Commentary

The interchangeability of innovator and generic drugs

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Prior to 1960s, it was considered to be illegal in many countries for a pharmacist to substitute a generic drug for the brand name version prescribed by the physician. Since then, manufacturers of generic drugs have grown tremendously. Even the laws governing bioequivalence and interchangeability of the brand and generic drugs have become the normal.[1] Even in the US healthcare system, generic pharmaceutical products play a vital role. Since the passage of the Drug Price Competition and Patent Term Restoration Act in 1984, generic drugs started completing the brand or innovator drug products especially as the rules have been set for such a competition. The US FDA has already approved around 11,000 generic products as of the end of 2008. As of December 2008 a total of 13,239 generic prescription and over-the-counter drugs were listed as marketed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluation (Orange Book).[2] Generic drugs offer a powerful approach to cost savings for the patients. As a result patient compliance to the treatment increases.[1,2] In the year 2008 alone, generic drugs accounted for 69% of all prescriptions dispensed in the USA, yet only 16% of the cost in US dollar were spent on such prescriptions.[2]

All prescriptions and over-the-counter generic drugs marketed in the USA must meet standards set by the US FDA. In approving a new generic drug for marketing, the FDA concludes that it is therapeutically equivalent to its corresponding reference product (usually the innovator product, but may be sometimes another generic product if the innovator product was withdrawn). The US FDA thus believes that therapeutically equivalent drug products can be substituted with full expectation that both drugs will produce the same clinical response.

A generic drug is approved in the USA if it is:[2]

1. Pharmaceutically equivalent to an approved safe and effective reference product in that it
   a. Contains identical amounts of the same active drug ingredient in the same dosage form and route of administration.
   b. Meets compendial or other applicable standards of strength, quality, purity, and identity.
2. Bioequivalent to the reference product in that it
   a. Does not present a known or potential bioequivalence problem and it meets an acceptable *in vitro* standard (usually dissolution testing).
   b. If it does present such a known or potential problem, it is shown to meet an appropriate bioequivalence standard.
3. Adequately labelled.
4. Manufactured in compliance with current Good Manufacturing Practice regulations.

The regulatory oversight of generic drug chemistry, manufacturing, and controls is identical to that imposed upon innovator drug products.[2]

Despite the steady growth of the market of generic drugs, scepticism regarding their use has persisted. There is still uncertainty regarding the differences that may exist in terms of efficacy and adverse events between the generic drugs and brand/innovator drugs. The basis of bioequivalence comparing the generic drug to the innovator product is of concern as bioequivalence compares the drug products in terms of pharmacodynamic parameters e.g. maximum plasma concentration. Another concern raised is that comparing a generic drug to an innovator product could fall within 80% bioequivalence while another generic version of the same drug may fall within the 125% bioequivalence limit leading to a variable plasma concentrations between the generics for the same drug.[1] On the other hand, a generic drug may be considered bioequivalent to an innovator drug manufactured at a European site of the pharmaceutical company while the same generic drug may not be considered bioequivalent to the innovator drug product manufactured at the US site of the pharmaceutical company. There have been cases where the bioequivalence study had to be repeated because the generic drug product has been compared to an innovator drug product different from the one used to compare the generic drug to the innovator product using *in vitro* dissolution testing.

This leads us to the question stating whether bioequivalence is a sufficient comparison form a clinical point of view. It has been observed that there is an increase in the occurrence of side effects when a generic drug product is used instead of the brand/innovator product. This may lead some physicians to warn against substitution between a generic version of the drug and the original innovator drug product. This is of special concern for drugs with a narrow therapeutic window such as immunosuppressants, anticoagulant agents, antiepileptic drugs, and antiarrhythmic products such as digoxin and amiodarone. The American Academy of Neurology opposes "generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval".[1] Some cases have been reported where patients suffering from epilepsy had more frequent seizures when they switched to a generic version of the drug. Similarly, a report by the American society of Transplantation recommended that generic immunosuppressant medications should be clearly labelled and distinguishable from innovator drugs and that the patients should be educated to inform their physicians of any switch to or among generic alternatives. It has been observed that some Istraeli patients

required a higher dose of warfarin sodium when they used a generic version of the drug. Some scientists and clinicians have thus expressed the opinion that the FDA's current bioequivalence standards may not be sufficient for certain patient populations being treated with certain classes of drugs (notably antiepileptic drugs and / or drugs with a narrow therapeutic window), drugs that display variable absorption patterns or drugs with nonlinear pharmacokinetics. Some of the controversy arises from misunderstanding the statistical evaluation of the bioequivalence study.[2]

Despite the lack of high quality data supporting real clinical differences between generic and brand/innovator drugs, some legislators in the US and Europe have already passed limits on generic substitution for certain drug classes especially anti-epileptic drugs and immunosuppresants. While some regulatory bodies have tightened their bioequivalence standards after a lot of political pressure.[1]

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Conflict of interest

The author declares no conflict of interest.

References

1. Keseelheim AS. The backlash against bioequivalence and the interchangeability of brand-name and generic drugs. *CMAJ*. 2011;183(12):1350–1351.

2. Davit BM, Nwakama PE, Buehler GJ, et al. Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration. *The Annals of Pharmacotherapy*. 2009;43(10):1583–1597.