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Letter to the Editors

Generic substitution: a need for clarification

Gregory M. Peterson

Unit for Medication Outcomes Research and Education, School of Pharmacy, University of Tasmania, Private Bag 26, Hobart 7001, TAS, Australia

As noted by Duerden & Hughes, there is considerable interest and debate concerning the place of generic substitution [1]. One of the causes of the ongoing debate is sadly confusion, often fuelled intentionally by the pharmaceutical industry, amongst health professionals and patients regarding the regulatory definition of bioequivalence. It is often erroneously stated, and was unfortunately perpetuated by Duerden & Hughes, that to be considered bioequivalent 'European regulations state that generic products must be shown to have bioavailability within the range of 80–125% of the reference product' [1]. This is false and implies there is a wide leniency allowed. Readers are referred to a recent industry-sponsored publication promoting this myth in the cause of preventing the generic substitution of anti-epileptic drugs [2].

Bioequivalence is usually assessed in healthy volunteers (typically between 18 and 24 subjects) by administering the two products on separate occasions under the same conditions. The peak plasma concentration (C_{max}, primarily reflecting the rate of absorption) and the area under the plasma concentration–time curve (AUC, reflecting the extent of absorption) of the generic product and the original brand are compared. To be considered bioequivalent, the 90% confidence intervals (CI) for the ratio (or its transformed natural log in Europe) of each pharmacokinetic variable must lie between 0.80 and 1.25 (or 80 and 125%) [3–5]. This is a numerical index that provides an indication of the certainty of the study results. Importantly, it does not mean that the actual observed C_{max} and AUC ratios or plasma concentrations can vary by –20 to +25%, which has often been misconstrued or implied [2]. In practice, the differences in the pharmacokinetic variables of the two products would have to be less than 10% to satisfy the 90% CI bioequivalence requirement [3].

Thus, the maximum degree of variability in the rate and extent of absorption from two different approved formulations can, in practice, be only around 10%. In reality, the differences in pharmacokinetic parameters between branded and generic medicines are likely to be even less than this. In fact, reviews of 127 [6] and over 2000 [7] US Food and Drug Administration (FDA) *in vivo* bioequivalence studies on generic medicines have found only a ±3–4% mean difference in AUC and C_{max} values between branded and generic medicines. In addition, regulatory authorities would look at the inter-subject variability for the two products within a bioequivalence study and seek explanations if there was a marked difference between them.

So, logically at least, because the therapeutic activity of a drug is usually related to the concentration in the blood stream, products satisfying the official bioequivalence requirements can reliably be assumed to produce similar clinical and adverse effects when used interchangeably in the same patient. This message needs to be made more clearly and frequently to all health professionals and patients. The licensed generic pharmaceuticals have been scientifically proven to be virtually identical in performance to the original brands. There are likely to be far more important sources of inter- and intra-patient variability in plasma concentrations of almost all medicines. There are other reasons why generic substitution may not be appropriate for a particular patient (e.g. risk of confusion), but these are not related to bioequivalence issues [8, 9].

Competing Interests

There are no competing interests to declare.

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CORRESPONDENCE
Professor Gregory M. Peterson PhD MBA, Unit for Medication Outcomes Research and Education, School of Pharmacy, University of Tasmania, Private Bag 26, Hobart 7001, TAS, Australia. E-mail: g.peterson@utas.edu.au