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DISSOLUTION PROFILE COMPARISON OF GENERIC AND INNOVATOR LEVOTHYROXINE TABLETS

ELENI ZERVAS[1]*, GONCALO FIGUEIREDO[2], JOHANNA GRUNEWALD[3]

Affiliation

[1]Department of Quality Assurance, Macedonia Plain Institute of Pharmacy, Serres, Greece
[2]Department of Quality Assurance, Douro Valley Institute of Pharmaceutical Sciences, Vila Real, Portugal
[3]Department of Quality Assurance, Fichtelgebirge Centre for Drug Research, Hof, Germany

*Corresponding author: Eleni Zervas, e.zervas@mpip.gr
ORCID iD: Eleni Zervas 0000-0001-3251-5242; Goncalo Figueiredo 0000-0001-1397-1867; Johanna Grunewald 0000-0001-4730-6312

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Abstract

Levothyroxine tablets are among the most widely prescribed medicines, and because the drug has a narrow therapeutic index, small differences between generic and innovator products can matter to patients. This review summarises published evidence on comparing in vitro dissolution profiles of generic and innovator levothyroxine tablets. It covers formulation and stability issues, dissolution test design, model-independent and model-dependent comparison methods, the similarity factor f2 and its limits, regulatory expectations, and clinical bioequivalence findings. Dissolution comparison is useful but cannot replace in vivo evidence for this drug, and published product-level data are limited. The article is a narrative review and reports no new data.

1. INTRODUCTION

Few medicines are taken as faithfully, for as long, or by as many people as levothyroxine. Hypothyroidism is common, and replacement with synthetic thyroxine restores normal thyroid function in most patients who take it correctly [1, 2]. The dose is adjusted against the serum level of thyroid-stimulating hormone (TSH), and a change of a few tens of micrograms can move that level out of range. Thyroid specialists have therefore long been careful about switching between products, and the question of whether a generic tablet can safely replace the innovator product has been argued for decades [1, 3, 4].

The therapeutic approach has changed little in decades. Levothyroxine monotherapy remains the standard, although debate continues over combination treatment with triiodothyronine and over the persistence of symptoms in a

minority of patients despite normal TSH [2, 5]. Wiersinga described the shifts in thinking about replacement, including the emphasis on individualised dosing and on better delivery systems [5]. This leaves the tablet itself, and its reproducible quality, as the foundation on which any refinement of therapy is built, and it explains why product comparison is treated seriously. Any improvement in practice therefore has to start from the quality of the product in the bottle.

Dissolution testing sits at the centre of that argument in a practical way. It is the only performance test that every batch of every tablet must pass, and it is the laboratory measure that regulators and manufacturers use to judge whether a changed or a copy product behaves like the original [6, 7]. When two products release the drug in the same way in vitro, there is a reasonable presumption that they will behave similarly in the gut. For most drugs that presumption is strong enough to waive human studies in some situations, but for levothyroxine it is not accepted so readily [8].

This review looks at how dissolution profiles of generic and innovator levothyroxine tablets are compared, and at what the comparison can and cannot tell us. It deals first with the drug and its formulation, then with the dissolution test, the mathematical and statistical methods for comparing profiles, regulatory expectations, and the clinical bioequivalence studies that provide the in vivo benchmark. Findings are collected in table 1, and fig. 1 shows how the entries are distributed between themes [9, 10, 11]. The aim is to show where the evidence is strong, where it depends on assumption, and where a reader should look for further information before drawing a conclusion.

The article is a narrative review of published sources up to 2023 and reports no new data. No tablets were tested for this article, and no new profile or f2 value is presented. Examples of calculation are given only to explain how a method works. Product-level dissolution data for specific brands are scattered and often held by manufacturers or regulators, so the review concentrates on principles, study designs and the strengths and weaknesses of the methods rather than on a ranking of products [10, 12, 13]. Where a general method is described, its relevance to levothyroxine is explained so the reader can judge its fit.

Terminology can be confusing, so a short note may help. Innovator or reference product means the original approved brand, and generic means a later product approved by showing that it is pharmaceutically equivalent and bioequivalent to it. Dissolution profile means the percentage of drug released over a series of time points, and similarity and equivalence are not the same thing. A profile may be called similar by f2, while bioequivalence is a statement about blood concentrations in people [10]. Keeping the three concepts apart avoids much of the confusion in the debate about generic substitution, where an in vitro finding is sometimes quoted as if it settled a clinical question.

2. LEVOTHYROXINE AND ITS FORMULATION

Levothyroxine sodium is the synthetic sodium salt of L-thyroxine, and it is given orally once daily, usually in the morning on an empty stomach. It is absorbed mainly in the jejunum and ileum, with an oral bioavailability that is commonly given as roughly 60 to 80 percent, and it has a long half-life of about a week that smooths out the effect of a missed or late tablet [1, 14]. Absorption depends on the stomach and small intestine environment, and it is reduced by food, coffee, calcium and iron salts, and some acid-suppressing drugs [15, 16].

The drug has some unusual physicochemical features. The sodium salt is poorly soluble in water and its solubility varies with pH, and it adsorbs readily to surfaces. The Biopharmaceutics Classification System, which groups drugs by solubility and permeability, has been applied to levothyroxine with differing conclusions, and its assignment has been described as uncertain in the literature [17, 18]. This matters because the classification system is the basis for waiving clinical studies in other drugs, and an unclear class makes a dissolution-only approach harder to defend [8, 18]. Differences between laboratories in

the way solubility is measured add to the confusion.

Table 1: Methods and findings relevant to dissolution comparison of levothyroxine tablets

Topic	Reported feature or finding	Ref.
Narrow therapeutic index replacement therapy	Small dose changes shift TSH, so product consistency matters for stable control.	[1, 2, 4]
Excipient interaction stability	Moisture, heat and some excipients accelerate degradation; potency may fall during shelf life.	[19, 20]
Absorption factors gastric pH	Food, coffee, calcium, iron and acid suppression reduce absorption of tablets.	[15, 16, 21]
Dissolution medium discrimination	Medium and apparatus must separate acceptable from unacceptable products.	[6, 22, 23]
Single-point specification release testing	Confirms batch acceptance but not the shape of the release curve.	[24, 25]
Similarity factor f2 model-independent	Value of 50 or more indicates similarity; needs at least 12 units and variability limits.	[7, 10, 12]
Bootstrap and multivariate methods variability	Provide confidence limits and handle high variability where f2 is unreliable.	[10, 13, 26]
Model-dependent fitting Weibull and others	Parameters can be compared statistically but model choice is partly arbitrary.	[26, 27]
BCS biowaiver classification	Limited use for narrow therapeutic index drugs; levothyroxine class debated.	[8, 17, 18]
Bioequivalence study healthy volunteers	Brand and generic judged bioequivalent, but baseline correction and extrapolation debated.	[9, 28, 29]

Absorption of levothyroxine from the intestine is not instantaneous. Delayed intestinal absorption has been described in some patients, with the peak serum concentration appearing later than expected, and the extent of absorption varies with the state of the stomach and small bowel [30]. Conditions that raise gastric pH, including atrophic gastritis and Helicobacter pylori infection, increase the dose needed in some patients, and the dose requirement falls when the infection is treated [15, 31]. These observations point to dissolution in the stomach as one step that matters for the drug.

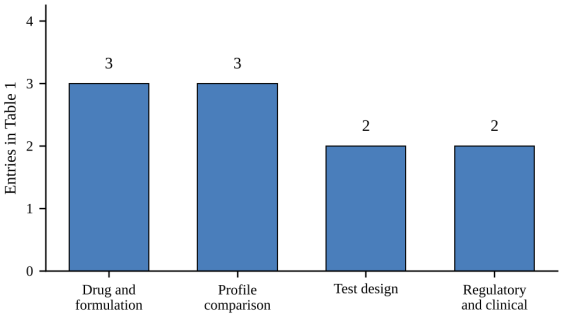


Fig. 1: Number of entries in table 1 by theme

Tablet formulation adds to the difficulty. A tablet may contain between 25 and 300 micrograms of drug in a mass of excipients that is thousands of times heavier, so content uniformity depends on very careful blending and on mixing the drug into the diluents evenly. The excipients are not inert in practice. Levothyroxine degrades in the presence of moisture, heat and light, and studies of its solid-state stability show that some common excipients accelerate decomposition, including carbohydrates that can react with the amino group of the drug [19, 20]. Segregation of the active ingredient during compression is another risk, so manufacturers pay close attention to blend uniformity and to the weight of each tablet.

These factors help to explain why products that look alike on paper behave differently. Reports on tablet instability and on differences between commercial products show that potency can fall over shelf life and that dissolution may change as tablets age, which can complicate the interpretation of a bioequivalence study and of a single in vitro comparison [19, 32]. Manufacturers have responded with different diluents, stabilisers and packaging, so that each brand has its own formulation strategy and the generic product usually differs from the innovator in several excipients [14, 19, 32].

Narrow therapeutic index is the label most often applied. Strictly it describes a drug for which small differences in dose or blood concentration lead to therapeutic failure or serious adverse effects. For levothyroxine the consequence of under-dosing is a return of hypothyroid symptoms, and of overdosing is

cardiac, bone and neuropsychiatric effect. These outcomes unfold slowly and are monitored by TSH, which is a sensitive marker, but they are what set the standard for control of product quality [1, 2, 4]. A narrow window has led some professional bodies to recommend a more cautious approach to product switching than for most other drugs.

3. DISSOLUTION TESTING FOR IMMEDIATE-RELEASE TABLETS

Dissolution testing measures how much of the drug goes into solution from a dosage form under controlled conditions. The standard apparatus are the paddle (apparatus 2) and the basket (apparatus 1), operated at a defined speed and temperature in a fixed volume of medium, with samples taken at set times and assayed [7, 24]. The test was originally designed as a quality control tool to detect batch-to-batch variation, and it later became a predictor of in vivo behaviour for some drugs and a surrogate for bioequivalence under certain conditions [6, 7].

The choice of medium is critical, and levothyroxine shows why. Because the drug's solubility depends on pH and because surfactants can enhance dissolution of a poorly soluble compound, the composition of the medium has a large effect on the profile. A medium that is too accommodating allows every product to dissolve completely and hides differences, while one that is too severe produces noisy, poorly reproducible results [6, 22]. A discriminating test is the aim, and it should be able to separate a product that is clinically acceptable from one that is not, a property that must be demonstrated rather than assumed [22, 23].

Analytical issues are as important as the dissolution conditions. Levothyroxine tablets are low-dose, so the concentration in each sample is small, and assay by high-performance liquid chromatography with ultraviolet detection must be sensitive and specific enough to quantify the drug in the presence of excipients and degradation products. Adsorption to filters, vessels and sampling tubes can also lower the measured concentration. Method validation should address these effects, and the sampling technique should be chosen to avoid loss of drug [24, 25]. The result is that a validated procedure for a one-hundred-microgram tablet may be no use for the lowest strength.

A single-point specification, such as a minimum percentage dissolved at a stated time, is what the pharmacopoeia and most registered specifications use for release testing [24, 25]. Such a specification indicates that the batch is acceptable, but it says little about the shape of the release curve. Two products can both pass a single-point test and yet release the drug at quite different rates earlier in the test. Multipoint profiles are used to reveal this, and are what regulatory comparisons of generic and reference products rely on [7, 25]. Specifications also differ between regions and pharmacopoeias, which complicates comparison of published results.

4. COMPARING DISSOLUTION PROFILES

Methods for comparing profiles fall into three groups: model-independent, model-dependent and statistical. The model-independent methods use the raw data points and include the difference factor f1 and the similarity factor f2, introduced by Moore and Flanner [12]. The f2 factor is a logarithmic transformation of the mean squared difference between the percentages dissolved at each time point. It equals 100 when profiles are identical, and a value of 50 or more is taken to indicate similarity, which corresponds to an average difference of about 10 percentage points at each time [10, 12].

Regulatory guidance specifies how f2 should be calculated. The test and reference products should be tested on at least 12 units each, the same conditions should be used for both, and at least three time points other than zero should be included. Only one point after 85 percent dissolution in both products should be used, and the coefficient of variation should be no more than 20 percent at the earliest time point and 10 percent at the others [7]. If both products dissolve very rapidly, 85 percent or more in 15 minutes, profile comparison is not needed [7].

The design of the comparison matters at least as much as the formula applied. Test and reference products should come from

representative batches, usually at least one pilot or commercial batch of the generic and several batches of the innovator, since the reference product itself varies [7]. Twelve individual tablets are tested for each, the same operator and equipment are used where possible, and the profiles are measured at identical time points. Where more than one medium is needed, as with pH 1.2, 4.5 and 6.8 for biowaiver work, comparisons are repeated in each [8, 10].

Wide dissolution specifications, as the Polli group argued for metoprolol tablets, may be justified when in vivo data show that products with different dissolution rates are still bioequivalent [33]. The reasoning is that a specification should reflect the range of release rates that are clinically acceptable and not just the range seen in a few batches. The logic applies in reverse for levothyroxine, where the in vivo link is unproven and there is little basis for relaxing limits, so tight specifications and comparison with the reference remain prudent [10, 33].

The f2 factor has well-documented limitations. It is not a formal statistical test, so it gives no confidence interval. It depends on the number of time points and is influenced by the choice of points, as a profile with many points in the plateau phase will have an inflated value. It treats the mean profile as the truth and ignores variability apart from the coefficient of variation limits, and its sampling distribution is skewed, which makes confidence statements awkward [10, 13]. Shah and colleagues analysed the statistical properties and recommended bootstrap approaches when variability is high [10].

Other model-independent methods have been proposed. Dissolution efficiency, the area under the dissolution curve up to a stated time as a percentage of the area for complete dissolution, offers a single number that reflects the whole profile and can be compared with an analysis of variance [13, 27]. Multivariate distance methods such as the Mahalanobis distance take account of variability and correlation between time points, and they have been recommended where the coefficient of variation is high. Anderson and colleagues compared fit factors with dissolution efficiency and found that the conclusions depend on the circumstances [10, 13].

Model-dependent methods fit the data to a mathematical function, such as the first-order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas or Weibull model, and compare the fitted parameters between products. The advantage is that the parameters have physical meaning and variability can be handled statistically. The disadvantage is that the choice of model is partly arbitrary and the fit may be poor outside the observed range [26, 27]. Freely available software has made fitting and comparison routine, but users must still check that the model suits the data [26, 27]. Fitted parameters can also be misleading if the number of points is small.

A frequent confusion deserves a separate mention. A high f2 value shows that two mean profiles are close under the chosen conditions. It does not show that the two products will give the same plasma concentrations in a patient, because absorption depends on permeability, gastrointestinal transit, food and drug interactions as well as release. For a drug whose absorption is as sensitive as levothyroxine's, a similarity result is best read as supporting evidence of comparable quality and not as proof of therapeutic equivalence [10, 15]. The number is best used to support a judgement about quality, not to replace it.

Scale-up and post-approval changes are another area where profile comparison is used. Guidance on changes to immediate-release products specifies when dissolution profiles in several media must be compared for a change in site, equipment, batch size or composition [34]. For levothyroxine, where formulation changes by a brand holder have occasionally led to reports of altered patient response, the comparison of profiles before and after a change helps to detect shifts early [32, 34]. Such comparisons form part of the file that supports the change and are examined at inspection. Reviewers at inspection can then check the evidence behind each decision.

5. REGULATORY FRAMEWORK AND BIOEQUIVALENCE

For most immediate-release drugs, regulators accept a biowaiver, which is approval without a human study, when the drug is highly soluble and the product dissolves very rapidly, subject to conditions about excipients and therapeutic index [8]. The Biopharmaceutics Classification System has been reviewed as a framework that links solubility, permeability and absorption to regulatory standards [17]. Systematic classification of the drugs on the WHO essential medicines list has shown that some are assigned to a class only provisionally, because solubility or permeability data are incomplete [18]. These approaches do not generally apply to narrow therapeutic index drugs, so generic levothyroxine products have to demonstrate bioequivalence in human studies [8, 28]. The quality of the supporting dissolution data therefore matters less for a final decision on equivalence than it does for a routine biowaiver.

Bioequivalence of levothyroxine is hard to demonstrate. The drug is also made by the body, so baseline endogenous thyroxine must be subtracted from measured concentrations, and the subtraction method influences the apparent result. The long half-life requires long sampling, and the single-dose studies in healthy volunteers must use doses above the usual replacement dose to give a measurable signal. For narrow therapeutic index drugs, regulators have proposed tighter approaches, such as European acceptance limits of 90.00 to 111.11 percent for the area under the curve, and sometimes for the peak concentration, relative to the usual 80 to 125 [28, 29].

The United States approach changed in 1997 and the years after. Levothyroxine was historically marketed without approved applications, and when the regulator required formal applications, innovator products were approved first and AB-rated generic products came later [3, 4]. Reviews by thyroid specialists describe this history and the continuing discussion about whether the existing bioequivalence standards are sufficiently sensitive for the drug [3, 4]. Professional guidelines advise caution, recommending that patients remain on the same product where possible and that TSH be rechecked after any change [1]. The regulatory history is therefore unusual among oral solid dosage forms.

Compendial and registered specifications form the daily framework for quality. The pharmacopoeial chapter on dissolution sets out the apparatus, calibration and acceptance stages, while the ICH guidance on specifications describes how acceptance criteria should be justified from batch and stability data and clinical experience [24, 25]. For a drug with a narrow therapeutic index, the guidance supports setting criteria close to the performance of batches shown to be clinically acceptable, instead of the widest limit that the manufacturing process can meet [7, 25]. Such specifications are rarely tested against clinical outcomes unless problems appear.

Pharmaceutical development under quality by design provides another response. The approach asks manufacturers to identify critical quality attributes, such as dissolution, and to relate them to the process and the clinical effect through a design space [11]. For levothyroxine, a better understanding of how excipients, particle properties and moisture affect dissolution and stability would support specifications that are clinically meaningful and not just historical [11, 19]. The compendial test and the quality attributes defined in ICH guidance provide the baseline for setting such specifications [24, 25]. The approach has had only limited application to levothyroxine so far.

6. EVIDENCE FOR GENERIC AND INNOVATOR EQUIVALENCE

The best-known comparison is the crossover study by Dong and colleagues, who gave single doses of brand and generic levothyroxine products to healthy volunteers and concluded that they were bioequivalent [9]. The study had a considerable influence on policy. Later commentary criticised its sample size, the approach to baseline correction and the choice of doses, and argued that bioequivalence in healthy volunteers might not predict behaviour in hypothyroid patients on long-term therapy, who have different gastrointestinal physiology and variable adherence [3, 4, 32]. Its design choices and their limits were not

widely appreciated at the time.

Observational and clinical reports on switching between products are mixed. Some describe changes in TSH after substitution, while others find that the TSH remains within range for most patients, and many reports are limited by retrospective design, lack of control for adherence and lack of information about the products involved [3, 4]. Reviews note that TSH variability between visits is high even in patients who stay on one product, so a single abnormal reading after a switch is hard to interpret [1, 4]. This weakens the case for strong conclusions in either direction.

Where does dissolution fit into this picture? Published analyses of levothyroxine products have noted differences between brands in release profiles under some test conditions, and they link these differences to formulation components. Tablet instability and changing potency add further variability [19, 32]. Studies that combine dissolution data with pharmacokinetic data for the same batches are rare, which limits the ability to establish an in vitro in vivo relationship for this drug. Without such a relationship, a dissolution specification remains a quality control tool and not a predictor of bioavailability [6, 32].

Variability within a product is a concern in its own right. Highly variable drugs show wide intra-subject differences in exposure, and regulators have analysed submitted data to develop approaches for them [35]. Levothyroxine is not usually listed in that group, since its variability stems mainly from the matrix and from patient factors, but some of the same reasoning about study size and design applies. In vitro tests that detect batch-to-batch variability thus remain valuable even when in vivo bioequivalence has been shown [32, 35]. Comparisons based on a single batch of each product can therefore be misleading.

Patient-level factors probably explain more of the variation in TSH than product differences do. Adherence, timing relative to meals, concurrent drugs, weight change and coexisting gastrointestinal disease all influence the dose needed [15, 16]. The shift in thinking on thyroid replacement over recent years has been to accept this complexity and to individualise treatment, with monitoring that tolerates modest fluctuations and a response to symptoms as well as laboratory values [2, 5]. Within that approach, the chief value of a consistent product is to remove one source of variation, not to guarantee control.

Alternative formulations offer indirect evidence about the role of release. Soft-gel capsules and liquid solutions have been reported to restore normal absorption in patients whose tablet absorption is impaired by proton pump inhibitors or gastric conditions, suggesting that tablet disintegration and dissolution can be a rate-limiting step in some people [21, 31]. These findings support the idea that dissolution matters for levothyroxine, at least in patients with altered gastric environments, while also showing that a standard test in simple media does not capture that variation [15, 21]. The suggestion is plausible but has been tested mainly in small series.

7. IMPLICATIONS FOR PRACTICE

For pharmacists, the practical points are straightforward. Dissolution similarity is one piece of evidence and should not by itself justify substitution of levothyroxine products on the shelf. Patients should be kept on one product where possible, told when the product changes, and advised to have TSH rechecked at about six to eight weeks after a change, in line with professional guidance [1, 2]. Counselling should include the timing of the dose relative to food and to drugs that bind or reduce absorption [15, 16]. Pharmacists are well placed to explain this to patients in plain language.

For manufacturers and quality teams, the implications concern method design and interpretation. Dissolution media and apparatus should be justified as discriminating, f2 conditions respected, and variability handled by a method that gives confidence limits where the coefficient of variation is high [10, 13, 26]. Comparisons should be made across multiple batches, as well as at the end of shelf life, to account for the instability that is a known feature of levothyroxine tablets [19, 32]. Changes to excipients or packaging deserve the same

scrutiny as a change of site [19, 34].

Reporting problems is part of good practice. Pharmacists who see patients with unexplained changes in TSH after a switch of brand can record the product names and batch numbers and pass them to the prescriber and to the regulator's reporting system. Such reports are weak evidence individually, but they are the only means of detecting a pattern across many patients, and the literature on adverse events and product switching shows how patchy such reporting has been [1, 3]. Their information may eventually feed into better guidance. Prescribers also benefit when the report is specific.

Dosing instructions carry weight beyond the product itself. The same tablet can behave differently depending on whether it is taken with breakfast, with coffee, or at bedtime, and the time between meals matters more than the brand in many cases. Patients with gastrointestinal disease or bariatric surgery may need higher doses or an alternative formulation, and these groups should not be forgotten when general statements about generic equivalence are made [15, 16]. Simple, consistent advice is often the most effective tool pharmacists have. Plain and consistent advice is probably the most useful tool a pharmacist has here.

8. LIMITATIONS AND FUTURE DIRECTIONS

This review is limited by what has been published. Product-level dissolution profiles for levothyroxine tablets are not widely available, many studies use different media and apparatus, and the clinical literature is dominated by observational reports. The statements about methods draw on general guidance and statistical papers that were written for immediate-release drugs as a whole, and their application to levothyroxine is partly an extrapolation [7, 10, 12]. The role of dissolution in the narrow therapeutic index setting remains less well characterised than for drugs with wide margins [28]. Product details are often commercially sensitive, and so regulators rarely publish them.

Statistical power is a further problem for the studies that do exist. Equivalence testing relies on two one-sided tests or confidence intervals within fixed limits, and a study that is too small cannot show equivalence even when the products are the same [29]. For dissolution comparisons, replicate numbers of six or twelve units are conventional, yet with highly variable tablets the uncertainty in the mean profile can be large relative to the difference of interest [7, 10]. Reporting of sample size, variability and the exact calculation method is often incomplete in published comparisons, which limits the use that can be made of them [10, 29].

Several lines of work would help. Paired in vitro and in vivo data from the same batches could test whether any dissolution medium predicts exposure. Bootstrap or multivariate methods could replace f2 when variability is high [10, 13, 26]. Physiologically based absorption models could incorporate gastric pH, transit and food, allowing simulation of the effect of dissolution differences in different patient groups [22, 23]. Randomised crossover studies in treated patients, with TSH and free thyroxine endpoints, would address the long-standing doubt about extrapolating from healthy volunteers [3, 9]. Together these steps would move the field from argument to measurement.

9. CONCLUSION

Dissolution profile comparison is a useful and inexpensive way to judge whether a generic levothyroxine tablet is made to the same standard as the innovator. Done well, with a discriminating medium, enough units, attention to variability and appropriate statistics, it detects differences in formulation and batch quality before they reach patients [7, 10, 12]. Done poorly, it can give false reassurance, particularly when f2 is applied to variable data or to profiles with many points on the plateau [10, 13]. The point carries practical weight, because the choice of medium and the number of units tested decide how far a result can be trusted.

For this drug the in vitro result cannot stand alone. Absorption is sensitive to the gastric environment, stability is fragile, and the clinical consequences of small differences are slow to appear and hard to attribute [1, 15, 19]. Bioequivalence in healthy volunteers supports substitution, but its limits are well

known [3, 4, 9]. The sensible position, supported by guidance, is to treat dissolution similarity as one strand of evidence, keep patients on a consistent product, and monitor TSH after any change [1, 2]. Better paired data on dissolution and exposure would let future reviews say more.

10. ABBREVIATIONS

BCS-Biopharmaceutics Classification System, f1-Difference factor, f2-Similarity factor, HPLC-High-performance liquid chromatography, ICH-International Council for Harmonisation, TSH-Thyroid-stimulating hormone, USP-United States Pharmacopeia, UV-Ultraviolet, AUC-Area under the concentration-time curve

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12. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

13. CONFLICT OF INTERESTS

Declared none

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