Development of Drug-Device Combination Products and Generic Substitution in the United States: An Overview

Ila Srivastava*, PharmD;[1] YoonJung Lee*, PharmD, PhD;[1] Katharine B. Feibus, MD;[1] Elizabeth R. Bielski, PhD;[1] Lolita Sterrett, PharmD;[1] Danielle M. Harris, PharmD;[1] Markham C. Luke, MD, PhD[1]

[1]Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 20993

*These authors contributed equally to this work

Abstract

Generic drug products approved and marketed in the United States include a variety of drug classes and dosage forms along with drug-device combination products (DDCPs). Development of DDCPs can pose scientific, regulatory, and legal challenges, and the Food and Drug Administration (FDA) has prioritized efforts to work with industry to improve scientific methodologies and application quality in an effort to provide quicker access to high-quality generic DDCPs. Once these products become available in the market, the roles of pharmacists and other healthcare providers (HCPs) become crucial. When prescribing, HCPs should provide risk/benefit counseling and, to prevent medication errors, teach patients about the proper use of these products. This review provides a comprehensive overview of the regulatory and developmental processes of generic DDCPs to help pharmacists and other healthcare professionals engage more effectively with patients.

Keywords: drug-device combination product, therapeutic equivalence, generic substitution, regulatory, generic, complex product

Introduction

Pharmacists play an essential role in providing pharmaceutical care to patients for management of various medical conditions. Pharmacists perform a number of clinical activities, including but not limited to appropriate medication selection and substitution, monitoring of drug-drug interactions, medication education, counseling patients about appropriate medication use and potential side effects, and promotion of medication adherence.[1] The pharmacist's role becomes especially critical when substituting a generic drug product for its brand product.

Generic drug products are approved based on their "sameness" to a particular innovator or brand name product (approved through a new drug application, or NDA), which is defined as a reference listed drug (RLD) by the United States (U.S.) Food and Drug Administration (FDA).[2] A generic drug is bioequivalent and pharmaceutically equivalent to its brand name product and has the same quality, performance characteristics, and intended use.[3-5] These regulatory requirements support the approval and marketing of generic drug products by ensuring that a generic has the same clinical effect and safety profile as its RLD. An RLD and its generics are called "therapeutic equivalents."

Corresponding Author:
YoonJung Lee
Yoonjung.Lee@fda.hhs.gov

A DDCP is a product comprised of both a drug constituent part and a device constituent part. Compared to simple drug products, like an oral tablet or capsule, the complexity of DDCPs may raise new questions about generic substitution for prescribers, pharmacists, patients, and caregivers. Patients and caregivers may raise questions about a generic DDCP, such as:

1. Why am I getting the generic instead of the product I usually get?
2. Does this product work in the same manner as the brand product I have been using?
3. How do I use this product?
4. How long has this product been on the market?
5. What are the side effects of this product?
6. What is the price difference between the generic and brand products?

There is a paucity of current scientific literature to support prescribers and pharmacists when making decisions about generic substitution for DDCPs. Therefore, the objective of this paper is to discuss how the Office of Generic Drugs (OGD) within the U.S. FDA evaluates generic DDCPs to ensure therapeutic equivalence and generic substitutability at the pharmacy level.

Current Status of Generic Drug Substitution in the United States

Throughout the U.S., and consistent with the laws of individual states, generic drugs are increasingly substituted for brand products. Each state has laws regulating whether and how pharmacists can substitute generics when filling prescriptions

for brand name drugs. This substitution may be mandatory or permissive, and prescriber and/or patient consent may be required. Insurance companies that provide prescription drug coverage often require generic substitution, and patients paying for medications out-of-pocket often rely on the cost savings offered by generic drugs.

The phrase "shall substitute" is used in the laws of states that mandate generic drug substitution, while the phrase "may substitute" is used in states that permit generic drug substitution. The number of states mandating generic drug substitution has grown, from 11 in 2008[6] to 16 in 2024 (see Figure 1 on page 10, Supplementary Table 1). This change may lead to an increase in the dispensing of generics at the pharmacy level, which plays a pivotal role in the growth of prescription drug expenditures. The increased use of generics also helps lower drug prices and improves access to drugs for American patients and consumers.[7]

Some states have additional requirements for generic drug substitution. In South Carolina,[8] for example, the pharmacist cannot substitute a drug product unless the practitioner authorizes generic drug substitution through either written (e.g., signing on the line stating "SUBSTITUTION PERMITTED" on the handwritten prescription) or verbal communication. Other states mandate generic drug substitution by the pharmacist. For example, in Washington state[9], generic drug substitution is mandated with the exception of authorizing refills for certain drug classes (i.e., antipsychotic, antidepressant, antiepileptic, chemotherapy, antiretroviral, immunosuppressive drug, immunomodulator/antiviral treatment for hepatitis C) or prescribers prohibiting generic drug substitution. Given the significant variations that exist among state laws for generic drug substitution, it is crucial for pharmacists to familiarize themselves with the most up-to-date requirements for the state(s) in which they practice. Pharmacists can also refer to FDA's *Approved Drug Products with Therapeutic Equivalence*, known as the Orange Book, to determine which products can be substituted for one another.[10] The Orange Book is a regulatory resource that provides a listing of drug products that are approved based on safety and effectiveness standards, along with patent and exclusivity information that is helpful for applicants to consider when submitting generic drug applications. Anyone can access the Orange Book online via https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.

Despite the impacts of U.S. state regulations on generic substitution, several studies have reported that generic drug substitution helps to lower drug costs and improve medication adherence.[11-18] In the U.S., both federal and state governments give pharmacists significant responsibility in helping control drug costs through effective generic substitution. Pharmacists consequently play a unique and vital role in the drug dispensing decision making process and in counseling patients about generic drug substitution.[19]

Regulatory Standards for Generic Products: Ensuring Sameness and Substitutability

The FDA approves an application for a generic drug product if the data submitted to the FDA demonstrate that the proposed generic product will have the same safety and effectiveness as its RLD. Before a generic product can be considered "therapeutically equivalent" to its RLD, it must demonstrate that it is bioequivalent and pharmaceutically equivalent to its RLD (Figure 2). The Federal Code of Regulations (CFR), at 21 CFR 314.3(b),[4] defines bioequivalence (BE) as the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in two pharmaceutically equivalent drug products becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

This same regulation also defines pharmaceutical equivalents as drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient or, for modified-release dosage forms, deliver identical amounts of the active drug ingredient over the identical dosing period, and meet identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. Due to the differences in criteria for BE and pharmaceutical equivalence (PE), certain products can be considered bioequivalent only, pharmaceutically equivalent only, or both; all approved generic drug products, however, must be both bioequivalent and pharmaceutically equivalent to their RLD. For example, even if there is a difference in rate (e.g., in certain extended-release dosage forms), certain pharmaceutical equivalents may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action.

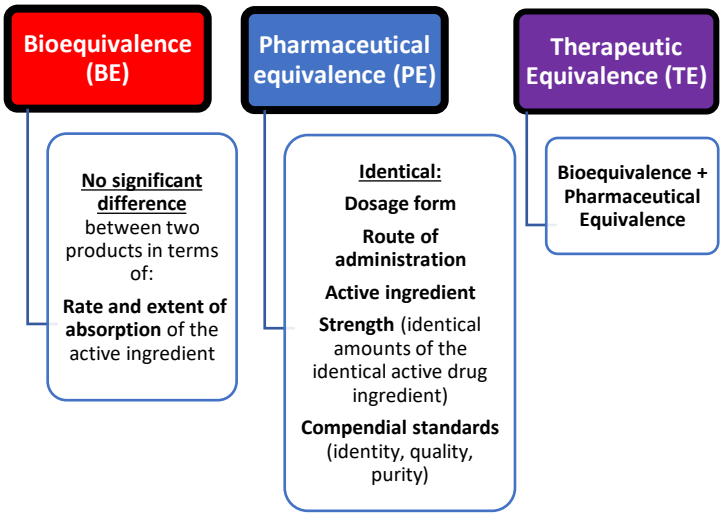


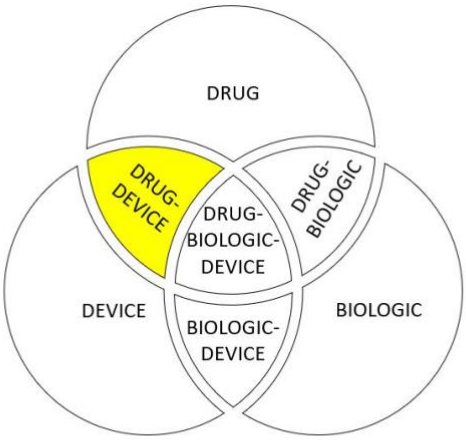
Figure 2. Illustration of the various aspects that constitute therapeutic equivalence (TE)

Therapeutic equivalents are approved drug products that are pharmaceutical equivalents for which BE has been demonstrated. Therapeutically equivalent products are expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.[4] A new drug application submitted to FDA for a generic drug is called an abbreviated new drug application (ANDA) because a generic drug relies on the demonstration of safety and efficacy for its RLD and does not need to submit additional toxicology and clinical studies to support those claims. However, an ANDA must include studies demonstrating that the proposed generic drug is bioequivalent to the RLD. As discussed in 21 CFR 320.24, BE studies may include in vivo and/or in vitro BE study designs and methods depending on the purpose of the study, the analytical methods available, and the nature of the drug product.[20] There are a couple of exceptions to the requirement to demonstrate BE between a generic and its RLD in an ANDA. For example, BE studies, for example, are waived for generic injectable solutions with formulations identical to the RLD because BE is considered self-evident. Otherwise, an ANDA includes the same types of quality, performance, stability, manufacturing, and compliance information and data as an NDA for an innovator drug.

The FDA approves a generic drug for marketing only if, based on review of all data and information submitted in the ANDA, it believes the generic drug will have the same safety, effectiveness, and quality as the RLD when used as recommended in product labeling. At the time of ANDA approval, a generic drug or DDCP is considered therapeutically equivalent to its RLD – it is expected to produce the same clinical effect and safety profile as the RLD under the conditions specified in the product labeling and can be substituted for its RLD. There have been instances where an approved generic drug product lost its TE rating to the RLD after a period of marketing because, as use of the generic drug expanded in a broader patient population, differences in clinical effectiveness or safety emerged. When a signal emerges suggesting that a generic drug may have a different risk profile than its RLD, experts from multiple scientific disciplines across multiple FDA offices collaborate to make an informed and thoughtful decision about whether to change a generic drug product's TE rating. When the TE rating is changed, the generic can no longer be substituted for its RLD at the pharmacy. While changes to TE ratings are rare, and less likely to occur with scientific advancements and with modernization of the generic drug program, the FDA continues to carefully monitor for post-approval signals suggesting differences between the risk profiles of a generic drug and its RLD.

Regulatory and Approval Standards for Generic Drug-Device Combination Products (DDCPs)

Federal Regulations define a combination product as a product comprised of two or more regulated components (e.g., drug and device, biologic and device, drug and biologic, or drug and device and biologic).[21] Figure 3 shows the various types of combination products.



Per 21 CFR 3.2(e), a combination product includes (1) drug/device, (2) biologic/device, (3) drug/biologic, or (4) drug/device/biologic that are physically, chemically, or otherwise combined or mixed and produced as a single entity.

Figure 3. The different types of combination products as per 21 CFR 3.2(e).[21]

Drug-device combination products (DDCPs) include a drug constituent part and a device constituent part. The FDA's Office of Combination Products determines whether the drug or the device provides the majority of the product's therapeutic effect, and this constituent is considered to be the primary mode of action. When a DDCP has a device primary mode of action, the product is reviewed and regulated by FDA's Center for Devices and Radiological Health (CDRH) in consultation with the FDA's Center for Drug Evaluation and Research (CDER). When a DDCP has a drug primary mode of action, the product is reviewed and regulated by CDER in consultation with CDRH. This paper focuses on DDCPs with a drug primary mode of action (also called "drug-led") that are approved under an ANDA. Examples of DDCPs include prefilled drug syringes, auto-injectors, metered-dose inhalers, dry powder inhalers, nasal sprays, transdermal delivery systems, and prefilled iontophoresis systems or microneedle "patches."

Most often, the RLD for a generic DDCP is also a DDCP, but not always. For example, some innovator injectable drugs are supplied in a glass vial. Before injection, the user must gather a syringe and a needle. Then, the user draws up the drug from the vial, adjusts the volume to the correct dose for administration, and injects the drug. In some cases, the FDA's Office of Generic Drugs has approved generic DDCPs presented in prefilled syringes or as drug vials packaged with a syringe and needles even though the generic product references an RLD that is a drug in a vial. These differences are

allowed because the generic drug presentation simplifies the drug preparation and administration process for the user.

As mentioned, there are different types of DDCPs based on how the drug and device constituent parts are supplied. Table 1 provides a summary of the regulatory definitions for single-entity DDCPs, co-packaged DDCPs, and cross-labeled DDCPs, along with some examples.

Table 1: Types of Drug-Device Combination Products

Single entity (21 CFR 3.2(e)(1)[21])	The drug and device constituent parts are physically, chemically, or otherwise combined into a single unit (e.g., metered dose inhalers, nasal sprays, auto-injectors, pen injectors, transdermal systems).
Co-packaged (21 CFR 3.2(e)(2)[21])	Separate drug and device constituent parts are packaged together (e.g., syringe packaged with vial of drug and vial adaptor, drug cartridge packaged with reloadable injection pen).
Cross-labeled (21 CFR 3.2(e)(3), 21 CFR 3.2(e)(4)[21])	The drug and device constituent parts are packaged and provided separately but the labeling (e.g., prescribing information, user guide, instructions for use) specifically state that the specific drug product and the device are intended for use only with each other or with a specific class of devices (e.g., nitric oxide and nitric oxide delivery systems, light-activated drug products such as Levulan Kerastick). Both the drug and the device are needed to administer the product.

The FDA regularly receives pre-application submissions and applications for generic versions of DDCPs. Some of these products have simple or non-complex devices such as oral dosing cups, oral dosing syringes, or a dosing card or dosing paper for topical application. Other DDCPs have complex devices such as various types of inhalers, injection pens and autoinjectors, transdermal systems, and inserters for subcutaneous and intrauterine drug-containing implants. DDCPs with a complex device are more likely to have multiple integrated parts and/or a more complicated user interface. Because some types of user interface differences could contribute to an increased risk of medication use errors when a generic is substituted, the FDA evaluates user interface differences between a proposed generic DDCP and its RLD to determine therapeutic equivalence.

Comparative Assessments for Generic Drug-Device Combination Products

Applications that support approval of a generic DDCP need to include comparative assessments to demonstrate that, when it is substituted for the RLD product, intended end-users (healthcare providers, patients, and/or caregivers) can use the generic as well as the RLD without any additional intervention by the health care provider and/or without additional training prior to use. While this does not mean the proposed generic needs to be identical to the RLD in all aspects, the user interfaces must be similar enough that the end user can use the generic product based on their knowledge of the RLD without an increased risk for medication use errors. User interface refers to all product components with which a user interacts, including the delivery device constituent part of the combination product, its associated controls and displays, and product labeling and packaging. Differences in the user interface between a proposed generic DDCP and its RLD must be identified and characterized in the ANDA. These differences may be permissible if they are adequately analyzed, scientifically justified, and if they do not add or change user tasks in a manner that could cause confusion and increase use errors that affect drug administration.

The analyses used to evaluate device user interface differences between a proposed generic combination product and its RLD are called "comparative analyses" (CA). As described in the FDA's draft guidance for industry, *Comparative Analyses and Related Comparative Human Use Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (January 2017)[22], CA should include three analyses:

- Physical comparison
- Task comparison
- Labeling comparison.

Critical Task Example: Tell the Story

A user is prescribed a dry powder inhaler. The instructions state that the user should insert a capsule into the inhaler, pierce the capsule with the piercing button, and then inhale the drug. Placing the capsule in the inhaler is a critical task, and piercing the capsule is another critical task. Failure to place the capsule in the inhaler could result in the patient swallowing the capsule instead of inhaling the contents. Failure to perform either one of these tasks could lead to lack of treatment effect and compromised medical care.

For the physical comparison assessment, the FDA recommends that the potential applicant of the proposed generic combination product acquire the RLD to examine its physical features, such as overall design, external dimensions/measurements, and external components, and compare them to those of the device constituent part(s) of the proposed generic combination product. In the comparative task analysis, the applicant should systematically dissect the use process for both the proposed generic product and the RLD, and analyze and compare the sequential and simultaneous manual and intellectual activities end-users must perform to correctly use each product. The FDA

recommends that applicants analyze the differences with the goal of characterizing the potential for use errors. In the labeling comparison assessment, the FDA recommends a side-by-side, line-by-line comparison of the full prescribing information, instructions for use, and descriptions of the delivery device constituent parts of the generic combination product and its RLD.

In general, the labeling (including the patient instructions for use) for a generic drug product should be the same as for the RLD product, except for permitted labeling changes as defined under 21 CFR 314.94(a)(8)(iv).[23] Permissible labeling differences are based on differences in manufacturer and include changing the following: the drug name from the brand name to the generic name, the name and contact information for the drug manufacturer, and the descriptive colors of device parts to accurately describe the generic device. On occasion, a specific difference in a labeled instruction will be viewed as permissible if it (1) relates to a device user interface difference between the RLD and proposed generic that the FDA considers "acceptable" and if (2) the difference accurately describes the correct use of the generic device. Other labeling differences between an RLD and its generics may occur based on an unexpired patent or an unexpired period of exclusivity on the RLD. For more information about patents and exclusivities, visit: https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-assistance-frequently-asked-questions-new-drug-product-exclusivity.

When performing CA between the user interfaces of a proposed generic DDCP and its RLD, the applicant should list one of the following three outcomes for each aspect of the user interface: no design differences, minor design differences, and other design differences. "No design difference" means that a particular user interface element is the same for the generic product and the RLD product. "Minor design differences" are differences in the generic user interface compared to the RLD that do not affect how users perform a critical task involved with drug administration. The FDA's draft guidance for industry, *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016),[24] defines critical tasks as user tasks that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user. "Harm" is defined to include compromised medical care (see "Critical Task Example" below).

"Other design differences" between the device user interfaces of the proposed generic and RLD are those that impact a design feature on which a user would rely to perform a critical task. Depending on the nature of the "other design difference," the applicant may need to include additional data in their ANDA to support that it will not affect the risk for medication use errors or the overall risk profile of the generic product when substituted for the RLD.

The types of information and/or data that can support the acceptability of other design differences between the user interfaces of a generic DDCP and its RLD may differ based on the drug product, the product's context of use (e.g., indication, user populations, use environment), and the specific other design differences.

Existing information and/or data can either demonstrate that the difference in design does not impact how users perform a critical task or, if the difference in design may impact how users perform a critical task, demonstrate that potential use errors related to the design difference do not preclude a finding that the generic DDCP and the RLD can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

If existing information and/or data are not available, applicants may provide new information and/or data to demonstrate that the design difference does not impact how users perform a critical task or, if the design difference may impact how users perform a critical task, demonstrate that potential use errors related to the design difference will not preclude the generic DDCP from having the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.

A comparative use human factors (CUHF) study is one method for providing additional data to demonstrate that certain user interface differences between a generic DDCP and its RLD will not increase the likelihood for medication use errors. CUHF studies enroll current users of the RLD in a study and place them in a simulated use scenario. A moderator asks each subject to demonstrate how they would use the proposed generic and the RLD. The subjects are randomized to order of interaction with the products.

Based on the additional data or information provided by the applicant, the FDA may or may not determine that the design difference(s) between the proposed generic DDCP and RLD user interfaces are acceptable. The FDA considers the need for additional data and the types of data that may address the "other design differences" on a case-by-case basis.

FDA Communication with Industry

There are several pathways through which the FDA communicates with industry to provide guidance about the development of generic DDCPs both prior to and after ANDA submission. The FDA developed its pre-ANDA program to increase the availability of complex generic products for the American public through enhanced transparency and support for complex generic product development and bioequivalence assessments. This program is designed to clarify regulatory expectations early in product development, assist applicants in developing more complete application submissions, promote a more efficient and effective ANDA assessment (review)

process, and reduce the number of FDA assessment cycles required to obtain ANDA approval.[25] The pre-ANDA program includes development of general guidances, development of product-specific guidances, and opportunities for the generic drug industry to submit questions to and/or meet with the FDA during generic drug product development (prior to submitting their drug application).

The FDA publishes guidances to communicate its current thinking on topics related to development of the products it regulates, including drugs, devices, biologics (e.g., vaccines and blood products), and combination products (Supplementary Table 2). All guidances are searchable from the FDA website titled "Search for FDA Guidance Documents."[26] To further support generic drug development, the FDA also publishes product-specific guidances (PSGs), which provide the generic drug industry with the agency's current thinking and recommendations about how to demonstrate that a proposed generic drug is therapeutically equivalent to a particular RLD.[27] The FDA works diligently to publish new and revised PSGs every three months. As of September 2024, it has published 2,223 PSGs. Any upcoming PSGs for complex drug products, including DDCPs, are regularly updated on the FDA's website.[28]

It is important to note that guidance documents do not establish legally enforceable responsibilities, but rather describe the FDA's current thinking on a topic; they should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The word "should" in FDA guidances indicates that something is suggested or recommended but not required.

The pre-ANDA program allows the generic drug industry to obtain answers to drug development questions through pre-ANDA meeting requests and controlled correspondence (a written inquiry submitted to FDA by or on behalf of a generic drug manufacturer about a specific element of generic drug product development[29]). Pre-ANDA program interactions are particularly helpful for firms developing complex drug products like complex generic DDCPs, as these products can raise unique scientific and regulatory considerations and challenges.

Generic Drug User Fee Amendments and the FDA Scientific Research Program

The FDA continues to advance generic drug development through expanded interactions with the generic drug industry, thoughtful and consistent application review, and advancement of generic drug science through funded research. Congress enacted the Generic Drug User Fee Act (GDUFA) in 2012 to ensure that patients have access to safe, high-quality, and affordable generic drugs.[30] GDUFA enables the FDA to assess industry user fees, which fund generic drug review resources (including scientific and clinical reviewers), allow greater predictability and timeliness of ANDA review, and support research to advance scientific methodologies for use in generic drug development. Every five years, the FDA's Office of Generic Drugs and representatives of the generic drug industry negotiate a GDUFA Commitment Letter that represents negotiated commitments from the two parties, and Congress decides whether to reauthorize GDUFA.

Complex generic drug products include DDCPs like pre-filled auto injectors and metered dose inhalers as well as drugs with complex active ingredients (e.g., peptides, polymeric compounds), complex formulations (e.g., liposomes, nanoparticles), and/or complex dosage forms (e.g., transdermal systems, oral suspensions, topical gels). FDA research and review priorities currently include development of complex generic products because they are often harder to develop and may face less generic competition, resulting in higher prices and decreased availability to patients. These priorities are reflected in the Commitment Letters for both GDUFA II (10/01/2017 through 09/30/2022) and GDUFA III (began 10/01/2022).[25] Furthermore, the GDUFA Science and Research Priority Initiatives for Fiscal Years 2023 and 2024 include specific research priorities for developing improved criteria for characterizing user interface differences, methods of comparative device user interface and performance assessment, and alternative data analysis approaches.[31] To learn more about complex DDCP development challenges and research efforts, please visit:

FDA/Center for Research in Complex Generics (CRCG) March 14-15, 2024 workshop "Drug-Device Combination Products: Updates and Challenges with Demonstrating Generic Substitutability" at https://www.complexgenerics.org/education-training/drug-device-combination-products-updates-and-challenges-with-demonstrating-generic-substitutability/

FY2023 GDUFA Science and Research Report: https://www.fda.gov/media/178640/download?attachment.

Take-Aways

Generic DDCPs play a critical role in the diagnosis and treatment of a wide range of disorders such as heart disease, cancer, respiratory disease, and diabetes. For some chronic disease states, such as diabetes, DDCPs offer new treatment options. Experts project a rise in new DDCP approvals in the future, which will lead to a continuous influx of generic DDCPs into the market. Increasing the availability of generic versions of DDCPs is essential for enhancing patient access to needed treatment. Availability of generic products increases patient access to needed therapies, and the reduced financial burden can enhance patient adherence to their drug treatment regimens. Despite these financial benefits, some patients may lack confidence that a generic DDCP will be as safe and effective as the brand name product, or they may have reservations about whether they can successfully use a generic product that looks different from their familiar brand

name product.[32] The FDA uses vigorous, science-based regulatory processes to ensure that generic DDCPs will achieve the same clinical therapeutic effect and safety profile as the RLD under the conditions of use specified in product labeling.

However, because patients and caregivers are unfamiliar with these regulatory review practices and how they affect the drug products they receive at the pharmacy and use at home, they may be anxious about switching to generic DDCPs. What can pharmacists and other healthcare providers do to educate, inform, and reassure patients as they experience generic substitution of DDCPs?

1. At the time you prescribe or dispense a new DDCP for a patient, check to see whether there are approved generic versions of the product that may be substituted at the pharmacy (download the Orange Book App or go to the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations at https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm). If there are approved generics, tell the patient what to expect. This information may include:
   - Inform the patient that their insurance company may require that the pharmacist dispense a generic version of the medication or that there is a generic version of the product that can reduce their cost.
   - For patients who are unfamiliar with generic drugs, inform them that generic drugs are medications created to be the same as marketed brand-name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. For helpful resources, pharmacists and healthcare professionals can review and access patient education materials at: https://www.fda.gov/drugs/generic-drugs/patient-education#New%20Patient%20and%20Prescriber%20Educational%20Materials
   - Reassure the patient that the generic version of the product may look a little different, but that it is as safe and will work just as well as the brand name version of the drug.
   - For the prescriber, if you have a trainer device in your office, show it to the patient and explain that, while the generic device may look a little different, it will work in a very similar way. Tell the patient to look for the "Instructions for Use" in the product package, to read them carefully before using the drug for the first time, and to follow these steps each time they use the drug.
   - For the pharmacist, if you have a trainer device at the pharmacy, use it to counsel the patient but also have the patient take the generic product out of the package to compare how the devices are both similar and different in appearance. Note any difference in the steps for correct use.
   - Inform the patient on how to reach you if they are confused about how to use their DDCP.
   - If patients mention adverse events due to device malfunctions, pharmacists are encouraged to report these concerns to the FDA MedWatch system; this can be accessed at https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program.
   - Some helpful patient and prescriber educational materials include the Generic Drugs: Questions and Answers FAQ and the Generic Drugs Stakeholder Toolkit; both can be found at https://www.fda.gov/drugs/generic-drugs/patient-education.
2. Be aware of and sensitive to differences among patients and caregivers in literacy, healthcare literacy, and personal experiences related to generic drugs and self-administration of DDCPs. Since all of these factors can influence how patients process information, learn new things, and deal with change, they can also affect how patients and caregivers navigate generic substitution of DDCPs.
3. The FDA makes generic drug approvals and TE determinations based on comparisons between a particular generic drug product and its RLD. However, once multiple generic versions of an RLD (brand name drug) enter the market, a patient may experience changes from a generic substituted for the RLD to one generic substituted for another generic. It may help patients and caregivers to know that their pharmacy may not always dispense the same generic for a particular brand name drug. Reassure the patient or caregiver that switching between generic versions of a drug product is okay, because each generic is as safe and effective as the brand name drug. In addition, for DDCPs, the devices should work in a very similar way.

Conclusions

Throughout the generic drug approval process, the FDA ensures, through vigorous testing and manufacturing standards, that generic DDCPs are safe and effective by holding them to the same standards of quality as required for brand-name DDCPs. Generic DDCPs increase access to high-quality, affordable medications required to manage a patient's health needs and improve medication adherence. This improves health outcomes, lowers health care costs for individuals and society, and reduces health disparities.[33] We hope that this publication provides pharmacists and other healthcare providers insight into how the FDA evaluates generic drug-device combination products to ensure generic

substitutability at the pharmacy. We hope that with this knowledge, we hope pharmacists and other healthcare providers can interact more effectively with patients and address any concerns relating to generic substitution.

Acknowledgements
The manuscript was supported in part by an appointment (Ila Srivastava and Yoonjung Lee) to the Research Participation Program at the FDA Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and the FDA.

The authors would also like to thank Dr. Betsy Ballard, MD (Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA) for her expert advice and support. We would also like to acknowledge Dr. Robert Lionberger (Director of Office of Research and Standards) and Dr. Lei Zhang (Deputy Director of Office of Research and Standards) for their leadership and vision on complex drug products as pertaining to generic drug development.

References

1. Lee Y, Gettman L. Descriptive Analysis of Acceptance by Prescribers and Economic Benefit of Pharmacist Recommended Interventions in a Critical Care Unit. *Innov Pharm*. 2018;9(2):1-20. doi:10.24926/iip.v9i2.958
2. Food and Drug Administration (FDA). Referencing Approved Drug Products in ANDA Submissions Guidance for Industry. FDA. Posted on October 2020. Accessed January 23, 2023. https://www.fda.gov/media/102360/download.
3. Alfonso-Cristancho R, Andia T, Barbosa T, Watanabe JH. Definition and Classification of Generic Drugs Across the World. *Appl Health Econ Health Policy*. Aug 2015;13 Suppl 1:S5-11. doi:10.1007/s40258-014-0146-1
4. Food and Drug Administration (FDA). CFR-Code of Federal Regulations Title 21, Volume 5, 21CFR314.3. FDA. Accessed June 30, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.3.
5. Food and Drug Administration. Generic Drug Facts. FDA. Accessed Nov 20, 2024. https://www.fda.gov/media/107601/download
6. Vivian, Jesse C. Generic-Substitution Laws. U.S.Pharmacist (OGD). Published June 19, 2008. Accessed July 13, 2022. https://www.uspharmacist.com/article/generic-substitution-laws.
7. Association for Accessible Medicines (AAM). The U.S. Generic & Biosimilar Medicines Savings Report SEPTEMBER 2022. AAM. Accessed on December 28, 2022. https://accessiblemeds.org/sites/default/files/2022-09/AAM-2022-Generic-Biosimilar-Medicines-Savings-Report.pdf.
8. Casetext. S.C. Code § 39-24-40. Section 39-24-40 - Prescription shall state whether substitution proper; form; consent of patient. Current as of 2024. Accessed September 27, 2024. https://casetext.com/statute/code-of-laws-of-south-carolina-1976/title-39-trade-and-commerce/chapter-24-drug-product-selection-act/section-39-24-40-prescription-shall-state-whether-substitution-proper-form-consent-of-patient
9. Washington State Legislature. Title 69 Chapter 69.41 Section 69.41.190 Preferred drug substitution—Exceptions—Notice—Limited restrictions (RCW 69.41.190). Current as of 2024. Accessed September 27, 2024. https://app.leg.wa.gov/rcw/default.aspx?cite=69.41.190.
10. Food and Drug Administration (FDA). Orange Book: approved drug products with therapeutic equivalence evaluations. FDA. Last updated on May 2023. Accessed May 2023. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm
11. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Medication adherence and use of generic drug therapies. *Am J Manag Care*. Jul 2009;15(7):450-6.
12. Ferdinand KC, Senatore FF, Clayton-Jeter H, et al. Improving Medication Adherence in Cardiometabolic Disease: Practical and Regulatory Implications. *J Am Coll Cardiol*. Jan 31 2017;69(4):437-451. doi:10.1016/j.jacc.2016.11.034
13. Shaw CR. Reducing the burden of medication costs to improve medication adherence. *Nurse Pract*. Jul 13 2014;39(7):43-7. doi:10.1097/01.NPR.0000450739.27061.e2
14. Shrank WH, Hoang T, Ettner SL, et al. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. *Arch Intern Med*. Feb 13 2006;166(3):332-7. doi:10.1001/archinte.166.3.332
15. Stein JD, Shekhawat N, Talwar N, Balkrishnan R. Impact of the introduction of generic latanoprost on glaucoma medication adherence. *Ophthalmology*. Apr 2015;122(4):738-47. doi:10.1016/j.ophtha.2014.11.022
16. Vrijens B, Antoniou S, Burnier M, de la Sierra A, Volpe M. Current Situation of Medication Adherence in Hypertension. *Front Pharmacol*. 2017;8:100. doi:10.3389/fphar.2017.00100
17. Cole AL, Jazowski SA, Dusetzina SB. Initiation of generic imatinib may improve medication adherence for patients with chronic myeloid leukemia. *Pharmacoepidemiol Drug Saf*. Nov 2019;28(11):1529-1533. doi:10.1002/pds.4893
18. Sanchez CK, Farrell N, Lapp E. Generic drugs, cost, and medication adherence. *US Pharm*. 2015;40(6):14-19.
19. Gershman J. Pharmacists Play a Vital Role in Generic Drug Product Selection. Pharmacy Times.

https://www.pharmacytimes.com/view/pharmacists-play-a-vital-role-in-generic-drug-product-selection
20. Food and Drug Administration (FDA). CFR-Code of Federal Regulations Title 21, Volume 5, 21CFR320.24. FDA. Accessed January 17, 2023. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=320.24.
21. Food and Drug Administration (FDA). CFR-Code of Federal Regulations Title 21, Volume 1, 21CFR3.2. FDA. Accessed June 30, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=3.2.
22. Food and Drug Administration (FDA). Comparative Analyses and Related Comparative Human Use Factors Studies for a Drug-Device Combination Product Submitted in an ANDA. FDA. Posted on January 2017. Accessed September 27, 2024. https://www.fda.gov/media/102349/download.
23. Food and Drug Administration (FDA). CFR-Code of Federal Regulations Title 21, Volume 5, 21CFR314.94. FDA. Accessed June 30, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=314.94.
24. Food and Drug Administration (FDA). Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development. FDA. Posted on February 2016. Accessed September 27, 2024. https://www.fda.gov/media/96018/download.
25. Office of Generic Drugs (OGD). GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years. 2023-2027. FDA. Accessed June 30, 2022. https://www.fda.gov/media/153631/download.
26. Food and Drug Administration (FDA). Search for FDA Guidance Documents. Accessed September 27, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch.
27. Office of Generic Drugs (OGD). Product-Specific Guidances for Generic Drug Development. FDA. Accessed June 30, 2022. https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.
28. Office of Generic Drugs (OGD). Upcoming Product-Specific Guidances for Complex Generic Drug Product Development. FDA. Accessed June 30, 2022. https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development.
29. Food and Drug Administration (FDA). Controlled Correspondence Related to Generic Drug Development Guidance for Industry. FDA. Posted on December 2020. Accessed January 23, 2022. https://www.fda.gov/media/109232/download.
30. Food and Drug Administration (FDA). Generic Drug User Fee Amendments. FDA. Accessed September 21, 2022. https://www.fda.gov/industry/fda-user-fee-programs/generic-drug-user-fee-amendments.
31. Office of Generic Drugs (OGD). Generic Drug User Fee Amendments (GDUFA) Science and Research Priority Initiatives for Fiscal Year 2023. FDA. Accessed November 21, 2022. https://www.fda.gov/media/162554/download.
32. Ray SE, Boudewyns V, Davis C, et al. Patient Perceptions of Switching to a Generic Dry Powder Inhaler - Increased Understanding Through Journey Mapping. *Int J Chron Obstruct Pulmon Dis*. 2022;17:1751-1768. doi:10.2147/COPD.S362696
33. Food and Drug Administration. Generic Drugs Can Help Promote Health Equity. Accessed Mar 04, 2025. https://www.fda.gov/media/173765/download#:~:text=Generic%20Drugs%20Can%20Help%20Improve%20Access%20to%20Medication&text=Generic%20drugs%20can%20help%20make,access%20needed%20medicines%20more%20easily.

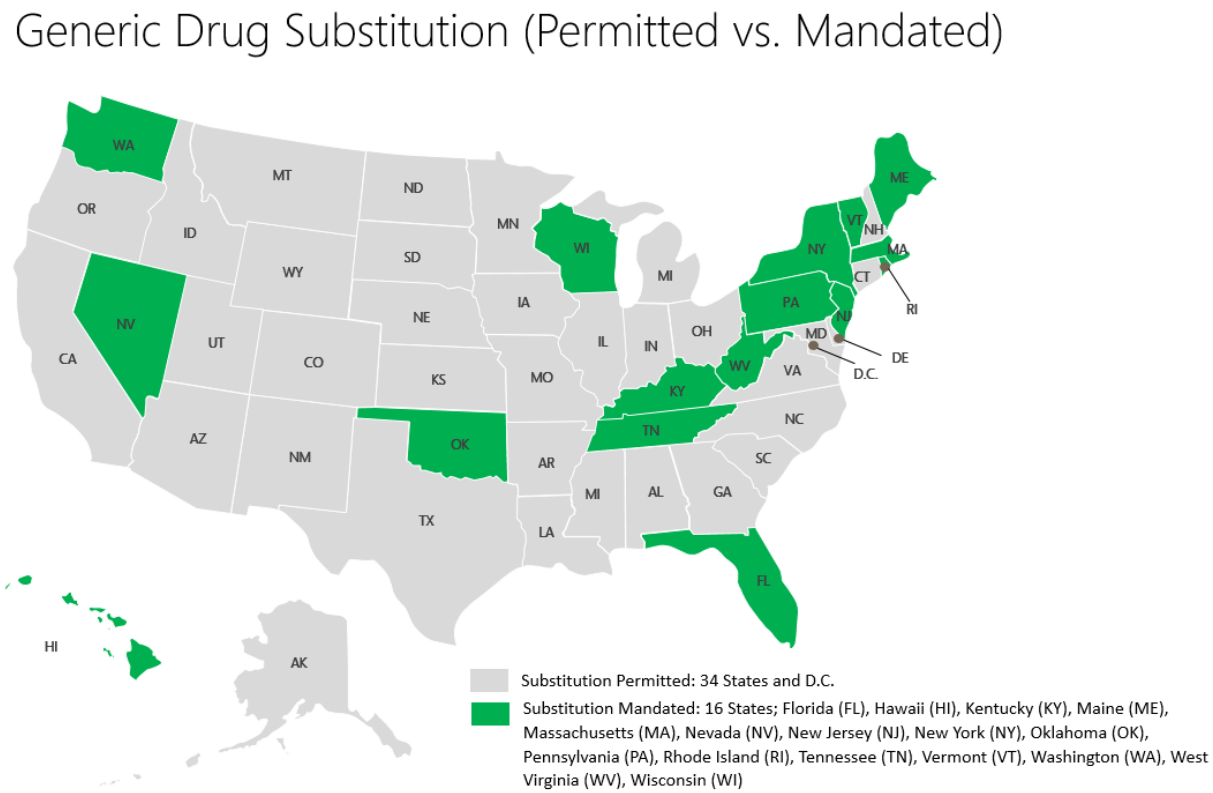


Figure 1. States that permit generic drug substitution (grey) vs. those with mandated substitution (green). Sixteen states mandate generic drug substitution while 34 states and Washington D.C. permit generic drug substitution. For more information on U.S. regulations per state, refer to Supplementary Table 1.