International Journal of Basic & Clinical Pharmacology
Samajdar SS et al. Int J Basic Clin Pharmacol. 2024 May;13(3):408-412
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20241004

Review Article

Truth in a pill

Shambo S. Samajdar[1], Shravan Venkatraman[2]*, Shashank Joshi[3], Kaushik Biswas[4], Bharat Saboo[5]

[1]Diabetes and Allergy-Asthma Therapeutics Specialty Clinic, Kolkata, West Bengal, India
[2]Department of Clinical Pharmacology, JIPMER, Puducherry, India
[3]Joshi Clinic, Mumbai, Maharashtra, India
[4]Department of Endocrinology, Medica Superspeciality Hospital, Kolkata, West Bengal, India
[5]Department of Diabetology, Prayas Diabetic Centre, Indore, Madhya Pradesh, India

Received: 06 February 2024
Accepted: 06 March 2024

***Correspondence:**
Dr. Shravan Venkatraman,
Email: shravandhawan18@gmail.com

ABSTRACT

In 1937, the elixir sulphanilamide disaster was one of the mass poisonings. It occurs due to the presence of the diluent diethylene glycol in the elixir preparation of sulphanilamide. Because of its therapeutic use, around 100 patients died. In response to the calamity, Federal Food, Drug and Cosmetic Act was passed in the year 1938 by U.S congress and this ensured the proof of safety before the drug comes to market. The similar incident occurred for thalidomide in late 1950s and early 1960s when the drug was used for the treatment of nausea in pregnant women and resulted in children with birth defects. The development of drugs is a complex and costly process and it takes around 10-15 years for the drug to develop. Because of these reasons, the development of generic drugs is essential and this review will deal about the use of generic drugs and also its advantages with limitations.

Keywords: Innovator, Generic, Bioavailability, Bioequivalent, BA/BE study

INTRODUCTION

In 1937, the elixir sulphanilamide disaster was one of the mass poisonings belonging to 20th century. It occurs due to the presence of the diluent diethylene glycol in the elixir preparation of sulphanilamide. Because of its therapeutic use, around 100 patients died. In response to the calamity, Federal Food, Drug and Cosmetic Act was passed in the year 1938 by U.S congress and this ensured the proof of safety before the drug comes to market.[1] The similar incident occurred for thalidomide in late 1950s and early 1960s when the drug was used for the treatment of nausea in pregnant women and resulted in children with birth defects.[2] The development of drugs is a complex and costly process and it takes around 10-15 years for the drug to develop. Because of these reasons, the development of generic drugs is essential and it is around 30-80% cheaper compared to originator equivalents.

NEED FOR GENERICS

Generic medicines are developed after the expiry of the original drugs and are produced by the manufacturers other than the patent-holding company. It is a pharmaceutical product which has the following properties: intended to be interchangeable with innovator product, manufactured without license from innovator company, and marketed after the expiry date of the patent.

The reasons to develop generic drugs are cost factor, accessibility, less health-related burden and export to other countries. It should contain the same active ingredient as the innovator product, identical in strength, dosage form and route of administration and used for the same indication. It should also be bioequivalent and meet the same batch requirements for identity, strength, purity and quality. The generic drugs should be manufactured under

similar strict criteria for FDA's GMP regulations required for originator products.

The definition of generic drug is "A drug product that is comparable to brand/reference listed product in dosage form, strength, route of administration, quality and performance characteristics and intended use".[3] It is different from generic name which is the approved name of the drug. The branded generic drug is the one which is developed by drug companies and sold under different companies' brand names.

The advantage of generic medicines is that it is 30-80% cheaper than the brand drugs.[4] The reason of generic medicine being cheap is that there is no burden to prove the efficacy and safety of the drug and this enables the generic drug to be sold at a low price in comparison with the branded equivalent. The new guidelines of NMC say that all registered medical practitioners (RMP) should prescribe drugs using generic names. The generic names should be written legibly and avoid unnecessary medications and irrational fixed-dose combination tablets.

REQUIREMENTS

The FDA approves generic drugs based on the two parameters measured in generic drugs. They include the rate of absorption and the bioavailability. The generic drug is considered bioequivalent and a therapeutic equivalent to the branded drug.

BIOEQUIVALENCE

Bioequivalence (BE) of a drug product is achieved if its extent and rate of absorption are not statistically significantly different from those of the reference product when administered at the same molar dose. According to Code of Federal Regulations (CFR 21), bioequivalence criteria is fulfilled when there is absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[5]

ACCEPTANCE CRITERIA FOR BIOEQUIVALENCE

There must be no more than a 20% difference between the AUC and C_{max} of brand name versus generic products. Bioequivalence criteria is explained below.

90% confidence interval (CI) acceptance criteria are 80.00-125.00% (0.80 and 1.25 when it is log-transformed data) for the test/reference ratio for all three parameters AUC, C_{max} and T_{max}.

There are exceptions to the criteria when the drug has narrow therapeutic index, wide therapeutic range or non-linear pharmacokinetics over linear range. For the drugs with narrow therapeutic index, the acceptance criteria for the bioequivalence are 90.00–111.11%.[6] The acceptance criteria should be stringent to assess bioequivalence. Various regulatory agencies like US FDA, European Medicines Agency, Health Protection and Food Branch (HPFB) of Canada have made the criteria to be stringent.

The generic form of imatinib has a different crystal form (alpha crystal form) than the branded imatinib (beta crystal form), which is less stable at room temperature. However, this polymorphism did not affect the solubility and bioavailability of the product, and it is generally considered clinically insignificant. FDA regulations for generic agents require bioequivalence studies demonstrating that the rate and extent of drug absorption fall within 80-125% of those of the original drug.

The approval process for generic pharmaceuticals involves a rigorous evaluation of adherence to good manufacturing practices (GMP) guidelines set forth by state drug regulators. These guidelines ensure that the manufacturing facilities and processes meet the highest standards of quality and safety. Additionally, generic drug manufacturers are required to conduct in-vitro dissolution studies, which assess the release of the active pharmaceutical ingredient (API) and its dissolution characteristics, ensuring that the generic product is bioequivalent to the reference brand. Furthermore, in-vivo bio-availability and bio-equivalence (BA-BE) testing are performed, measuring crucial pharmacokinetic parameters such as C_{max} (peak plasma concentration), T_{max} (time to reach C_{max}), and area-under-the-curve (AUC).

This comprehensive evaluation process ensures that generic drugs are not only manufactured to the same quality standards as their brand-name counterparts but also provide the same therapeutic benefits to patients, making them a cost-effective and safe alternative in the pharmaceutical market.

In vivo method

Pharmacokinetic parameters measured include C_{max}, T_{max} and AUC

The extent of the drug absorption is measured using AUC. The measure of the total exposure of the drug to the body up to the last sampling time is known as AUCt and AUCinf is a theoretical measure of the total exposure of drug to the body from administration till the drug is eliminated completely.

C_{max} is the maximum concentration that a drug achieves in tested area after the drug has been administered and prior to the administration of second dose. C_{min} is the minimum concentration that a drug achieves after dosing.

T_{max} is the time at which the C_{max} is observed.

Pharmacodynamic study

The response should be a pharmacological effect and it should be measured through a double blinded study. A pilot study can be conducted to assess non responders. The study design can be a cross-over/parallel design.[7]

IN VITRO METHODS

Dissolution

Dissolution testing has been used for developing and approval of generic drugs of solid oral dosage forms. *In-vivo* performance of certain products can be predicted by dissolution testing which also play a vital role in identification of the bioequivalence studies related with scale-up and post approval changes (SUPAC).

Dissolution method should be appropriate for the generic product to be tested. Dissolution profile should be characterized to generate the dissolution data by sampling the dissolution medium at appropriate time points. Three or more time points are essential for rapidly dissolving drugs whereas for extended formulations, more time points are required to characterize the complete dissolution profile.[8]

Biopharmaceutical classification system

Biopharmaceutical classification system (BCS) is used for classifying medicines based on dissolution, water solubility, and intestinal permeability. These are the factors which affect the absorption of active pharmaceutical ingredients (API) from immediate-release solid oral forms.

There are 4 classes in biopharmaceutical classification system (BCS). In class I, there is high permeability and solubility and the drugs are well absorbed indicating a higher absorption rate than excretion. The class II drugs have high permeability and low solubility. In this class, the bioavailability of the products is limited by low solubility. In class III, there is high solubility but a low permeability limiting its absorption. In class IV, there is low permeability and solubility resulting in low bioavailability of the drug due to lack of absorption from the intestinal mucosa.

In India, the BCS plays a significant role in determining the regulatory requirements for generic drug approval. BCS class I and III drugs, which typically have well-understood and predictable pharmacokinetics, are eligible for bioequivalence waivers, implying that they may not require a full-fledged BA-BE study for generic drug approval. Instead, the focus may primarily be on in vitro dissolution studies, ensuring that the generic versions of BCS class III drugs like Dapagliflozin, Empagliflozin, and Linagliptin demonstrate comparable dissolution profiles to the innovator products.[9] This streamlined approach can expedite the availability of affordable generic alternatives for patients while maintaining the necessary quality and efficacy standards, particularly for drugs in this class with specific pharmacokinetic characteristics. However, it's crucial to note that the US FDA, for instance, only allows BCS class I drugs to have bioequivalence waivers, while class III drugs require a BA-BE study. This variance in regulatory practices between countries raises questions about the appropriateness of granting bio-waivers for BCS class III drugs and highlights the importance of rigorous evaluation to ensure patient safety and therapeutic equivalence in all regions.[10]

IN VITRO- IN VIVO CORRELATION (IVIVC)

The correlation means a scientific approach to describe the relationship between an *in vitro* attribute of a dosage form (e.g., the rate or extent of drug release) and a relevant *in vivo* response (e.g., plasma drug concentration or amount of drug absorbed). This model relationship facilitates the rational development and evaluation of extended-release dosage forms as a surrogate for bioavailability and/or BE testing, as well as a tool for formulation screening and setting of the dissolution/drug release acceptance criteria.

CONDUCT OF BA/BE STUDIES

BA/BE study should be conducted only in the BA or BE study centre registered with the Central Licencing Authority under rule 47 and to be registered with CTRI maintained by the ICMR before enrolling the first subject for the study. It is to be conducted in accordance with the approved study protocol and other related documents and as per requirements of GCP guidelines and provisions of these rules.

BA/BE studies are done for the reasons: BE study is a surrogate marker for clinical effectiveness and safety data, as it would not normally be necessary to repeat clinical studies for generic products; and to reduce the cost and the time taken for introducing the drug in the market.

IMPACT OF THE DRUG SWITCHING

Reference and generic drugs are not the same although they contain the same active pharmaceutical ingredient (API). Small differences will result in the change of efficacy or safety of the drug. The clinicians should avoid unplanned or unnecessary switching (reference product to generic or the vice-versa). The patient should be informed to report soon if there is presence of negative consequences following switching. In case of doubt, the clinicians should directly communicate with pharmacists to make sure that the pharmacists recognize the differences between the reference and generic products. The below mentioned examples show that switching of the drugs is not required unless the patient has adverse effects or non-compliant.

Generic and brand name Levothyroxine are not bioequivalent in hypothyroidism due to decreased thyroid reserve. This shows that the levothyroxine formulations

should not be substituted in children less than 3 years of age having congenital hypothyroidism. Before switching of the formulations, the clinician should be aware of the important implications where precise titration of levothyroxine is essential. Generic substitution should be made very cautious in formulations involving levothyroxine formulations since small differences between the formulations can cause significant changes in TSH levels.[11] In the study done by Narayanasamy et al where there is comparison between generic and branded latanoprost, the magnitude of lowering of intra-ocular pressure in primary open angle glaucoma is different. Latanoprost developed by Pfizer has better reduction in IOP in comparison with generic latanoprost.[12]

Imatinib is used as standard therapy for patients with chronic myeloid leukaemia (CML). In 2016, a generic formulation of imatinib entered the market in USA. The study done by Dalle et al showed that a change from original to generic imatinib maintained the efficacy and safety of the drug.[13] The shifting of original to generic drugs was done in 38 patients and adverse events were well tolerated. Major molecular response (MMR) was taken as the outcome parameter and it is defined as *BCR-ABL1/ABL1* transcript ratio ≤0.1% on international scale (IS), and molecular response being 4.5 as a ratio of ≤0.0032% IS. This study finding needs to be confirmed in a larger sample size with longer duration of follow-up period.

The therapeutic drug levels achieved with innovator itraconazole is higher compared to the generic one in patients with chronic pulmonary aspergillosis. The levels were measured at 2 weeks, 3 months and 6 months and 73% of innovator group of drugs achieved therapeutic drug concentration at 2 weeks in comparison with 29% of the levels in generic group.[14]

The impact of generic is high since the physician should not change the brand of the drug since it may affect the normally controlled blood pressure and may result in sudden rise of BP leading to cardiac arrest.[15]

In a recent cross-sectional observational study focusing on the post-off-patenting period of vildagliptin, a key antidiabetic medication, the availability of its branded generics and the resultant switching patterns among patients were scrutinized over a three-month interval. This study unveiled that patient, on average, needed to visit pharmacies 2.29 times to find their prescribed branded generic vildagliptin, underscoring the challenge of consistent drug availability. Notably, when faced with unavailability, 28% of patients shifted to the innovator brand, 41% opted for alternative branded generics, while only 31% adhered to the initially prescribed branded generic. These findings highlight a significant deviation from prescribed medication regimens, potentially jeopardizing treatment adherence and outcomes. The study calls for improved strategies to ensure the availability and accessibility of branded generics, advocating for better coordination among healthcare providers, pharmaceutical companies, and pharmacies to bolster patient care without sacrificing affordability.[16]

ROLE OF EXCIPIENTS

Excipient reactions occur due to the presence of toxic substances like diethylene glycol or due to use of the excipients in low-birth-weight neonates or in patients having history of asthma. The package insert regarding the drug should enlist the presence of excipients in accordance with good manufacturing procedures to make aware of the practitioners and to the drug information centres. Excipients will not be always biologically inert.[17]

The active pharmaceutical ingredient (API) does not differ between generic and innovator products while other active ingredients called excipients are found to cause toxicity and side effects.[18] The cough syrups contaminated with diethylene glycol or ethylene glycol imported to Gambia from India has resulted in acute kidney injury in children.

DATA WITH STATINS

The data with generic statins (e.g. atorvastatin) contain a methylated impurity that reduces HMG-CoA reductase inhibitory effects. All the generic formulations of atorvastatin contain high levels of methyl ester impurity (16.0±6.5% by relative mass signal) tested by LC-MS analysis in comparison with the trace levels observed with crystalline sustained release preparation of atorvastatin.[19] The generic form of atorvastatin is found to produce increase risk of adverse events in comparison with innovator drug. This will affect globally the management of patients with hypercholesterolemia who take generic group since due to the increased presence of the impurities. The impurity present in rosuvastatin affects the shelf-life of the drug and the stability of the drug formulation.

DATA WITH DAPAGLIFLOZIN

Dapagliflozin, a SGLT2 inhibitor, a chiral molecule with 5 stereogenic centres. The right stereogenic centre is vital for the drug's bioavailability, rate of metabolism, metabolites, excretion, potency and selectivity for receptors, transporters and/orenzymes, and toxicity. Cardiorenal benefits were shown only with innovator dapagliflozin and not with the generic drug.[20]

The statement "generics only prove bioequivalence to innovators" underscores the critical importance of demonstrating bioequivalence for generic pharmaceuticals compared to their innovator (brand-name) counterparts. In the realm of organic molecules, even a slight spatial rearrangement can result in a completely different compound, and this is particularly relevant when dealing with chiral molecules like dapagliflozin, which boasts five stereogenic centers. Having the right stereogenic center configuration is the key to ensuring appropriate bioavailability, rate of metabolism, metabolite formation,

excretion rates, potency, selectivity for receptors, transporters, and/or enzymes, as well as toxicity. These factors can vary significantly between enantiomers of a chiral drug like dapagliflozin, which highlights the necessity for generic pharmaceuticals to not only be chemically equivalent to innovator drugs but also demonstrate precise bioequivalence. This stringent requirement ensures that the spatial arrangement of atoms within the molecule aligns closely with the innovator product, guaranteeing both efficacy and safety for patients.

CONCLUSION

To conclude, the generic drug is accessible to all population at a cheaper rate but the presence of impurities should be borne in mind while selecting the drug and the clinician should monitor the shifting of branded drug since that will affect the therapeutic outcomes in a patient. The criteria of bioequivalence should be made stringent in our country to use generic drug rather than using the innovator product.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Swaters D, van Veen A, van Meurs W, Turner JE, Ritskes-Hoitinga M. A History of Regulatory Animal Testing: What Can We Learn? Altern Lab Anim. 2022;50(5):322-9.
2. Ridings JE. The thalidomide disaster, lessons from the past. Methods Mol Biol. 2013;947:575-86.
3. Al-Jazairi AS, Bhareth S, Eqtefan IS, Al-Suwayeh SA. Brand and generic medications: are they interchangeable? Ann Saudi Med. 2008;28(1):33-41.
4. Joshi SS, Shetty YC, Karande S. Generic drugs - The Indian scenario. J Postgrad Med. 2019;65(2):67-9.
5. Chow SC. Bioavailability and Bioequivalence in Drug Development. Wiley Interdiscip Rev Comput Stat. 2014;6(4):304-12.
6. Jiang W, Makhlouf F, Schuirmann DJ, Zhang X, Zheng N, Conner D, et al. A Bioequivalence Approach for Generic Narrow Therapeutic Index Drugs: Evaluation of the Reference-Scaled Approach and Variability Comparison Criterion. AAPS J. 2015;17(4):891-901.
7. BPAC-Better Medicine. Available at: https://bpac.org.nz/bpj/2009/generics/docs/bpjse_generics_bio_pages_ 4-8.pdf. Accessed on 12 September 2023.
8. Larregieu CA, Benet LZ. Drug discovery and regulatory considerations for improving in silico and in vitro predictions that use Caco-2 as a surrogate for human intestinal permeability measurements. AAPS J. 2013;15(2):483-97.
9. Benet LZ. The role of BCS (biopharmaceutics classification system) and BDDCS (biopharmaceutics drug disposition classification system) in drug development. J Pharm Sci. 2013;102(1):34-42.
10. Benet LZ, Larregieu CA. The FDA should eliminate the ambiguities in the current BCS biowaiver guidance and make public the drugs for which BCS biowaivers have been granted. Clin Pharmacol Ther. 2010;88(3):405-7.
11. Carswell JM, Gordon JH, Popovsky E, Hale A, Brown RS. Generic and brand-name L-thyroxine are not bioequivalent for children with severe congenital hypothyroidism. J Clin Endocrinol Metab. 2013;98(2):610-7.
12. Narayanaswamy A, Neog A, Baskaran M, George R, Lingam V, Desai C, et al. A randomized, crossover, open label pilot study to evaluate the efficacy and safety of Xalatan in comparison with generic Latanoprost (Latoprost) in subjects with primary open angle glaucoma or ocular hypertension. Indian J Ophthalmol. 2007;55(2):127-31.
13. Abou Dalle I, Kantarjian H, Burger J, Estrov Z, Ohanian M, Verstovsek S, et al. Efficacy and safety of generic imatinib after switching from original imatinib in patients treated for chronic myeloid leukemia in the United States. Cancer Med. 2019;8(15):6559-65.
14. Sehgal IS, Vinay K, Dhooria S, Muthu V, Prasad KT, Aggarwal AN, et al. Efficacy of generic forms of itraconazole capsule in treating subjects with chronic pulmonary aspergillosis. Mycoses. 2023;66(7):576-84.
15. Blier P. Brand versus generic medications: the money, the patient and the research. J Psychiatry Neurosci. 2003;28(3):167-8.
16. Samajdar SS, Mukherjee S, Sarkar S, Sen S, Tripathi SK, Joshi SR. Availability of different branded generic vildagliptin after off-patenting: An observation from India. J Diabetol. 2023;14(4):236-38.
17. Tyrer JH, Eadie MJ, Sutherland JM, Hooper WD. Outbreak of anticonvulsant intoxication in an Australian city. Br Med J. 1970;4(5730):271-3.
18. Dunne S, Shannon B, Dunne C, Cullen W. A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. BMC Pharmacol Toxicol. 2013;14:1.
19. Richard Preston Mason, Robert F. Jacob, Seth A. Gerard. Atorvastatin Generics Obtained from Multiple Sources Worldwide Contain a Methylated Impurity that Reduces Their HMG-CoA Reductase Inhibitory Effects. J Clin Lipidol. 2013;7(3):287.
20. Dhillon S. Dapagliflozin: A Review in Type 2 Diabetes. Drugs. 2019;79(10):1135-46.

Cite this article as: Samajdar SS, Venkatraman S, Joshi S, Biswas K, Saboo B. Truth in a pill. Int J Basic Clin Pharmacol 2024;13:408-12.