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By Electronic Submission

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

Encore Dermatology, Inc. (Encore) respectfully submits this citizen petition under section 505(q) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 10.30, 314.94, and 314.127, among other provisions of law. Encore is the holder of the new drug application (NDA) for Impoyz® (clobetasol propionate) 0.025% topical cream, which is indicated for moderate to severe plaque psoriasis. Impoyz is a novel formulation of clobetasol propionate that maintains effectiveness using half the amount of active ingredient contained in previously approved clobetasol propionate cream products. The key characteristic of the formulation is that it uses Transcutol® (diethylene glycol monoethyl ether or DEGEE) without propylene glycol. Transcutol "increase[s] cutaneous retention of active ingredient (i.e., expanded intracutaneous depot) while limiting systemic exposure" and is associated with "a lack of irritancy and allergenicity."[1] In addition to local advantages, Impoyz represents an important development in topical formulation because systemic absorption of clobetasol propionate is associated with safety risks, such as suppression of hypothalamic-pituitary-adrenal axis (HPA axis suppression). In 2018, Podiatry Today featured Impoyz as one of the "Top Ten Innovations in Podiatry."[2]

Recently, Encore received a Paragraph IV notice letter from a generic drug sponsor, Glenmark Pharmaceuticals Limited (Glenmark), stating that Glenmark submitted an abbreviated new drug application (ANDA) for a generic version of Impoyz. Glenmark's notice letter asserts that its proposed generic product contains more than 10% propylene glycol, a well-known topical penetration enhancer. The notice letter does not assert that the Glenmark product contains Transcutol. By describing a proposed formulation that differs from Impoyz in the selection and proportion of penetration enhancers (assuming the notice letter is accurate), Glenmark's product

[1] Del Rosso, J., Topical corticosteroid therapy for psoriasis – A review of clobetasol propionate 0.025% cream and the clinical relevance of penetration modification, J CLIN AESTHET DERMATOL. 2020;13(2):22-29, 27 (Tab 1).

[2] McCurdy, B., Top ten innovations in podiatry, PODIATRY TODAY. 2018;31(7):26-34 (Tab 2).

raises questions of safety and efficacy that cannot be answered by relying on the clinical data for Impoyz. Accordingly, Encore submits this citizen petition to ensure that Glenmark and other similarly situated generics who claim to use formulations that rely significantly on propylene glycol instead of, or in addition to, Transcutol must provide independent clinical data (through a new drug application) to establish the safety and effectiveness of their proposed products.

ACTIONS REQUESTED

Encore respectfully requests that the Commissioner take the following actions:

1. Refuse to approve the Glenmark generic topical clobetasol propionate product submitted under ANDA 214191, and any similarly formulated generic products, because there is a reasonable basis to conclude that Glenmark made formulation changes, including significant changes to the vehicle, that likely increase absorption and raise unanswered questions of safety and effectiveness.

2. Require Glenmark and similarly situated generic applicants to submit their new formulations under a new drug application with adequate data demonstrating safety and effectiveness.

3. If FDA does allow Glenmark, and similarly situated generic applicants, to proceed with an ANDA, require Glenmark and others to:

    a. establish bioequivalence with a comparative clinical endpoint study; and

    b. support their ANDAs with (i) systemic exposure data, (ii) HPA axis suppression data, and (iii) local safety data to ensure that the proposed formulations have the same safety profile as Impoyz.

STATEMENT OF GROUNDS

I. FACTUAL BACKGROUND

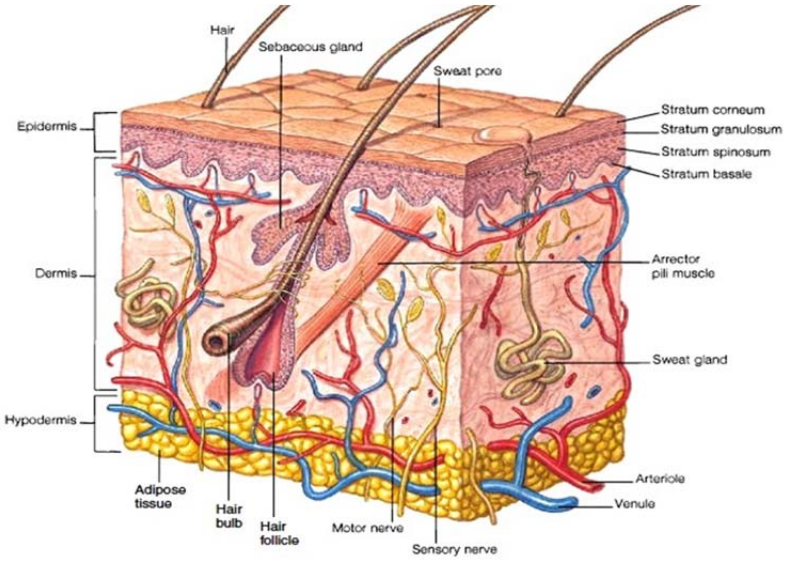
A. Plaque Psoriasis

Psoriasis is a chronic, immune-mediated inflammatory disease of the skin and joints, affecting approximately 7.4 million adults in the United States.[3] In plaque psoriasis, the most common clinical type of psoriasis, cells build up rapidly on the surface of the skin, resulting in

[3] *See* Rachakonda, T.D., *et al.*, Psoriasis prevalence among adults in the United States, J AM ACAD DERMATOL. 2014 Mar;70(3):512-16, 512 (Tab 3); *see also* National Psoriasis Foundation, Statistics, https://www.psoriasis.org/content/statistics (Tab 4).

raised oval-shaped "plaques" over the skin.[4] The hyperproliferation of skin cells causes the formation of scaling on the plaques. The disease is difficult to treat, with frequent acute flares and relapses, which can progress to a more severe subtype.[5]

Studies suggest that the chronic inflammation in psoriasis is mediated by T helper (Th)17 and Th1 cells; expression of chemerin induces plasmacytoid dendritic cells to infiltrate the dermis and epidermis, where they release interferon-alpha.[6] This, in turn, leads to the activation of myeloid dendritic cells, which migrate to lymph nodes and further inflammatory response. The cells move to the epidermal and dermal tissues and cause the continued proliferation of keratinocytes and feedback loops of T cells. An image showing the different layers and complexities of the skin is provided below.



Topical corticosteroids are the cornerstone of treatment of psoriatic lesions, alone or in combination with other treatments.[7] Corticosteroids "exert anti-inflammatory and immunosuppressive effects by stimulation or inhibition of the genes involved in inflammatory pathways, including inhibition of cytokine production and reduction of such mediators of inflammation as prostaglandins and leucotrienes, inhibition of T-cell proliferation and T-cell dependent immunity, and suppression of fibroblast and endothelial cell functions."[8]

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[4] *See* Badri, T., *et al.*, Plaque psoriasis, StatPearls Publishing. 2020 Jan (Tab 5).

[5] *Id.*

[6] Coates, L.C., *et al.*, Psoriasis, psoriatic arthritis, and rheumatoid arthritis: Is all inflammation the same? SEMINARS IN ARTHRITIS AND RHEUMATISM. 2016 Dec;46(3):291-304, 292 (Tab 6).

[7] Sitter, B., *et al.*, Metabolic changes in psoriatic skin under topical corticosteroid treatment, BMC DERMATOLOGY. 2013;13:8 (Tab 7).

[8] *Id.*

Additionally, corticosteroids have been shown to interfere with cell cycle functions by delaying DNA synthesis and decreasing the mitotic rate, resulting in an anti-proliferative effect.[9]

B. Impoyz

FDA approved Impoyz (clobetasol propionate) on November 28, 2017, as a topical cream in 0.025% strength for the treatment of moderate to severe plaque psoriasis in patients 18 years of age and older. Clobetasol propionate is a corticosteroid with anti-inflammatory, anti-pruritic, and vasoconstrictive properties. The approval of Impoyz was based on two adequate and well-controlled clinical endpoint studies in patients with moderate to severe plaque psoriasis. Impoyz is classified as a high potency topical corticosteroid. Topical administration to the affected skin areas is limited to twice daily for up to two consecutive weeks of treatment.[10] Treatment beyond two consecutive weeks is not recommended, and the total dosage should not exceed 50 g per week because of the potential for the drug to suppress the HPA axis.

Impoyz is an oil-in-water emulsion intended for topical application. Each gram of Impoyz contains 0.25 mg clobetasol propionate. Notably, the Impoyz formulation is half the strength of previously approved clobetasol propionate products, which have a strength of 0.05%.[11] The formulation is designed to reduce the incidence of local and systemic adverse effects seen with the 0.05% products, including HPA axis suppression, while maintaining effectiveness. It achieves this result by using the pharmaceutical excipient, Transcutol, without propylene glycol. In addition to Transcutol, Impoyz contains the following excipients: butylated hydroxytoluene, cetostearyl alcohol, cyclomethicone, glyceryl stearate and PEG 100 stearate, isopropyl myristate, methyl paraben, propyl paraben, purified water and white wax.

C. The Proposed Glenmark Product

Glenmark has submitted ANDA 214191 for a generic clobetasol propionate topical cream product that relies on Impoyz as the reference listed drug (RLD). According to Glenmark's notice letter (assuming it is accurate), Glenmark's purported product has a different formulation than Impoyz. In particular, the notice letter states that Glenmark's proposed product contains propylene glycol in an amount greater than 10% and, based on that assertion, it seems unlikely that Glenmark's purported formulation includes Transcutol. Impoyz contains Transcutol and

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[9] *Id.*

[10] *See* Impoyz Prescribing Information (PI) at Section 2 (Dosage and Administration) (Tab 8).

[11] Clobetasol propionate is marketed in the U.S. at 0.05% strength in several topical dosage forms: cream, ointment, solution, lotion, shampoo, spray, aerosol, foam, and gel. Previously approved topical cream products include Temovate and Temovate E, which were discontinued for reasons other than safety and/or efficacy, and related generic products, including a 0.05% generic cream product by Glenmark.

does not contain any propylene glycol. The Glenmark product also is described as not containing at least 60% w/w water.[12]

II. FDA SHOULD REFUSE TO APPROVE THE GLENMARK ANDA BECAUSE THE FORMULATION CHANGES EXCEED THE TYPES OF CHANGES PERMITTED UNDER FDA REGULATIONS

A. Legal Framework Governing Generic Topical Formulations

Generic products are approved based on a showing of sameness to an RLD and not based on supporting clinical trials demonstrating safety and effectiveness. Establishing that a generic topical product is the same as the RLD raises a specific set of issues because such products are intended to act locally, within the complex systems of the skin. To address those issues, FDA regulations impose enhanced formulation requirements for generic topical products: "a [generic] drug product intended for topical use … shall contain the same inactive ingredients as the [RLD]. However, an ANDA may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product."[13] Furthermore, FDA's regulation governing the approval of ANDAs states that:

> FDA will consider the inactive ingredients or composition of a drug product unsafe and refuse to approve an ANDA under paragraph (a)(8)(i) of this section if, on the basis of information available to the agency, there is ***a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy***…. Examples of the changes that may raise serious questions of safety or efficacy include, but are not limited to, the following: …
>
> (7) If the drug product is intended for topical administration, ***a change in the properties of the vehicle or base that might increase absorption of certain potentially toxic active ingredients*** thereby affecting the safety of the drug product, or a change in the lipophilic properties of a vehicle or base, e.g., a change from an oleaginous to a water soluble vehicle or base.[14]

[12] Letter from J. Reisman to R. Moccia (January 24, 2020) (excerpt, Tab 9). Encore does not concede the accuracy of Glenmark's assertions in its notice letter. Encore is currently in Paragraph IV patent litigation that Encore commenced against Glenmark.

[13] 21 CFR 314.94(a)(9)(v).

[14] 21 CFR 314.127(8)(ii)(A) (emphasis added).

B. Glenmark's Claimed Change to the Impoyz Vehicle Exceeds the Types of Changes Allowed Under FDA's Regulations for Generic Topical Products

1. Propylene Glycol is Significantly Different than Transcutol

Impoyz utilizes a novel formulation that is specifically designed to maintain effectiveness for the treatment of moderate to severe plaque psoriasis using half the amount of clobetasol propionate as the previously approved products. As discussed below, the use of Transcutol without propylene glycol in the Impoyz formulation "provides penetration modification and formation of an intracutaneous depot (i.e., reservoir effect)"[15] essential to Impoyz's clinical profile. Encore is not aware of any information showing that propylene glycol can achieve the same type of depot effect that can be achieved with Transcutol.

Assuming Glenmark's assertions in its notice letter are accurate, Glenmark has changed the key ingredients of Impoyz. Importantly, Glenmark asserts that its formulation contains at least 10% propylene glycol and, based on that assertion, it seems unlikely that Glenmark's formulation includes Transcutol. Transcutol is a distinctly different penetration enhancer than propylene glycol.[16] Transcutol is a hydrophilic solvent with "unique physicochemical properties" and "a unique ability to swell the intercellular path of the skin's barrier [that] gives rise to both skin retention (the intracutaneous skin depot) and skin penetration enhancement…."[17] In fact, Transcutol has been described as a penetration modifier instead of a traditional penetration enhancer, like propylene glycol, because of its ability to "enhance[] a permeant's solubility in the skin without significantly influencing the diffusivity of the permeant in the skin."[18] This activity of Transcutol can result in an intracutaneous depot:

> [Transcutol (TC)] has been found to increase the flux and ***retention of drugs***. Recently, Haque *et al.* showed that TC as a solvent penetrated and retained in the human skin in highest quantities compared with other selected hydrophilic solvents…. TC has been reported to [be] present inside the SC as ***intraceutaneous depot***. TC being a hydrophilic molecule, is inserted into the aqueous region between the polar head group and induce swelling of the bilayer region without altering the bilayer structure. Therefore, the swollen lipids hold the drugs soluble in the SC. In this way, TC aids to accumulate drugs

[15] Del Rosso, J., Topical corticosteroid therapy for psoriasis – A review of clobetasol propionate 0.025% cream and the clinical relevance of penetration modification, J CLIN AESTHET DERMATOL. 2020;13(2):22-29, 27 (Tab 1).

[16] *See* Osborne, D.W., Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products, J COSMETIC DERMATOL. 2011;10:324-329, 327 (Tab 10).

[17] Osborne, D.W. & Musakhanian, J., Skin penetration and permeation properties of Transcutol® – Neat or Diluted Mixtures, AAPS PHARMSCITECH. 2018;19(8):3512-3533, 3518 (Tab 11).

[18] Osborne, D.W., Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products, J COSMETIC DERMATOL. 2011;10:324-329, 327 (Tab 10).

> in the SC (Pull effect)…. The barrier function of the SC was not altered by TC…. Caon *et al*. showed that skin permeation of ioniaside in TC was reduced but ***skin retention was increased*** and the statement goes well with the '[int]ranscutaneous depot' theory.[19]

In contrast, propylene glycol is a hydrophilic penetration enhancer that alters the stratum corneum structure by disrupting intercellular lipids and proteins and increasing the partitioning of active ingredient and solvents used in the vehicle.[20] Generally, propylene glycol solvates the α-keratin and reduces drug-tissue binding. The effect of Transcutol and propylene glycol are very different. Propylene glycol does not provide a depot effect similar to Transcutol. As one article concluded, "Ultimately, DEGEE [Transcutol], as a penetration modifier, differs from conventional penetration enhancers, such as PG [propylene glycol] and ethanol."[21] Consistent with the differences between Transcutol and propylene glycol, Encore is not aware of any information showing that the use of propylene glycol instead of, or in addition to, Transcutol in a topical clobetasol propionate formulation would not result in a different clinical profile.

2. Glenmark's Claimed Use of Propylene Glycol Raises Safety and Efficacy Issues

The use of Transcutol without propylene glycol is integral to the performance and clinical profile of the Impoyz formulation. It allows Impoyz to maintain effectiveness using half the clobetasol propionate as the other approved 0.05% products, which generally use propylene glycol. Prior to Impoyz, FDA had approved approximately 13 clobetasol propionate cream products at 0.05% strength, and they all seem to use propylene glycol without Transcutol. The clobetasol propionate products approved after Impoyz also seem to have similar formulations containing propylene glycol but not Transcutol.

Impoyz's use of Transcutol without propylene glycol provides effectiveness at a lower strength while limiting systemic absorption. Generally, percutaneous absorption occurs when a drug passes through the epidermis and dermis, and into the circulation.[22] The depot effect of Transcutol in Impoyz means that less drug is available for systemic absorption. As explained in the literature:

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[19] Haque, T., *et al*., Chemical enhancer: A simplistic way to modulate barrier function of the stratum corneum, ADV PHARM BULL. 2018;8(2):169-179, 173 (Tab 12) (emphasis added); *see also* Osborne, D.W., Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products, J COSMETIC DERMATOL. 2011;10:324-329 (Tab 10).

[20] *See* Haque, T., *et al*., Chemical enhancer: A simplistic way to modulate barrier function of the stratum corneum, ADV PHARM BULL. 2018;8(2):169-179, 174 (Tab 12).

[21] Del Rosso, J., Topical corticosteroid therapy for psoriasis—A review of clobetasol propionate 0.025% cream and the clinical relevance of penetration modification, J CLIN AESTHET DERMATOL. 2020;13(2):22–29, 27 (Tab 1).

[22] Dhar, S., *et al*., Systemic side-effects of topical corticosteroids, INDIAN J DERMATOL. 2014 Sep-Oct;59(5):460–464 (Tab 13).

> Many studies evaluating DEGEE [Transcutol] as a skin penetration modifier have shown that DEGEE enhances a permeant's solubility in the skin without significantly influencing the diffusivity of the permeant in the skin, that is, stratum corneum. For the permeants dexamethasone and hydrocortisone, the presence of DEGEE resulted in enhanced skin retention although the permeability and therefore the systemic uptake were significantly decreased. This effect has been called the intracutaneous depot and can be conceptualized as DEGEE increasing the reservoir capacity of the stratum corneum.[23]

In *ex vivo* permeation and penetration testing with Impoyz and Temovate® (clobetasol propionate) topical cream (0.05%), Impoyz showed a statistically lower mean cumulative amount of clobetasol propionate (ng/cm^2) delivered to receptor solution at 24 hours post-application compared to Temovate.[24] The testing, which was conducted by MedPharm Ltd. on behalf of Encore, used MedPharm's methodology and involved application to combined donor skin, with the mean cumulative amounts of clobetasol propionate (ng) recovered from the epidermis, dermis, and receptor solution 24 hours post-application. The amount of drug that permeates through the skin layers is represented by the amount in the receiver solution under the skin samples. Temovate, which was formulated with propylene glycol and twice the clobetasol propionate as Impoyz, delivered about 17-fold more drug than Impoyz to the receptor solution. Impoyz achieved statistically the same level of clobetasol propionate in the dermis as Temovate[25] with half the amount of the active ingredient and only 6% of the potential systemic exposure.[26] Similarly, the *in vivo* relative bioavailability study comparing Impoyz and Temovate E® topical cream (0.05%) that was submitted to support the approval of Impoyz showed that mean plasma concentrations of clobetasol propionate at Day 15 (post-treatment) were approximately 2.6 fold higher in the Temovate E® group (152.5 ± 140.9 pg/mL (95% CI of mean (90.0 to 214.9)) compared to the Impoyz group (56.3 ± 104.7 pg/mL (95% CI of mean (9.9 to 102.7)).[27]

The potential effects of Transcutol versus propylene glycol on the properties of a topical vehicle, including lower systemic absorption, are described in the literature:

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[23] Osborne, D.W., Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products, J COSMETIC DERMATOL. 2011;10:324-329, 327 (Tab 10).

[24] *See* MedPharm Study Data (confidential) (Tab 14).

[25] Statistical analysis was performed using a one-way ANOVA with post hoc Tukey's HSD.

[26] The potential systemic exposure value was calculated by dividing the mean cumulative amount of clobetasol propionate in the receptor solution at 24 hours following application of Impoyz (3.28 ng/cm^2) by the mean cumulative amount at 24 hours following application of Temovate (56.39 ng/cm^2). *See id.*

[27] Impoyz (clobetasol propionate) cream, NDA 209483, Clinical Pharmacology & Biopharmaceutics Review(s), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000ClinPharmR.pdf at 2, 7-8 (excerpt, Tab 15).

> The properties that make DEGEE [Transcutol] so valuable in vehicle technology are its abilities to increase solubility of compounds in suitable solvents, including poorly soluble agents, provide immediate dissolution and suspension of active ingredient (i.e., reservoir effect), and increase cutaneous retention of active ingredient (i.e., expanded intracutaneous depot) while limiting systemic exposure.
> …
> Pharmaceutical-grade DEGEE provides important vehicle characteristic advantages over PG [propylene glycol] and ethanol. DEGEE provides a unique intracutaneous depot effect that prolongs retention of the active ingredient within skin, with the added benefit of lower systemic exposure.[28]

Lower systemic absorption of clobetasol propionate is particularly important because systemic absorption of corticosteroids is related to serious safety issues, such as HPA axis suppression, iatrogenic Cushing's syndrome, and growth retardation in children. Corticosteroids can suppress the hypothalamic cortisol releasing hormone and pituitary adrenocorticotropic hormone (ACTH), which can result in suppression of HPA axis and adrenal insufficiency with adrenal gland atrophy.[29] The increased blood level of corticosteroids also can induce features of hypercortisolism or iatrogenic Cushing's syndrome. The labeling for Impoyz includes the following warnings and precautions related to systemic absorption:

- Clobetasol propionate has been shown to suppress the HPA axis at the dose tested. (5.1)

- Cushing’s syndrome, hyperglycemia, and glucosuria can also result from systemic absorption of topical corticosteroids. (5.1)

- Systemic absorption may require periodic evaluation for HPA axis suppression. Modify use if HPA axis suppression develops. (5.1)

Furthermore, children are considered especially susceptible to systemic toxicity from the use of topical corticosteroids. According to the Impoyz labeling, “Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of systemic

[28] Del Rosso, J., Topical corticosteroid therapy for psoriasis – A review of clobetasol propionate 0.025% cream and the clinical relevance of penetration modification, J CLIN AESTHET DERMATOL. 2020;13(2):22–29, 27 (Tab 1). To the extent that Glenmark has added propylene glycol to a formulation that also contains Transcutol, the literature suggests that the combination leads to further increases in the flux rate of an active ingredient compared to Transcutol alone. *See* Osborne, D.W. & Musakhanian, J., Skin penetration and permeation properties of Transcutol® – Neat or Diluted Mixtures, AAPS PHARMSCITECH. 2018;19(8):3512-3533, 3522 (describing the influence of the combination of 10% Transcutol and 50% propylene glycol on clonazepam permeation through artificial membrane and rabbit ear skin) (Tab 11).

[29] Dhar, S., *et al*., Systemic side-effects of topical corticosteroids, INDIAN J DERMATOL. 2014 Sep-Oct; 59(5): 460–464 (Tab 13).

toxicity, including HPA axis suppression, when treated with topical drugs."[30] Similarly, the scientific literature has recognized that "[c]hildren are more susceptible to the systemic adverse effects because of enhanced percutaneous absorption through their tender skin."[31] An article published in 2014 analyzed the number of Cushing's syndrome cases over the previous 35 years and determined that the majority of cases were in children, with only a few in adults.[32]

Impoyz has been proven safe and effective through significant clinical testing. Despite the fact that FDA already had approved numerous clobetasol propionate cream products at a higher 0.05% strength, FDA still required Impoyz to be supported with two adequate and well-controlled clinical trials. The two clinical trials, DFD-06-CD-004 (N=267) and DFD-06-CD-005 (N=265), involved patients with moderate to severe plaque psoriasis who were randomized to Impoyz or vehicle treatment. Impoyz was shown to be significantly superior to vehicle in both trials, based on the primary efficacy endpoint of proportion of subjects with treatment success, defined as IGA=0 or 1 and at least 2 grade reduction from baseline at the Day 15 visit.[33] The treatment effect was similar across both trials.

Impoyz also was supported with local safety data and systemic/HPA axis suppression data. The amount of data needed to support the approval of Impoyz underscores that a change in formulation of a topical corticosteroid, even a change involving a lower strength, can have significant clinical effects. This is particularly the case when the change involves the formulation vehicle and might increase absorption of the active ingredient.

3. FDA Regulations Preclude Glenmark From Submitting its Proposed Formulation Change Under an ANDA

The significant and serious risks of increased systemic exposure clearly establish a reasonable basis to conclude that the propylene glycol in Glenmark's proposed product (as described in the notice letter) raises serious questions of safety or efficacy, such that FDA must refuse to approve the application.[34] Glenmark's claimed formulation change is precisely the type of change that FDA regulations state should not be approved in an ANDA, because the purported use of propylene glycol "might increase absorption of certain potentially toxic active ingredients."[35] Accordingly, FDA must refuse to approve the Glenmark ANDA, and Glenmark

[30] Impoyz PI at Section 8.4 (Tab 8).

[31] Dhar, S., *et al*., Systemic side-effects of topical corticosteroids, INDIAN J DERMATOL. 2014 Sep-Oct; 59(5): 460–464 (Tab 13).

[32] *Id.*

[33] Impoyz (clobetasol propionate) cream, 0.025%, NDA 209483, Medical Review(s), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000MedR.pdf at 6 (excerpt, Tab 16).

[34] *See* 21 CFR 314.127(a)(8)(ii)(A).

[35] 21 CFR 314.127(a)(8)(ii)(A)(7).

should submit its new formulation under a new drug application with appropriate data demonstrating that the proposed product is safe and effective.

III. GLENMARK MUST SUPPORT ITS CLAIMED NEW FORMULATION WITH CLINICAL ENDPOINT BIOEQUIVALENCE DATA AND ADDITIONAL SAFETY DATA

Establishing that a generic product is bioequivalent to the RLD is an important part of the generic sameness requirements and ensures that the generic product has the same clinical profile as the RLD. Generally, bioequivalent products provide the same rate and extent of drug absorption at the site of action.[36] For systemic products, bioequivalence typically is established through drug blood levels. However, blood levels are not correlated with clinical effectiveness in the case of topical products intended for local treatment. Thus, bioequivalence for topical products can be demonstrated through other measurements, such as pharmacodynamic effect studies, comparative clinical endpoint studies, and *in vitro* studies.[37] To establish bioequivalence of topical corticosteroids, FDA generally relies on a vasoconstrictor assay, which is a pharmacodynamic test that measures skin blanching.

A. Vasoconstrictor Assay

In June 1995, FDA issued its *Guidance for Industry: Topical Dermatologic Corticosteroids: In Vivo Bioequivalence* (*Topical Corticosteroids BE Guidance*), which sets forth the assessment of bioequivalence of topical corticosteroids using the vasoconstrictor assay, or skin blanching study. The *Topical Corticosteroids BE Guidance* recommends two *in vivo* studies that use the vasoconstrictor assay – a pilot study in the reference product alone and a pivotal study comparing the test and reference products.[38] The pilot study determines the appropriate dose duration to be used in the pivotal study by evaluating the degree of skin blanching on healthy human subjects after topically applying the corticosteroid formulation for different durations of time. The *Topical Corticosteroids BE Guidance* states that the skin blanching should be measured at multiple times.[39] For the pivotal study, the same pharmacodynamics vasoconstrictor assay should be used, with the appropriate dose duration identified from the pilot study.

The vasoconstrictor assay relies on the property of topical corticosteroids to cause vasoconstriction or blanching of the skin microvasculature.[40] As explained in the *Topical*

[36] 21 USC 355(j)(8)(B)(i); 21 CFR 320.21(e).

[37] 21 CFR 320.24(b).

[38] *Topical Corticosteroids BE Guidance* at 3 (Tab 17).

[39] *See id.* at 6, 12.

[40] *Id.* at 2.

Corticosteroids BE Guidance, "This property presumably relates to the amount of drug entering the skin and thus becomes a possible basis for the comparison of drug delivery from two potentially equivalent topical corticosteroid formulations."[41]

B. The Vasoconstrictor Assay is not Sufficient to Ensure the Bioequivalence and Safety of Glenmark's Claimed New Formulation

Based on FDA's use of the vasoconstrictor assay for topical corticosteroids, the Glenmark ANDA probably relies on vasoconstrictor data to demonstrate bioequivalence to Impoyz without providing any systemic drug level data, HPA axis suppression data, or other safety data.[42] Due to the significant formulation differences in this situation (based on Glenmark's assertions in its notice letter), the vasoconstrictor assay is not sufficient by itself to support approval of the Glenmark ANDA.

1. Comparative Clinical Endpoint Data

Vasoconstrictor assays do not establish a sufficient scientific bridge, to allow one sponsor to rely solely on another sponsor's data, when the formulations of the two products contain a significant difference. This has been widely recognized, including by government regulators. The European Medicines Agency (EMA), for example, has recognized that the vasoconstrictor assay is not an appropriate test when a generic product incorporates more than minor formulation differences. As explained by the EMA, qualitative changes to a topical corticosteroid formulation must be supported with clinical efficacy data:

> The vehicle itself may have a great impact on efficacy and may modify the dermal absorption…. ***Therefore, a pharmacodynamic model, e.g. the vasoconstriction assay (VCA) is sufficient only if the generic medicinal product possesses the same or a similar qualitative and quantitative composition to that of the reference product.***
>
> Differences in excipients have to be considered case by case. In case of only minor changes, e.g. slight differences in the quantity of the same excipients in generic applications, VCAs can be accepted instead of clinical efficacy studies***. However, qualitative changes in the composition imply the need for clinical efficacy data***.[43]

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[41] *Id*.

[42] FDA has issued two product-specific bioequivalence draft guidance documents related to clobetasol propionate topical cream products: one for Temovate cream 0.05% and the other for Temovate E cream emollient 0.05%. Both draft guidances recommend two vasoconstrictor studies consistent with FDA's *Topical Corticosteroids BE Guidance*.

[43] EMA, Questions and Answer on Guideline Title: Clinical Investigation of Corticosteroids Intended for Use on the Skin (Nov. 16, 2006) at 2 (emphases added), https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answer-guideline-title-clinical-investigation-corticosteroids-intended-use-skin_en.pdf (Tab 18).

This is particularly the case for products, like Impoyz, that are designed to have a particular dermatokinetic profile. The Impoyz formulation promotes retention of the drug in the skin and allows Impoyz to use half the amount of active ingredient compared to other approved clobetasol propionate products, while reducing the amount of active ingredient available for systemic absorption. An alternative formulation, with more than a minor formulation change (particularly as to penetration enhancer), cannot be assumed to have the same kinetic profile as Impoyz. Instead, it must be independently tested, using a testing model that is appropriately calibrated to identify a difference in the performance of the formulation, including the potential of the formulation to increase systemic drug absorption.

In this situation, the vasoconstrictor assay is not sufficiently sensitive to distinguish important formulation differences. The vasoconstrictor assay measures a pharmacodynamic effect involving a comparative measurement of skin color. This is a reasonable proxy for reasonably similar formulations, but has been shown to be inadequate when bridging between qualitatively different formulations of the same drug. Further, the utility of the vasoconstrictor assay has been questioned when applied to drugs formulated to have a depot effect, like Impoyz:

> The VCA [vasoconstrictor assay] measures blanching effects of topical products as a surrogate marker for bioavailability. Skin blanching occurs as a result of vasoconstriction in the lower skin layers, and VCA measures if the drug has passed through the skin, but not necessarily whether the drug is within the skin. The "depot effect" of designer vehicles allows a steroid to penetrate the stratum corneum layer of skin and remain in position in the epidermis and dermis to topically treat psoriasis.[44]

In fact, even FDA has recognized the limits of using the vasoconstrictor assay to bridge significantly different topical corticosteroid formulations. Typically, a 505(b)(2) applicant bridges to the listed drug relied on for approval through a bioequivalence study. Similar to an ANDA, a 505(b)(2) bridge demonstrates that reliance on the listed drug is scientifically justified. With respect to topical corticosteroids, using bioequivalence as a bridge would mean that a 505(b)(2) applicant should be able to bridge to the listed drug using the vasoconstrictor assay. However, that is not FDA's approach. Instead, FDA recommends that the bridge include a clinical endpoint trial. As FDA explained with respect to a 505(b)(2) application for a new halobetasol propionate 0.05% lotion product that relied on an approved halobetasol propionate 0.05% cream product: "For a topical product, this [bridge] is accomplished through conduct of

[44] Updates in psoriasis management: Based on selected presentations from Maui Derm 2018, J CLIN AESTHET DERMATOL. 2018;11(10):S5–S23, https://jcadonline.com/oct-2018-psoriasis-supplement/ (Tab 19).

well-controlled trials with clinical endpoints and for a topical corticosteroid, also includes assessment of the effect of the products on the HPA axis."[45, 46]

Similarly, in situations where a 505(b)(2) applicant for a new topical corticosteroid formulation seeks to rely solely on the listed drug for safety and efficacy data (akin to an ANDA), FDA has described the need for a clinical endpoint study:

> If the application is submitted as a 505(b)2 with a bridge for both safety and efficacy:
> One multi-armed study (product, vehicle, and reference listed drug product) demonstrating superiority to vehicle and non-inferiority to a reference listed product at the pre-specified time of assessment.[47]

For the purported Glenmark product (as described in its notice letter), and any similarly formulated generic, FDA must require a bioequivalence bridge to Impoyz based on a comparative study with clinical endpoints. This will ensure that the Glenmark generic product provides the same local effectiveness as Impoyz and would be consistent with the scientific approach used by FDA to bridge significantly different topical corticosteroid formulations under 505(b)(2) applications. Furthermore, to ensure that Glenmark's purported product provides the same systemic safety as Impoyz, FDA should require the Glenmark ANDA to be supported with systemic and HPA axis suppression data.

2. Systemic and HPA Axis Suppression Data

The Glenmark ANDA also should be supported with systemic exposure and HPA axis suppression data to address potential safety issues. Even though Impoyz is a topical product, systemic exposure to clobetasol propionate is associated with numerous safety issues, including HPA axis suppression, Cushing's syndrome, hyperglycemia, and glucosuria. Systemic absorption of a topical corticosteroid is influenced by, among other factors, product formulation. The Impoyz formulation is specifically designed to limit systemic absorption, and its positive systemic safety profile was supported with systemic and HPA axis testing.

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[45] Ultravate (halobetasol propionate) lotion, NDA 208183 End-of-Phase 2 Meeting Minutes, Admin. and Corr. Documents at 6 (excerpt, Tab 20), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208183Orig1s000Admincorres.pdf (pdf 84).

[46] The fact that this 505(b)(2) example involves a new dosage form does not make it irrelevant. FDA routinely approves 505(b)(2) applications for new dosage forms based only on a showing of bioequivalence. *See* Nityr (nitisinone) tablets, NDA 209449 (a 505(b)(2) application for a new tablet dosage form that was approved based on a showing of bioequivalence to the capsule listed drug).

[47] Desonate (desonide) gel, NDA 021844 Guidance Meeting Minutes, Admin. and Corr. Documents at 5 (excerpt, Tab 21), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021844s000_AdminCorres.pdf (pdf 88).

Impoyz was compared to Temovate® E cream (0.05%) under maximal use conditions in a relative bioavailability study in subjects with moderate to severe plaque psoriasis. One third fewer Impoyz subjects showed evidence of HPA axis suppression.[48] Further, the results showed that Day 15 post-treatment plasma concentrations of clobetasol propionate were 2.6 fold higher in the Temovate E group compared to the Impoyz group. At the same time, the systemic exposure in patients with HPA axis suppression was approximately 3 fold higher compared to the systemic exposure in patients without HPA axis suppression. FDA reviewers concluded, "This indicates that higher systemic exposure leads to the incidence of HPA axis suppression."[49]

FDA has previously stated that HPA axis suppression testing is not necessary for generic products that show bioequivalence using the vasoconstrictor assay.[50] As FDA explained, "if bioequivalence is shown using a multiple-point vasoconstrictor assay, the test and reference products can be expected to perform similarly with respect to HPA axis suppression and HPA axis suppression testing would not be necessary."[51] Further, FDA stated that its determination not to require HPA axis suppression testing is based on the underlying principle that "local availability will correlate with potential systemic exposure."[52]

However, the scientific literature contradicts the underlying principle of FDA's determination. As explained in one publication, "No correlation exists between the availability of drug in the skin and with the resulting blood levels."[53] The vasoconstrictor assay only measures the local blanching response and does not provide any quantification of drug that is not involved in that response. Drug that is not involved in the blanching response might be on the skin's surface or may already be absorbed systemically. In fact, one *in vitro* skin study described in the literature measured topical corticosteroid absorption after administration and found that distribution of the active ingredient is highest on the skin surface followed by the stratum corneum, epidermis, dermis, and receptor fluid.[54] Further, the article noted that drug "concentrations retained by the SC [stratum corneum] were not absorbed by the skin and did not contribute to the systemic dose."[55] The vasoconstrictor assay, which involves a comparison of

[48] Impoyz (clobetasol propionate) cream, NDA 209483, Clinical Pharmacology & Biopharmaceutics Review(s), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000ClinPharmR.pdf at 2 (excerpt, Tab 15).

[49] *Id*. at 7.

[50] *Topical Corticosteroids BE Guidance* at 1 (Tab 17).

[51] FDA Citizen Petition Response to Docket No. FDA-2010-P-0570 at 13 fn 38 (Apr. 27, 2011) (Tab 22).

[52] FDA Citizen Petition Response to Docket Nos. FDA-2011-P-0565, FDA-2011-P-0593 at 12 (Jan. 18, 2012) (Tab 23).

[53] Nair, A. *et al*., Basic considerations in the dermatokinetics of topical formulations, EBRAZILIAN J PHARM SC. 2013 (49):423-434, 425 (Tab 24).

[54] Carrer, V., *et al*., Effect of propylene glycol on the skin penetration of drugs, ARCH DERMATOL RES. 2019 (Tab 25).

[55] *Id*.

skin color, is not sufficiently sensitive to provide the type of comparative systemic absorption information needed to compare two very different topical corticosteroid formulations.

The claimed significant formulation differences and the serious risks associated with systemic levels of clobetasol propionate require that Glenmark conduct a direct measurement of HPA axis suppression.[56] In fact, FDA requires significantly different formulations of topical corticosteroids submitted under 505(b)(2) applications to be supported with HPA axis suppression testing to bridge to the listed drug relied on for approval. As FDA stated:

> If the application is submitted as a 505(b)2 with a bridge for safety only:
> Two independent studies demonstrating superiority to vehicle at the pre-specified time of assessment are needed. In addition, a comparative bridging study to the reference listed product demonstrating lack of superiority is needed to allow the Agency to use its findings for local safety for the reference listed product. The study to compare to the reference listed product may be incorporated into the study design for one of the two pivotal clinical studies if desired. ***Also, systemic safety may be inferred if an HPA axis suppression study and/or desonide blood levels comparing test and reference products show no greater systemic exposure with your test product***.[57]

The requirement that HPA axis suppression testing be performed to establish a bridge for systemic safety data holds true even for applicants that complete a multiple time-point vasoconstrictor assay. For example, a new betamethasone valerate foam 0.1% product was submitted under a 505(b)(2) application. At the pre-IND meeting, FDA agreed that the product could be approved based on a showing of "comparative bioavailability" to the listed drugs.[58] The applicant performed a multiple time-point vasoconstrictor assay that assessed skin blanching at 1 hour before drug application, after drug removal, and at 2, 4, 6, 19, and 24 hours after drug removal.[59] Despite the fact that the applicant had to complete a multiple time-point vasoconstrictor assay, the applicant also had to complete HPA axis suppression testing and a comparative clinical endpoint trial to establish comparable bioavailability.[60]

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[56] Glenmark would be required to submit its new formulation under a 505(b)(2) application instead of an ANDA if FDA determines that HPA axis suppression testing is needed and such testing is not considered limited confirmatory safety testing. *See FDA Guidance for Industry: Determining Whether to Submit an ANDA or a 505(b)(2) Application* at 7 (May 2019).

[57] Desonate (desonide) gel, NDA 021844 Guidance Meeting Minutes, Admin. and Corr. Documents at 5 (excerpt, Tab 21) (emphasis added).

[58] Luxiq (betamethasone valerate) foam, NDA 20934, Pre-IND Meeting Minutes, Admin. and Corr. Documents Pt. 2 (excerpt, Tab 26), https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20934_admindocs_P2.pdf (pdf 12-13).

[59] Luxiq (betamethasone valerate) foam, NDA 20934, Medical Review at 3, https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20934_medr_P1.pdf (excerpt, Tab 27).

[60] *See id.*

The scientific principles underlying the need for the additional HPA axis suppression testing and clinical endpoint testing with respect to 505(b)(2) applicants for topical corticosteroid products seeking to establish comparable bioavailability to the listed drug relied on for approval apply equally to ANDA applicants that must demonstrate comparable bioavailability to rely on the RLD. If a multiple time-point vasoconstrictor assay is always a sufficient test to assess both local and systemic bioavailability, it is not clear why FDA would require the additional clinical testing for topical corticosteroid products submitted under 505(b)(2), particularly as unnecessary clinical testing raises ethical issues.

Systemic and HPA axis suppression data are particularly important with respect to Glenmark's purported formulation because Impoyz obtained a right of reference to the Temovate products and relied on them for safety data. The reliance was scientifically appropriate because the Impoyz HPA axis suppression testing established a bridge to Temovate.[61] By using Impoyz as the RLD, Glenmark is indirectly relying on Temovate as well. However, Glenmark has not conducted any comparative testing with Temovate to establish that reliance on Temovate is scientifically appropriate. In this situation, Glenmark must, at a minimum, conduct HPA axis suppression testing with Impoyz to establish an accurate assessment of this critical risk and provide evidence supporting reliance on both Impoyz and Temovate. The vasoconstrictor assay is not sufficient to identify any drift that may occur with respect to Glenmark's new formulation that would make reliance by Glenmark on Temovate improper.

Furthermore, establishing specific and accurate comparable systemic data is important because Impoyz received several clinical waivers based on its positive systemic exposure profile. FDA did not require Impoyz to be supported with a TQT assessment based, in part, on a showing "that the mean systemic exposure of DFD-06 cream [Impoyz] was lower than Temovate E® cream."[62] Similarly, FDA waived drug interaction assessments for Impoyz. As FDA explained, "since the systemic exposure and HPA axis suppression rate of DFD-06 cream [Impoyz] was lower than Temovate E® cream, the drug interaction assessments are not needed."[63] By relying on Impoyz as the RLD, Glenmark seeks to rely on those clinical waivers; however, such reliance would not be scientifically appropriate if Glenmark's purported formulation results in higher systemic absorption than Impoyz.

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[61] *See* Impoyz (clobetasol propionate) cream, NDA 209483 Pre-NDA Meeting Minutes, Admin. & Corr. Documents at 5 (excerpt, Tab 28), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000Admincorres.pdf (pdf 38).

[62] *See* Impoyz (clobetasol propionate) cream, 0.025%, NDA 209483, Clinical Pharmacology & Biopharmaceutics Review(s) at 3, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000ClinPharmR.pdf (excerpt, Tab 15).

[63] *Id.*

3. Local Safety Data

Glenmark's assertion that its proposed product uses propylene glycol also raises local safety issues. The local safety profile of Impoyz was established with significant data. In addition to clinical safety data, Impoyz was supported with repeat-dose dermal toxicity studies in rats up to 13 weeks and in minipigs up to 4 weeks, an acute dermal study in rabbits, an ocular irritation study using the bovine corneal opacity and permeability (BCOP) assay, a dermal photoirritation study in mice, and a dermal sensitization study in guinea pigs.[64]

Propylene glycol is known to produce eczematous skin reactions, allergic responses, and irritant contact dermatitis.[65] In fact, a study has shown that propylene glycol is the most common allergen in topical corticosteroids,[66] and propylene glycol was named the American Contact Dermatitis Society's "Allergen of the Year" in 2018 for these well-documented reactions.[67] Allergic reactions have typically been associated with propylene glycol concentrations of greater than 10%,[68] which is the purported amount in Glenmark's new formulation. In contrast, the Transcutol in Impoyz is associated with "the relative absence of irritancy, allerginicity, adverse alteration of the skin microbiome, or toxicity."[69]

Based on Glenmark's claimed use of propylene glycol, there is a reasonable basis to conclude that Glenmark's formulation may have a less favorable local safety profile than Impoyz. If Glenmark's proposed product is approved as therapeutically equivalent to Impoyz, then the Glenmark product will be "expected to have the same clinical effect and safety profile" as Impoyz and will have the same labeling as Impoyz.[70] The adverse event information in the Impoyz labeling states that rash occurred in less than 1% of subjects. It also states that "[t]he

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[64] *See* Impoyz (clobetasol propionate) cream, 0.025%, NDA 209483, Non-Clinical Review(s) at 3, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000PharmR.pdf (excerpt, Tab 29).

[65] *See, e.g.*, McGowan, M., *et al.*, Propylene glycol in contact dermatitis: A systematic review, DERMATITIS. 2018;29(1):6-12 (Tab 30); Al Jasser, M., *et al.*, Propylene glycol: An often unrecognized cause of allergic contact dermatitis in patients using topical corticosteroids, SKIN THERAPY LETT. 2011 May;16(5):5-7 (Tab 31); Lessmann, H., *et al.*, Skin-sensitizing and irritant properties of propylene glycol, CONTACT DERMATITIS. 2005 Nov;53(5):247-59 (Tab 32); Catanzaro, J., *et al.*, Propylene glycol dermatitis, J AM ACAD DERMATOL. 1991 Jan;24(1):90-5 (Tab 33).

[66] Coloe, J., *et al.*, Allergens in Corticosteroid Vehicles, DERMATITIS. 2008;19(1):38-42, 39 (Tab 34).

[67] McGowan, M., *et al.*, Propylene glycol in contact dermatitis: A systematic review, DERMATITIS. 2018:29(1):6-12, 6 (Tab 30).

[68] *See* Del Rosso, J., Topical corticosteroid therapy for psoriasis—A review of clobetasol propionate 0.025% cream and the clinical relevance of penetration modification, J CLIN AESTHET DERMATOL. 2020;13(2):22–29, 26 (Tab 1).

[69] *Id.* at 27.

[70] 21 CFR 314.3 (defining "Therapeutic equivalents"); Orange Book Preface, https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface.

adverse reaction that occurred in at least 1% of subjects treated with IMPOYZ Cream and at a higher incidence than in subjects treated with vehicle cream was application site discoloration (2% versus 1%)." In contrast, the labeling for another clobetasol propionate cream product with a high level of propylene glycol states that burning/stinging "occurred in 5% of treated patients."[71]

The Glenmark product must be supported with local safety data showing that it has the same local safety profile as Impoyz and that the Impoyz labeling is applicable to the Glenmark product. Otherwise, Glenmark's product would not be therapeutically equivalent to Impoyz and use of Impoyz's labeling with Glenmark's product would be false and misleading. To the extent that Glenmark's product contains propylene glycol and has a different safety profile that requires different labeling, Glenmark should submit its new formulation under a new drug application.

IV. CONCLUSION

For all of the reasons described above, Encore respectfully requests that FDA grant the actions requested in this citizen petition.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

[71] *See* Temovate E PI (rev. Nov. 2012), https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020340s007lbl.pdf (Tab 35).

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: January 24, 2020. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Encore Dermatology, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

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Enclosures