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Prior publication: Nil
Support: This work was supported by AstraZeneca Pharma India Ltd Medical writing support was provided by BioQuest Solutions, which was in accordance with Good Publication Practice (GPP3) and funded by AstraZeneca Pharma India Ltd.
Conflicts of interest: Sanjay Kalra has received speaker fees from AstraZeneca Pharma India Ltd. Boehringer Ingelheim, and Jannsen Pharmaceuticals.
Vijay Kher has received consultancy agreements from Torrent Pharmaceuticals, India; Novartis, India; Roche, India; Panacea, India; Sanofi Aventis, India; Intas Pharmaceuticals, India; Biocon Pharmaceuticals, India; GSK, India; RPG Life Sciences; AstraZeneca Pharma India Ltd. India; and Emcure (Gennova) India. He has also received research funding from Novartis India, Sanofi Aventis India, Astellas India; and Medtronics. He has been a Scientific Advisor for Roche, India; Novartis, India; Torrent; Sanofi Aventis; Dr. Reddy's Laboratories Ltd., India, Biocon, India; Medtronics; Wockhardt, India. He has been part of the Speakers Bureau for Novartis, India; Roche, India; Panacea, India; Sanofi Aventis, India; Intas, India; Biocon, India; Pfizer; JB pharmaceuticals; AstraZeneca Pharma India Ltd., India; Boehringer Ingelheim, India.
Manoj Chawla has no conflicts of interest; however, he has speaker contracts with Astra Zeneca Pharma India Ltd., Boehringer Ingelheim, Novo Nordisk, Merck & Co., Inc. (MSD), Sanofi India, Biocon Ltd., Cipla Ltd., USV Pvt. Ltd., Lupin Ltd., Eris Lifesciences Ltd., and Abbott Laboratories Ltd.
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Manuscript Title Innovator vs. Generic: The Real McCoy vs. the Pretender?
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- ❑ ✓Signed by all contributors
- ❑ ×Previous publication / presentations mentioned
- ❑ ✓Source of funding mentioned
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Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i3.4806

INNOVATOR VS. GENERIC: THE REAL MCCOY VS. THE PRETENDER?

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Source(s) of support: Nil
Presentation at a meeting:Nil

Conflicting Interest (If present, give more details):

Sanjay Kalra has received speaker fees from AstraZeneca Pharma India Ltd. Boehringer Ingelheim, and Jannsen Pharmaceuticals.
Vijay Kher has received consultancy agreements from Torrent Pharmaceuticals, India; Novartis, India; Roche, India; Panacea, India; Sanofi Aventis, India; Intas Pharmaceuticals, India; Biocon Pharmaceuticals, India; GSK, India; RPG Life Sciences; AstraZeneca Pharma India Ltd. India; and Emcure (Gennova) India. He has also received research funding from Novartis India, Sanofi Aventis India, Astellas India; and Medtronics. He has been a Scientific Advisor for Roche, India; Novartis, India; Torrent; Sanofi Aventis; Dr. Reddy's Laboratories Ltd., India, Biocon, India; Medtronics; Wockhardt, India. He has been part of the Speakers Bureau for Novartis, India; Roche, India; Panacea,

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The rest of the authors declare no conflicts of interest.

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Manuscript preparation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
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All authors have contributed equally to the conception, design, drafting, review, and finalization of the manuscript.

Title of the article: Innovator vs. Generic: The Real McCoy vs. the Pretender? Abstract Page

Abstract:
Generic drugs with active ingredients are generally developed and marketed following the expiry of the patent and the other exclusivity rights of the innovator drug. Generic drugs are given preference due to better affordability in many instances. Many health agencies and governments encourage the use of generic drugs due to cost parameters; however, not much data are available about the quality of generics. Generics do not undergo complete clinical development as the original innovator drug; hence, there have been differences in the effects of generic drugs in the real world. The study of properties such as stereoisomerism is important, as the shape of the drug molecule (especially in generics) not only impacts the desired biological activity but also influences the potential adverse effects (AEs). Generic drugs are considered therapeutically equivalent if they are pharmaceutically equivalent and have similar pharmacokinetics. However, the bioavailability of the drug is a prime concern among generics. Additionally, bioequivalence does not assure similar therapeutic responses and AEs as that of the reference drug. In addition, concerns related to the effect of excipients have also been raised. Nevertheless, generic drugs are considered an alternative to address the increasing cost of healthcare in developing countries where most patients pay for healthcare out of their pockets. However, generic drugs should meet the same standards of quality, safety, and efficacy as those of innovator drugs as they are prescribed widely. Hence, it is important to implement generic switching policies with caution until the quality, efficacy, and safety of generics are convincingly at par with innovator drugs.

Key-words: Generics, Innovator, Equivalence, Clinical efficacy

Key Messages (Provide appropriate messages of about 35-50 words to be printed in centre box):Text

Introduction:

Drug discovery and development is a highly complicated and challenging process that comprises several stages, including identification and validation of the target cells; identification and optimization of the leads; along with formulation, characterization, and development of the test product. The product then undergoes rigorous evaluation via preclinical research, clinical research, and clinical trials before being made available in the market.[1]

According to the available reports, the time required (including discovery, development, and clinical research) for a new drug to be introduced in the market is at least 10 years, while the probability of the new drug being eventually approved is less than 12%.[2] Owing to all these aspects, the overall cost of researching and developing a new drug becomes substantially high. According to an estimate, the cost of getting a new drug approved by the United States Food and Drug Administration (US-FDA) between 2009 and 2018 was $985 million.[3] The prices of the innovator drugs significantly decrease following the expiry of the patent and the availability of generic drugs. According to a systematic review, the reduction in the innovator drug prices ranged from 6.6% to 66% following 1–5 years of patent expiry.[4]

Generic drugs with active ingredients are allowed to be developed and marketed after the patent and the other exclusivity rights of the innovator drug expire. A generic drug is defined as "a drug product that is comparable to a brand/reference-listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use".[5] The production of generic drugs has been allowed in the US since 1984 per the Hatch Waxman Act amendments (Patent Term Restoration Act) passed by the United States Congress.[6] A generic drug is approved by the US-FDA if it is: "1. pharmaceutically equivalent to the reference product in that it (a) contains identical amounts of the same active drug (the same dosage form and route) and (b) meets compendial or other applicable standards of strength, quality, and purity; 2. bioequivalent to the reference product in that it (a) meets an acceptable in vitro standard (usually dissolution testing) or (b) it is shown to meet an appropriate bioequivalence standard; 3. adequately labeled; and 4. manufactured in compliance with current Good Manufacturing Practice regulations."[7] However, some scientists and clinicians believe that the FDA's current bioequivalence standards may not be sufficient for certain classes of drugs (notably, antiepileptic drugs, immunosuppressants, and/or drugs with a narrow therapeutic index), drugs that display variable absorption patterns, or drugs with nonlinear pharmacokinetics.[8]

The difference between generics and biosimilars should also be understood to be aware of variations in the drug dosages and actions. While generics are usually manufactured from chemicals, resulting in an active ingredient, which is the same in all manufactured batches, biosimilars are manufactured from living systems (such as bacteria, yeast, or animal cells) and hence, inherent variations (especially in protein molecules) are expected across manufactured batches.[9] Therefore, a head-to–head comparison of the biosimilar product with the reference drug in terms of function, structure, pharmacokinetics, and pharmacodynamics, along with clinical effectiveness and safety is suggested.[10]

The prescription of generics is encouraged across the world.[11] Generics are preferred in developing countries (as they are cheaper than innovator drugs by 30%–80%) where the per capita out-of-pocket expenditure for healthcare is high.[6] The use of generic medicines is considered a vital facilitator for decreasing expenditure, improving access, and extending medical coverage.[12] Even developed countries have adopted policies and regulations to improve the use of generic medicines.[12]

However, there is a significant concern among physicians about the quality of generics. One of the main reasons for this concern is the lack of stringent regulatory requirements for the approval of generics and the permissible impurities in them.[6] The presence of inactive ingredients (often referred

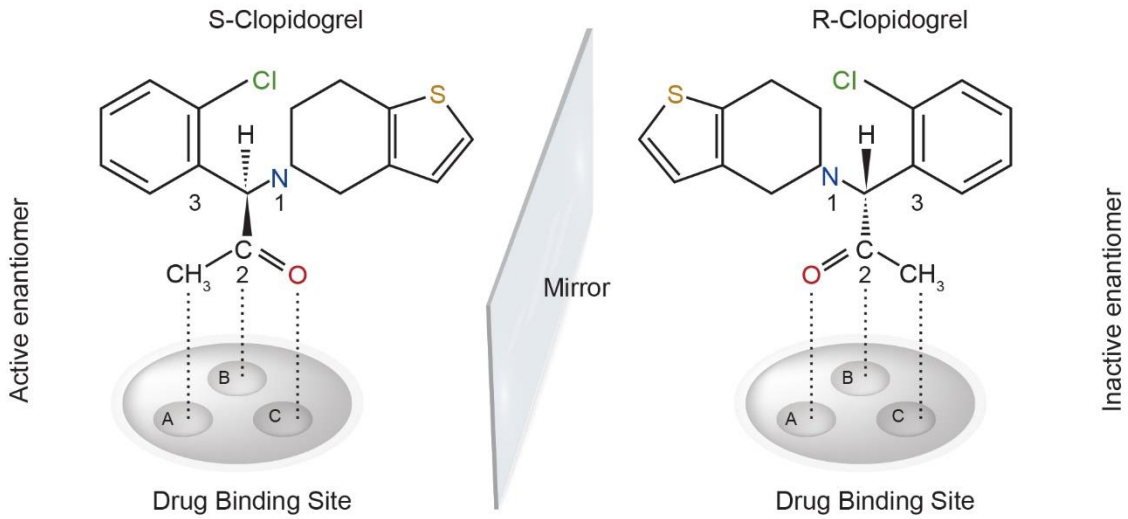
to as excipients) can lead to AEs, thereby affecting the prognosis of the condition being treated.[13] According to the recommendations of the American Society of Transplantation, generic immunosuppressant medications should be distinguishable from innovator drugs and clearly labeled. Further, patients should also inform their physicians when they plan to switch to generic alternatives.[8]

Comparing the bioequivalence of originator immunosuppressive drugs with generic versions is also important. Even if generic drugs are approved, there may be differences among generics and switching a patient from one generic to another may be problematic, especially owing to the possibility of changes in dosage levels. Additionally, trials conducted in healthy volunteers may not match real-world scenarios, especially in patients who are renally compromised. Further, comparative studies commonly evaluate single doses, which may not reflect the steady states achieved with chronic dosing.[14] A pharmacokinetic study with a cross-over design would be needed to produce data about the effects of switching from innovator to generic drugs (or between generic drugs) to prove noninferiority among them.

Impact of Molecular Structure on Efficacy

Molecules with identical atomic constitutions but different three-dimensional atomic arrangements are called stereoisomers. Although stereoisomers have identical atomic constitutions, they have different pharmacokinetic and pharmacodynamic properties.[15] Studying these properties is an important aspect of pharmaceutical chemistry as the shape of the drug molecule not only impacts the desired biological activity but also influences potential AEs.[16] Stereoisomers can occur either as enantiomers (molecules that are non-superposable mirror images of each other) or as diastereomers (molecules that are not mirror images of each other) (Figure 1). Chirality refers to the geometric property of these molecules. Notably, 25% of the available drugs are a mixture of more than one stereoisomer and such forms are referred to as racemic mixtures. Interactions between the different stereoisomers in the racemic mixtures may increase the risk of AEs.[17]

Figure 1: Stereoisomerism and chirality



Stereoisomerism and Chirality- Stereoisomers are identical molecules with differing three-dimensional atomic arrangements. Chiral molecules are non-superimposable. Enantiomers are chiral molecule mirror images. The active enantiomer's three-dimensional structure lets drug domains interact and bind to drug-binding sites. The inactive enantiomer cannot align itself and attach to the drug binding site, and its bioavailability, metabolism, metabolite excretion, potency and selectivity for receptors and transporters, pharmacokinetics, and pharmacodynamics change.

The pharmacological activity of each enantiomer in a racemic drug can be similar, null, opposite, or different.[18] Furthermore, the metabolism, bioavailability, selectivity, potency, excretion, and toxicity of the two enantiomers of a chiral drug may be different.[19] For example, the chiral molecule ticagrelor has six stereogenic centers, which would account for 64 possible stereoisomers owing to the potential structural orientations in space.[20] To prevent platelet activation, the right stereoisomer is essential for blocking the adenosine diphosphate (ADP) receptor (subtype P2Y12).[21] The pharmacokinetics of a drug can be improved by developing separate enantiomers, which can also help in reducing AEs. This was evident with amlodipine. Conventionally, amlodipine is a mix of S- and R-enantiomers; S-amlodipine (S-AM), is an S-enantiomer of amlodipine, which is available in India and has been proven to have a greater affinity to the receptor sites (1000 times higher than the R-enantiomer), less variable pharmacokinetics, longer half-life, better tolerability, and lesser risk of AEs compared with conventional amlodipine.[22] Similarly, S metoprolol, a chirally pure form of the conventional racemate metoprolol was noted to have fewer side effects and was considered safer for hypertensive patients with diabetes or chronic obstructive pulmonary disorder.[23]

Impact of Increased or Decreased Bioavailability

Bioavailability refers to the extent and rate at which a therapeutically active component of the drug enters the systemic circulation and becomes available to the body.[24] According to regulatory agencies, generic drugs can be considered therapeutically equivalent if they are pharmaceutically equivalent (in terms of active ingredients, route of administration, dose, and concentration) and have similar pharmacokinetics.[25] However, there are concerns about the bioavailability of a generic drug compared with that of the innovator drug.

The quality and performance of drugs are influenced by the bioavailability, and the bioavailability of a generic drug may not be similar to that of an innovator drug. This difference may lead to therapeutic failure, subtherapeutic effect, or prolongation of the illness. Aspects such as potency, purity, drug release, and stability have a critical role in the efficacy of a drug, and these need to be controlled to ensure the desired quality of a drug.[6]

Importance of Bioequivalence

Bioequivalence refers to the biological equivalence of two proprietary preparations of a drug. To be considered bioequivalent, the drugs should be able to provide the same therapeutic effect.[26] Properties such as maximum concentration (Cmax) and area under the curve (AUC) are generally evaluated to compare the bioequivalence of two preparations. The Cmax reflects the rate and extent of absorption, while the AUC provides insights on the extent of exposure to a drug and its clearance rate from the body. According to the FDA regulations, the 90% confidence intervals (90% CI) for the ratio between Cmax and AUC of the two drugs must lie between 0.8 and 1.25 (~20%–25%) to be considered bioequivalent. Based on this calculation, the active plasma concentrations of the innovators and generics can vary by up to 45%; however, this is considered acceptable.[24] The actual difference in exposure to the active ingredient between generics and innovators is typically less than 5%.[8] For drugs with a narrow therapeutic index, it should be 90%–111%. However, such a degree of variation in the bioequivalence (±20%) can significantly impact the therapeutic efficacy of a generic drug in comparison with that of an innovator.[27] Further, bioequivalence does not guarantee a similar therapeutic response and rate of AEs as those of the innovator drug.[28]

Another concern is the age group and the number of volunteers involved in the studies conducted to establish the bioequivalence of generics with innovators. Such studies usually involve small groups of healthy young adult males who are not receiving any other therapy.[29] However, drug handling characteristics in this population may not be similar to those of the general population or the population that the drug is most useful/prescribed for. Further, the influences of gender differences and drug–disease interactions on the efficacy and safety of generic drugs may be unclear.[30]

According to the researchers who reviewed 12 years of bioequivalence data submitted to the FDA, comparing 2070 single-dose clinical bioequivalence studies of generic drugs approved by the FDA between 1996 and 2007, the mean difference in the extent and rate of drug absorption between generic and innovator drugs was 3.56% and 4.35%, respectively. Additionally, a 10% difference was noted in the extent of drug absorption of the generic drug compared with the innovator drug in nearly 98% of the bioequivalence studies.[8] Such differences in drug absorption can significantly affect the bioequivalence parameters of generic and innovator drugs.[31]

Therefore, it has been suggested that physicians exercise caution when substituting a branded drug with a generic equivalent.[31]

Impact of Manufacturing Processes: Impurities in Generics

Apart from variations in bioequivalence, the AEs associated with generic medicines may be attributed to the presence of inactive ingredients referred to as excipients. Generic preparations containing excipients that are not part of the innovator drug preparations may cause AEs in individuals who were tolerant of the innovator drug.[31] The cost of producing a pure form of a drug is high and usually requires sensitive isolation techniques, which may be expensive. To overcome this and to allow price reduction, the concept of "safety of a drug substance impurity" has been introduced in the acceptance criteria of generic drugs.[32]

However, high levels of impurities or excipients in a drug can reduce its efficacy as the amount of the active ingredient in the formulation may be reduced.[32] According to the studies that compared generic drugs with innovators, a total impurity rate of >3% was noted in the generic formulations, which could negatively impact the bioavailability and therapeutic efficacy.[27] Other studies have also demonstrated differences in the clinical outcomes and AEs when original drugs were substituted with generics. For example, if a lactose-intolerant arrhythmia patient is switched to an antiarrhythmic generic containing a lactose-based excipient, he/she may experience gastrointestinal disturbances, which may, in turn, impact the absorption, and consequently, the systemic levels of the drug.[31] Such aspects may be critical in patients being treated for cardiovascular disorders.

In a study published in 2013 that evaluated the presence of impurities in generic atorvastatin formulations obtained from 15 countries, it was noted that the generic medications contained elevated levels of a specific methyl ester impurity. Additionally, the 3 hydroxy 3 methylglutaryl coenzyme A reductase (HMGR) enzyme activity was not inhibited by this impurity, which could compromise the effective management of hypercholesterolemia in patients at risk of developing cardiovascular issues.[33] In another similar 2016 study from India that evaluated impurities in rosuvastatin, the percent relative standard deviation (% RSD) for impurities like process impurity, adduct, anti-isomer, lactone, and 5-keto acid was found to be 0.6, 0.6, 0.6, 0.7, and 0.5, respectively. The presence of such impurities can impact the stability of the rosuvastatin formulation and the overall shelf-life of the tablet.[34] Another 2020 study conducted in India reported that generic clopidogrel tablets available for free at government-run hospitals did not meet the recommended percentage purity standards.[35]

Other Concerns

Several studies have reported that switching to generics negatively impacts medication adherence, leads to poorer clinical outcomes, and increases the risk of AEs. Although switching to generics results in cost savings, the overall cost of care increased owing to increased physician visits and hospitalizations. Suggestions toward a mandatory switch to generic medications may increase the potential for unintended consequences. This may be especially true for drug classes with narrow therapeutic indices, such as antiarrhythmic, antiepileptic, anticoagulant, and thyroid medications, where even minor variations in dosage could lead to subtherapeutic drug levels or increase the risk of toxicity.[36]

Patient concerns related to the efficacy of generic medications have also been reported in a few studies. Patients felt that the effects of generics were lower than those of the innovator drugs. For example, improvements in depression symptoms were observed after patients were switched back to the innovator medications after a shift to generic medications.[31]

Clinical Evidence

Evidence for antiplatelets

A more than two-fold increase in stent thrombosis (ST) was reported with the use of generic clopidogrel in patients who underwent percutaneous coronary intervention (PCI) at a single center in the USA. The incidence of ST following generic clopidogrel was compared with the 3 year historical data during which the innovator drug was used. Generic clopidogrel usage was associated with an ST incidence of 0.38% compared with the 0.14% in the 3-year historical data, representing a 2.7-fold increase in the incidence of 30-day ST.[37]

Comparator studies	Patient population	Findings
Branded vs. generic clopidogrel [37]	Patients undergoing percutaneous coronary intervention	Incidence of stent thrombosis: 0.14% vs. 0.38% (branded vs. generic)
Branded vs. generic clopidogrel [38]	Patients with acute coronary syndrome	Incidence of high platelet reactivity: 25.4% vs. 42.4% (branded vs. generic)
Branded vs. generic clopidogrel [39]	Adverse events across different patient populations	Rash/dermal events, hemorrhagic events, and cardiac events were higher with generics compared with branded clopidogrel
Branded vs. generic statins [40]	Adherence and adverse events among cardiovascular patients prescribed branded vs. generic statins	31% higher incidence of cardiovascular events, 36% increase in the probability of all-cause death, and lower achievement of therapeutic goals with generic statins
Switch to generics [41,42]	Patients with epilepsy	Increase in seizure frequency and risk of adverse events with generics

In a 2013 study from Italy that evaluated 1579 patients with acute coronary syndrome (ACS), the incidence of high platelet reactivity following the administration of generic clopidogrel was significantly higher compared with the innovator clopidogrel (42.4% vs. 25.4%; $p<0.0001$). High platelet reactivity is associated with an increased risk of ischemic recurrence in patients with ACS undergoing PCI for stent implantation. The study concluded that there is a need for accurate postmarketing surveillance of generic drugs.[38]

A 2019 study that compared the incidence of AEs (using data from the US-FDA Adverse Event Reporting System) following the administration of generic clopidogrel or branded clopidogrel reported a higher incidence of AEs with generic clopidogrel. The study concluded that the branded version had a better safety profile compared with generic clopidogrel.[39]

Evidence for statins

A retrospective cost–consequences study in 2018 in Spain that evaluated the medical records of 13,244 patients reported poorer treatment adherence and persistence with generic statins compared with those on branded statins. On average, the probability of experiencing cardiovascular events was 31% higher with generic statins compared with that of innovator statins. Further, there was a 36% increase in the adjusted probability of all-cause death with generics. Among patients without previous cardiovascular disease, generic statins were associated with a lower achievement of therapeutic goals (decrease in low-density lipoprotein–cholesterol levels) compared with innovator statins (37.2% vs. 39.46%). Patients on generic statins had a 13% lower probability of reaching their therapeutic goals during the 60-month follow-up period than those using innovator statins.[40]

Evidence for cardiovascular drugs

According to a systematic review and meta-analysis by Kesselheim et al. (2008), which evaluated 47 publications comparing the efficacy of generic and brand-name cardiovascular drugs, brand-name

drugs were not superior to generic drugs. However, about 53% of the editorials recommended against interchanging generic drugs.[43]

Evidence for other drug classes

In a systematic literature search of 70 publications on antiepileptic drugs, it was reported that therapeutic failure was associated with increased episodes of seizures in a quarter of the study subjects after a brand-to–generic switch.[28] According to another study in 2011 in the US, involving 260 patients, 42.9% of patients with epilepsy on generic medication were switched back to the innovator brand owing to an increase in seizure frequency (19.6% vs. 1.6%; $p<0.0001$) and AEs.[41] A survey involving 196 neurologists reported that the generic substitution of antiepileptic drugs was associated with increased seizure frequency, decreased clinical efficacy, and increased risk of AEs. Neurologists reported an increase in AEs in 56% of cases and increased seizure frequency in two-thirds of the cases on switching over to generic drugs.[42]

The Generic Drug Approval Process in India

The generic drug approval process in the US is mainly governed by the US-FDA regulatory requirements enlisted earlier. An abbreviated new drug application (ANDA) needs to be submitted to the regulatory authorities by the pharmaceutical companies for obtaining approval to market a generic drug. The review process is carried out by the US-FDA and the Center for Drug Evaluation and Research (CDER) to compare the therapeutic bioequivalence of the generic drug with that of the innovator before marketing approval is granted.[44]

Generic drugs that are pharmaceutically equivalent (same active ingredient as the innovator, and administered in the same route, concentration, and dose as the innovator) and have similar pharmacokinetics (mainly bioequivalence) as the innovator drug are approved for marketing. Notably, bioequivalence can be established based on studies involving only
12-24–36 healthy young men. The assessment is based on a comparison between the rates of drug absorption–peak concentration (Cmax) and the extent to which it occurs within the AUC.[45]

The regulatory guidelines related to the approval of generic drugs in India are similar to those in other developing countries.[6] The CDSCO, which operates under the purview of the Ministry of Health and Family Welfare, oversees the approval of generic drugs, ensuring their safety, efficacy, and quality. Notably, the term “generic drug” is neither defined nor mentioned in the Indian regulations. According to rule 122-A, applicants applying for new drug registration in India for the first time should provide information related to local clinical trials. On the contrary, according to Appendix I-A of Schedule Y, subsequent applicants wanting to register the same drug need not submit the results of local clinical trials; data related to bioavailability/bioequivalence along with comparative dissolution studies are sufficient for oral drugs.[46] However, bioequivalence studies are not mandatory for drugs (generic products) whose “reference formulations” have been available in the Indian market for 4 years.[46]

Most of the medicines sold in India have a brand name and these medicines are commonly referred to as “branded medicine” or “branded-generics”. In many instances, both these types are produced by the same pharmaceutical company. The branded generics closely resemble the generic formulations sold worldwide. The price-to-patient for the branded medicine is generally higher than that of the branded generic.[47]

Conclusion

Generic drugs are a viable alternative in developing countries where most patients pay out of their pockets. Better affordability and compliance have been suggested as benefits noted with generics. As generic drugs are not required to demonstrate efficacy and safety through clinical trials as innovators have already established these, generics are cheaper. Despite this, generic drugs still need to meet the

same standards of quality, safety, and efficacy as those of innovator drugs. Also, it is important to implement generic switching policies with caution. On one hand, the use of generic drugs may be related to increased disease days (time to relapse) and therapeutic failure; on the other hand, patients may experience more side effects if the drug concentration is higher than that in the brand formulation. Further, stringent regulations, clarifications on the definition of generic drugs, and larger prospective studies to evaluate the efficacy and safety of generics can help improve the quality and uptake of generics. In general, it is advisable to identify and evaluate the effects of generic formulations when treatment is provided.

Funding statement:
This work was supported by AstraZeneca Pharma India Ltd.

Acknowledgement:
The authors would like to thank BioQuest Solutions for medical writing support, which was funded by AstraZeneca Pharma India Ltd. The manuscript building was done in accordance with GPP 2022 guidelines (https://www.ismpp.org/gpp-2022).

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