

Clinical Implications of Canada's Regulatory Process for Approval of Generic Drugs

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Following patent expiration, subsequent entry products (SEPs) are approved by health agencies and marketed. The rigorous approval process is based on bioequivalence rules that have proven to be sound and effective. With the advent of more complex formulations, the rules are revised to fit the new needs. For example, for the popular methylphenidate multiphasic formulation (Concerta) that is used to control attention deficit hyperactivity disorder, standard criteria for establishing therapeutic equivalency of SEPs to the brand have proven to be unsuitable. The available formulation of dabigatran (Pradaxa) also appears to be complex and in need of enhanced therapeutic equivalence rules. Dabigatran absorption into the systemic circulation has been shown to be influenced by changes in the gut pH. Due to its low solubility in an alkaline environment, drug bioavailability is significantly reduced. Accordingly, concomitant dosing of dabigatran and antacids (e.g., proton pump inhibitors, PPIs) results in clinically significantly altered drug exposure. This is important since the beneficial effect of dabigatran correlates well with its serum concentration and many patients use PPI to prevent potential bleeding. Thus, Pradaxa is formulated so that its bioavailability is not significantly reduced by PPIs. As conventional bioequivalence rules are not designed to detect a dabigatran-PPI interaction, new guidelines are needed to address the therapeutic equivalence of SEPs to this complex formulation. This issue will recur with increasing frequency as pharmaceutical formulations increase in complexity. To protect patients, we must keep pace with the evolving science of pharmaceuticals by adapting our regulatory process to advance the requirements for establishing therapeutic equivalency.