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QUALITY EVALUATION OF MARKETING BRANDS OF CIPROFLOXACIN TABLETS: IN VITRO EQUIVALENCE

MAAIKE DIJKSTRA^{1*}, MATHILDE DELACROIX², ELENA VITALE³

Affiliation

¹Department of Pharmaceutical Analysis, Twente Institute of Pharmaceutical Technology, Enschede, Netherlands

²Department of Analytical Chemistry, Jura Centre for Medicinal Chemistry, Lons-le-Saunier, France

³Department of Pharmaceutical Analysis, Cilento Institute of Pharmaceutical Sciences, Salerno, Italy

*Corresponding author: Maaïke Dijkstra, m.dijkstra@tipt.nl

ORCID iD: Maaïke Dijkstra 0000-0001-2680-7978; Mathilde Delacroix 0000-0001-0558-4517; Elena Vitale 0000-0001-2036-1960

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1. INTRODUCTION

Ciprofloxacin is among the most widely used oral antibiotics in the world. It is prescribed for urinary tract, gastrointestinal, respiratory, bone and sexually transmitted infections, and it features on essential medicines lists in many countries. A fluoroquinolone with broad activity, it acts by inhibiting bacterial DNA gyrase and topoisomerase IV [1, 2, 3]. Because the drug is old, off-patent and cheap, dozens of brands are sold in some markets, often at a wide spread of prices. For the physician and the patient those brands are expected to be interchangeable. Whether they truly are depends on the quality of

Abstract

Ciprofloxacin tablets are sold under many brand names, and clinicians assume that they can be interchanged. This narrative review examines how the published literature judges that assumption in vitro. It covers the biopharmaceutical properties of the drug, pharmacopoeial and physical tests, dissolution profile comparison and the similarity factor, biowaiver and correlation concepts, and evidence on substandard antimicrobials. It reports no new laboratory data and names no brand. The literature supports multi-medium dissolution testing with validated assays and several batches per brand, while showing that many evaluations rely on single-medium, single-batch designs. In vitro similarity is consistent with, but does not prove, bioequivalence, and reporting standards need to improve.

manufacture and on whether each product releases its drug in a way that delivers comparable exposure, which is the question that in vitro equivalence testing sets out to

answer.

Quality matters more for an antibiotic than for many other drugs. A tablet that releases drug slowly or incompletely may give sub-inhibitory concentrations, and sub-inhibitory exposure favours the selection of resistant organisms, which with the fluoroquinolones has become a serious clinical problem [3, 4]. Failure of therapy may then be attributed to the organism or to the patient when the product was the weak link. For these reasons regulators and pharmacopoeias treat dissolution as the main in vitro surrogate for the performance of oral solid forms, and comparing the dissolution profile of a multisource product with that of a reference has become the routine first step in judging whether brands can be regarded as equivalent [5, 6, 7].

This review addresses the evidence behind in vitro equivalence assessment of ciprofloxacin tablets as it appears in the literature. It does not present new laboratory data, and it does not identify or rank any marketed brand. The topics are the biopharmaceutical properties that make the drug an interesting test case, the pharmacopoeial and non-compendial tests applied to tablets, the statistics used to compare dissolution profiles, the regulatory frameworks for waiving in vivo studies, and the evidence on substandard antimicrobial products. Practical methodological points are given where the literature supports them, because small differences in apparatus, medium or sampling can decide whether a product appears to pass or fail [6, 8, 9].

Terms need to be fixed at the outset. Pharmaceutical equivalence means the same active substance, strength and dosage form meeting comparable standards; bioequivalence means that exposure in the body falls within agreed limits of the reference; and in vitro equivalence usually means similar dissolution profiles under defined conditions [10, 11]. The last is a surrogate and the first two are the goal. Only a well-designed human study establishes bioequivalence, but in vitro testing is cheap enough to be applied to many batches and brands. That is why it is the tool of choice for quality surveys and post-marketing monitoring, and why its limits deserve to be

understood by anyone who reads the results of such surveys.

Interest in this topic is long-standing in countries where many brands compete. In such markets prescribing is often by brand name, regulators may lack the capacity to inspect every manufacturing site, and pharmacists substitute according to price and availability. A quality evaluation that compares marketed tablets with the innovator or with pharmacopoeial standards is a practical way to check whether the system is delivering what it promises [12, 13]. Published evaluations of this kind exist for many antibiotics and are typically small, using a limited number of brands and batches. Their value is real but local, and the conclusions of one survey should not be carried over to another country or period.

2. CIPROFLOXACIN BIOPHARMACEUTICS

The pharmacology of ciprofloxacin explains why exposure matters. The drug is bactericidal, its killing is concentration-dependent, and clinical and microbiological outcomes are related to the ratio of the area under the plasma concentration–time curve to the minimum inhibitory concentration of the pathogen [1, 2]. Resistance arises mainly through mutations in the target enzymes and through efflux, and exposure that is too low favours the stepwise accumulation of such mutations [3, 14]. Dosing in practice is based on the assumption that a tablet from any approved source delivers the expected exposure. If a brand delivers materially less, the margin for the organism's own variability in susceptibility narrows, and the product may fail where another would succeed [4, 14].

Ciprofloxacin is a zwitterion with a carboxylic acid group and a basic piperazinyl nitrogen, so its charge and solubility change with pH. Solubility is lowest around neutral pH, where the molecule is closest to its isoelectric point, and rises substantially in acidic media, which is why the hydrochloride salt is used in most marketed tablets [15, 16]. In the stomach the drug dissolves readily. As it moves into the small intestine, the rising pH may allow precipitation of the free base, so

dissolution testing at pH 1.2 alone does not tell the whole story [15, 17]. Multi-pH testing is therefore sensible for this drug, and the point has been made repeatedly in biopharmaceutical assessments of the molecule.

After oral dosing ciprofloxacin is absorbed rapidly, reaching peak plasma concentrations within about one to two hours, and absolute bioavailability is typically reported as roughly 70 per cent, with an elimination half-life of around four hours [1, 2]. Absorption occurs mainly in the proximal small intestine. Food delays absorption without greatly reducing its extent. Because bioavailability is incomplete rather than near-total, small formulation effects on release could show up as differences in exposure, and this partly explains the reluctance of regulators to treat the drug as a simple candidate for biowaivers [2, 17]. The relatively short half-life also means that peak and trough concentrations are sensitive to the rate at which each dose is absorbed.

The classification of ciprofloxacin in the biopharmaceutics system has varied between analyses, reflecting borderline solubility across the physiological pH range and moderate permeability [17, 18]. The biowaiver monograph for the hydrochloride reviewed the evidence and advised caution about waiving in vivo studies. Dose and solubility interact: a 500 mg tablet needs a large volume of fluid to dissolve if solubility is low, so the dose-to-solubility ratio can exceed the volume of fluid available at intestinal pH [17, 19]. The classification framework introduced by Amidon and colleagues, and later reviewed for biowaiver purposes, links such properties to the relationship between dissolution and absorption, and it is the reason dissolution in several pH media carries information that a single test cannot [5, 19].

Interactions with polyvalent cations are the best-known formulation-related concern. Ciprofloxacin chelates aluminium, magnesium, calcium and iron, and co-administration with antacids lowers bioavailability by amounts that depend on the cation and on timing [20, 21]. This matters for product quality because excipients containing

such ions, for example calcium or magnesium salts used as fillers or lubricants, could in principle form complexes in the dissolution medium or in the gut. The effect of the small quantities present in a typical tablet is generally considered limited, but the possibility is one reason why in vitro studies of brands should look at the excipient declaration as well as the label claim [20, 22].

Salt form is a further variable between products. Most ciprofloxacin tablets use the hydrochloride monohydrate, but the free base and other salts exist, and a change in salt can alter dissolution rate and sometimes dose equivalence when strength is expressed as the base [16, 23]. Verbeeck and colleagues argued that products containing different salts of the same moiety should be assessed case by case, rather than assumed to be interchangeable. For brand surveys the lesson is practical: label claims should be read carefully to see whether the strength refers to the base or to the salt, since a labelled 500 mg may correspond to different amounts of the active moiety.

3. PHARMACOPOEIAL AND PHYSICAL TESTS

A quality evaluation of tablets starts with simple physical tests. Weight variation, thickness, hardness, friability and disintegration are quick and cheap, and they reveal gross manufacturing problems such as poor compression or inadequate binding [22, 24]. A friability of less than one per cent is the usual benchmark, and disintegration is expected to be complete within the pharmacopoeial limit, commonly in the region of half an hour for film-coated tablets. These tests are not a measure of efficacy. A tablet can pass every one of them and still dissolve poorly, or fail one and perform adequately in a patient. Their value lies in flagging batches for further testing and in identifying gross defects that can be corrected at the factory.

Manufacturing choices behind the physical attributes also deserve notice. Compression force, granule properties, the type and level of disintegrant and the nature of the film coat all influence how fast a tablet breaks up and how fast drug becomes available [22]. Hard tablets

made at high compression force may disintegrate slowly, while an over-lubricated blend with a hydrophobic lubricant can slow wetting. Two brands with identical labels may therefore differ in dissolution because of process decisions invisible to the buyer. This is part of the reason that identical active content does not guarantee identical performance, and it is an argument for testing release and not merely content.

Assay and content uniformity address whether the tablet contains what the label claims. Pharmacopoeial monographs set assay limits generally in the region of 90 to 110 per cent of the labelled amount for ciprofloxacin tablets, and uniformity of dosage units is assessed by weight variation or content uniformity depending on strength [24]. Methods include ultraviolet spectrophotometry in dilute acid, with absorbance near 275 to 280 nm, and high-performance liquid chromatography (HPLC) on a C18 column with an acidic mobile phase [9, 24]. Chromatography is preferred when degradation products or excipient interference are possible, because ultraviolet methods cannot distinguish the parent drug from other absorbing species.

Any analytical method used in a comparison has to be validated. Validation guidance defines the characteristics to be demonstrated: specificity, linearity, range, accuracy, precision, detection and quantitation limits where relevant, and robustness [9]. For dissolution samples the matrix is a buffer or dilute acid, and filtration, sample stability and sink conditions deserve attention. Filters can adsorb drug, particularly at low concentrations, and ciprofloxacin in solution is photosensitive, so protection from light is prudent. Where results from different laboratories or surveys are compared, differences in the quality of validation may account for more of the apparent variation between brands than the products themselves.

Compendial dissolution testing for immediate-release tablets is a single-point test intended to confirm batch quality. Monograph conditions for ciprofloxacin tablets have been described using dilute hydrochloric acid, a paddle apparatus at moderate speed and a specified minimum percentage dissolved at a

fixed time of about half an hour [24]. A product that meets the monograph is considered to be of acceptable quality, but passing a single-point test does not show that two brands behave alike at other times and pH values [5, 6]. Hence the use of profile comparisons at several time points and in several media when brands are compared with one another or with an innovator.

Practical details of the monograph test deserve attention because they decide whether a result can be trusted. The medium has to be deaerated, the temperature held within a narrow band, and the apparatus checked for vibration and shaft wobble, since small mechanical faults change the hydrodynamics at the tablet surface [24]. Ciprofloxacin tablets that are film-coated may show a short lag before drug appears, and a sampling time placed too early can make a sound product look slow. Analysts therefore benefit from reading the whole profile rather than only the pharmacopoeial point. Coating polymer, thickness and curing also affect the lag, which is one reason why identical active content does not guarantee identical early release [22]. Where a brand narrowly misses the monograph limit, repeating the test on additional units from the same pack, with the apparatus qualified, is a sensible step before any conclusion is drawn about the product itself.

4. DISSOLUTION PROFILE COMPARISON

Dissolution profile comparison has become the standard in vitro tool for judging multisource products, and the main methods and conditions reported in the literature are collected in table 1. Regulators recommend using at least twelve units of each product, sampling at enough time points to define the profile, and testing in media across the physiological pH range, typically 1.2, 4.5 and 6.8, at 37 °C [6, 7]. The paddle apparatus at 50 rpm in 900 mL is the common choice for tablets, with 75 rpm sometimes used if coning occurs. The reference should be the innovator or the comparator named by the regulator. Choice of medium is not a technical detail, since it determines which differences will be detected.

Table 1: Methods and concepts used in published in vitro equivalence assessment of ciprofloxacin tablets

Method or concept	Reported feature or criterion	Ref.
Similarity factor f2 Dissolution profile comparison	Values from 50 to 100 indicate similarity, subject to conditions on variability and sampling.	[8, 25]
Difference factor f1	Percentage difference between profiles, acceptable between 0 and 15.	[25]
Multi-pH dissolution Media at pH 1.2, 4.5 and 6.8	Recommended to compare products across the physiological pH range.	[7, 26]
Compendial single-point test	Minimum percentage dissolved at a fixed time in dilute acid.	[24]
Analytical method validation	Specificity, linearity, accuracy, precision and robustness are demonstrated.	[9]
BCS-based biowaiver	Limited to suitable classes with rapid dissolution; caution advised for ciprofloxacin.	[17, 18, 26]
Human bioequivalence study	Ratio of AUC and $C_{\max}$ with 90% interval within 80 to 125 per cent.	[10, 11, 27]
Kinetic model fitting Weibull, first-order, Korsmeyer–Peppas	Parameters compared; fit quality judged by adjusted R^2 or information criteria.	[28, 29, 30]
Noyes–Whitney relation	Dissolution rate proportional to surface area and concentration gradient.	[31, 32]
Polyvalent cation interaction	Antacids containing aluminium or calcium reduce ciprofloxacin bioavailability.	[20, 21]
Salt form and excipients	Different salts or excipients may alter dissolution and need case-by-case assessment.	[16, 23]

Survey design comes before any test is run. A fair comparison needs the reference product to be purchased in the same market, within its shelf life, and brands to be sampled from several outlets, preferably including more than one batch [12]. Storage and transport conditions need recording. The number of brands tested is often dictated by availability, and ignoring batch-to-batch variation can turn

a chance difference into an apparent quality problem. Studies that report only one batch should say so, and should word their conclusions accordingly, since the sample can describe the tablets that were tested and little else [12, 13].

The similarity factor, f2, is the most widely used statistic. It is a logarithmic transformation of the mean squared difference between the percentages dissolved for reference and test products across time points, and values between 50 and 100 are taken to indicate similarity, corresponding to an average difference of no more than about 10 per cent at each point [6, 8, 25]. The difference factor, f1, expresses the percentage difference and is acceptable between 0 and 15. Use of the formulas is subject to conditions: only one measurement after 85 per cent dissolution, a minimum of three time points, and low variability, with a coefficient of variation not above 20 per cent at early points and 10 per cent later [7, 25]. Where both products dissolve very rapidly, 85 per cent or more in 15 minutes, profiles are considered similar without calculation [7].

Critics have pointed out weaknesses in f2. The statistic is a point estimate, takes no account of variability except through the rule of thumb on coefficients of variation, and can mislead when profiles cross or when few points are available [8, 28]. Liu and colleagues examined the statistical properties of f2 and showed that the value depends on the number and timing of sampling points, and they discussed approaches that account for variability. Bootstrap methods, multivariate confidence regions based on the Mahalanobis distance and model-based comparisons have all been proposed [8, 28, 30]. Regulatory practice remains largely tied to f2 for the sake of simplicity, but a careful report states the variability and the points used.

Model-dependent approaches describe each profile with an equation and compare the fitted parameters. Commonly used models are zero-order, first-order, Higuchi, Hixson–Crowell, Korsmeyer–Peppas and Weibull, and the choice is judged by goodness of fit such as adjusted R^2 or the Akaike criterion [28, 29, 31]. The

Noyes–Whitney relation underlies many of them, expressing the dissolution rate as proportional to surface area and to the concentration gradient [32]. For an immediate-release tablet the Weibull function and first-order models usually fit well, while the Higuchi and Korsmeyer–Peppas models belong more naturally to matrix systems. The Weibull function, brought into dissolution work by Langenbucher, describes cumulative release with a scale and a shape parameter, which is a reminder that a good fit alone should not be read as proof of any particular mechanism [30]. A good fit shows that a model describes the data, not that the mechanism is understood.

Dissolution efficiency, mean dissolution time and the time for 50 or 85 per cent release are simpler summary measures with the advantage of transparency. They let readers see directly whether a brand is slower than the reference, which a single f_2 number may conceal [5, 28]. Presenting them alongside the profiles, with standard deviations, helps interpretation. The measures can also be compared statistically using analysis of variance with post-hoc tests, provided the assumptions are checked. The choice of method should be stated before testing, because selecting the statistic after seeing the data invites bias, and surveys of brand quality are as vulnerable to this as clinical studies [8, 11]. The distribution of the methods in table 1 by group is given in fig. 1.

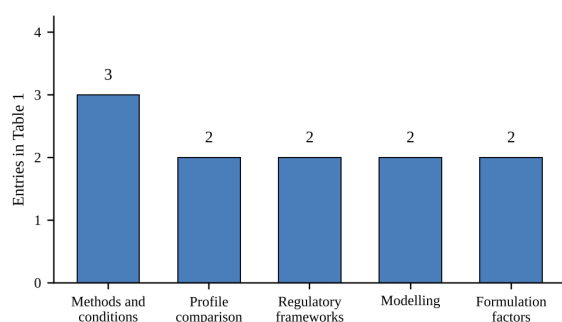


Fig. 1: Number of entries in table 1 by group

Sampling and apparatus details can swing a result. Paddle speed, vessel centring, degassing of the medium, the position of the sampling probe and the choice of sinker affect hydrodynamics, and a tablet that coned at the bottom of the vessel may seem slower than it is [6, 22]. Sampling volumes should be replaced or corrected for. Automated systems

reduce operator effects, but they need calibration, and apparatus suitability tests with calibrator tablets remain part of good practice. When brands are compared in a survey, running them in the same session with the same batch of medium and the same analyst reduces noise that would otherwise be mistaken for product differences.

5. BIOWAIVERS AND IN VIVO CORRELATION

The case for waiving in vivo studies rests on the Biopharmaceutics Classification System, which sorts drugs by solubility and permeability [19, 26]. Regulatory guidance allows biowaivers for rapidly dissolving products containing class I drugs and, under WHO and EMA rules, extends the option to some class III substances with very rapid dissolution [7, 26]. For ciprofloxacin, the biowaiver monograph and subsequent commentary advise caution, because borderline solubility and the interaction potential with excipients weaken the argument that dissolution alone ensures bioequivalence [17, 18, 33]. Where a regulator accepts a waiver, it will usually demand similar dissolution in three media. Where it does not, a human study is required.

In vitro–in vivo correlation is a related concept but a more demanding one. A level A correlation links the whole dissolution profile to the plasma concentration–time curve, and it could allow dissolution to stand in for in vivo studies after certain changes [5, 33]. For drugs such as ciprofloxacin, with rapid absorption and moderate bioavailability, developing correlations is difficult because dissolution is unlikely to be the rate-limiting step once the tablet has disintegrated. Dissolution testing in biorelevant media can improve prediction, although this has seldom been applied to brand surveys [5, 33]. The sober conclusion is that dissolution similarity is consistent with bioequivalence and dissimilarity is a warning, but neither is a proof.

Human bioequivalence studies remain the reference standard. A typical design is a randomised, two-period crossover in healthy volunteers, usually fasting, in which the 90% confidence interval for the ratio of geometric

means of the area under the curve (AUC) and of peak concentration ($C_{\max}$) must lie between 80 and 125 per cent [10, 11]. A review of generic bioequivalence studies by the US regulator reported that generics differed little from innovators on average, which supports the premise that approved generics are broadly interchangeable [27]. That finding applies to products that went through approval. Many brands sold in markets with limited oversight never did, and in vitro surveys of such products are less reassuring [12, 13].

Statistics for bioequivalence and for dissolution are not interchangeable, and confusion between them appears in the literature. Bioequivalence uses a confidence interval of a ratio and requires adequate numbers of subjects, whereas f_2 is a descriptive index of two mean profiles. A brand with an f_2 of 48 is not therefore inequivalent in vivo, nor is a brand with an f_2 of 60 guaranteed to be bioequivalent. Reports that call products bioequivalent on the strength of in vitro testing alone overstate what the method can show, and careful wording such as in vitro equivalent or similar dissolution is preferable [8, 11].

6. POOR-QUALITY MEDICINES

Concern about brand quality does not arise from nothing. Reviews of substandard and falsified antimicrobials describe products with too little active ingredient, the wrong ingredient, poor dissolution or unlabelled impurities, found in a range of countries and especially in regions with weak regulation [12, 13, 34]. Antibiotics appear in these reviews alongside antimalarials, and the problem is not confined to low-income settings, though it is more severe there. Definitions differ: substandard products fail specifications through poor manufacture or storage, whereas falsified ones are deliberately misrepresented. A dissolution failure in a brand survey is most likely substandard in this sense, and not falsified, unless identity testing says otherwise.

Surveys of antimalarial quality in Southeast Asia and sub-Saharan Africa found substantial proportions of samples failing chemical analysis in some studies, with

consequences that include treatment failure, toxicity and the selection of resistance [35]. Similar mechanisms apply to antibiotics. The worrying element is the dependence of a study's conclusion on sampling: surveys that buy from informal outlets find more problems than those that sample licensed pharmacies, and results that are positive in one location may not be repeated in another [34, 35]. Sampling plans, sample size and a statement of how products were purchased and stored are therefore essential in any report that characterises the quality of marketed brands.

Poor storage can cause degradation after the product leaves the factory. Heat and humidity speed hydrolysis and alter tablet hardness and dissolution, and these conditions are normal in many tropical pharmacies [13, 24]. A tablet that complied at release may therefore fail on the pharmacy shelf. Ciprofloxacin is photosensitive in solution but film-coated tablets are generally considered stable, so loss of potency from storage may be less likely than for some other antibiotics, yet physical changes such as moisture uptake can still occur [1, 24]. Reports should record batch numbers, manufacturing and expiry dates and storage conditions, and where possible compare more than one batch of each brand.

The public health stakes extend beyond the individual patient. Fluoroquinolone resistance among urinary and enteric pathogens has risen in many regions, and exposure to sub-therapeutic concentrations of a poorly performing product is one of several plausible contributors, alongside overuse and unregulated sale [3, 4, 14]. The relative importance of poor-quality products is hard to quantify, and it would be wrong to assign resistance trends to them without evidence. What can be said is that quality assurance is consistent with antimicrobial stewardship: a drug that is dispensed correctly but delivers less than the labelled dose weakens the effect of every other measure intended to preserve the usefulness of the class [12, 13].

Regulatory enforcement determines how often poor products reach patients. Countries with strong inspection and post-marketing surveillance find fewer failures, but even in them, recalls for dissolution failure or impurities happen. Quality systems depend on

good manufacturing practice, supplier qualification and batch release testing, all of which cost money and are harder to sustain where margins are thin [12, 13]. Procurement policy matters as well, since tenders that award contracts on price alone may drive down quality unless prequalification of suppliers is required. Independent laboratory surveys complement regulation but cannot replace it, because they test a few samples at one moment.

7. LIMITATIONS AND FUTURE DIRECTIONS

The limitations of the evidence on in vitro equivalence deserve plain statement. The majority of published brand evaluations study few brands, usually one batch each, in a single laboratory, so between-batch variability goes unmeasured [12, 13]. Many apply the f_2 statistic without checking its conditions, test in one medium only, or compare against a pharmacopoeial limit when an innovator reference was available. Some conflate pharmaceutical equivalence with bioequivalence in their conclusions. A pass in vitro tells the reader that tablets met a test, and a fail suggests investigation, but an individual finding rarely establishes more than that [6, 8].

Methodological improvements are available at low cost. Studies should test several batches per brand, use innovator reference products purchased in the same market, apply at least three pH media for comparison, report variability along with mean profiles, and describe the statistics before analysis [6, 7]. Using validated assays with stated specificity strengthens credibility [9]. Reporting dissolution efficiency and the time to 85 per cent dissolution as well as f_2 helps readers who want to judge clinical relevance. Where a product fails, confirmatory testing in a second laboratory and a report to the regulator are more useful than publication alone, because they allow a recall or an inspection to follow.

How findings are communicated also matters. A report that names a brand as substandard on the basis of one batch and one medium can damage a manufacturer unfairly and confuse prescribers, while a report that anonymises

everything gives regulators nothing to act on. A reasonable compromise is to share product identities with the regulator and the manufacturer for verification and to publish aggregate findings, with methods described in enough detail for repetition [12, 13]. Prescribers want a plain message: the brands tested met or did not meet a stated standard under stated conditions. Overstatement in either direction undermines trust in generic medicines as a whole [11, 27].

Future work could usefully link in vitro findings with in vivo ones. Physiologically based absorption models, using solubility, permeability and dissolution inputs, offer a way to predict whether a given difference in dissolution would translate into a difference in plasma concentration, and may allow risk-based decisions about which brands need human studies [5, 33]. Low-cost screening tools could extend surveillance to places without full laboratories, and publication of survey results in open databases would let regulators track trends over time. Ciprofloxacin remains a useful model drug for this work because it is widely used, inexpensive and sensitive enough to formulation for differences to be detectable [12, 17].

A word on terminology may help future authors. Several papers describe their results as quality control, quality evaluation or bioequivalence assessment interchangeably, although the three differ in scope. Quality control checks a batch against a specification; quality evaluation compares marketed products with each other and with a standard; bioequivalence assessment belongs to the regulatory approval process and needs human data [10, 11]. Titles and abstracts that say what was actually done, and conclusions that stay within it, make the literature easier to synthesise. A cautious phrase such as in vitro equivalence under the stated conditions costs nothing and avoids the impression of a regulatory ruling that the data cannot support [6, 8].

8. CONCLUSION

In vitro equivalence testing is a useful and inexpensive way to judge whether marketed ciprofloxacin brands are likely to behave

alike, provided that it is done carefully. The literature favours validated assays, several batches per brand, an innovator comparator, dissolution in at least three media and transparent statistics, with f2 supplemented by variability measures and model-based or summary comparisons [6, 7, 8, 28]. The drug's pH-dependent solubility and cation interactions make it a reasonable test case for this approach.

The limits are equally clear. Dissolution similarity is consistent with bioequivalence but does not prove it, many published brand evaluations use single batches and single media, and findings from one market do not generalise to another [12, 13, 27]. Better reporting, confirmation of failures and cooperation with regulators would make surveys more useful, and would help sustain confidence in affordable antibiotics, an aim that sits comfortably alongside the wider effort to protect the fluoroquinolones from resistance [3, 4].

9. ABBREVIATIONS

AUC-Area under the concentration–time curve, BCS-Biopharmaceutics Classification System, C_{max}-Peak plasma concentration, EMA-European Medicines Agency, f1-Difference factor, f2-Similarity factor, HPLC-High-performance liquid chromatography, WHO-World Health Organization

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

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Declared none

13. REFERENCES

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