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Perceptions and Challenges for Adoption of Generics and Biosimilars in Oncology

Amit Garg, Deepak CSN and Tarveen Jandoo

Abstract

Cancer care is increasingly becoming challenging in low resource settings. With the improved availability and access of generic medicines and biosimilars, cost-effective and affordable treatment can be offered to cancer patients. However, generics and biosimilars continue to be plagued with negative perceptions that impact the adoption of these products. Lack of understanding and negative perceptions regarding the quality, safety, effectiveness, integrity and stability, formulations, manufacturing, and costs of generics and biosimilars are more common in the developing countries. Their equivalence to innovator counterparts is often doubted. Collaborative efforts for enhanced utilization of generics and biosimilars in oncology should be made by physicians, healthcare professionals, manufacturers and sponsors of these drugs, and national healthcare systems. Steps to improve access and utilization of these drugs include procurement of high-quality generics and biosimilars, formulary management, supply chain integrity, continued safety surveillance, and educational programs to improve knowledge mitigate fears in healthcare professionals and patients. Objective and standard frameworks should be developed and used to identify the perceptions and factors impacting the adoption of generics and biosimilars. Outcomes in hematological malignancies can be improved with the adoption of generics and biosimilars, in particular in low-income countries where access and affordability of chemotherapy is challenging.

Keywords: generics, biosimilars, perceptions, adoption, oncology

1. Introduction

Generic medicines find application in both chemotherapy and supportive care in oncology. Generics are increasingly available for small molecules and biologic agents used in oncology treatment regimens.

Generic medicines are pharmaceutical drugs that have the same chemical substance, i.e., the same active pharmaceutical ingredient (API), as that of the originator drug. According to the US Food and Drug Administration (FDA), “a generic drug is a medication created to be the same as an existing approved brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use [1].” According to the European Medicines Agency (EMA), “a generic medicine is developed to be the same as a medicine that has already been authorized, called the reference

Parameter	Generic drug	Biosimilar
Manufacturing	Simple and predictable	Stepwise to produce compound as similar as possible to the originator biologic
Immunogenicity	Low potential	No increase in comparison to the reference biologic
Regulatory approvals	Small trials in healthy volunteers/patients	At least one study including assessments of pharmacokinetics, pharmacodynamics, and immunogenicity

Table 1.
Key differences between generic medicines and biosimilar agents.

medicine [2].” These regulatory directions of similarity imply the possible substitution of innovator products with generic medicines. According to the World Health Organization (WHO), a generic is a ‘multisource pharmaceutical product which is intended to be interchangeable with the comparator product.’ This also includes an originator brand for which the patent has expired. WHO has distinguished between originator brand, regardless of its patent status, and lowest-priced generic equivalents [3]. Biosimilars are defined as biologic products that are highly similar to reference products, notwithstanding minor differences in clinically inactive components. Biosimilars have no clinically meaningful differences to the reference product in terms of safety profile, purity, and potency [4]. Both generics and biosimilars are widely used in cancer care. However, there are several differences between the two agents (**Table 1**) [5].

Generic medicines may differ from the originator products in the manufacturing processes. There may be subtle differences in the excipients, color, and packaging. Sometimes, generic medicines may also have different formulations. According to the EMA, “a generic medicine’s inactive ingredients, name, appearance and packaging can be different [2].” Approval of generics and biosimilars are granted after confirmation of evidence of biophysical similarity to the originator reference products. This is a proxy to similarity in the clinical effectiveness and safety of generics and biosimilars. Generics and biosimilars are approved only when there is ‘totality of evidence’ for similarity to the reference originator product. This includes robust scientific data for parameters of structural analysis, preclinical, pharmacokinetic, efficacy and safety, and immunogenicity.

2. Regulations around generics

Various countries have regulations for the development and availability of generic medicines. Generic medicines can be marketed in a country only after a marketing authorization has been obtained. The US FDA requires generics to be identical to the originator products in pharmacokinetic and pharmacodynamic properties. There are defined parameters for establishment of bioequivalence of generic medicines to their branded counterparts. The FDA’s Office of Generic Drugs (OGD) has a vigorous review process facilitating the approval of generic medicines of high quality [6]. The FDA also has clear directions for the development, review, and approval of biosimilars [7]. In the EU, the EMA reviews the quality standards and other parameters to establish the equivalence of a generic medicine to its innovator counterpart [8]. Various countries have described regulations for the production, review, and approval of generics though the regulatory frameworks are not equally mature in all countries [9, 10].

3. Use and impact of generics

Generic medicines are increasingly being used in most countries across the world. In the US, 9 out of 10 prescriptions are said to have a generic drug [1]. In the European Union (EU), about 20–80% prescriptions are filled with generics [11]. However, lower utilization of generics is reported in the lesser developed countries [12]. Not all generic medicines are available in all countries. Both generics and biosimilars are widely used in hematological malignancies. Examples include lenalidomide for multiple myeloma, rituximab for Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and filgrastim for febrile neutropenia.

3.1 Cost reduction

Generic medicines are lesser priced when compared to the innovator products and offer affordable options in management of various disease conditions including cancer [4, 13]. This has special relevance in low-income countries as it improves access and compliance to therapeutic options. Treatment regimens are associated with huge costs in oncology settings. The lesser price of generics and biosimilars is reflective of the abbreviated pathways to regulatory approvals.

The widespread use of generics has favorably influenced the national health-care spending. The utilization of generics is influenced by various factors such as physician recommendations, pharmacy practices, patient preferences, and the economic status of the patient. The use of biosimilars is reported to have an average of 20–30% cost-saving effect [14].

3.2 Improved compliance

The affordability of generics and biosimilars offers an opportunity for sustained engagement and adherence of patients to the treatment regimens [15]. This is of greater relevance in oncology where therapeutic options are expensive and treatments last long periods [16]. High costs of treatment are a common impediment in the management of cancer. Reduction of costs leads to enhanced access and adoption of generics [17, 18].

4. Perceptions and adoption of generics

Though generic medicines have been available for several decades, there is paucity of knowledge about what these medicines are and how these differ from their innovator counterparts. There is also a lack of understanding about the standards described for the approval and market authorization of generics and how these drugs have a lower cost [19].

There are lacunae in knowledge about generics in physicians, healthcare professionals, and patients. This is evident in the perceptions that healthcare professionals and patients have for generics and biosimilars. These perceptions drive the apathy or antipathy for generics and impact the adoption of generics in routine practice. There are mixed perceptions regarding the use of generic medicines. The perceptions differ in various countries. While physicians in the high-income countries generally have positive perceptions for generics, those in the low-income countries generally have more negative perceptions [12, 20]. Controversies have emerged regarding the adoption of generics for brand substitution [21]. The differences in perceptions can be attributed to various factors including the regulatory milieu, healthcare policies, educational initiatives, and drug information sources.

Perceptions regarding generics and biosimilars and attitudes of physicians, healthcare providers, and patients impact the use of generics (**Figure 1**). Several factors may impact the acceptance and use of generics. These factors are diverse and include increased knowledge about the regulated approval of generics and biosimilars and the increased awareness regarding generics from the access to information in social and scientific platforms.

Perceptions and levers for adoption of generics may be grouped into four broad categories (**Figure 2**).

4.1 Effectiveness

Though generic medicines have an established equal effectiveness to their innovator counterparts and are intended to be interchangeable with the latter, they

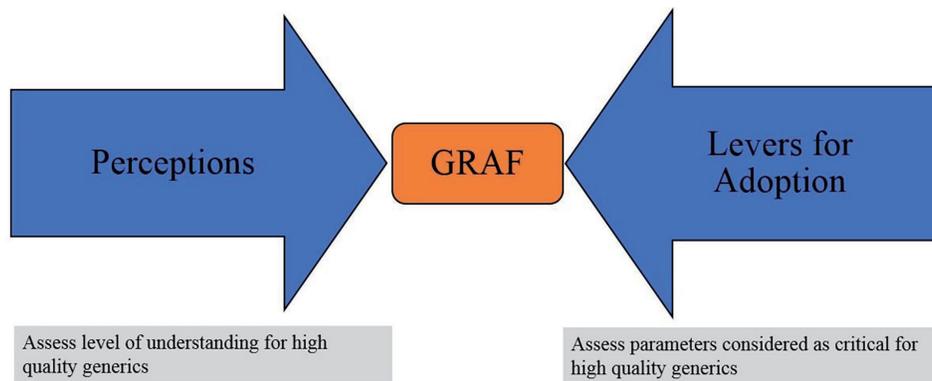


Figure 1. Use and adoption of generics and biosimilars. GRAF (generic dRug adoption framework) is a tool to identify and differentiate high quality generics.

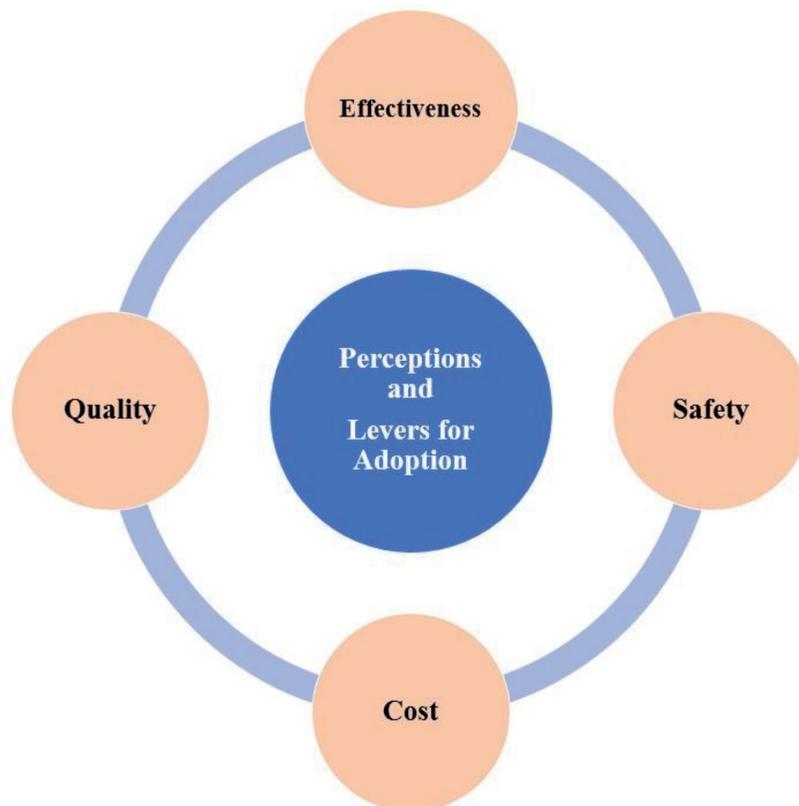


Figure 2. Components of perceptions and levers for adoption of generics.

are perceived to be less efficacious effective. Physicians and healthcare professionals need to understand how confirmation of similar clinical outcomes is key to the regulatory review process for the approval of generics and biosimilars. Bioequivalence is a standard and reliable measure to confirm the similar effectiveness of generics and their branded counterparts. Bioequivalence is a dependable proxy for similar clinical effects [22]. Therapeutic benefits are maintained when patients receiving innovator drugs are switched over to generic options of the same dosing. In the setting of oncology, this switch is not reported to impact the cytogenetic or molecular response [23]. The demonstration of equivalence and increasing awareness for the same can help physicians and healthcare professionals in easy decision making for a switch to generic options.

4.2 Safety

The likely differences in manufacturing and excipients between generics and innovator products raise concerns about the safety of generics. Safety is usually measured in terms of the number and frequency of adverse effects with the clinical use of a pharmaceutical product. There is no established evidence for the inferiority of generic medicines for any safety parameters. However, there is a growing trend towards the enhanced reporting of safety experiences with generics. This is suggestive of increased surveillance for the safety of generics [24, 25].

Continued safety monitoring is increasingly being applied to generics and biosimilars. Any efforts made to set up such systems build trust and acceptance for the generic molecules. The exposure of generics to stringent pharmacovigilance practices in the regulated markets are a proxy to established safety of the products. The safety monitoring systems in the regulated markets are mature and reliable. These systems allow for the easy identification of generics in the reports. For example, in the US, the FDA adverse event reporting system (FEARS) enables the identification of generic drugs in the safety reporting systems [26]. If approved and marketed in countries with such regulations, generic medicines are perceived to hold a promise of safety. This facilitates the easy adoption of such approved products.

4.3 Cost

Generic medicines and biosimilars are perceived as low-cost alternatives to expensive originator anticancer drugs. Many patients perceive generics as less efficacious; physicians and pharmacists continue to doubt the safety of generics [27]. These perceptions impact the utilization of generics.

There are smaller price differentials between biosimilars and biopharmaceuticals when compared to generics and their comparator originators. This is explained by the longer development time and larger research costs for biosimilars. Cost-effectiveness and cost-utility analyses are being used to establish the economic benefits of adopting biosimilars. Such economic evaluations have a role in checking the rapidly rising healthcare expenditures [28]. However, there is a lack of regulatory directions for the most appropriate techniques of economic evaluation for generics and biosimilars.

The benefits of cost saving options are manifold. Patients may seek affordable options, physicians may be reassured by the willingness and ability of patients to complete the therapy, and payers may view this as a pharmacoeconomic reform. The WHO has described cost of therapy as a key component of rational prescribing [29].

Payers, physicians, and patients are developing an incline to evaluate the pharmacoeconomics of generics and biosimilars periodically throughout the life cycle of the product. This is explained by the increasingly available experience in the

real-world settings with these products. Economic efficiency is not solely determined by the relative costs of generics and comparators. It is ideally defined by the attainable levels of efficiency and safety with the use of lower-priced options. This eventually constitutes the quality of the generics and biosimilars [30]. In a cost minimization study in Colombia, use of generic equivalents of bortezomib, decitabine and capecitabine resulted in substantial savings of 63% (USD 4.68 million), 26% (USD 0.29 million), and 46% (USD 1.50 million), respectively [31].

4.4 Quality

Quality is a key parameter that impacts the utilization of generics. It is important to understand the perceptions about quality of generics and also define what parameters define quality of generics.

The regulatory standards for approval of generics and biosimilars are guided by the principles of quality by design (QbD) [32]. This implies that science-driven and risk-based concepts underlie the development, scale-up, and manufacturing of generics and biosimilars. The yield of this approach is a high-quality generic product or biosimilar molecule with an implied clinical equivalence which may be validated in research studies and clinical experience. Quality is not alone limited to structural and chemical similarities during development; it also spans to the similarities of generic drugs to comparators in final formulations and packaging. Quality is also defined by testing for stability, sterility, and impurities. These data are an important and mandatory component of abbreviated new drug applications (ANDAs) [33]. The WHO has defined standards for good manufacturing practices (GMP) as a guide to the quality assurance of pharmaceutical products [34].

5. Challenges for switch and adoption

With the prevalent perceptions about generics, there are several likely challenges that physicians and patients can confront for the adoption of these drugs. Observational studies have confirmed doubts and unfavorable attitudes in physicians, pharmacists, and lay people for the effectiveness, safety, and quality of generic medicines [27]. There may be questions regarding the dependable and acceptable evidence for the effectiveness and safety of generics and biosimilars. There may be uncertainties regarding the acceptance of bioequivalence as a marker of similarity. These uncertainties may lead to cohesive discussions in media and scientific platforms which in turn may influence the decision-making for switch and substitution with generics and biosimilars.

Physicians may want to go for facility visits to understand and inspect the development and manufacturing of generics. This can build trust in the products and facilitate their early and easy adoption. Consistent product supply may be taken as a proxy to dependable quality and this can safeguard the trust in the product of a particular supplier. On the other hand, physicians may feel reassured regarding safety if the generic or biosimilar has been approved in a regulated market with clear guidance for development and approval of these products.

6. Efforts by companies and physicians

Physicians should make sustained efforts to discuss the most cost-effective therapeutic options with patients and help them to achieve desired outcomes at lower costs [35, 36]. This may be an important aspect of therapy in low income

countries with majority of patients belonging to the poorer segments [37]. Many of these countries have ill-defined reimbursement policies and healthcare management is largely an out-of-pocket expense. Not alone physicians, pharmacists have an important role in the switch and substitution of generics and biosimilars [14].

Company sponsored patient assistance programs (PAP) have a huge potential to improve access to generics and biosimilars. These programs offer medicines to eligible patients at no or minimal costs [38]. Companies should also make efforts to educate patients, inform physicians, and demonstrate benefits to payers for their products.

7. Role of healthcare systems

Healthcare systems should prepare for increased adoption of generics and biosimilars by procurement and formulary management, continued safety surveillance, and transformational reforms for mitigating the economic and operational challenges. A healthcare system should aim to allow an equitable access to essential medicines of assured quality, efficacy, and safety [39]. Policies and programs should aim to not only improve access but also build trust in medicine quality and healthcare systems [40].

Procurement of high-quality generics is the first and key step that acts as a gatekeeper to the access and adoption of generics and biosimilars in a particular country. These practices need to be standardized and implemented as nation-wide initiatives for successful utilization of generics. Efforts should be made to develop and design a prequalification scheme to assist countries lacking strong regulations in procurement of anticancer generics and biosimilars of assured quality [13].

Regulators are making constant efforts to improve the knowledge and understanding for the development and clinical use of biosimilars. In collaboration with the European Commission, the EMA has formulated an information guide for healthcare professionals to educate them about the development, approval, effectiveness, safety, switch, substitution, and interchangeability of biosimilars [8]. Such efforts need to be replicated by the healthcare systems in countries with poor regulations. Manufacturers can collaborate with the healthcare systems to plan and implement educational programs for physicians, pharmacists, and patients. Physicians should be educated for the criteria of equivalence, safety and vigilance, and manufacturing processes adopted for developing high-quality generics and biosimilars.

There is lack of unawareness for the costs of pharmaceutical therapies in physicians [41]. Educational programs should aim to improve understanding for the lower costs of generics and biosimilars and the implications of this on overall cost of therapy.

Payers should be encouraged to develop appropriate reimbursement policies that will encourage the use of generic medicines in routine clinical practice. Further, a pool of generic suppliers should be identified to ensure an uninterrupted availability of these medicines [13]. Generic medicines and biosimilars should be included in the national lists of essential medicines and should be part of national formularies. The integrity of supply chains should be maintained and circulation of counterfeit or substandard products should be discouraged. Lack of constant drug supplies can lead to mistrust in patients and lack of confidence in physicians and healthcare systems. All these factors compromise clinical care in oncology where treatments are phased and last longer.

8. Recommendations

Most experience about the knowledge and perceptions regarding generics comes from interviews and surveys conducted in cross sections of populations in various

countries [12, 27, 42, 43]. There is lack of a standard approach for the assessment of knowledge, attitudes, and perceptions about generics. In addition, factors impacting the utilization of generics have not been precisely determined. Sustained and collaborative efforts should be made to understand the perceptions for generic medicines and mitigate the same.

Educational initiatives should be introduced by manufacturers of generics and biosimilars and healthcare systems to improve knowledge about these drugs and develop positive attitudes towards their adoption. This will empower physicians, patients, and pharmacists to make rational choices in therapy and improve outcomes of cancer care.

Uniform standards should be developed for high-quality generics and these need to be implemented at global levels. Maiden efforts in this direction include tools like the generic dRug adoption framework (GRAF) (**Figure 1**). This framework, comprising a 20-item questionnaire, has been developed to enable physicians and pharmacists to make decisions to identify and differentiate high quality generics and facilitate interchangeability. Currently available in three languages (English, Spanish, and Portuguese), the framework has successfully been implemented in Brazil and Colombia. More and more countries should adopt such objective measures to evaluate the perceptions and adoption of high-quality generics. Insights gained from the experience of such frameworks can help to make further reforms to allow the identification, procurement, and prescription of high-quality generic medicines. This can advance the use of cost-effective solutions in cancer care.

9. Conclusions

Availability of generics and easier access to these drugs can impact the outcomes in oncology settings. The low-priced and affordable generic medicines and biosimilars can improve the adoption and compliance with treatment options in cancer care. However, the low price of these drugs is often construed as compromise in quality. There are myriad perceptions for the use of generics and biosimilars in routine practice. The perceptions are different among physicians in high- and low-income countries; these can possibly be due to differences in regulations and policies, educational opportunities and available drug information sources. Factors like cost, quality, effectiveness, and safety impact the understanding for and adoption of generics and biosimilars. There are several challenges in the substitution and switch from originator products to generics and biosimilars. The widespread and confident adoption of generics requires collaborative efforts of prescribers, healthcare professionals, payers, and the manufacturers of these agents.

Conflict of interest

The authors have no conflicts of interest.

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