintegration testing to replace dissolution testing for certain rapidly dissolving immediate-release products containing highly soluble drug substances (Source: database.ich.org). When a generic manufacturer can demonstrate that its product's dissolution profile is statistically similar to the reference product's, and when the drug substance qualifies under the **Biopharmaceutics Classification System (BCS)**, the manufacturer may be able to obtain a **biowaiver**: regulatory permission to skip an expensive in vivo bioequivalence (BE) study entirely and rely on in vitro data instead.

The stakes of getting this right are large. FDA's Office of Generic Drugs (OGD) had published **2,187 product-specific guidances (PSGs)** by April 2024, providing drug-specific dissolution and BE testing recommendations for individual molecules (Source: www.fda.gov), and generic drugs filled roughly **9 of every 10 U.S. prescriptions** in 2024 (Source: accessiblemeds.org). Yet high-profile strength-extrapolation and complex modified-release cases have required regulators to revisit therapeutic-equivalence ratings for already-marketed products, as detailed later in this report's case studies section.

For life-sciences organizations building regulatory strategy, quality systems, or the underlying data infrastructure that supports dissolution and BE submissions, understanding this framework in granular technical detail (apparatus selection, media chemistry, f2 calculation mechanics, BCS classification thresholds, and IVIVC levels) is a prerequisite to designing compliant, cost-efficient development programs. Consultancies operating at the interface of regulatory science and enterprise technology, including **IntuitionLabs**, an AI and Veeva-focused life-sciences consultancy, note that

the industry's compliance obligations extend well beyond the laboratory bench into the data systems that must document, trace, and defend every dissolution result and biowaiver justification submitted to regulators; the firm describes its regulatory-facing work as "built-in compliance with FDA, EMA, and global regulations" across the enterprise software it implements for pharmaceutical clients (Source: intuitionlabs.ai).

This report explains, in sequence: USP <711> dissolution apparatuses, specialized drug-release apparatuses, and dissolution media selection; the mathematics, validity conditions, and limitations of the f2 similarity factor; the BCS framework and biowaiver eligibility under FDA, EMA, WHO, and ICH M9, including named eligible and ineligible drug substances; bioequivalence study design with international comparison; the three levels of in vitro in vivo correlation and a worked case example; and practical implementation guidance. It closes with quantitative data, five named case studies, and an assessment of where this framework is headed as of August 2026.

# Understanding Dissolution Testing: Apparatus, Media, and Regulatory Purpose

**Dissolution testing** measures the rate and extent to which an active pharmaceutical ingredient (API) is released from a solid oral dosage form (tablet, capsule, or similar) into a defined liquid medium under controlled, reproducible mechanical and thermal conditions. It serves two related but distinct regulatory functions: as a **quality control (QC) release specification** that confirms batch-to-batch manufacturing consistency, and as an **in vitro surrogate** for how a drug will behave in the gastrointestinal tract, used to support bioequivalence claims and biowaivers.

## USP <711> Apparatuses and Specialized Drug-Release Apparatuses

USP <711> describes four dissolution apparatuses: basket, paddle, reciprocating cylinder, and flow-through cell. USP provides additional specialized apparatuses for drug-release testing, including apparatuses used with transdermal systems. *Table 1* distinguishes these groups and summarizes their operating principles and typical applications.

| APPARATUS | COMMON NAME | OPERATING PRINCIPLE | TYPICAL DOSAGE FORMS |
|---|---|---|---|
| **USP <711> Apparatus 1** | Rotating basket | Dosage form held in a cylindrical wire mesh basket rotating in the medium | Capsules, tablets that float or disintegrate slowly |
| **USP <711> Apparatus 2** | Paddle | A paddle stirs the medium above a freely resting dosage form; used in roughly 70% of FDA dissolution methods for commercial products (Source: pmc.ncbi.nlm.nih.gov) | Immediate-release tablets, most solid oral forms |
| **USP <711> Apparatus 3** | Reciprocating cylinder | Dosage form oscillates vertically through a series of media-filled rows | Extended-release and chewable tablets |
| **USP <711> Apparatus 4** | Flow-through cell | Fresh medium continuously flows through a cell containing the dosage form; used for extended-release forms, soft and hard gelatin capsules, powders, granules, pellets, suppositories, and implants (Source: pmc.ncbi.nlm.nih.gov) | Poorly soluble drugs, implants, microspheres |
| **Specialized apparatus 5** | Paddle over disk | Paddle apparatus with the dosage form mounted on a disk assembly | Transdermal patches |
| **Specialized apparatus 6** | Rotating cylinder | Dosage form affixed to or contained within a rotating cylinder | Transdermal patches |
| **Specialized apparatus 7** | Reciprocating holder | Dosage form mounted in a holder that reciprocates through media vessels | Transdermal systems, implants, non-disintegrating forms |

The **paddle method (Apparatus 2)** dominates in practice. FDA's foundational 1997 dissolution guidance recommends mild test conditions using "basket method at 50/100 rpm or paddle method at 50/75 rpm" (Source: www.fda.gov) for setting new-molecule dissolution specifications, and EMA's 2017 reflection paper on dissolution specifications recommends the same starting point on the EU side, stating that method development "should start with a stirring speed of 50 rpm" for the paddle apparatus (Source: www.ema.europa.eu). A representative commercial method illustrates real-world parameters: one published method for a poorly soluble drug used **Apparatus 2 at 75 rpm in 1,000 mL** of 0.1 N hydrochloric acid with an added surfactant to achieve adequate solubilization (Source: pmc.ncbi.nlm.nih.gov). USP General Chapter <711> additionally requires a **two-step dissolution method** for enteric-coated solid oral dosage forms, testing coating integrity in acid medium before transitioning to a neutral pH phosphate buffer stage (Source: pmc.ncbi.nlm.nih.gov), and USP <711> itself is being progressively harmonized with the corresponding chapters of the European and Japanese pharmacopoeias (Source: doi.usp.org). The European Pharmacopoeia imposes its own apparatus-qualification discipline: GMP trade publisher ECA Academy notes that "critical test parameters that have to be monitored periodically during use include volume" of the dissolution medium across all four Ph. Eur. apparatus types (Source: www.gmp-compliance.org).

Testing is generally performed at **37 degrees Celsius**, matching human body temperature, and for drugs lacking a compendial (USP-published) method, FDA maintains a **Dissolution Methods Database**, curated by the Division of Bioequivalence within OGD and updated on a **quarterly** cycle (Source: www.fda.gov). Under EMA's own EU-specific dissolution-specification convention, a fixed acceptance value, denoted **Q**, must be set at **at least 80 percent** for immediate-release products under discriminatory test conditions (Source: www.ema.europa.eu), and the European Pharmacopoeia definition EMA applies classifies an oral product as immediate-release when "at least 75% (Q) of the active substance is dissolved within 45 minutes" (Source: www.ema.europa.eu), a somewhat different reference point than the 85 percent in 15 or 30 minute thresholds used in FDA's rapid-dissolution classifications discussed below.

## Dissolution Media Selection and Biorelevant Testing

Selecting an appropriate **dissolution medium** requires balancing physiological realism against reproducibility. Under ICH M9, a drug substance is highly soluble when its highest single therapeutic dose is completely soluble in **250 mL or less** of aqueous media across pH **1.2 to 6.8** at 37 ± 1°C. If that dose does not meet the criterion but the highest reference-product strength does, additional data are needed to justify a BCS-based biowaiver. When a reference product's own dissolution method is not publicly disclosed, FDA recommends comparative testing across **pH 1 to 6.8**, with surfactant addition and varied agitation, using Apparatus 1 and 2, to characterize the reference product's behavior before designing a generic method (Source: www.fda.gov).

For **poorly soluble drugs**, achieving **sink conditions** (a medium volume sufficiently large relative to drug solubility that dissolution is not artificially rate-limited by saturation) is critical. Sink conditions are commonly defined as a medium volume containing **at least three times** the saturated solubility of the API, using the minimum surfactant concentration needed to reach that threshold (Source: pmc.ncbi.nlm.nih.gov). **Sodium lauryl sulfate (SLS)** is reported as the most commonly used surfactant added to dissolution media for this purpose (Source: pmc.ncbi.nlm.nih.gov).

**Biorelevant media** attempt to more closely mimic actual gastrointestinal fluid composition than simple buffers. **Fasted-state simulated gastric fluid (FaSSGF)** contains pepsin along with low concentrations of bile salt and lecithin to better represent fasted gastric conditions than earlier simulated gastric fluid formulations (Source: pmc.ncbi.nlm.nih.gov). Because the proximal small intestine in the fasted state typically holds only around 300 to 500 mL of fluid, a dissolution test volume of **500 mL or less** is recommended when using fasted-state simulated intestinal fluid (FaSSIF) (Source: pmc.ncbi.nlm.nih.gov). Its postprandial counterpart, **fed-state simulated intestinal fluid (FeSSIF)**, models small-intestinal conditions after a meal at a higher pH of approximately 5.0, and is buffered with acetate rather than the phosphate buffer typically used in FaSSIF (Source: pmc.ncbi.nlm.nih.gov). FDA guidance also describes **two-tiered dissolution testing**, using simulated gastric fluid with and without pepsin, or simulated intestinal fluid with and without pancreatin, to better reflect how enzymatic activity affects release (Source: www.fda.gov). On sampling design, WHO's Prequalification Team guidance for BCS-based biowaiver applications requires that comparative dissolution profiles be generated under matched conditions, since "dissolution profiles for the test and comparator products should be generated in the same laboratory" rather than compiled from historical data (Source: extranet.who.int), and specifies that "samples should be collected at 5, 10, 15, 20, and 30 minutes" for standard comparative profiling (Source: extranet.who.int).

Beyond biorelevance, ICH Q6A guides how much dissolution data a specification needs: **single-point measurements** (one sampling time, one acceptance criterion) are generally sufficient for immediate-release dosage forms, while modified- or extended-release forms require multi-time-point testing that characterizes the full release profile (Source: database.ich.org). FDA's 2018 guidance, **"Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances,"** provides recommendations for setting these criteria in NDA, IND, and ANDA submissions for orally administered immediate-release drug products containing highly soluble drug substances (Source: www.fda.gov).

# The f2 Similarity Factor: Calculation, Requirements, and Limitations

## What f2 Measures and How It Is Calculated

The **f2 similarity factor** is a model-independent statistic, meaning it assumes no particular mathematical model of drug release kinetics, that quantifies how closely a test product's dissolution profile matches a reference profile across multiple sampling time points. It was proposed alongside a companion metric, **f1 (the difference factor)**, by Moore and Flanner in 1996 as a practical way to compare dissolution curves without complex curve-fitting (Source: dissolutiontech.com). The two are conceptually distinct: **f1** tracks the average percent difference at each time point, while **f2**, inversely related to the sum of squared differences, weights larger deviations more heavily, which is why the two were described as the "difference factor" and "similarity factor" respectively (Source: dissolutiontech.com).

Both the harmonized ICH M9 guideline and the EMA's bioequivalence guideline define f2 using the mean percent dissolved of the reference product, R(t), and test product, T(t), summed across **n** time points, and regulators worldwide, including FDA and EMA, have converged on **f2 greater than or equal to 50** as the threshold for "similar" dissolution profiles (Source: www.fda.gov) (Source: www.ema.europa.eu). The result is a single number bounded between 0 and 100, where 100 indicates identical profiles, a standard an FDA-authored publication describes as "a public standard of f2 value between 50-100 to indicate similarity between two dissolution profiles" (Source: dissolutiontech.com).

## Conditions for Valid f2 Calculation

An f2 value is only statistically meaningful, and only accepted by regulators, when several preconditions are met. ICH M9 and the parallel EMA guideline on oral modified-release products converge on the same core requirements:

- **A minimum of three time points**, excluding the initial zero-time measurement, and **at least 12 dosage units per product**, with an individual value from each unit measured at every time point and the mean used in the calculation (Source: www.fda.gov); EMA's oral modified-release quality guideline states the same requirement, requiring dissolution similarity be "established with at least 12 individual values per time point" (Source: www.ema.europa.eu)
- **Not more than one mean dissolution value exceeding 85%** across either product's profile, combined with **bounded variability**, a coefficient of variation (CV) of no more than roughly **20% at early time points** (up to 10 minutes) and no more than **10% at later time points**, since high inter-unit variability makes the point estimate of f2 unreliable (Source: www.fda.gov)

A key exception applies to fast-dissolving products. When more than 85 percent of the labeled drug amount dissolves within **15 minutes** for both products, most regulators consider a formal f2 comparison unnecessary, treating the profiles as inherently similar. FDA-authored guidance states plainly: "For products which are rapidly dissolving, i.e., more than 85% in 15 minutes or less, a profile comparison is not necessary" (Source: dissolutiontech.com), and the EMA bioequivalence guideline similarly states that "where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation" (Source: www.ema.europa.eu). A 2015 peer-reviewed AAPS Journal analysis reaches the same conclusion, noting f2 is "not needed when greater than 85% of the labeled amount of drug in the drug products has been dissolved within 15 min" across the three standard compendial media (Source: www.ncbi.nlm.nih.gov).

## Limitations and Alternatives to f2

The f2 formula's chief weakness is its sensitivity to variability: when dissolution data exceed the CV thresholds above, the resulting f2 value cannot be interpreted with statistical confidence, and regulators generally will not accept it as evidence of similarity. In those situations, FDA has accepted alternative, model-independent multivariate confidence-interval approaches, sometimes called **bootstrap methods**, where similarity is established by confirming the lower bound of a calculated confidence interval is 50 or greater, rather than relying on a single point estimate (Source: www.ncbi.nlm.nih.gov). FDA has applied this in practice; the AAPS Journal analysis reports "the bootstrap method was applied by the FDA when they evaluated the reformulated 400 mg mesalamine delayed-release" capsule against its original predecessor, because ordinary variability was too high for a standard f2 calculation to be defensible (Source: www.ncbi.nlm.nih.gov).

f2 also has an important use beyond biowaivers: as a **method discrimination check**, deliberately manufacturing batches with altered critical variables and confirming the method detects the change, since "the calculated similarity factor (f2) for the altered batches should be <50 when compared to the bio-, pivotal, or clinical batches" (Source: www.fda.gov). EMA's parallel guideline expresses the same expectation, requiring dissolution testing capable of "discriminating between batches with respect to critical process parameters" (Source: www.ema.europa.eu), the inverse use case from a biowaiver comparison: proving a method is sensitive enough to fail meaningfully different batches, not just pass similar ones.

## Statistical Critique and Ongoing Refinement of f2

The f2 formula's limitations have drawn sustained academic scrutiny since shortly after its adoption. The methodology's original statistical validation, published in Pharmaceutical Research in 1998, established the bootstrap resampling approach now used by FDA, finding "a relatively robust distribution could be obtained after more than 500 'Bootstraps'" (Source: pubmed.ncbi.nlm.nih.gov), while separately showing "f2 values were found to be sensitive to number of sample points" taken after the dissolution plateau is reached (Source: pubmed.ncbi.nlm.nih.gov) (Source: link.springer.com), meaning study design choices can materially shift the resulting score.

Subsequent research has continued to probe f2's boundaries. A 2017 simulation study concluded that f2 "is an acceptable metric when used according to the regulatory requirements, but loses its applicability when variability increases" (Source: pubmed.ncbi.nlm.nih.gov), while an alternative multivariate statistical distance approach sometimes "presented contradictory results in several of the simulation scenarios, which makes it an unreliable metric" (Source: pubmed.ncbi.nlm.nih.gov). A 2020 software comparison found divergent bootstrap confidence-interval results between tools depending on the platform used (Source: pubmed.ncbi.nlm.nih.gov), and a 2025 Pharmaceutical Research analysis proposed a decision-tree framework for choosing among f2 and newer alternatives, finding the multivariate statistical distance approach "was most stringent as compared to others" (Source: pubmed.ncbi.nlm.nih.gov). European trade press summarizes the driver behind this refinement plainly, noting the underlying statistic "is complex and does not allow for the analytical calculation of a confidence interval" using standard closed-form methods (Source: www.pharmafocuseurope.com), which is why regulators turned to bootstrap resampling instead.

# The Biopharmaceutics Classification System and BCS-Based Biowaivers

## The Four BCS Classes

The **Biopharmaceutics Classification System (BCS)** classifies drug substances into four categories based on two properties: aqueous **solubility** and intestinal **permeability**. The original 1995 paper by Gordon Amidon, Hans Lennernas, Vinod Shah, and John Crison proposed the four-class framework and anticipated today's biowaiver logic directly, stating that "for very rapidly dissolving high solubility drugs, e.g. 85% dissolution in less than 15 minutes, a simple one point dissolution test, is all that may be needed" to establish equivalence (Source: pubmed.ncbi.nlm.nih.gov), while also cautioning that certain drug types, such as rapidly dissolving but poorly permeable compounds, may show "no in vitro-in vivo correlation" at all (Source: pubmed.ncbi.nlm.nih.gov). FDA guidance defines the four resulting classes as "Class 1: High Solubility, High Permeability" through "Class 2: Low Solubility, High Permeability," with Class 3 (high solubility, low permeability) and Class 4 (low solubility, low permeability) completing the matrix (Source: www.gmp-navigator.com).

*Table 2* below summarizes the practical solubility and permeability thresholds, current biowaiver eligibility, and a representative named example for each class.

| BCS CLASS | SOLUBILITY | PERMEABILITY | BCS-BASED BIOWAIVER ELIGIBLE | DOCUMENTED EXAMPLE |
|---|---|---|---|---|
| **Class 1** | High: highest dose soluble in ≤250 mL across pH 1 to 6.8 (Source: cdn.who.int) | High: ≥85% of dose absorbed (Source: www.gmp-navigator.com) | **Yes, conditionally**: both products must be very rapidly dissolving, or rapidly dissolving with similar profiles under all defined conditions; if one is rapid and the other very rapid, f2 similarity is required (Source: www.fda.gov) | Widely applicable |
| **Class 2** | Low | High: dissolution rate-limited absorption (Source: link.springer.com) | No | **Ibuprofen** (Source: pmc.ncbi.nlm.nih.gov) |
| **Class 3** | High | Low | **Yes, conditionally** under ICH M9; requires very rapid dissolution and tight excipient similarity (Source: database.ich.org) | **Metformin**, **ranitidine** (biowaiver recommended despite Class 3) (Source: pubmed.ncbi.nlm.nih.gov) |
| **Class 4** | Low | Low | No | **Ciprofloxacin**, for which "biowaiver based approval... cannot be recommended" (Source: pubmed.ncbi.nlm.nih.gov) |

Under FDA's guidance, "highly soluble" means the highest labeled strength of the drug substance is soluble in **250 mL or less** of aqueous media across the pH range of **1 to 6.8** (Source: www.gmp-navigator.com), and "high permeability" means systemic bioavailability or extent of absorption in humans has been determined to be **85 percent or more** of the administered dose (Source: www.gmp-navigator.com). Dissolution rate classification also matters: FDA defines an IR product as **"very rapidly dissolving"** when 85 percent or more dissolves within **15 minutes**, and merely **"rapidly dissolving"** within **30 minutes**, both using USP Apparatus 1 or 2 (Source: www.gmp-navigator.com).

As Table 2 illustrates, BCS classification alone does not guarantee a favorable biowaiver outcome. The biowaiver monograph series published under the International Pharmaceutical Federation (FIP) has evaluated numerous high-volume generics individually: ibuprofen (BCS Class II) does not qualify for a biowaiver under any current framework (Source: pmc.ncbi.nlm.nih.gov); ranitidine hydrochloride (Class 3) does qualify, with its monograph concluding "a biowaiver can be recommended for IR solid oral dosage forms" (Source: pubmed.ncbi.nlm.nih.gov); and ciprofloxacin hydrochloride (Class 4) is explicitly disqualified, its monograph stating "biowaiver based approval of ciprofloxacin hydrochloride containing IR solid oral dosage forms cannot be recommended" (Source: pubmed.ncbi.nlm.nih.gov).

## Regulatory Harmonization: FDA, EMA, WHO, PMDA, and ICH M9

For years, BCS-based biowaiver policy diverged meaningfully by region. EMA's original bioequivalence guideline, adopted January 2010 and effective from August 2010, included its own recommendations on BCS-based biowaivers (Source: ema.europa.eu), while FDA maintained a separate biowaiver guidance line. As EMA itself later summarized, prior to harmonization "BCS-based biowaivers for these two classes [1 and 3] are not recognized worldwide. This means that pharmaceutical companies have to follow different approaches in the different regions" (Source: www.ema.europa.eu), creating duplicated testing burdens for globally marketed generics.

The **ICH M9 guideline** resolved much of this divergence. It was adopted "by the Regulatory Members of the ICH Assembly under Step 4" on **20 November 2019** (Source: database.ich.org), took legally effective status in the EU on **30 July 2020** (Source: www.ema.europa.eu), and FDA formally finalized its own harmonized guidance in May 2021, explicitly stating the new "guidance replaces the existing FDA guidance issued December 26, 2017" (Source: www.federalregister.gov); that December 2017 document had itself already broken new ground by extending U.S. biowaiver policy to include BCS Class 3 drug substances for the first time, adding excipient and dissolution-rate criteria that had not existed in FDA's earlier Class 1-only biowaiver guidance. In 2024, the **World Health Organization** published an updated, separate BCS-based biowaiver annex that it said was intended to align with ICH M9 principles (Source: cdn.who.int).

Beyond the FDA-EMA-WHO harmonization axis, other major regulators maintain broadly consistent but separately documented frameworks. WHO's own multisource (generic) pharmaceutical products guideline requires modified-release oral products undergo bioequivalence testing under both fasted and fed conditions because of dose-dumping risk (Source: www.who.int), and sets a minimum comparative bioavailability enrollment, requiring "a minimum of 12 subjects" (Source: www.who.int). Japan's PMDA issued its own 2013 notice governing bioequivalence for post-approval manufacturing changes, Japan's functional analog to the SUPAC framework discussed later, intended to "assure bioequivalence between the formulations before and after the manufacturing process change" (Source: www.pmda.go.jp), and separate PMDA guidance frames dissolution testing as central to "assure the consistency of bioavailability, bioequivalence, or interchangeability of multisource drug products" (Source: www.pmda.go.jp). Health Canada's comparative bioavailability standards define modified-release forms partly by their capacity "to delay disintegration, de-aggregation, or dissolution so that the drug's rate of degradation is altered" (Source: www.canada.ca), broadly consistent with the FDA and EMA frameworks described throughout this report.

## Excipient and Formulation Requirements for BCS-Based Biowaivers

ICH M9 explicitly excludes certain drug categories from biowaiver eligibility regardless of BCS class: **narrow therapeutic index (NTI)** drugs, where small differences in exposure could cause therapeutic failure or toxicity, are categorically excluded, since "drug products having a narrow therapeutic index are excluded from consideration for a BCS-based biowaiver in this guidance" (Source: database.ich.org). The exclusion has a documented clinical rationale: patient-safety literature summarized by the generics-industry publication GaBI Online has raised concern that "switching from branded anti-epileptics to generic versions might result in increased risk" of therapeutic failure (Source: www.gabionline.net), precisely the kind of narrow-margin risk the NTI exclusion is designed to prevent. The biowaiver route is also dosage-form limited: GaBI Online's coverage of FDA's final M9-aligned guidance confirms a "BCS-based biowaiver can only be used for immediate release, solid orally administered dosage forms" (Source: www.gabionline.net), excluding modified-release and non-oral products regardless of BCS class.

For Class 3 products, ICH M9 imposes materially stricter excipient-comparability requirements than for Class 1, since "BCS Class III drug substances are considered to be more susceptible to the effects of excipients" on absorption, given their permeability is already the limiting factor (Source: database.ich.org). Concretely, excipients that could affect absorption must be **"within ± 10% of the amount of excipient in the reference product, and the cumulative difference for these excipients should be within ± 10%"** (Source: database.ich.org), and Class 3 eligibility additionally demands "both the test product and reference product should display very rapid (≥85% for the mean percent dissolved in ≤15 minutes) in vitro dissolution characteristics" (Source: database.ich.org).

These excipient limits are not merely academic. Both ICH M9 and WHO's 2024 guideline give the same illustrative example of a formulation that fails eligibility despite satisfying individual excipient limits, because total tablet composition deviated too far in aggregate: "the total core weight of the proposed product deviates by more than 20% from the total core weight of the comparator product, making the product ineligible for a biowaiver" (Source: cdn.who.int). This illustrates why formulation scientists must assess the complete ICH M9 Table 1 limits and the total permitted core-weight change, rather than applying a uniform ±10% threshold to every excipient. A 2007 peer-reviewed review argued the BCS permeability boundary may be drawn more generously than the solubility boundary, finding "near complete uptake has been shown for a drug product" with an extremely high calculated Dose number, proposing the system instead be organized around whichever mechanism actually limits absorption for a given molecule (Source: pubmed.ncbi.nlm.nih.gov). GaBI Online's coverage of complex generic drug development traces this tension back further: a 2006 FDA advisory committee reportedly declared "current OSFA-based bioequivalence (BE) guidelines... to be Procrustean" (one-size-fits-all, forcing dissimilar products into an identical mold) (Source: www.gabionline.net), with researchers concluding "developing scientifically sound, product-specific requirements is imperative" for complex generics such as long-acting injectables (Source: www.gabionline.net).

# Bioequivalence Study Design for Generic Drugs

## The Standard Crossover Design and Statistical Acceptance Range

When a generic drug candidate does not qualify for a BCS-based biowaiver, a pharmacokinetic bioequivalence study is commonly used to demonstrate bioequivalence. For many oral products, the recommended design is **administration of either single or multiple doses of the test (T) and reference (R) products to healthy subjects on separate occasions** with randomized sequence assignment, formally known as the **two-treatment, two-period, two-sequence crossover design**, commonly called the "two-way crossover design". Scientifically justified alternative designs may be used; for example, a randomized parallel design may be appropriate when a crossover design is impractical because it would require a prolonged washout period (Source: www.fda.gov), in which each subject receives both products on separate occasions, separated by a washout period long enough to eliminate carryover effects, serving as their own statistical control.

Bioequivalence is established when the **90 percent confidence interval** for the ratio of the test product's average AUC (area under the plasma concentration-time curve) and Cmax (peak plasma concentration) to the reference product's average falls entirely within **80.00 percent to 125.00 percent** (Source: www.fda.gov). This is not a statistical accident but a deliberate regulatory judgment, "based on a clinical judgment that a test product with BA [bioavailability] measures outside this range should be denied market access" (Source: www.fda.gov). The World Health Organization applies functionally the same standard internationally, requiring pharmacokinetic parameters to fall within the same bioequivalence limits for log transformed data (Source: www.who.int), demonstrating that the 80 to 125 percent window functions as a de facto global standard rather than a purely domestic FDA convention.

For **highly variable drugs** (generally those with within-subject variability greater than roughly 30 percent), FDA may recommend partial or fully replicate crossover designs and a **reference-scaled average bioequivalence (RSABE)** approach, which can scale bioequivalence limits to the reference product's variability. For **narrow therapeutic index (NTI)** drug products, FDA recommends a fully replicated design with additional variability controls; the standards are intended to allow less, not more, variation. FDA notes that a replicate design can use fewer subjects than a nonreplicate design for highly variable drugs (Source: www.fda.gov). FDA's statistical approach has continued to evolve: a 2021 revision added a methodological appendix that "provides a step-by-step guide to for using a reference-scaled average BE approach" (Source: www.raps.org), and FDA finalized two companion guidances in May 2026, one explicitly "applicable to non-orally administered drug products such as transdermal and certain rectal" and nasal products (Source: www.raps.org), while the companion guidance clarifies that "missing data is distinct from intercurrent events; however, both can introduce problems" into BE analysis (Source: www.raps.org).

## Product-Specific Guidances and the Scale of the ANDA System

Because bioequivalence study design (fasting versus fed conditions, sampling schedule, analyte selection, acceptable study population) varies enormously by molecule, FDA publishes individualized **product-specific guidances (PSGs)** for the vast majority of generic candidates. As of April 2024, OGD had published **2,187 PSGs**, of which roughly 40 percent addressed complex products requiring specialized study designs (Source: www.fda.gov). These guidances function as the practical rulebook that translates the general statistical and BCS frameworks above into molecule-specific study protocols.

The resulting approval pipeline is large. In calendar year 2024, FDA approved **76 first-time generic drugs**, a category the agency describes plainly as "just what they sound like, the first approval by FDA" of a generic version of a given reference product, including prucalopride tablets and deutetrabenazine tablets among the year's approvals (Source: www.fda.gov). In fiscal year 2019, FDA reported what was then a record year, with "1,171 generic drug approvals, 935 of them full approvals and 236 tentative approvals" (Source: www.biospace.com), a scale of throughput that depends directly on the standardized dissolution and BE evidentiary framework described in this report to keep review timelines and study costs manageable.

# In Vitro In Vivo Correlation (IVIVC) and Its Regulatory Uses

## Levels A, B, and C

**In vitro in vivo correlation (IVIVC)** is a predictive mathematical model linking an in vitro property of a dosage form, typically its dissolution rate, to a relevant in vivo response, typically the rate or extent of drug absorption. FDA's 1997 guidance on extended-release oral dosage forms defines IVIVC's core purpose as "applying an IVIVC as a surrogate for in vivo bioequivalence when it is necessary to document bioequivalence" for certain initial approvals and post-approval changes (Source: www.fda.gov). EMA's own guideline on oral modified-release products recognizes the same logic from the EU side, noting an established Level A correlation "may reduce the number of in vivo studies during product development" (Source: www.ema.europa.eu).

*Table 3* below summarizes FDA's three principal IVIVC levels, with Multiple Level C shown as a variant of Level C, ordered from most to least predictive.

| IVIVC LEVEL | DEFINITION | REGULATORY UTILITY |
|---|---|---|
| **Level A** | A point-to-point relationship between the entire in vitro dissolution profile and the entire in vivo input (absorption) rate curve (Source: www.fda.gov) | Most predictive; when established and validated, may support formulation and manufacturing change biowaivers |
| **Level B** | Uses statistical moment analysis, comparing mean dissolution time to mean in vivo residence time; does not uniquely define the plasma curve (Source: www.fda.gov) | Limited standalone regulatory use |
| **Multiple Level C** | Relationships between several dissolution time points and one or more pharmacokinetic parameters | Can be as useful as a Level A correlation and may support a biowaiver when established across the dissolution profile |
| **Level C** | A single-point relationship between one dissolution parameter and one pharmacokinetic parameter such as Cmax or AUC (Source: www.fda.gov) | A single-point correlation is generally insufficient alone to support a biowaiver |

**Level A** correlations are by far the most commonly developed and most regulatorily valuable, with FDA guidance noting "Level A correlations are the most common type of correlation developed in NDAs, and it will permit certain formulation and manufacturing changes without an in vivo bioequivalence study" once validated, while Level B and multiple Level C correlations are only infrequently pursued and carry much less standalone regulatory weight (Source: www.fda.gov).

### Building and Applying an IVIVC Model

Developing a defensible IVIVC requires disciplined study design. In FDA's historical review of accepted IVIVC data sets, underlying human bioavailability studies used between **6 and 36 subjects**, generally in the fasted state, and required manufacturing consistency be tightly controlled, with the coefficient of variation for mean dissolution profiles of a single batch held below 10 percent (Source: www.fda.gov), a considerably tighter tolerance than the 20 percent CV permitted for ordinary f2 comparisons.

A frequently cited example of Level A IVIVC development is the 1998 case study of an extended-release metoprolol tartrate tablet, where researchers tested dissolution across multiple apparatus, agitation, and pH combinations before finding "Apparatus I operated at 150 rpm, and pH of 6.8 was found to be the most discriminating dissolution method" for correlating in vitro release with in vivo absorption (Source: pubmed.ncbi.nlm.nih.gov). The resulting model achieved an "average percent prediction error of less than 10% [which] indicates that the correlation is predictive and allows the associated dissolution data to be used as a surrogate for bioavailability studies" (Source: pubmed.ncbi.nlm.nih.gov), illustrating the empirical bar a Level A correlation must clear before regulators accept it in place of new clinical BE data.

Once validated, a Level A IVIVC becomes a durable regulatory asset that outlives the original approval. It is most commonly leveraged under FDA's **SUPAC-MR** framework, which classifies post-approval manufacturing and formulation changes by risk level and ties the highest-risk **Level 3 changes**, such as adding or deleting release-controlling excipients, to IVIVC-based waiver logic, since an in vivo bioequivalence "study may be waived in the presence of an established in vitro/in vivo correlation" (Source: www.fda.gov). The EU does not maintain a single document directly equivalent to SUPAC-MR; instead, post-approval changes are governed through the EU variations classification system, under which bioequivalence studies used "to support quality changes to the marketing authorisation" must be filed under the applicable quality variation category (Source: www.ema.europa.eu), achieving a broadly similar outcome through a differently structured process.

## Implementation Guidance: Building a Defensible Dissolution and Biowaiver Strategy

Translating the regulatory framework above into a working development and compliance program requires attention to sequencing, documentation, and cross-functional data governance. Based on the guidance and case evidence assembled in this report, several practical principles emerge for sponsors and generic manufacturers.

- **Classify early.** BCS classification should be established as early as possible, since it determines whether a biowaiver pathway is even available and shapes the dissolution method development strategy, particularly given that classification alone (as the ibuprofen, ranitidine, and ciprofloxacin examples show) does not guarantee a favorable outcome.
- **Match apparatus and media to the molecule, not convention.** While Apparatus 2 (paddle) covers roughly 70 percent of methods, poorly soluble or modified-release molecules may require Apparatus 4 (flow-through cell) or biorelevant FaSSIF/FeSSIF media rather than a familiar default configuration.
- **Design for discrimination, not just for passing.** A dissolution method should be validated by confirming it can detect a deliberately altered batch (f2 below 50 against the pivotal batch), a requirement shared explicitly by both FDA and EMA quality guidance.
- **Budget for excipient-level documentation on Class 3 biowaiver claims.** ICH M9 requires qualitative sameness of excipients (other than permitted coating or capsule-shell exceptions) and compliance with the excipient-class-specific quantitative limits in Table 1, including a 10% total permitted change for all excipients relative to core weight; formulation records must support that assessment quantitatively.
- **Consult product-specific guidances before finalizing study design.** With over 2,187 PSGs published as of April 2024, a molecule-specific guidance frequently already answers questions about fed versus fasted conditions, sampling windows, and acceptable reference standards.
- **Treat IVIVC development as a manufacturing-quality investment, not just a regulatory one.** The sub-10 percent CV requirement for IVIVC-supporting dissolution data means IVIVC-ready manufacturing processes are also, by construction, higher-consistency processes, as the metoprolol case study above illustrates.
- **Plan for cross-system traceability.** Every f2 calculation, BCS classification decision, and IVIVC dataset submitted to a regulator must be reconstructable years later, during inspections, post-approval change reviews, or litigation, which places real weight on the underlying laboratory information management and quality systems that capture raw dissolution data.

This last point is where regulatory science and enterprise data infrastructure intersect. Life-sciences organizations increasingly rely on specialized technology partners to build the systems, quality data pipelines, and audit-ready analytics that keep dissolution and BE evidence defensible over a product's lifecycle. Consultancies such as **IntuitionLabs**, which positions itself around "strategic guidance on digital transformation, AI adoption, and technology roadmapping," frame this documentation burden as a systems-architecture problem as much as a laboratory one (Source: intuitionlabs.ai). A biowaiver package or IVIVC-based post-approval change justification is only as strong as the traceable data trail supporting it, and that trail increasingly lives in enterprise quality and regulatory systems rather than paper laboratory notebooks.

# Data Analysis and Evidence

## Regulatory Fee Structure and Application Throughput

The dissolution and bioequivalence framework operates within a defined economic structure funded largely by industry user fees. Under the **Generic Drug User Fee Amendments (GDUFA III)**, FDA's fiscal year 2025 fee schedule set the standard **ANDA filing fee at $321,920** and the **Drug Master File (DMF) fee at $95,084** (Source: www.federalregister.gov). Facility fees for the same fiscal year included **$41,580** for domestic API manufacturing facilities, **$56,580** for foreign API facilities, and **$231,952** for domestic finished dosage form (FDF) facilities (Source: www.federalregister.gov). In aggregate, the statutory GDUFA III base revenue target for fiscal year 2025 was set at **$613,538,015** (Source: www.federalregister.gov).

FDA's own performance tracking shows both throughput and persistent backlog pressure. The agency's FY2024 reporting shows mean total ANDA approval time, from original filing acceptance through final approval across all review cycles, ranging from approximately **39.8 to 42.7 months** across quarters (Source: www.fda.gov), underscoring that even a strong dissolution and biowaiver strategy operates within a multi-year approval timeline once deficiency-response cycles are included.

## Market Scale and Economic Impact

Quantifying the dissolution testing market itself, commercial market-research firm BIS Research estimated the **global pharmaceutical dissolution testing market at $649.4 million in 2024** and forecast growth to **$1,311.2 million by 2033** at a CAGR of **8.12 percent** (Source: bisresearch.com). These are BIS's commercial market estimates, not official market statistics; BIS attributes projected growth in part to regulatory testing requirements (Source: bisresearch.com). A separate analysis from Verified Market Reports similarly frames dissolution test apparatus as core infrastructure: "represents a critical segment within the pharmaceutical quality control and research infrastructure" (Source: www.verifiedmarketreports.com). A third estimate from IndexBox forecasts the global dissolution-testing equipment market growing at a more conservative "approximately 4.8%" CAGR

through 2035 (Source: www.indexbox.io) and identifies pharmaceutical quality control as "the largest end-use segment for dissolution testers" (Source: www.indexbox.io). This 4.8 to 8.12 percent spread across analyst firms illustrates the inherent imprecision of market-sizing forecasts, and readers should treat any single figure as directional rather than definitive.

The downstream economic impact of the generics system this testing infrastructure supports is substantial, though exact figures vary by source. The Association for Accessible Medicines (AAM), an industry trade association, and the IQVIA Institute estimated that generic and biosimilar medicines saved the U.S. healthcare system **$467 billion in 2024**, up from $445 billion in 2023 (Source: accessiblemeds.org). Their report also states that generics "comprised 90% of all prescriptions filled, but only 12% of the total" prescription drug spending (Source: accessiblemeds.org). DrugPatentWatch offers a broadly consistent estimate for an earlier year, reporting "$408 billion in savings for the U.S. healthcare system" in 2022 while generics accounted for "roughly 91%" of prescriptions filled (Source: www.drugpatentwatch.com) (Source: www.drugpatentwatch.com), an asymmetry between volume and spend that the dissolution and bioequivalence framework exists to make possible: without a credible, low-cost substitute for full clinical trials on every generic candidate, that volume of medicine could not reach patients on comparable timelines.

Against this backdrop, the Tufts Center for the Study of Drug Development's widely cited (though separately scoped) estimate that developing and winning marketing approval for a new drug costs approximately **$2.6 billion** in 2013 dollars (Source: contractpharma.com) helps contextualize why the generics pathway, anchored in dissolution testing and BCS-based biowaivers rather than de novo trials, exists as a distinct, far less expensive regulatory track for products whose reference molecule has already been proven safe and effective.

# Case Studies and Real-World Examples

## Budeprion XL 300 mg: A Strength-Extrapolation Bioequivalence Failure

In December 2006, FDA approved a generic 300 mg extended-release bupropion product, Budeprion XL, manufactured by Impax and marketed by Teva, as therapeutically equivalent to GlaxoSmithKline's brand product Wellbutrin XL 300 mg (Source: web.archive.org). Critically, the original approval's bioequivalence data came not from a direct study of the 300 mg strength, but from extrapolation, since "the bioequivalence studies were performed using the 150 mg strength" and biowaiver logic was applied to justify the higher strength (Source: web.archive.org).

Years of patient and physician reports of reduced efficacy at the 300 mg strength prompted FDA to commission its own direct crossover bioequivalence study. The results, announced in October 2012, confirmed a pharmacokinetic basis: FDA determined the generic "tablets fail to release bupropion into the blood at the same rate" as the brand (Source: web.archive.org), and "FDA has changed the therapeutic equivalence rating for this product" in the Orange Book, withdrawing equivalence for the 300 mg strength specifically while the directly tested 150 mg strength remained unaffected (Source: web.archive.org). This episode became a widely cited case for why strength-to-strength extrapolation, rather than direct testing at every marketed strength, carries real clinical risk.

## Generic Concerta (Methylphenidate Extended-Release): FDA Changes Equivalence Rating and Proposes ANDA Withdrawal

A second, related episode involved generic Concerta (methylphenidate hydrochloride extended-release), used to treat attention-deficit/hyperactivity disorder. In November 2014, FDA changed the therapeutic equivalence rating for products from Mallinckrodt and Kudco, announcing "the FDA has changed the therapeutic equivalence (TE) rating for the Mallinckrodt and Kudco products" from AB (equivalent) to BX (not yet demonstrated) (Source: www.fda.gov). The action was grounded partly in the agency's own laboratory work, since "FDA laboratory tests of products manufactured by Mallinckrodt and Kudco have raised concerns" (Source: www.fda.gov), and by October 2016 FDA moved to withdraw ANDA approval outright, stating the firms "have failed to demonstrate that their products provide the same therapeutic effect" (Source: www.fda.gov). Because Concerta relies on an osmotic, controlled-release mechanism, this case illustrates limits in then-current bioequivalence approaches for complex modified-release products. FDA states that the sponsors' original data met the approval standards in force at the time; subsequent adverse-event reports, re-examination of the data, and FDA laboratory testing prompted re-evaluation.

## Aligning BCS Biowaiver Frameworks: ICH M9 and WHO’s Separate Guideline

Unlike the two cases above, the multi-year process of finalizing and adopting **ICH M9** represents a regulatory success story of harmonization reducing, rather than exposing, cross-region testing risk. As detailed earlier, ICH's M9 guideline was adopted at Step 4 by the ICH Assembly's regulatory members on 20 November 2019 (Source: database.ich.org), became legally effective in the EU on 30 July 2020 (Source:

www.ema.europa.eu), and was formally finalized by FDA in May 2021 (Source: www.federalregister.gov); WHO's 2024 update closed the loop for prequalification-track products (Source: cdn.who.int). This case demonstrates the practical value of closer alignment: a sponsor developing a BCS Class 3 generic may be able to use a more consistent excipient-comparability and dissolution strategy across FDA, EMA, and WHO prequalification submissions. Each application remains subject to the relevant authority's separate requirements and review.

### Metformin: A Documented BCS Class 3 Biowaiver Candidate

**Metformin hydrochloride**, the first-line oral therapy for type 2 diabetes, is a well-documented example of a BCS Class 3 drug substance now eligible for biowaiver treatment under the harmonized framework. A peer-reviewed biowaiver monograph published in the Journal of Pharmaceutical Sciences classifies metformin as Class 3 because it is "highly soluble, but only 50% of an orally administered dose is absorbed" (Source: pubmed.ncbi.nlm.nih.gov), placing it squarely in the high-solubility, low-permeability quadrant despite its excellent aqueous solubility. Under the Class 3 biowaiver framework described earlier, the same monograph confirms that a metformin biowaiver requires "in vitro dissolution from both [products to] be very rapid (i.e. at least 85%" dissolved within the specified short time window) (Source: pubmed.ncbi.nlm.nih.gov), directly applying the ICH M9 standard to a specific, high-volume generic molecule.

### SUPAC-MR and Ibuprofen: When Biowaiver Logic Extends Manufacturing Flexibility, and When It Proves Too Strict

Two contrasting cases illustrate the outer boundaries of the biowaiver framework. On the permissive side, FDA's SUPAC-MR framework allows an in vivo bioequivalence "study [to] be waived in the presence of an established in vitro/in vivo correlation" (Source: www.fda.gov) for high-risk, Level 3 post-approval manufacturing changes, meaning a manufacturer that has invested in developing and validating a Level A IVIVC model (such as the metoprolol case described earlier) can move a manufacturing site or adjust certain formulation variables across a product's lifecycle using dissolution data alone, avoiding a new clinical study for each qualifying change.

On the restrictive side, not every documented case shows the biowaiver framework being too permissive. A 2011 peer-reviewed study applying the WHO/FIP BCS-based biowaiver procedure to two multisource ibuprofen products that had already been shown clinically bioequivalent in a real in vivo study found that the same in vitro procedure nonetheless flagged them as non-similar: "two in vivo bioequivalent tablets were declared bioinequivalent by this procedure, indicating that [the] procedure seems to be over-discriminatory" (Source: pmc.ncbi.nlm.nih.gov). Because ibuprofen is independently classified as BCS Class II (Source: pmc.ncbi.nlm.nih.gov), it would not qualify for a biowaiver under current FDA, EMA, or ICH M9 criteria in any case, but the finding illustrates a structurally important point that regulators continue to study: in vitro dissolution similarity criteria can, in some circumstances, be stricter than what clinical pharmacokinetic data show is actually necessary for interchangeability.

## Implications and Future Directions

The trajectory of dissolution and bioequivalence regulation over the past decade points toward continued **international alignment**. ICH M9 was implemented in the EU in 2020 and by FDA in 2021, while WHO issued a separate 2024 guideline aligned with M9 principles. PMDA and Health Canada maintain their own frameworks. These developments can reduce duplicated work, but future applications remain subject to each authority's requirements.

At the same time, the Budeprion XL and generic Concerta cases show the framework's biggest residual risk sits not at the level of the f2 mathematics itself, well-validated when its preconditions are met, but at the level of **extrapolation and complex release mechanisms**: applying bioequivalence conclusions from one strength or a simplified model to a different strength or delivery system without direct testing. Regulators appear to have internalized this through more granular, molecule-specific PSGs, a shift that also responds to the "Procrustean" criticism leveled at earlier one-size-fits-all guidelines discussed above.

The ongoing academic critique of f2 itself, from the 1998 bootstrap paper through the 2025 Pharmaceutical Research decision-tree analysis, also suggests the statistical toolkit for dissolution comparison is likely to keep evolving rather than remaining fixed at the 1996 Moore-Flanner formula (Source: pubmed.ncbi.nlm.nih.gov). The ibuprofen over-discrimination finding, and the 2007 review questioning where exactly the BCS permeability boundary should sit (Source: pubmed.ncbi.nlm.nih.gov), point toward continued refinement of exactly where BCS class boundaries and biowaiver dissolution thresholds should be drawn, balancing the risk of approving a non-equivalent product against the risk of needlessly blocking equivalent, lower-cost generics from reaching patients. FDA's own May 2026 guidance finalization suggests this refinement is an active, ongoing process rather than a settled one (Source: www.raps.org).

Finally, the data infrastructure supporting this entire evidentiary chain, laboratory information management systems, electronic batch records, and regulatory submission platforms, is itself under active transformation as pharmaceutical and life-sciences organizations adopt AI-assisted quality and regulatory tooling. Consultancies operating in this space observe that regulatory compliance increasingly functions as a systems-design requirement built into enterprise software from the start, rather than a downstream audit exercise (Source: intuitionlabs.ai). As dissolution and bioequivalence data volumes grow alongside expanding PSG coverage and more complex generic products, the traceability and auditability of that underlying data infrastructure is likely to become as consequential to successful biowaiver and BE strategy as the underlying pharmaceutical science itself.

## Frequently Asked Questions (FAQs)

**What is the f2 similarity factor in dissolution testing?** The f2 similarity factor is a model-independent statistic that compares two dissolution profiles across multiple time points and produces a single value between 0 and 100 (Source: dissolutiontech.com). When the applicable conditions are met, a value of **50 or greater** indicates similar dissolution profiles; it does not by itself establish bioequivalence or product interchangeability (Source: www.fda.gov).

**What are the USP dissolution apparatus types?** USP <711> describes four dissolution apparatuses: Apparatus 1 (rotating basket), Apparatus 2 (paddle, used in about 70% of methods) (Source: pmc.ncbi.nlm.nih.gov), Apparatus 3 (reciprocating cylinder), and Apparatus 4 (flow-through cell) (Source: pmc.ncbi.nlm.nih.gov). Apparatuses 5, 6, and 7 are specialized drug-release apparatuses, used primarily for transdermal systems and other specialized dosage forms; Table 1 distinguishes them from the USP <711> apparatuses.

**What are the biowaiver requirements under FDA guidance?** FDA permits BCS-based biowaivers for Class 1 (high solubility, high permeability) and, since 2017 and reaffirmed under the harmonized 2021 M9-based guidance, Class 3 (high solubility, low permeability) drug substances, provided the formulation demonstrates rapid or very rapid dissolution and meets excipient-comparability requirements (Source: www.federalregister.gov). Narrow therapeutic index drugs are categorically excluded (Source: database.ich.org).

**What is in vitro in vivo correlation (IVIVC) and how does it relate to bioequivalence?** IVIVC is a predictive model linking in vitro dissolution data to in vivo pharmacokinetic outcomes, with Level A correlations (point-to-point) being the most common and most regulatorily useful type (Source: www.fda.gov). A validated Level A IVIVC, such as the metoprolol tartrate case discussed in this report, can substitute for a new in vivo bioequivalence study when qualifying post-approval manufacturing changes occur (Source: pubmed.ncbi.nlm.nih.gov).

**How is dissolution media selected?** Media selection balances physiological realism (pH range, biorelevant FaSSIF/FeSSIF/FaSSGF media) against reproducibility and sink conditions, generally requiring a medium volume holding at least three times the API's saturated solubility, with surfactants such as SLS added for poorly soluble drugs (Source: pmc.ncbi.nlm.nih.gov).

**What is the Biopharmaceutics Classification System (BCS)?** BCS is a framework, proposed by Amidon and colleagues in 1995, that classifies drug substances into four classes based on aqueous solubility and intestinal permeability, used to determine biowaiver eligibility and guide formulation strategy (Source: pubmed.ncbi.nlm.nih.gov).

**How do I calculate the f2 similarity factor, and are there known limitations?** Using the mean percent dissolved values at each sampling time, calculate $f_2 = 50 \log_{10}{[1 + (1/n)\sum_{t=1}^{n}(R(t)-T(t)^2]^{-0.5} \times 100}$, where **n** is the number of time points and **R(t)** and **T(t)** are the mean percent dissolved for the reference and test products at time *t*. The calculation requires at least three non-zero time points and at least 12 dosage units per product (Source: www.fda.gov). Peer-reviewed research has shown the resulting estimate is statistically "biased and conservative" and highly sensitive to variability, which is why bootstrap and other alternative statistical approaches exist for highly variable dissolution data (Source: pubmed.ncbi.nlm.nih.gov).

**What is the study design used for generic drug bioequivalence?** For many oral products, the usual design is a randomized two-treatment, two-period, two-sequence crossover study, typically in healthy volunteers. FDA allows scientifically justified alternatives, including parallel designs when crossover is impractical. For unscaled average bioequivalence, the 90% confidence interval for AUC and Cmax ratios is generally evaluated against 80.00% to 125.00%, a standard applied consistently by FDA and WHO (Source: www.fda.gov) (Source: www.who.int).

## Conclusion

Dissolution testing and bioequivalence evaluation together constitute the scientific and regulatory infrastructure that makes low-cost, interchangeable generic medicines possible at scale. The f2 similarity factor gives regulators a standardized, mathematically transparent way to compare dissolution profiles, while the Biopharmaceutics Classification System and its harmonized ICH M9 biowaiver pathway determine when in vitro data alone can substitute for an expensive clinical bioequivalence study. For many molecules that cannot qualify for a biowaiver, a two-way crossover study using the

80.00 to 125.00 percent confidence-interval standard for unscaled average bioequivalence remains a common approach; product-specific guidance and special cases can call for other designs or analyses. In vitro in vivo correlation models can extend this logic across a product's post-approval lifecycle.

This framework is neither purely theoretical nor immune to failure, and it cuts in both directions. The Budeprion XL case shows the risk of strength extrapolation, while the generic Concerta case shows limits in then-current bioequivalence approaches for a complex modified-release product; the ibuprofen over-discrimination finding documents the opposite failure mode. In each case, regulators and researchers responded by refining rather than abandoning the framework: tightening extrapolation rules, re-evaluating evidence using updated approaches and laboratory testing where appropriate, and continuing to publish statistical critiques of f2 more than two decades after its adoption. ICH M9 was adopted by ICH in 2019, became legally effective in the EU in 2020, and was finalized as FDA guidance in 2021. WHO issued a separate BCS-based biowaiver guideline in 2024 that aligns with M9 principles; PMDA and Health Canada maintain separately documented frameworks. These developments support greater alignment, but applications remain subject to each authority's requirements.

For life-sciences organizations, the practical takeaway is that dissolution testing, f2 analysis, BCS classification, and IVIVC modeling function as a single interconnected evidentiary chain rather than isolated technical exercises. Getting BCS classification right early, designing discriminating dissolution methods, and maintaining rigorous, traceable documentation of excipient comparability and manufacturing consistency are what ultimately determine whether a biowaiver strategy withstands regulatory scrutiny years after initial approval. As generic and biosimilar medicines continue to account for roughly 90 percent of U.S. prescription volume while delivering hundreds of billions of dollars in annual healthcare savings, the technical rigor of the dissolution and bioequivalence framework described in this report remains a foundational, if often underappreciated, pillar of accessible modern medicine.

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Tags: dissolution testing, bioequivalence, f2 similarity factor, biowaiver, biopharmaceutics classification system, bcs, ivivc, usp apparatus, generic drugs, fda guidance

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