Authors' Reply to Lechat et al.: " New and Old Formulations: Are they Switchable for Millions of Patients?"

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LETTER TO THE EDITOR

Authors' Reply to Lechat et al.: "Levothyrox® New and Old Formulations: Are they Switchable for Millions of Patients?"

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We are pleased to respond to the letter of Lechat et al. [1] as follows. First, as clarified in our response to the letter of Castello-Bridoux et al. [2], we now emphasize yet again that the conclusion of our paper [3] clearly distinguished the two possible explanations for a lack of switchability between the new and the old Levothyrox® formulations. To be clear, these are: (1) a subject-by-patient formulation interaction and (2) a large within-subject variability. Moreover, we again point to the differing consequences, in terms of management of these two explanations, these being the necessity of reconsidering the development of the new formulation in the case of high within-subject variability on the one hand, whereas an interaction could be managed by the prescriber supervising all patients during transition from the old to the new formulation, on the other hand. In their letter to the Editor, Lechat et al. [1] suggest, from their simulations, that the subject-by-formulation is very unlikely. This implicitly favors a large intra-subject variability and hence reconsideration of development of the new formulation, for which a residual having a high coefficient of variation of 23.7% was reported [4]. However, we recommend greater prudence for two reasons. First, it is simply impossible to determine the origin of a large residual variability (as reported in this average bioequivalence study, using a classical 2×2 cross-over design) because, in the analysis of standard two-period cross-over trials, any subject-by-formulation interaction is included in the residual mean squares from the analysis of variance. Second, when simulations are carried out to explore the influence of a possible subject-by-formulation interaction, it is generally appropriate for a limited sub-group (e.g., 20%) of patients [5], and not for all subjects enrolled in the trial. Therefore, it is advisable to also explore scenarios corresponding to sub-groups of differing size to definitively exclude any possible subject-by-formulation factor for the new formulation of Levothyrox®.

More importantly, Lechat et al. [1] propose a new hypothesis, as stimulating as it is challenging from a regulatory point of view, to explain what might have occurred during the 2018 switch in France from the old to the new formulation, a switch that was imposed on almost 3 million patients. They stated, "The upper limit of levothyroxine tablet content of the old Levothyrox® formulation at release was 110%, higher than the standard 105% limit used for other pharmaceutical formulations. This was, at that time, authorized worldwide in relation to the progressive levothyroxine degradation over time due to spontaneous oxidation". If we fully comprehend this statement (and expressing it more technically), Lechat et al. have hypothesized that, from a bioequivalence perspective, the old formulation cannot be considered in a regulatory trial as a "fixed" effect but rather as a "random" effect. This is because, in reality, patients might have been exposed randomly at the time of the switch to an old formulation, for which relative bioavailability ranged from 90 to 110% of the nominal value, depending on the date of manufacture and the rate of degradation of the old formulation. If this hypothesis is accepted, a valid bioequivalence trial would have compared the new formulation not to a recent formulation having a perfect nominal composition (as suggested by the results of the Merck trial

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with a ratio close to unity) but rather to a random sample of already marketed Levothyrox® formulations as existed in France before the switch. Ironically, this hypothesis simply assumes the existence, for the target population of 3 million patients, of an unavoidable subject-by-formulation interaction for the two sub-groups being treated at the time of the switch either with an over- or under-dosed old formulation. This justifies our encouragement to Lechat et al. to now proceed with simulations to test their own hypothesis.

Compliance with Ethical Standards

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Conflict of interest Didier Concordet, Peggy Gandia, Jean-Louis Montastruc, Alain Bousquet-Mélou, Peter Lees, Aude A. Ferran, and Pierre-Louis Toutain have no conflicts of interest that are directly relevant to the content of this reply.

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