Levothyrox® new and old formulations: are they switchable for millions of patients?

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Short title: Levothyrox®: average bioequivalence vs. switchability

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Abstract

In France more than 2 million patients are currently treated by levothyroxine, mainly under the marketed product Levothyrox®. In March 2017, at the request of French Authorities, a new formulation of Levothyrox® was licensed with the objective of avoiding stability deficiencies of the old formulation. Before to launch this new formulation, an average bioequivalence trial based on EU recommended guidelines was performed. The rational was to implicitely assume that the two products being bioequivalent, they are also switchable allowing a substitution and avoiding the often tedious step of individual calibration of the dosage regimen of thyroxine using TSH concentration as the end-point as it is the case for a new patient who is initiating his/her treatment. Despite the fact that both formulations were shown to be bioequivalent, adverse drug reactions were reported in several thousand patients after taking the new formulation. In this opinion paper we report that more than 50% of healthy volunteers enrolled in a successful regulatory average bioequivalence trial were actually outside the *a priori* bioequivalence range. Therefore, we question the ability of an average bioequivalence trial to guarantee the switchability within patients of the new and old levothyroxine formulations. We further propose analysis of this problem using the conceptual framework of individual bioequivalence. This involves investigating the bioavailability of the two formulations within a subject by comparing not only the population means (as established by average bioequivalence) but also by assessing two variance terms, namely the within-subject variance and the variance estimating subject-by-formulation interaction. A higher within individual variability for the new formulation would lead to reconsideration of the appropriateness of the new formulation. Alternatively, a possible subject-by-formulation interaction would allow a judgement on the ability, or not, of doctors to manage patients effectively during transition from the old to the new formulation.

In France, more than 2 million patients are under treatment with levothyroxine (reference); most are administered the product Levothyrox®. In March 2017, Merck Serono, the French subsidiary of the German pharmaceutical company, Merck KGaA, launched a new formulation of Levothyrox®. It is anticipated that this new formulation will soon be marketed in 21 EU countries

[1]. Despite the fact that both formulations were shown to be bioequivalent (BE), several thousand patients reported adverse drug reactions (ADRs), following this replacement [2]. In this opinion paper we report that more than 50% of healthy volunteers, enrolled into a study which demonstrated average bioequivalence (ABE), were actually outside the *a priori* bioequivalence range. We therefore question the ability of an ABE trial to guarantee the switchability, within a patient, of the new and old levothyroxine formulations.

The objectives in developing a new formulation of Levothyrox® (hereafter named Levothyrox®NF) were two-fold; to improve pharmaceutical stability and to ensure a potency specification over a shelf-life of at least 18 months. The active drug (synthetic L-thyroxine, levothyroxine, or L-T4) was the same as in the original formulation (hereafter named Levothyrox®OF). The excipients only were changed, with the replacement of lactose by mannitol and citric acid, both of which having been claimed by French Authorities as excipients not known to have a recognized action or to affect on the administered dose of Levothyrox®NF [3]. Following this substitutiion and over 13 months of marketing of the new formulation (from 27 March 2017 to 17 April 2018), as many as 31,411 patients had declared ADRs to the French network of pharmacovigilance centres, after switching from the old to the new Levothyrox formulation, i.e.about 1.43% of patients treated with Levothyrox®NF. Most ADRs occurred shortly after this imposed change and the official pharmacovigilance review reported that for 1745 patients documented for their thyroidal status before and after the switch between the two formulations that 23% have an hypothyroidism, 10% an hyperthyroidism and that 67% were normal regarding their TSH status [2]. The conclusion of the French regulatory agency is that it is not possible, from their data analysis, to suggest an hypothesis to account for these ADRs. The possibility of bio-inequivalence between the old and the new formulations has been excluded, following a large trial comparing the formulations [4]. This conclusion was based on the 90% confidence interval (CI) for the area under the curve (AUC) plasma concentration, which is a measure of internal exposure within the pre-defined European regulatory limits of 90.00-110.00 %, hereafter reported as 0.9-1.11 limits.

1-What can be exactly demonstrated with an average EU or FDA bioequivalence trial?

It is important to recognize that a BE trial, conducted in healthy volunteers according to both the EU 2010 revised guidance [5] as well as for the corresponding US Food and Drug Administration (FDA) guideline [6], does not guarantee that each individual patient in the target population, who switches from an older reference (R) formulation to a new test (T) formulation, will be "similarly" exposed to levothyroxine, nor is it intended to do so. In the overview of comments received on the draft EU BE guideline (reference), one can read the following comment from stakeholders "*The draft guideline deals only with average bioequivalence. The Population and Individual bioequivalence approaches are not mentioned anywhere; therefore, it is not clear as to whether these approaches are acceptable*". The European Medicines Agency's (EMA) succinct but uninformative answer was, "*The average bioequivalence approach is the recommended method to establish bioequivalence*". In commenting on the 2010 revision of the EU guideline, Morais and Lobato [7] pointed out to the conceptual EMA shift between the previous and the 2010 revised EU guideline on BE with the replacement of a clinically orientated guideline by a quality control oriented guideline. This explains why the notion of "essential similarity", which was the basis for comparability of two medicinal products, in order to support their interchangeability in clinical use, was deleted due to lack of a solid legal basis. Conversely, the adoption of a '*quality-like'* approach implies "*less reliance on judgment based on clinical considerations* [7] . The new objective is to ensure that formulation differences can be detected, because "*pharmacokinetic parameters such*

as AUC and Cmax are more sensitive to difference in formulation and manufacturing process than to clinical endpoints" [7]. This new EU position is legally more supportable than the previous guidance, but it implicitly considers healthy subjects involved in an ABE trial to be equivalent to homogeneous 'walking' chromatographic columns, rather than being representative of a future heterogeneous targeted patient population.

2-The EU legislation does not deal with substitution that is subject to national regulation.

The EU legislation does not deals with switchability that is the scientific concept to address to support a substitution (*vide infra*) and the substitution policy is a national issue and not one regulated by the EU [5]. In contrast, in the USA, the concept of individual bioequivalence (IBE) and its merits compared to ABE have been extensively investigated [9-11] [8] [9] [10]. It should be understood that the aim of ABE studies is solely to compare the population means between T and R products and thus to ensure that the mean (median) AUCs of the two formulations are sufficiently close to guarantee that their ratio is contained within the acceptable pre-defined regulatory limits. ABE is typically used in the pre-marketing. approval of new generic formulations. However, Levothyrox®NF is not a new generic formulation offered as a possible alternative to Levothyrox®OF for a new patient. It is a new formulation designed to replace Levothyrox®OF and the number of patients for which this change was imposed in France between March and June 2017 is estimated to be 2,188,432 [2]. Hence, the key question that should have been addressed before the marketing of Levothyrox®NF is: can a patient already treated with Levothyrox®OF be safely and effectively switched from this no longer available formulation to the new one? A study demonstrating ABE does not answer this question i.e. the demonstration of ABE between Levothyrox®OF and Levothyrox®NF does not ensure their switchability.

3- The appropriate conceptual framework to document switchability between two formulations is Individual bioequivalence

The concept underlying switchability is that each patient has his/her *own individual Therapeutic Window (TW)*, that is a range of plasma concentrations providing appropriate efficacy and safety. If a formulation change is made, the new formulation should ensure a drug exposure profile precisely located in this *individual TW,* thereby ensuring unchanged safety and efficacy [10].

For thyroxine, the TW is narrow; it is classified as a Narrow Therapeutic Index (NTI) drug [11], dosage for which each patient should be carefully titrated. This is provided for, first, by the availability of multiple dosage product strengths and, second, by reduction of the classical BE acceptance interval from 0.80-1.25 to 0.90-1.11.

The appropriate conceptual framework to document switchability is Individual BE (IBE); the explicit aim is to document the switchability between two formulations. The concept of IBE was introduced more than 25 years ago [12] to address the limitations of ABE trials in addressing the issue of switchability. An IBE study compares the exposure obtained with each formulation *within each individual subject*, thereby ensuring that each individual will respond similarly to the two formulations. Investigation of IBE requires comparing the closeness of the distribution of bioavailability between T and R formulations by establishing not only population means (as for ABE) but also two variance terms, namely, the within-subject variance and the variance estimating subject-by-formulation interaction (for further detail and critical comments see [9] [10] [13]). This interaction term documents the extent to which the individual *differences* between T and R formulations are similar across individual subjects. The FDA reported that an interaction is important when about 10% or more of individuals' R/T ratios are outwith the pre-defined *a priori* BE range [10]. IBE has been both extensively discussed and challenged and then, finally, not adopted by regulatory authorities. It is beyond the scope of this paper to discuss in detail

advantages and limitations of IBE. However, simply concluding that the IBE concept is not clinically relevant, because it has been considered by some authors or organizations that there is no evidence for failure of ABE for approved generics, as [14] is not acceptable. Compared to ABE, IBE studies require more complicated and expensive designs and are associated with several regulatory issues. These include defining IBE, how to measure it and how to analyze data (for detailed review, see a series of 13 articles published in a special issue of Statistics in Medicine in 2000 expressing pros and cons [15]).

We concur with the opinion of the FDA Individual Population Bioequivalence Working group [10] that subject-by-formulation interaction, the most critical variance term to explore for switchability, is highly relevant. In this commentary, it is proposed that the BE of the two formulations of Levothyrox®, and more especially the subject-by-formulation interaction to assess whether (or not) IBE is established for the formulations, merits further consideration.

4-For Levothyrox®, more than 50% of subjects enrolled into a large EU regulatory average bioequivalence trial were actually outside the *a priori* bioequivalence range

Because of public and media concerns, and the wish of the French Regulatory Authorities to ensure full transparency for this major public health crisis, the BE dossier*,* including its raw data, have been made public: it can be down-loaded on the Agence Nationale de Sécurité du Médicament et produits de santé (ANSM) [16]. The dossier provided data on L-T4, hereafter named T4. The T4 concentration-time profiles of 204 healthy individuals, for both old and new formulations, were retrieved. Blood samples were taken before administration (base-line) and regularly up to 72 hours (h) post-administration. For individual subject concentration-time profiles, AUC was computed by trapezoidal methods. According to the 2010 EMA guideline "*If the substance being studied is endogenous, the calculation of pharmacokinetic parameters should be performed using baseline correction so that the calculated pharmacokinetic parameters refer to the additional concentrations provided by the treatment"* [5] .In our analysis, both base-line-adjusted AUC, obtained by subtracting base-line concentration from each post-administration concentration, and unadjusted AUC were calculated, to take account of overall T4 exposure, when evaluating IBE. It is rational to recognize, from the patient perspective, that it is this overall exposure that is clinically relevant.

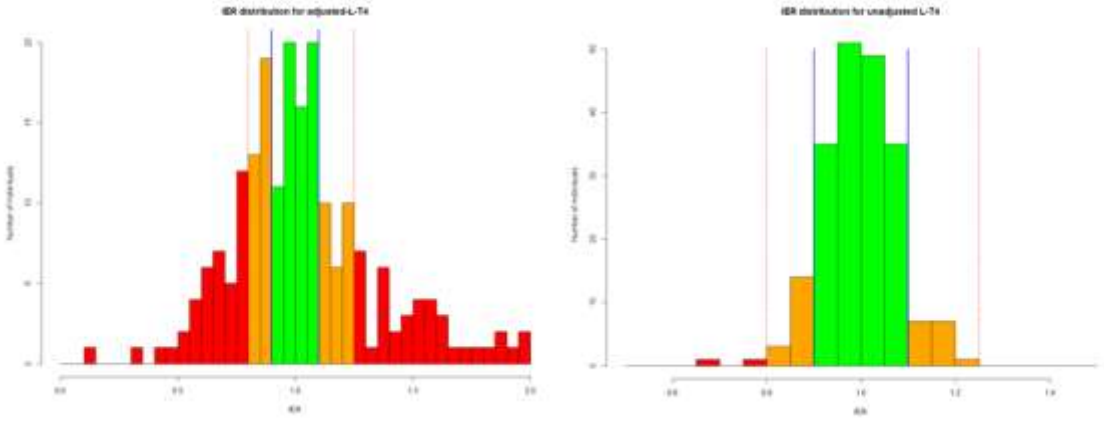
The experimental design was a 2x2 cross-over. As the sequence of administration of the formulations to each individual was not reported in the public dossier, possible period or sequence effects were not considered in our analysis. However, for each individual subject, the exposure ratios AUCnew/AUCold (hereafter named IER) were computable for adjusted and non-adjusted T4 concentrations. This is of interest when documenting IBE, because as indicated above, the proportion of subjects outwith the *a priori* BE interval (here 0.90-1.11) is directly related to the variance term measuring the subject-by-formulation interaction. This variance can, under some conditions, be estimated from the standard deviation of the individual mean formulation differences on a logarithmic scale (see [10] for explanation and [17] for demonstration). For example, assuming that the ratio of overall T/R means is 1 (as is the case for LEVOTHYROX®) and assuming a bivariate normal distribution for the between-subject distribution, the proportion of individuals T/R ratios outwith the *a priori* BE interval 0.80-1.25 is 13.7% for a standard deviation of 0.15 for the Subject-by-formulation interaction, 0.15 being the cut-off value selected by FDA[10].

The data and the R-script used to perform the computation and details of data analysis including management of missing data are available on the journal web site.

Individuals were then classified into 5 groups, respectively corresponding to an IER in one of the following intervals [0 ; 0.8[, [0.8 ; 0.9[, [0.9 ; 1.11],]1.11 ; 1.25],]1.25, ∞[(Table 1). Figure 1 illustrates the distributions of IER computed for T4 with and without adjustment for the base-line.

For the base-line-adjusted ratio (Figure 1, left panel; Table 1), less than 50% of subjects (32.8%) were located in the a priori BE interval of 0.9-1.11, with an expected percentage having a 95% CI of 26.4-39.7%. The corresponding percentage for the unadjusted IER (Figure 1, right panel; Table 1) was 83.3%, with a 95% CI of 77.5-88.20%.

Figure 1: *Distribution of IER (AUCnew/AUCold) obtained with base-line adjusted T4 (left panel), and unadjusted T4 (right panel) plasma concentrations. Blue vertical straight lines are the acceptable pre-defined limits, namely 0.9 and 1.11. An individual with an IER within these limits has an observed variation of exposure of less than 10% when switching from the old to the new formulation. Red dotted vertical straight lines, 0.8 and 1.25, are respectively, the limits below and above which the variation of exposure is greater than 20% when switching from the old to the new formulation. IER = individual exposure ratio.*



Class Intervals	Unadjusted T4 AUCnew/AUCold ratio	Base-line-adjusted T4 AUCnew/AUCold ratio
<0.8	2 1.0% (0.1 ; 3.5%)	40 19.6% (14.4 ; 25.7%)
[0.8 ; 0.9[	17 8.3% (4.9 ; 13.0%)	32 15.7% (11.0 ; 21.4%)
[0.9 ; 1.11]	170	67

(*a priori* regulatory interval)	83.3 % (77.5 ; 88.2 %)	32.84% (26.4 ; 39.7%)
]1.11-1.25]	15 7.4% (4.2 ; 11.8%)	26 12.7% (8.5 ; 18.1%)
>1.25	0 0.0% (0 ; 1.8%)	39 19.1% (14.0 ; 25.2%)

Table 1: *Number of individuals from 204 investigated subjects in each class of IER. This Table gives, for the base-line adjusted T4 and the unadjusted T4, the number and the percentage of individuals from the 204 investigated subjects in each class of IER (AUCnew/AUCold) and the corresponding 95% confidence interval (Clopper-Pearson). It is of note that less than 50% of subjects were located in the a priori BE interval of 0.9-1.11, when the regulatory adjusted AUC is considered, whereas the unadjusted AUC provided more homogeneous IER results with some 83% of patients located in the a priori bioequivalence interval. IER = individual exposure ratio.*

In the dossier, the ABE was established on the adjusted AUC (0-72h) and, even if statistical re-analysis of the data set had not been possible, as a consequence of lack of public information on trial design, it is acknowledged that the trial [4] and analyses were conducted professionally according to current EU guidelines. However, it is proposed that the IBE, focusing on intra-individual variability, as well as on a possible subject-by-formulation interaction, merits consideration.

The published experimental design [4] was not planned for statistical analysis of an IBE and this report does not claim with statistical protection that the two formulations are not switchable. Nevertheless, plotting the observed IER highlights a major "*warning signal*" requiring consideration for two reasons. First, less than 50% of subjects are within the *a priori* BE interval of 0.90-1.11 when (in compliance with the EU guideline) the base-line adjusted AUC is considered. Second, there is an apparently more favorable finding, when unadjusted AUC is considered. Whilst such data analysis is not recommended by the EU guidelines, it constitutes an important consideration, when discussing the relevance of IBE. Indeed, for the healthy subjects in this trial, having normal thyroid function, the administered T4 likely triggered a negative feedback on endogenous T4 secretion, with a buffering effect on T4 plasma concentration, thus resulting in smaller IER dispersion than when adjusted AUC is considered. Axiomatically, it can be hypothesized that such rapid physiological adjustments will be less efficient or even absent in the targeted clinical population, these patients having either reduced or total lack of thyroid

function. In this case, it is ADRs that triggered the required dosage adjustment to ensure an individual euthyroidal status. Therefore, the appropriateness of using healthy euthyroidal subjects to assess BE for Levothyrox® formulations is questionable.

5- As more 50 % of individuals were outside the *a priori* BE range, existence of subject-by-formulation interaction is not unlikely.

The fact that more 50 % of individuals were outside the *a priori* BE range suggests the existence of subject-by-formulation interaction, as reported for several drugs (for recent review see [18]). Indeed, such findings have been reported previously for thyroxine. It was shown that the magnitude of the influence of pH on levothyroxine pharmacokinetics is formulation-dependent and that two formulations that are considered as BE in healthy volunteers under fasting condition may be not necessarily BE in patients with altered gastric pH [19] but that absorption of a liquid formulation of T4 was not altered by proton-pump inhibitors [20] . Likewise, liquid T4 formulations are more efficacious than tablets in patients with malabsorption receiving T4 either for replacement or for suppressive therapy, whereas there were no significant differences in patients in the absence of malabsorption [21]. These literature reports indicate that there are clinical situations in which establishing equivalence for thyroxine in healthy volunteers may not translate unequivocally to equivalence in all patients. They illustrate potential concerns for many patients treated with Levothyrox®NF.

6- The new, but not the old, Levothyrox formulation contains mannitol, an excipient considered to be critical for drugs as levothyroxine having a low permeability

A subject-by-formulation interaction can arise when either a sub-group of subjects or individual subjects have differing pharmacokinetic profiles for either T or R formulation from the remainder of the population enrolled in a BE trial [17]. Mechanistically, it is attributable to some characteristic of this sub-population leading to altered drug absorption. Levothyroxine is classified in the Biopharmaceutical Classification System (BCS) as a Class III substance i.e. one having high solubility but low permeability [22].The new, but not the old, Levothyrox formulation contains mannitol, an osmotic excipient considered to be critical [23], especially for class III drugs (for a general review of the impact of osmotically active excipients on bioavailability and BE of BCS class III drugs, see [24]). Indeed, low permeability compounds are often subject to site-dependent absorption, and their bioavailability can be dependent on gastro-intestinal tract transit time, which may be influenced by mannitol. For example, the bioavailability of the H2-receptor antagonist, cimetidine, in a chewable tablet containing 2.264 g of mannitol, was reduced by 29% and this was due to a reduction in small intestine transit time of 20% [25]. The magnitude of effect of mannitol was shown to be dose-dependent in the range 0.755 and 2.265g [26]. For the new formulation of Levothyrox, the amount of mannitol is approximately 70 mg for a 100 mg tablet [27] and a patient may take two tablets. Whether a small amount of mannitol, of some 140 mg, can affect small intestine transit time and thereby be associated with decreased bioavailability of levothyroxine is not known. Moreover, according to Chen and Yu [24] the quantitative dose-response relationship for mannitol on cimetidine/ranitidine absorption may not be extrapolable to other substances because, as well as an osmotic effect, an osmotically active excipient may influence either absorption mechanism or absorption site. For sorbitol, an isomer of mannitol, it has been reported that very small amounts (7, 50 or 60 mg) can affect drug absorption and this effect appears to be subject-dependent [28].

6-Concluding comments

In conclusion, a statistical analysis conducted in the conceptual framework of IBE would have enabled: (i) documentation of possible higher intra-individual variability for the new compared to

the old formulation and, hence, possible reconsideration of development of this new formulation; indeed a fine individual calibration with a day-to-day undue variability in bioavailability would be very difficult and rendered of lower informativeness a snapshot TSH concentration, when seeking to guarantee a chronic appropriate exposure to thyroxine, as would be the case with a formulation giving lower variability in bioavailability (ii) consideration of a possible subject-by-formulation interaction, thus allowing both regulatory authorities and prescribing clinicians to be better placed to manage and systematically supervise all patients during transition from the old to the new formulation; and (iii) thereby to anticipate a possible new titration for patients on whom the new formulation has been imposed. ABE as the regulatory recommended BE approach notwithstanding, a requirement to explore a possible subject-by-formulation interaction to ensure switchability between products is justified, especially when millions of patients are involved. Such was the case for Concerta® (methylphenidate) and associated generic products; a subject-by-formulation analysis for each pharmacokinetic metric was recommended by FDA *in addition to* the establishment of ABE [29]. Such analysis is warranted on grounds of optimal risk management both for the millions of existing patients and for future EU patients undergoing thyroid-deficiency treatment with a drug, for which replacement of an old with a new formulation, has been known for many years to be problematic internationally [30].

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PG retrieved and validated raw data, AF validated raw data, DC performed the statistical analysis,

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