How Does the Food and Drug Administration Approve Topical Generic Drugs Applied to the Skin?

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KEYWORDS

• Dermatologic • Locally applied • Topical • Generics • Skin diseases

KEY POINTS

- Topical dermatologic drug products are a multibillion-dollar industry in the United States and are widely used for the treatment of various diseases, such as acne, psoriasis, actinic keratosis, and basal cell carcinoma.[1]
- Topical dermatologic drug products encompass a wide array of dosage forms including solutions, gels, creams, lotions, and ointments, among others.
- The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98–417), informally known as the Hatch-Waxman Amendments, established a pathway for approval of generic drug products, including topical dermatologic products, to enhance patient access to such products.
- Approved generic drug products that are therapeutically equivalent to a preidentified brand name drug product (a reference listed drug) are pharmaceutical equivalents for which bioequivalence has been demonstrated. They are expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.
- The types of studies used to evaluate the bioequivalence of such drug products typically depends on the site/mechanism of action of the drug product and the complexity of the dosage form.

INTRODUCTION

Topical dermatologic drug products, that is, drug products that are applied to the outer surface of the skin for treatment of skin diseases, are a vital part of a practicing dermatologist's treatment armamentarium. Pastore and colleagues[2] summarized the historic use of oils, fats, perfumes, creams, and so forth to treat disease conditions and wear as cosmetics. The 1966 publication by Bender and Thom[3] discussed the formulation of an ancient cold cream, which was similar to the cream formulations that are available on the market today. However, despite the similarities with ancient formulations, most of the topical dermatologic drug products that are available on the market today are carefully designed using one or more active therapeutic agents (otherwise known as active ingredients) and inactive ingredients to deliver a specific amount of active ingredient per unit area of the skin. Both the formulation development and manufacturing of topical dermatologic drug products have evolved significantly from the days when Galen's Cerate (Cérat de Galien), a cold cream, was one of the most renowned formulas for a dermatologic drug product.

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Topical dermatologic drugs are one of several pharmaceutical dosage forms that allow for targeted application of a drug to a localized area of the body. This allows for focused therapeutics that minimize the systemic bioavailability (BA) and potential toxicity of the applied drug. There are some drugs that are applied on the skin, which may have an underlying systemic site of action (either in addition to, or exclusive of, any local skin effect). In other instances, a topical dermatologic drug product may be applied to diseased skin, which may or may not be intact. Some topical products exhibit therapeutic effects that rely on the fact that the diseased or wounded skin is not intact (ie, the rate-limiting barrier to skin permeation, the stratum corneum, is nonexistent or compromised). Yet other topical dermatologic drug products may actually target a localized infestation, which may be exterior to the surface of the skin. Finally, concern for some locally acting drugs' systemic toxicity may prompt the need to assess that formulation's systemic availability.

HISTORY OF TOPICAL DRUG REGULATIONS IN THE UNITED STATES

In 1906, the Pure Food and Drug Act was one of the first laws enacted by Congress to ensure consumer protection against mislabeled vaccines; it led to the development of the US Bureau of Chemistry, which eventually became the US Food and Drug Administration (FDA).[4] Following the sulfanilamide crisis in 1932, Congress enacted the Federal Food, Drug, and Cosmetic Act (FD&C), which gave the FDA authority to veto the marketing of a drug product unless the safety of the product could be established.[5] Between 1938 and 1962, approximately 4500 new drug applications (NDAs) were submitted to the FDA and subsequently marketed in the United States; these drug products included many topical dermatologic products, such as the Kenalog (triamcinolone acetonide) topical ointment, which is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Eventually, following the thalidomide tragedy in Europe, the 1962 Kefauver-Harris Amendments to the FD&C Act were enacted, which required premarket approval of all drug products, including topical dermatologic drug products sold in the United States.[6] Most significantly, the 1962 amendments to the FD&C Act led to the requirement for safety and efficacy data using adequate and well-controlled clinical studies to support the approval of a drug product. Drug products that were authorized for marketing at the time (between 1932 and 1968) had to be reviewed by the FDA for efficacy in addition to the previously reviewed safety data. The administrative process that was used to review the effectiveness of such drug products is known as the drug efficacy study implementation.[7] Topical dermatologic drug products, such as the triamcinolone acetonide topical ointment, among others, were reviewed and found to be efficacious under the drug efficacy study implementation program.

In 1984, to enhance patient access through streamlining the approval of therapeutically equivalent generic drug products, Congress enacted the Drug Price Competition and Patent Term Restoration Act,[8] informally known as the Hatch-Waxman Amendments. The amendments to the FD&C Act made it possible for companies to manufacture and obtain FDA approval for generic drug products by submitting an Abbreviated New Drug Application (ANDA) instead of an NDA. Compared with a drug product that is submitted under an NDA, which contains full reports of investigations of safety and effectiveness, a drug product submitted under an ANDA relies on FDA finding that the preidentified reference listed drug (RLD) is safe and effective and generally must show that the generic drug product is among other things, bioequivalent to the corresponding RLD. The Code of Federal Regulations (CFR) Title 21, Part 320 outlines the kind of data that can be used to establish the bioequivalence (BE) of a given generic product. Within the scope of the current review, the goal is to discuss the rigorous methodologies and different types of evidence that are typically used to support the approval of generic topical dermatologic drug products (small molecules). Such evidence is often related to the complexity of the topical dermatologic dosage form involved.

During the last decade, the use of biologics has been widely recognized as one of the major breakthroughs in the treatment of topical dermatologic diseases, such as psoriasis. Biologics are typically complex mixtures that are sourced from humans, animals, or microorganisms, and represent a different class of drugs compared with the chemically synthesized small molecules with known structures. Biologic drug products are submitted for approval under Section 351 of the Public Health Service Act[9] and are beyond the scope of the current review, which focuses exclusively on pathways used to support the approval of small molecules via the ANDA pathway.

COMMONLY USED TOPICAL DERMATOLOGIC DOSAGE FORMS

Topical dermatologic dosage forms, such as Galen's Cerate (Cérat de Galien), a cold cream,

and medicated plasters (*emplastra*), which were generally applied to the skin for local conditions, are traced back to Ancient Greek and Chinese civilizations. Currently, numerous topical dermatologic dosage forms outlined in **Fig. 1** are available on the US market. The most commonly used topical dermatologic dosage forms include gels, creams, lotions, ointments, foams, solutions, and others; they are routinely used to treat a wide array of diseases. Some examples include topical dermatologic drug products that contain antiparasitic agents used in the treatment of head lice. These topical products, which include malathion or benzyl alcohol topical lotions, are applied to the scalp and work on an organism that is external to the human body. Antifungal products, such as efinaconazole and tavaborole solutions, are used for the treatment of onychomycosis of the toenail. More commonly, retinoid- and antibiotic-containing products, such as the tretinoin topical gels and creams, tazarotene topical gels and creams, and clindamycin topical gels, are used for the treatment of acne vulgaris; and antibiotic-containing products, such as the metronidazole topical gels and creams, are used for the treatment of rosacea. Topical ointments and creams products containing synthetic vitamin D_3 derivates, such as calcipotriene, are used in the treatment of psoriasis; whereas topical calcineurin inhibitors, such as pimecrolimus, and immunosuppressive agents, such as tacrolimus, are used for the treatment of atopic dermatitis.

The previously outlined examples illustrate that numerous active ingredients in a wide array of dosage forms are used to treat different skin diseases. The selection of the dosage form is typically driven by the feasibility of formulating the active ingredient in a given dosage form and influenced by factors, such as patient perceptions and ease of use. For example, although an occlusive topical ointment may be preferred for the treatment of atopic dermatitis, a rapidly evaporating gel or cream may be preferred for the treatment of facial acne.

A topical dermatologic dosage form usually contains one or more active ingredients. A 2005 publication briefly outlined a scientifically based, systematic classification of dosage forms for topical drugs.[10] From a technical perspective, a solution is a dosage form where the active ingredient is completely solubilized in the drug product. A topical suspension is a dosage form where the active ingredient is partially suspended in the continuous phase; in such cases the active ingredient is expected to dissolve before it is available for diffusion across the stratum corneum barrier of the skin. Gels are typically manufactured by adding a polymerizing/gelling agent to a mixture of active and inactive ingredients. Both aqueous-based and alcohol-based gels are available on

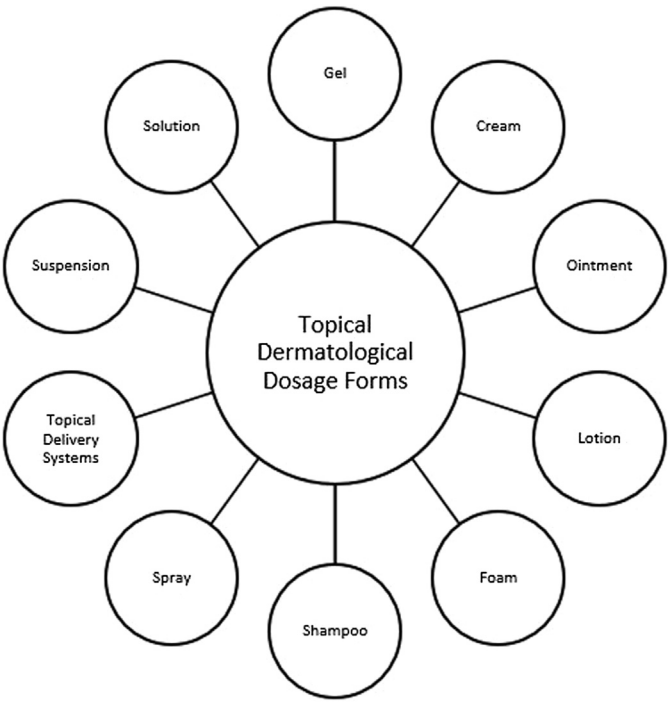

Fig. 1. The 10 most commonly used topical dermatologic dosage forms in the United States.[12]

the US market, and most gels are single-phase systems where the active ingredient is either fully or partially dissolved in the continuous phase. Emulsion-based gels (ie, gels that are manufactured to be biphasic systems) are less common, but such products (eg, diclofenac sodium [emulsion-based] gels) are also available on the US market.[11] Lotions and creams are typically biphasic vehicle (emulsion) dosage forms where the active ingredient is either fully or partially dissolved in one or both phases. An ointment is typically manufactured using either a petrolatum base or polyethylene glycols, where the active ingredient is fully or partially dissolved. Unlike the gels, creams, and lotions that undergo rapid drying (metamorphosis) following application on the surface of the skin, ointments typically tend to form an occlusive film following application and, therefore, are often used in the treatment of diseases involving a compromised barrier function of the stratum corneum, such as atopic dermatitis. Foams and sprays are typically manufactured by either adding a propellent to a solution or emulsion dosage form, or by using an air-spray foam pump. Shampoos are solution or emulsion type formulations that contain surfactants, and these drug products are typically manufactured for treatment of diseases of the scalp, such as seborrheic dermatitis. Lastly, topical delivery systems (also known as patches) are conceptually similar to medicated plasters where the drug is loaded onto an adhesive matrix or hydrogel-based system; the delivery systems are expected to adhere to the skin and deliver drug across the surface area of application over a specific period of time. Note that the discussion related to the most commonly used dosage forms within the current review is focused on dosage forms that are typically used as pharmaceutical interventions for the treatment of skin diseases with limited and controlled exposure to the active and inactive ingredients, compared with using similar dosage forms in cosmetics where the exposure to the components of the dosage form may be significantly higher.

APPROACHES FOR ESTABLISHING THERAPEUTIC EQUIVALENCE OF GENERIC TOPICAL DERMATOLOGIC DRUG PRODUCTS

For a product to be considered therapeutically equivalent to a preidentified brand name drug or RLD, the generic product must be pharmaceutically equivalent and bioequivalent to the RLD. The Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book)[12] defines a pharmaceutically equivalent drug product as one that contains an identical amount of the same active ingredient, in an identical dosage form, administered by the same route of administration. Approved generic drug products are considered to be therapeutic equivalents to the preidentified RLD if they are pharmaceutical equivalents for which BE has been demonstrated and can be substituted with the full expectation that the substituted product will have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the drug product label. The type of evidence that is typically required for establishing the BE of a generic topical dermatologic product depends on the site/mechanism of action of the drug product and the complexity of the dosage form.

According to 21 CFR 320.24, the following in vivo and in vitro approaches are acceptable for establishing the BE of a drug product: (1) an in vivo test in humans where the concentration of the active ingredient or active moiety, and, when appropriate, its active metabolites, in whole blood, plasma, serum, or other appropriate biologic fluid is measured as a function of time; (2) an in vivo test in humans where the urinary excretion of the active moiety and, when appropriate, its active metabolites, are measured as a function of time; (3) an in vivo test in humans in which an appropriate acute pharmacologic effect of the active moiety, and, when appropriate, its active metabolites, are measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility; (4) appropriately designed comparative clinical end point studies, for purposes of demonstrating BE; (5) a currently available in vitro test acceptable to FDA that ensures human in vivo BA; or (6) any other approach deemed adequate by FDA to establish BE.

The overall goal of studies conducted to evaluate the BE of a prospective generic product to the predefined RLD is predominantly to assess the impact of differences in formulation, if any, on the rate and extent to which the active ingredient becomes available at the site of action, from the drug products. In general, for drug products that are indicated for systemic action, the BE of a generic drug compared with the RLD is typically established based on an evaluation of the pharmacokinetics (PK) of the active ingredient in the blood (serum/plasma). However, when a drug product is not intended for systemic action, as is the case for topical dermatologic drug products, systemic PK studies are generally not relied on for establishing BE.[13] The following section of the review discusses the types of studies that are

typically used for establishing the BE of topical dermatologic dosage forms.

Comparative Clinical End Points Bioequivalence Studies

Historically, a BE study with a comparative clinical end point has routinely been used for establishing the BE of locally acting topical dermatologic products, such as those mentioned previously. Such studies span weeks to months and are usually conducted in a patient population relevant to the indication of the drug product identified within the product labeling. Typically, hundreds to thousands of patients are required to adequately power such a study to demonstrate the BE of a proposed generic product compared with the predefined RLD. Both products are also expected to demonstrate superiority over a placebo formulation in such studies, as a control. Although comparative clinical end point studies have been successfully used for establishing the BE of topical dermatologic dosage forms, such studies are expensive and time consuming (given the large number of patients and the long duration of the study before the comparative clinical end point may be achieved), and may not be the most sensitive or discriminating method for evaluating differences in the BA of an active ingredient from a proposed generic product compared with the predefined RLD.

Pharmacodynamic Bioequivalence Studies

In addition to the comparative clinical end point BE studies, in limited instances, a pharmacodynamic BE study that uses a vasoconstrictor response for corticosteroids has been used for topical dermatologic dosage forms containing glucocorticoids. However, over the last decade, the FDA has systematically invested in research[14] to develop more efficient approaches for evaluating the BE of locally acting topical dermatologic dosage forms. Based on the FDA's current understanding of the complexity of the different topical dermatologic dosage forms, the following approaches can typically be used for establishing the BE of such drug products.

Waiver of In Vivo Bioequivalence Studies for Topical Solutions

The 21 CFR 320.22(b) (3) states that for certain drug products, the in vivo BA or BE of the drug product may be self-evident. To be able to use this waiver, topical solutions that are applied to the skin must contain the same active ingredient at the same concentration and dosage form as the predefined RLD and not contain any inactive ingredient or other change in formulation that may significantly affect the local or systemic availability of the active ingredient.

Characterization-Based Approaches for Topical Gels, Creams, Lotions, and Ointments

The FDA has recently published several product-specific guidances[15] for generic drug development for topical products in which efficient characterization-based approaches have been recommended for establishing BE, as a complement to comparative clinical end point BE studies. In some instances, the comparative in vitro characterization data of the drug products are used to establish the pharmaceutical equivalence of a prospective generic product compared with the predefined RLD, or to gain additional evidence to mitigate the risk of potential failure modes for BE that may be unique to a drug product. In several other instances, efficient characterization-based approaches are recommended as a stand-alone option, offered as an alternative to a comparative clinical end point BE study. From a scientific perspective, the characterization-based approaches are developed such that the methodology is used to design a prospective generic product that is essentially identical to a predefined reference product with respect to the composition and the microstructure of the drug product, and any differences between a prospective generic product and the predefined reference product are similar to what would be expected across multiple batches of the reference product itself.

Currently, efficient characterization-based approaches are used for establishing the BE of prospective generic drug products that contain no difference in inactive ingredients or in other aspects of the formulation relative to the predefined reference product that may significantly affect the local or systemic availability of the active ingredient. For example, if a prospective generic and the predefined reference product are qualitatively (Q1) and quantitatively (Q2) the same, as defined in the guidance for industry ANDA Submissions–Refuse-to-Receive Standards (December 2016), the BE of such a prospective generic product may be established using a characterization-based BE approach. Such formulation sameness of the drug products is expected to mitigate the risk of known failure modes for therapeutic equivalence related to irritation, sensitization, and issues related to interaction of the formulation with the abnormal, diseased anatomy, physiology, and morphology of the skin, which may arise when there are differences in inactive ingredients between a prospective generic product and the

corresponding reference product. Additionally, formulation sameness generally ensures that the stability, solubility, and physical state of the active ingredient in the formulation, which can potentially impact the diffusion and partitioning of active ingredient from the drug product into the skin, are identical for the prospective generic and predefined reference product. Sameness of formulation may also mitigate the risks associated with differences in contribution of the vehicle toward efficacy of drug products.

In general, as the complexity of the dosage form increases (eg, solution ⇒ gel ⇒ cream), the number of potential failure modes for BE often also increases. Therefore, the precise type of physicochemical and structural (Q3) characterizations that are recommended as a component of the characterization-based approaches is determined rationally based on the nature of the dosage form, and the potential differences in product quality that may impact the therapeutic performance of a given drug product. Such comparative studies typically include the following:

- An evaluation of visual appearance and microstructural characterization (including microscopic images at multiple magnifications) to be able to visualize and identify differences in the microstructure of the prospective generic and reference products, if any.
- Based on the microscopic evaluation, for products that contain suspended active ingredients, comparative evaluation of particle size distribution and polymorphic form of the active ingredient is recommended because differences in the particle size distribution and/or the polymorphic form of the active ingredient can lead to differences in the solubility of the active ingredient in the drug product and/or the rate of dissolution of the suspended active ingredient. Based on Fick's laws of diffusion, soluble drug can diffuse in molecular form across the stratum corneum. Therefore, differences in the amount of solubilized drug or the rate of dissolution of the active ingredient can impact the BA of the active ingredient from the dosage form.
- For a monophasic system, such as a gel, an evaluation of the microstructure of the dosage form using high-resolution microscopy is usually informative to compare the microstructure of such polymeric gel-based systems. However, for biphasic systems, such as the lotions and the creams that were previously described within the review, an evaluation of the globule size distribution of the emulsion is recommended, because differences in globule size distribution can impact the interaction of the different phases of the dosage form with the skin, especially as the dosage form dries, which in turn can impact the BA of the active ingredient from the dosage form.
- A comparative evaluation of the rheology of the non-Newtonian semisolid formulations is recommended, given that rheologic differences between a prospective generic and the reference product may impact the look and feel of the product and the corresponding patient perception of quality, and the patient acceptance of the product. Additionally, differences in rheologic properties can also lead to differences in the diffusion of the active ingredient within the dosage form and the amount of the active ingredient that is dispensed before application of the drug product. For example, most topical dermatologic drug product labeling recommends that patients should dispense and use a sufficient amount of the drug product to cover the intended treatment area rather than specifying a predetermined amount/dose. Therefore, it is possible that a smaller amount of a less viscous drug product may be used to treat a surface area that would typically require a larger amount of a more viscous drug product. Such potential differences in rheology, if any, can thereby impact the BA of the active ingredient from the drug product in addition to patient perception and therapeutic compliance.
- A comparative evaluation of the specific gravity/density is also used to ensure that the amount of entrapped air that may be introduced in the formulation during manufacturing processes (eg, the homogenization or emulsification steps used during the manufacture of biphasic formulations, or the gelling of single-phase gels) is consistent between the prospective generic and reference product. Differences in the amount of entrapped air also has the potential to impact the amount of drug product/active ingredient that is dispensed and applied to the skin, and thereby the BA from a given drug product.
- A comparative evaluation of pH is recommended to mitigate the risk of potential irritation, which can impact the patient's acceptability of the product and to ensure a similar solubility and stability of the active ingredient in the drug product, especially in situations where the pKa of the active ingredient is similar to the target pH of the drug product. Small differences in pH between a prospective generic product and the corresponding reference product in such instances can lead to

differences in the amount of solubilized active ingredient in the drug product and thereby the BA of the active ingredient from the drug product.

- Additional comparative Q3 tests may include an evaluation of water activity, that is, a comparative evaluation of the amount of unbound/free water molecules in biphasic formulations and/or an evaluation of the drying rate to understand differences, if any, in the metamorphosis of a prospective generic product and the reference product. Such differences in turn could impact the BA of the active ingredient from the drug product.

An in vitro release test (IVRT), which is designed to evaluate the apparent rate of release of the active ingredient from a drug product, is typically recommended to detect differences, if any, in the apparent rate of release of the active ingredient from the prospective generic and reference products, which may arise because of differences in the microstructure of the drug product that may not be detectable using the previously mentioned comparative Q3 characterization. An adequately validated IVRT is sensitive to differences in the rate of release of the active ingredient from the drug product, and thereby, is useful to mitigate potential failure modes for BE that may arise because of differences in manufacturing processes between a prospective generic product and a reference product.

For complex dosage forms, such as biphasic emulsions, a comparative evaluation of the interaction of the drug product with the skin during metamorphosis (drying of the drug product following application to the skin) may be used to evaluate the BA of the active ingredient from a prospective generic product and the corresponding reference product following application of the drug product to the skin. Such studies that involve a comparison of the cutaneous PK of the drug product in vitro, can be conducted using an in vitro model, such as the in vitro permeation test.[16,17]

As previously noted within the review evaluating the systemic BA using a PK study is typically not relevant for locally acting topical dermatologic drug products where the site of action of the drug product is not systemic. However, in limited instances a crossover in vivo study with PK end points may be used to evaluate the rate and extent of systemic availability of the active ingredient in situations where the site and/or mechanism of action of a topically applied drug product may be partially systemic. An example of a product where such studies have been used includes the diclofenac sodium topical (emulsion-based) gel where the perceived site of action of the drug product is the synovial fluid[18] and the product is indicated for the relief of osteoarthritic pain.

Combination of Multiple In Vivo Studies

In limited instances, a BE study with PK end points and a BE study with comparative clinical end points may be used for certain drug products when there are differences in the formulation between a prospective generic drug product and the corresponding reference product. For example, for the diclofenac sodium topical (emulsion-based) gel, although the drug is detectable in the plasma, there have been speculative concerns that because of the low BA of diclofenac following topical application of the drug product, only a small difference may be observed between systemic levels of diclofenac delivered from the generic and corresponding reference drug products, despite a potentially significant difference in the amounts of diclofenac delivered locally to the site of application. Additionally, because the exact mechanism of action of diclofenac in osteoarthritis is not well understood and the site of action of the drug product is not well defined (believed to be the structures around the joint or in the synovial fluid), a BE study with comparative clinical end point in addition to the BE study with PK end points is used for establishing BE of such drug products.

Therefore, generic topical dermatologic products may use one or more approaches for establishing BE. An in vivo BE approach, which includes a BE study with comparative clinical end point, or an in vivo vasoconstrictor assay for corticosteroid products, may be used by many proposed generic products (irrespective of the differences in formulation with respect to the reference product) because the recommended in vivo studies are expected to mitigate the risks associated with potential failure modes for BE, regardless of the formulation of the test product. However, a characterization-based BE approach may be applicable to a subset of proposed generic products that contain no difference in inactive ingredients or other aspects of the formulation relative to the reference product that may significantly affect the local or systemic availability of the active ingredient. In addition to “no difference” in the formulation, the recommendations within the characterization-based BE approach may include the following studies to support a demonstration of BE, depending on the complexity of the dosage form and the mechanism/site of action of the drug product: comparative Q3 characterization of the test and reference products, a comparative IVRT study, a comparative in vitro permeation test study, and a BE study with PK end points. The

types of studies that are recommended by the FDA to systematically mitigate the risks associated with potential failure modes for BE for a specific product are typically outlined within a product-specific guidance.[15] These product-specific guidances, in conjunction with relevant general guidance for industry,[19] are an excellent resource that can be used by the generic industry to develop high-quality generic products in a manner compatible with regulatory expectations. Additionally, such tools as physiologically based modeling and simulation tools are currently being developed to support the characterization-based approaches for establishing BE.

SUMMARY

According to a US Government Accountability Office report,[20] 57% of topical drug products experienced a price increase of more than 100% between 2010 and 2015, with the average price of topical generic drugs being 276% higher by 2015. Therefore, it is critically important to use efficient approaches for establishing the BE of topical dermatologic drug products to be able to increase market competition and to enhance patient access to such products. This current review systematically discusses the complexity of topical dermatologic dosage forms that are available on the US market and are used to treat a wide array of common dermatologic diseases. Current methodologies used for evaluating the equivalence of a prospective generic product involve a systematic and rigorous comparative evaluation of the drug products using one or more studies to ensure that the rate and extent of BA of the active ingredients at or near the site of action is comparable between the prospective generic and corresponding brand name product.

CLINICS CARE POINTS

- Approved generic drug products are expected to have the same clinical effect and safety profile as the brand name drug when administered to patients under the conditions specified in the labeling.
- Current methodologies used for evaluating the equivalence of a prospective generic product involves a systematic and rigorous comparative evaluation of the drug products using one or more studies.
- FDA works to ensure that generic topical dermatologic drug products are easily accessible to prescribers and patients.

DISCLOSURE STATEMENT

The authors have nothing to disclose.

This article reflects the views of the authors and should not be construed to represent FDA views or policies.

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