

November 13, 2020

***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<sup>®</sup> (clobetasol propionate) 0.025% topical cream, which is indicated for moderate to severe plaque psoriasis. On May 22, 2020, Encore filed a citizen petition regarding an abbreviated new drug application (ANDA) referencing Impoyz that was submitted by Glenmark Pharmaceuticals Limited (Glenmark). Encore's prior citizen petition concerned the legal, safety, and efficacy issues raised by Glenmark's claimed formulation. Encore supplemented its petition with experimental data on August 10, 2020. On October 16, 2020, FDA stated that it was not ready to make a final determination regarding the Glenmark application and denied the citizen petition "without comment on whether we will take the actions you request."<sup>1</sup> The agency has not addressed the substantive issues raised by Encore. Accordingly, Encore submits this petition to ensure that FDA considers and addresses the issues raised by Encore, and has adequate time to do so, in conjunction with any final decision reached as to the Glenmark application. This citizen petition combines the prior petition and supplement, and is substantively the same as those documents.

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<sup>®</sup> (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."<sup>2</sup> In addition to local

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<sup>1</sup> FDA Petition Response, Docket No. FDA-2020-P-1421-0041 (October 16, 2020) at 1.

<sup>2</sup> 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).

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.”<sup>3</sup>

Encore received a Paragraph IV notice letter from Glenmark stating that Glenmark submitted an 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 raises questions of safety and efficacy that cannot be answered by relying on the clinical data for Impoyz. Furthermore, *in vitro* permeation testing (IVPT) conducted by an independent contract provider demonstrates that there is a significant difference in clobetasol propionate permeation (both flux and cumulative amount of drug) between Impoyz and a propylene glycol-based formulation. 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

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<sup>3</sup> McCurdy, B., Top ten innovations in podiatry, *PODIATRY TODAY*. 2018;31(7):26-34 (Tab 2).

- 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.<sup>4</sup> In plaque psoriasis, the most common clinical type of psoriasis, cells build up rapidly on the surface of the skin, resulting in raised oval-shaped “plaques” over the skin.<sup>5</sup> 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.<sup>6</sup>

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.<sup>7</sup> 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.

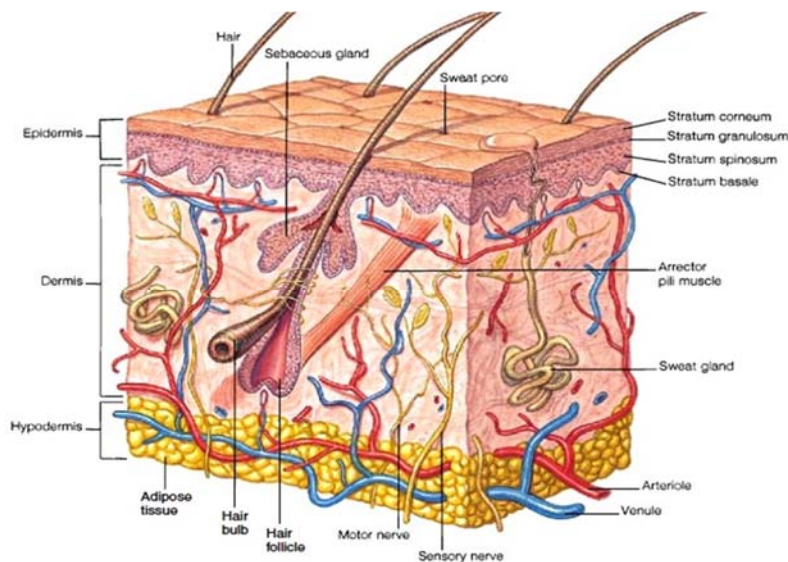
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<sup>4</sup> See Rachakonda, T.D., *et al.*, Psoriasis prevalence among adults in the United States, J AM ACAD DERMATOL. 2014 Mar;70(3):512-16, 512 (Tab 3); *see also* National Psoriasis Foundation, Statistics, <https://www.psoriasis.org/content/statistics>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

<sup>5</sup> See Badri, T., *et al.*, Plaque psoriasis, StatPearls Publishing. 2020 Jan (Tab 5).

<sup>6</sup> *Id.*

<sup>7</sup> 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).



Topical corticosteroids are the cornerstone of treatment of psoriatic lesions, alone or in combination with other treatments.<sup>8</sup> 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.”<sup>9</sup> 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.<sup>10</sup>

## 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.<sup>11</sup> 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.

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

<sup>9</sup> *Id.*

<sup>10</sup> *Id.*

<sup>11</sup> See Impoyz Prescribing Information (PI) at Section 2 (Tab 8).

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%.<sup>12</sup> 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 does not contain any propylene glycol. The Glenmark product also is described as not containing at least 60% w/w water.<sup>13</sup>

## **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

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<sup>12</sup> 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.

<sup>13</sup> 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.

identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.”<sup>14</sup> 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.<sup>15</sup>

**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)”<sup>16</sup> 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

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<sup>14</sup> 21 CFR 314.94(a)(9)(v).

<sup>15</sup> 21 CFR 314.127(8)(ii)(A) (emphasis added).

<sup>16</sup> 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, 28 (Tab 1).

propylene glycol.<sup>17</sup> 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....”<sup>18</sup> 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.”<sup>19</sup> 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 **intracutaneous 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 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.<sup>20</sup>

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.<sup>21</sup> Generally, propylene glycol solvates the  $\alpha$ -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.”<sup>22</sup> Consistent with the differences between Transcutol and propylene glycol, Encore is not aware of any

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<sup>17</sup> 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).

<sup>18</sup> Osborne, D.W. & Musakhanian, J., Skin penetration and permeation properties of Transcutol® – Neat or Diluted Mixtures, AAPS PHARMSciTECH. 2018;19(8):3512-3533, 3513, 3518 (Tab 11).

<sup>19</sup> Osborne, D.W., Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products, J COSMETIC DERMATOL. 2011;10:324-329, 327 (Tab 10).

<sup>20</sup> 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).

<sup>21</sup> 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).

<sup>22</sup> 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).

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.<sup>23</sup> The depot effect of Transcutol in Impoyz means that less drug is available for systemic absorption. As explained in the literature:

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.<sup>24</sup>

In *in vitro* 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<sup>2</sup>) delivered to receptor solution at 24 hours post-application compared to Temovate.<sup>25</sup> 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

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<sup>23</sup> Dhar, S., *et al.*, Systemic side-effects of topical corticosteroids, INDIAN J DERMATOL. 2014 Sep-Oct;59(5):460–464 (Tab 13).

<sup>24</sup> Osborne, D.W., Diethylene glycol monoethyl ether: an emerging solvent in topical dermatology products, J COSMETIC DERMATOL. 2011;10:324-329, 327 (Tab 10).

<sup>25</sup> See MedPharm Study Data (confidential) (Tab 14).



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<sup>26</sup> with half the amount of the active ingredient and only 6% of the potential systemic exposure.<sup>27</sup> Similarly, the *in vivo* relative bioavailability study comparing Impoyz and Temovate E<sup>®</sup> 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<sup>®</sup> group ( $152.5 \pm 140.9$  pg/mL (95% CI of mean (90.0 to 214.9)) compared to the Impoyz group ( $56.3 \pm 104.7$  pg/mL (95% CI of mean (9.9 to 102.7))).<sup>28</sup> Additional IVPT results comparing Impoyz to formulations containing propylene glycol are described in section IV below. Those results also show that propylene glycol-based formulations have significantly different dermatopharmacokinetics compared to Impoyz.

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

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.<sup>29</sup>

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<sup>26</sup> Statistical analysis was performed using a one-way ANOVA with post hoc Tukey's HSD.

<sup>27</sup> 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<sup>2</sup>) by the mean cumulative amount at 24 hours following application of Temovate (56.39 ng/cm<sup>2</sup>). *See id.*

<sup>28</sup> Impoyz (clobetasol propionate) cream, NDA 209483, Clinical Pharmacology & Biopharmaceutics Review(s), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/209483Orig1s000ClinPharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000ClinPharmR.pdf) at 2, 7-8 (excerpt, Tab 15).

<sup>29</sup> 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<sup>®</sup> – 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).

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 adrenocorticotrophic hormone (ACTH), which can result in suppression of HPA axis and adrenal insufficiency with adrenal gland atrophy.<sup>30</sup> 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 toxicity, including HPA axis suppression, when treated with topical drugs."<sup>31</sup> 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."<sup>32</sup> 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.<sup>33</sup>

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,

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<sup>30</sup> Dhar, S., *et al.*, Systemic side-effects of topical corticosteroids, INDIAN J DERMATOL. 2014 Sep-Oct; 59(5): 460–464 (Tab 13).

<sup>31</sup> Impoyz PI at Section 8.4 (Tab 8).

<sup>32</sup> Dhar, S., *et al.*, Systemic side-effects of topical corticosteroids, INDIAN J DERMATOL. 2014 Sep-Oct; 59(5): 460–464 (Tab 13).

<sup>33</sup> *Id.*

defined as IGA=0 or 1 and at least 2 grade reduction from baseline at the Day 15 visit.<sup>34</sup> 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.<sup>35</sup> 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."<sup>36</sup> Accordingly, FDA must refuse to approve the Glenmark ANDA, and Glenmark 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.<sup>37</sup> 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.<sup>38</sup> To establish bioequivalence

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<sup>34</sup> Impoyz (clobetasol propionate) cream, 0.025%, NDA 209483, Medical Review(s), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/209483Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000MedR.pdf) at 6 (excerpt, Tab 16).

<sup>35</sup> See 21 CFR 314.127(a)(8)(ii)(A).

<sup>36</sup> 21 CFR 314.127(a)(8)(ii)(A)(7).

<sup>37</sup> 21 USC 355(j)(8)(B)(i); 21 CFR 320.21(e).

<sup>38</sup> 21 CFR 320.24(b).

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.<sup>39</sup> 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.<sup>40</sup> 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.<sup>41</sup> As explained in the *Topical 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.”<sup>42</sup>

**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.<sup>43</sup> 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.

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<sup>39</sup> *Topical Corticosteroids BE Guidance* at 3 (Tab 17).

<sup>40</sup> *See id.* at 6, 12.

<sup>41</sup> *Id.* at 2.

<sup>42</sup> *Id.*

<sup>43</sup> 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*.

## 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.***<sup>44</sup>

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:

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<sup>44</sup> 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](https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answer-guideline-title-clinical-investigation-corticosteroids-intended-use-skin_en.pdf) (Tab 18).

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.<sup>45</sup>

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 well-controlled trials with clinical endpoints and for a topical corticosteroid, also includes assessment of the effect of the products on the HPA axis.”<sup>46, 47</sup>

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.<sup>48</sup>

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<sup>45</sup> 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).

<sup>46</sup> 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](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208183Orig1s000Admincorres.pdf) (pdf 84).

<sup>47</sup> 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).

<sup>48</sup> 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](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021844s000_AdminCorres.pdf) (pdf 88).

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.

Impoyz was compared to Temovate<sup>®</sup> 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.<sup>49</sup> 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."<sup>50</sup>

FDA has previously stated that HPA axis suppression testing is not necessary for generic products that show bioequivalence using the vasoconstrictor assay.<sup>51</sup> 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."<sup>52</sup> Further, FDA stated that its determination

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<sup>49</sup> Impoyz (clobetasol propionate) cream, NDA 209483, Clinical Pharmacology & Biopharmaceutics Review(s), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/209483Orig1s000ClinPharmR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000ClinPharmR.pdf) at 2 (excerpt, Tab 15).

<sup>50</sup> *Id.* at 7.

<sup>51</sup> *Topical Corticosteroids BE Guidance* at 1 (Tab 17).

<sup>52</sup> FDA Citizen Petition Response to Docket No. FDA-2010-P-0570 at 13 fn 38 (Apr. 27, 2011) (Tab 22).

not to require HPA axis suppression testing is based on the underlying principle that “local availability will correlate with potential systemic exposure.”<sup>53</sup>

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.”<sup>54</sup> 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.<sup>55</sup> 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.”<sup>56</sup> The vasoconstrictor assay, which involves a comparison of 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.<sup>57</sup> 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***

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<sup>53</sup> FDA Citizen Petition Response to Docket Nos. FDA-2011-P-0565, FDA-2011-P-0593 at 12 (Jan. 18, 2012) (Tab 23).

<sup>54</sup> Nair, A. *et al.*, Basic considerations in the dermatokinetics of topical formulations, BRAZILIAN J PHARM SC. 2013 (49):423-434, 425 (Tab 24).

<sup>55</sup> Carrer, V., *et al.*, Effect of propylene glycol on the skin penetration of drugs, ARCH DERMATOL RES. 2019 (Tab 25).

<sup>56</sup> *Id.*

<sup>57</sup> 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).



***suppression study and/or desonide blood levels comparing test and reference products show no greater systemic exposure with your test product.***<sup>58</sup>

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.<sup>59</sup> 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.<sup>60</sup> 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.<sup>61</sup>

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.<sup>62</sup> 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

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<sup>58</sup> Desonate (desonide) gel, NDA 021844 Guidance Meeting Minutes, Admin. and Corr. Documents at 5 (excerpt, Tab 21) (emphasis added).

<sup>59</sup> 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](https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20934_admindocs_P2.pdf) (pdf 12-13).

<sup>60</sup> Luxiq (betamethasone valerate) foam, NDA 20934, Medical Review at 3, [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/99/20934\\_medr\\_P1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20934_medr_P1.pdf) (excerpt, Tab 27).

<sup>61</sup> See *id.*

<sup>62</sup> 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](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000Admincorres.pdf) (pdf 38).

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<sup>®</sup> cream."<sup>63</sup> 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<sup>®</sup> cream, the drug interaction assessments are not needed."<sup>64</sup> 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.

### 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.<sup>65</sup>

Propylene glycol is known to produce eczematous skin reactions, allergic responses, and irritant contact dermatitis.<sup>66</sup> According to one study, propylene glycol is the most common

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<sup>63</sup> 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](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000ClinPharmR.pdf) (excerpt, Tab 15).

<sup>64</sup> *Id.*

<sup>65</sup> 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](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000PharmR.pdf) (excerpt, Tab 29).

<sup>66</sup> 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).

allergen in topical corticosteroids.<sup>67</sup> In fact, propylene glycol was named the American Contact Dermatitis Society's Allergen of the Year for 2018.<sup>68</sup> The potential risks of a propylene glycol allergy are not speculative. Allergic reactions typically have been associated with propylene glycol concentrations greater than 10%,<sup>69</sup> which is the purported amount in Glenmark's formulation. In contrast, the Transcutol in Impoyz is associated with "the relative absence of irritancy, allergenicity, adverse alteration of the skin microbiome, or toxicity."<sup>70</sup> Moreover, Impoyz was supported with dermal safety studies that FDA determined "did not demonstrate a potential for phototoxicity, photoallergenicity, or cumulative irritancy/contact sensitization ...."<sup>71</sup> Those studies would not support the approval or labeling of Glenmark's claimed formulation.

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.<sup>72</sup> The adverse event information in the Impoyz labeling states that rash occurred in less than 1% of subjects. It also states that "[t]he 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%)."<sup>73</sup> 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."<sup>74</sup>

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

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<sup>67</sup> Coloe, J., *et al.*, Allergens in Corticosteroid Vehicles, DERMATITIS. 2008;19(1):38-42, 39 (Tab 34).

<sup>68</sup> McGowan, M., *et al.*, Propylene glycol in contact dermatitis: A systematic review, DERMATITIS. 2018;29(1):6-12 at 6 (Tab 30).

<sup>69</sup> 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).

<sup>70</sup> *Id.* at 27.

<sup>71</sup> Impoyz (clobetasol propionate) cream, 0.025%, NDA 209483 Medical Review(s) at 8, *available at* [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/209483Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209483Orig1s000MedR.pdf) (Tab 16).

<sup>72</sup> 21 CFR 314.3 (defining "Therapeutic equivalents"); Orange Book Preface, <https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface>.

<sup>73</sup> See Impoyz PI at Section 6 (Tab 8).

<sup>74</sup> See Temovate E PI (rev. Nov. 2012), [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/020340s007lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020340s007lbl.pdf) (Tab 35).

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.

#### **4. *In Vitro* Permeation Testing Results**

The IVPT results detailed in section IV below also show that FDA's typical reliance on the vasoconstrictor assay is not sufficient in this case. Glenmark claims that it has changed the key ingredients in the Impoyz formulation, creating its own clobetasol propionate formulation. The IVPT results indicate that Glenmark's claimed formulation has significantly different dermatopharmacokinetics than Impoyz and is not bioequivalent to Impoyz.<sup>75</sup>

The lack of sensitivity of the vasoconstrictor assay compared to IVPT has been described in the literature. According to one article co-authored by several FDA employees: "It has also been confirmed that vasoconstrictor assays and clinical endpoint studies are less sensitive, accurate, and reproducible than the in vitro permeation test approach for bioequivalence evaluation."<sup>76</sup> Another publication describes a study that compared the sensitivity of the vasoconstrictor assay with IVPT to assess the relative bioavailability of topical clobetasol propionate products. The study assessed the pharmacokinetics of clobetasol propionate absorption from five commercial products and compared the results to those obtained by vasoconstrictor assay using the same products.<sup>77</sup> The results show "a striking disparity in the sensitivity of the two tests,"<sup>78</sup> as well as greater variability with the vasoconstrictor assay:

A comparison of two surrogate tests has revealed that the use of the IVPT to quantify differences in relative BA between five marketed clobetasol propionate products provides a much greater level of sensitivity than that afforded by the VC assay. The permeation test found total clobetasol absorption from the five products to vary over a ten-fold range whereas the vasoconstrictor assay found this same difference was less than two-fold. The discriminating power of vasoconstriction was constrained by much higher variability as well as apparent saturation of the response at the high levels of clobetasol absorption exhibited by these products.<sup>79</sup>

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<sup>75</sup> Impoyz does not have any propylene glycol; however, even varying the amount of propylene glycol can render formulations inequivalent. See Trottet, L., *et al.*, Are all aciclovir cream formulations bioequivalent? INT. J. PHARM. 2005;304:63–71 (studies suggesting that generic versions of Zovirax<sup>®</sup> (aciclovir) cream were not bioequivalent to Zovirax<sup>®</sup> because they contained different amounts of propylene glycol) (Tab 36).

<sup>76</sup> Raney, S.G., *et al.*, Pharmacokinetics-based approaches for bioequivalence evaluation of topical dermatological drug products, CLIN. PHARMACOKINET. 2015; 54:1095–1106 at 1102 (Tab 37).

<sup>77</sup> The five products were Temovate ointment, cream, emollient cream, gel, and scalp application.

<sup>78</sup> Lehman, P.A., *et al.*, Assessing topical bioavailability and bioequivalence: A comparison of the in vitro permeation test and the vasoconstrictor assay, PHARM. RES. 2014; 31:3529–3537 at 3534 (Tab 38).

<sup>79</sup> *Id.* at 3536–37.

The difference in sensitivity between IVPT and the vasoconstrictor assay is clinically relevant: “Differences in the discriminatory power of permeation and vasoconstrictor data have been noted before and, in at least one case, have definite clinical implications.”<sup>80</sup> For example, a clinical trial comparing foam and lotion betamethasone valerate products found the foam product to be 50% more effective in the treatment of scalp psoriasis.<sup>81</sup> Consistent with the clinical results, IVPT found a 3-fold greater rate of betamethasone valerate absorption from the foam product. The vasoconstrictor assay, in contrast, did not find any difference between the two products. The vasoconstrictor assay also may not be sufficiently sensitive to detect systemic toxicity in all situations. According to the article, “The disparity between absorption data and the blanching response also suggests that differences in the potential to cause systemic toxicity, namely adrenal suppression, may not be detectable by VC assay.”<sup>82</sup>

Glenmark’s claimed formulation changes raise new questions of safety and effectiveness that cannot be answered by relying on the vasoconstrictor assay to establish bioequivalence in this instance, particularly as the IVPT results indicate that Glenmark’s claimed formulation is not bioequivalent to Impoyz.

#### **IV. IN VITRO PERMEATION TESTING DATA SHOW THAT A FORMULATION CONTAINING PROPYLENE GLYCOL BUT NOT TRANSCUTOL PERFORMS DIFFERENTLY THAN IMPOYZ**

To investigate the potential formulation differences, an independent contract provider of topical product testing services, MedPharm, performed a series of IVPT experiments. The test results clearly show that there is a significant difference in clobetasol propionate permeation (both flux and cumulative amount of drug) between Impoyz and a propylene glycol-based formulation. The testing also measured the permeation of propylene glycol, which is associated with distinct safety issues like allergic and contact dermatitis. The test results support the conclusion that changing the key ingredients of Impoyz in the manner described by Glenmark would result in a generic product with a different clinical profile than Impoyz.

##### **A. Background on *In Vitro* Permeation Testing**

IVPT uses excised human skin to measure the cutaneous pharmacokinetics of topical drugs. A diffusion cell maintains the skin, which may be dermatomed to a thickness that includes the epidermis (with the stratum corneum) and part of the dermis, at a physiological hydration and temperature. The underside of the skin is bathed in a physiologically based receptor solution. The drug product is administered to the skin, and the receptor solution is

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<sup>80</sup> *Id.* at 3536.

<sup>81</sup> *See id.*

<sup>82</sup> *Id.*

sampled at various timepoints to determine the amount of drug that has diffused through the skin. The sampling is sufficient to maintain sink conditions that adequately mimic the clearance created by the dermal microcirculation and is analogous to pharmacokinetic blood sampling.

Under the Generic Drug User Fee Amendments (GDUFA), FDA is conducting a research program regarding *in vitro* approaches to bioequivalence for topical products, including IVPT. FDA has determined that IVPT can correlate with clinical performance and “that IVPT studies are a sensitive and discriminating approach by which to evaluate the cutaneous PK of topical drugs.”<sup>83</sup> Similarly, the scientific literature has recognized that IVPT is a valid measurement of bioequivalence. One article, co-authored by several FDA employees, states: “The utility of the *in vitro* permeation test model for the determination of bioequivalence is supported by numerous studies demonstrating that the results correlated with and were predictive of human *in vivo* bioavailability data.”<sup>84</sup> Consistent with the research, FDA has incorporated IVPT into numerous product-specific bioequivalence guidance documents for generic topical products.<sup>85</sup>

## **B. Description of the MedPharm IVPT Studies**

MedPharm conducted IVPT studies comparing Impoyz with propylene glycol-based formulations representing Glenmark’s claimed product. MedPharm is a contract research organization that specializes in the formulation of topical delivery systems. The lead investigator was Prof. Marc B. Brown B.Sc. (Hons), Ph.D., CChem FRSC., who is the Chief Scientific Officer and co-founder of MedPharm. Prof. Brown specializes in *in vitro* testing, including IVPT. He holds several academic positions and is the author of numerous publications.<sup>86</sup>

The testing investigated seven formulations, including three 0.025% clobetasol propionate formulations with various amounts of propylene glycol representing Glenmark’s claimed potential ANDA product. The formulation of Glenmark’s proposed product is not public. However, Glenmark has asserted that its formulation contains more than 10% propylene glycol and does not contain at least 60% (w/w) water.<sup>87</sup> Furthermore, Glenmark has not asserted that its formulation contains any Transcutol.<sup>88</sup>

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<sup>83</sup> FDA, FY2018 GDUFA Science and Research Report: Topical Dermatological Drug Products at 2, <https://www.fda.gov/media/130622/download> (Tab 39).

<sup>84</sup> Raney, S.G., *et al.*, Pharmacokinetics-based approaches for bioequivalence evaluation of topical dermatological drug products, CLIN. PHARMACOKINET. 2015; 54:1095–1106 at 1101 (Tab 37).

<sup>85</sup> See, e.g., Acyclovir topical cream (Dec. 2016); luliconazole topical cream (Sept. 2018); oxymetazoline hydrochloride topical cream (Nov. 2019); crisaborole topical ointment (Feb. 2019); pimecrolimus topical cream (Nov. 2019); ivermectin topical cream (May 2019); tacrolimus topical ointment (Sept. 2018).

<sup>86</sup> See Prof. Marc Brown *Curriculum Vitae* (Tab 40).

<sup>87</sup> Letter from J. Reisman to R. Moccia (January 24, 2020) (excerpt, Citizen Petition Tab 9).

<sup>88</sup> See *id.*

The composition of the three 0.025% test formulations believed to be representative of Glenmark's asserted formulation were based on the deformation of Glenmark's approved and publicly available 0.05% clobetasol propionate cream product (ANDA 209095), which indicated a high level of propylene glycol [REDACTED]. Suitable rheological methods were developed to fully characterize and develop formulations that matched the commercial product profile. [REDACTED]

[REDACTED] providing test formulations with 36%, 48%, and 60% propylene glycol concentration (% w/w). The other test formulations included Impoyz and three 0.05% clobetasol cream formulations. [REDACTED]

<sup>89</sup> The compositions of the three propylene-glycol based formulations (CRO2, 3, and 4) and the Impoyz 0.05% formulation are provided confidentially in Tab 41. Clobetasol Propionate IVPT Study Data (confidential) (excerpt, Tab 41) at slide 14. Note that the references to "Sponsor" in Table 1 refer to Encore.

<sup>90</sup> See Study No. 370-1701-02 Slides (confidential) (excerpt, Tab 42); see also MedPharm Study Plan, *In Vitro* Permeation Testing of Clobetasol Propionate Creams (confidential) (Tab 43). Study reports and Standard Operating Procedures are on file with MedPharm.

The testing measured both clobetasol propionate and propylene glycol permeation. As detailed below, the results show significant differences between Impoyz and the propylene glycol-based formulations.

**C. The IVPT Results Show a Significant Difference in Permeation of Clobetasol**

The clobetasol propionate IVPT results are striking. The testing measured two key parameters: (1) cumulative amount of clobetasol propionate ( $\text{ng}/\text{cm}^2$ ) delivered to the receptor solution at 24 hours; and (2) flux ( $\text{ng}/\text{cm}^2/\text{hr}$ ). The results show that propylene glycol-based formulations have significantly different dermatopharmacokinetics than Impoyz, indicating that propylene glycol-based formulations are not bioequivalent to Impoyz.

**1. Total Cumulative Amount of Clobetasol Permeated into Receptor Solution**

All three of the propylene glycol-based formulations (0.025% clobetasol propionate) delivered significantly more ( $p < 0.05$ ) clobetasol propionate to the receptor solution at 24 hours ( $\text{ng}/\text{cm}^2$ ) compared to Impoyz (0.025% clobetasol propionate). Specifically, the formulation with 60% concentration of propylene glycol (% w/w) resulted in a 10.35 fold difference in clobetasol propionate delivery compared to Impoyz. Similarly, the formulations with 48% and 36% concentrations of propylene glycol resulted in 9.48 and 6.52 fold differences, respectively.



Confirming the significant effect of propylene glycol on the delivery of clobetasol propionate, the three propylene glycol-based formulations (0.025% clobetasol propionate) even delivered more clobetasol propionate to the receptor solution than a test formulation of Impoyz containing 0.05% clobetasol propionate, despite the fact that the propylene glycol formulations had half the clobetasol propionate compared to the Impoyz 0.05% formulation. The correlation between increasing amounts of propylene glycol and increased delivery of clobetasol propionate was consistent across the 0.05% formulations. The 0.05% Glenmark cream [REDACTED] and 0.05% Temovate<sup>®</sup> cream delivered significantly more clobetasol propionate to the receptor solution compared to the 0.05% formulation of Impoyz. There were no statistical differences in the delivery of clobetasol propionate between the two propylene glycol-based 0.05% formulations (*i.e.*, the 0.05% Glenmark cream and the 0.05% Temovate Cream).<sup>91</sup>

Importantly, the results show that all of the formulations with propylene glycol delivered significantly more clobetasol propionate to the receptor solution than Impoyz.<sup>92</sup> [REDACTED]

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<sup>91</sup> See Clobetasol Propionate IVPT Study Data (confidential) (excerpt, Tab 41) at slide 6 [REDACTED]

<sup>92</sup> See *id.* at slide 18 [REDACTED]

[REDACTED]

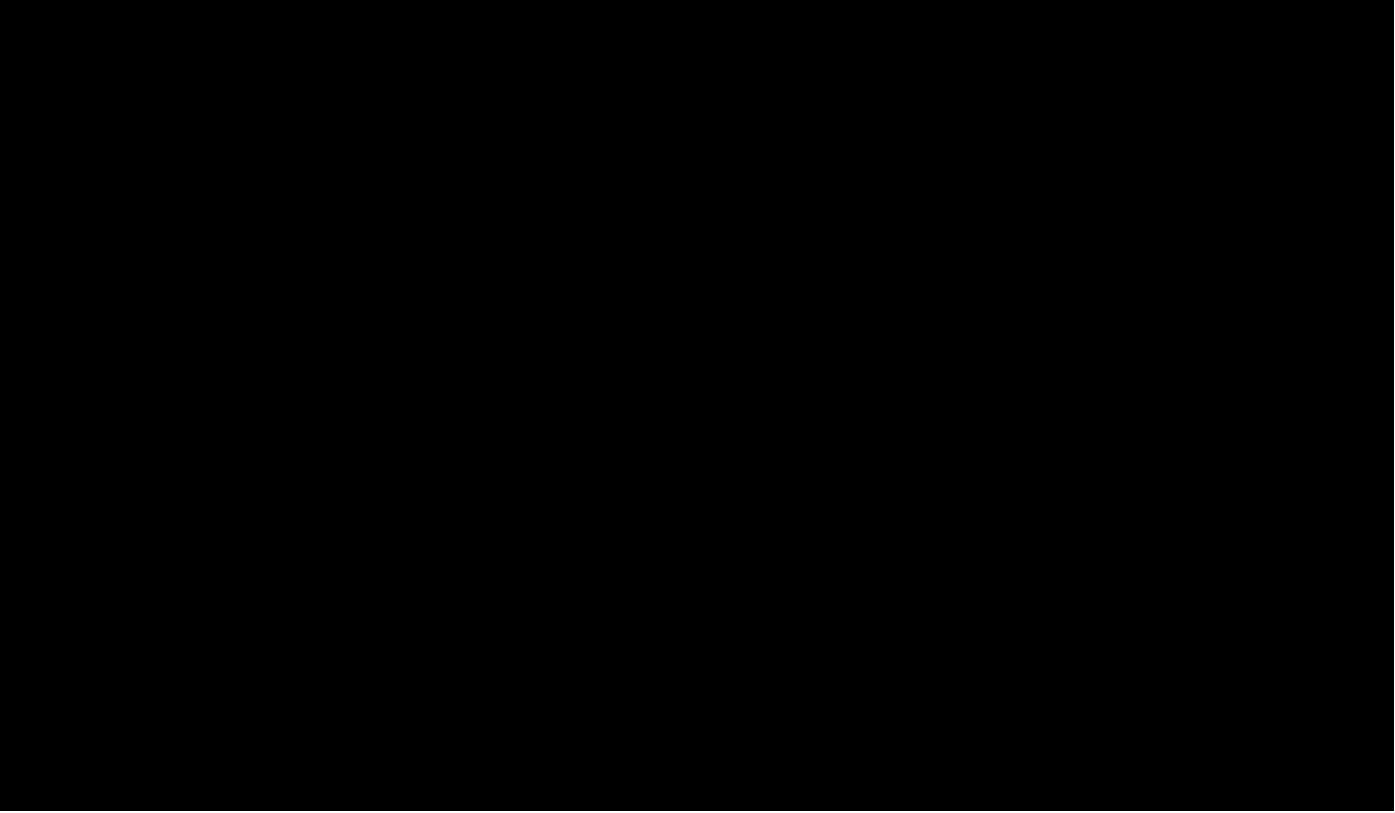
Notably, these amounts were obtained through permeation testing of healthy skin donors. Permeation and systemic absorption can be even higher with diseased skin, particularly when the skin's barrier function is impaired.<sup>94</sup> Glenmark's proposed product would be indicated for moderate to severe plaque psoriasis, a condition that results in an impaired stratum corneum.

## 2. Flux

The flux results are consistent with the results regarding the cumulative amounts of clobetasol propionate in receptor solution. All three of the propylene glycol-based formulations (0.025% clobetasol propionate) had a significantly higher peak flux (ng/cm<sup>2</sup>/hour) compared to Impoyz (0.025% clobetasol propionate). The formulation with 60% concentration of propylene glycol (% w/w) resulted in a 15.22 fold difference, while the 48% and 36% propylene glycol formulations resulted in 14.13 and 9.60 fold differences, respectively. [REDACTED]

<sup>93</sup> See *id.* at slides 15, 16 [REDACTED]

<sup>94</sup> See Dhar, S., *et al.*, Systemic side-effects of topical corticosteroids, INDIAN J. DERMATOL. 2014;59(5):460-64 ("Diseased skin has impaired barrier function resulting in enhanced percutaneous absorption.") (Tab 13).



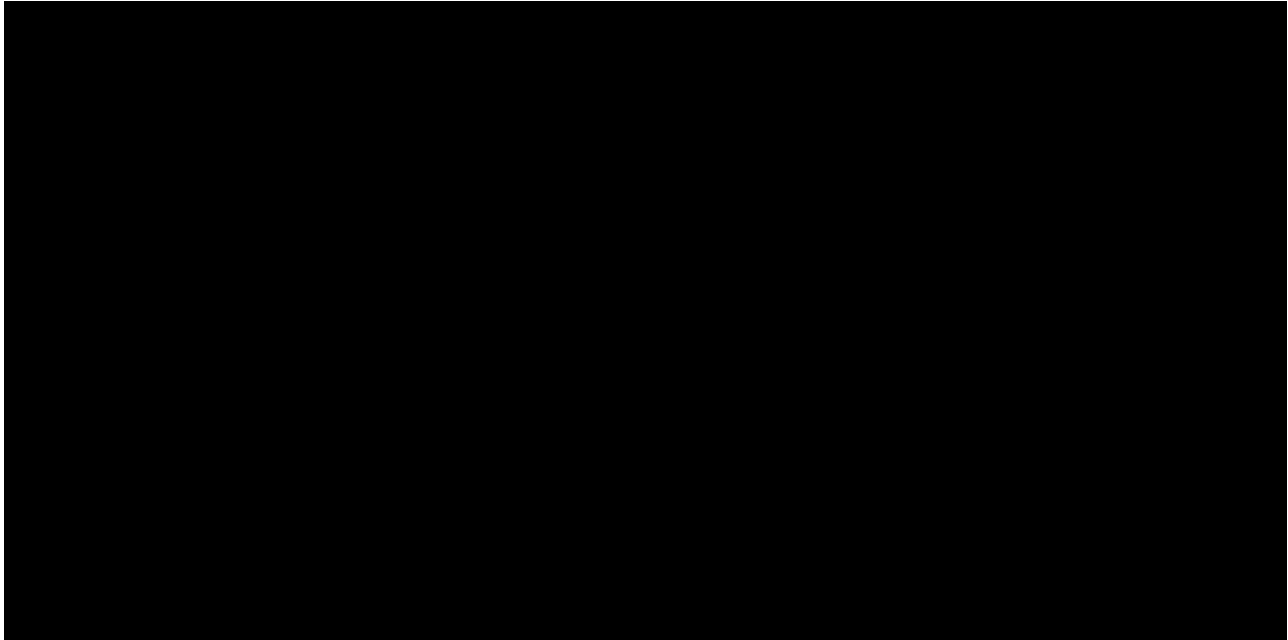
Furthermore, the three propylene glycol-based formulations (0.025% clobetasol propionate) even had a higher peak flux compared to Impoyz (0.05% clobetasol propionate). Similarly, the 0.05% Glenmark cream [REDACTED] and 0.05% Temovate cream [REDACTED] had a higher peak flux compared to the 0.05% formulation of Impoyz.<sup>95</sup>

Consistent with the cumulative amount results, the flux data show that all of the formulations with propylene glycol had a significantly higher peak flux (ng/cm<sup>2</sup>/hr) of clobetasol propionate over 24 hours following application than Impoyz.<sup>96</sup> The rank order of all formulations based on peak flux is provided in Table 4 and is the same as the rank order based on the delivered cumulative amount of clobetasol propionate.

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<sup>95</sup> See Clobetasol Propionate IVPT Study Data (confidential) (excerpt, Tab 41) at slide 10 [REDACTED]  
[REDACTED]

<sup>96</sup> See *id.* at slide 19 [REDACTED]  
[REDACTED]



**D. The IVPT Results Indicate that Glenmark's Claimed Formulation is Not Bioequivalent to Impoyz**

The IVPT results show that Impoyz and Glenmark's asserted formulation have significantly different pharmacokinetic profiles and support the conclusion that they are not bioequivalent. Generally, bioequivalent products provide the same rate and extent of drug absorption at the site of action.<sup>97</sup> With respect to IVPT data, FDA has stated that the rate of permeation is characterized by the flux and the extent of permeation is characterized by the total cumulative amount of drug in the receptor solution. As FDA explained in the draft product-specific bioequivalence guidance on acyclovir topical cream:

The cutaneous pharmacokinetic endpoints for the IVPT pivotal study are based upon parameters that characterize the rate and extent to which acyclovir permeates into and through the skin, and becomes available in the receptor solution. Specifically, the rate of acyclovir permeation is characterized by the flux (J) and the extent of acyclovir permeation is characterized by the total cumulative amount of acyclovir permeated into the receptor solution across the study duration.<sup>98</sup>

Impoyz had significantly different results than the propylene glycol-based formulations with respect to both flux and cumulative amounts of clobetasol propionate delivered into the

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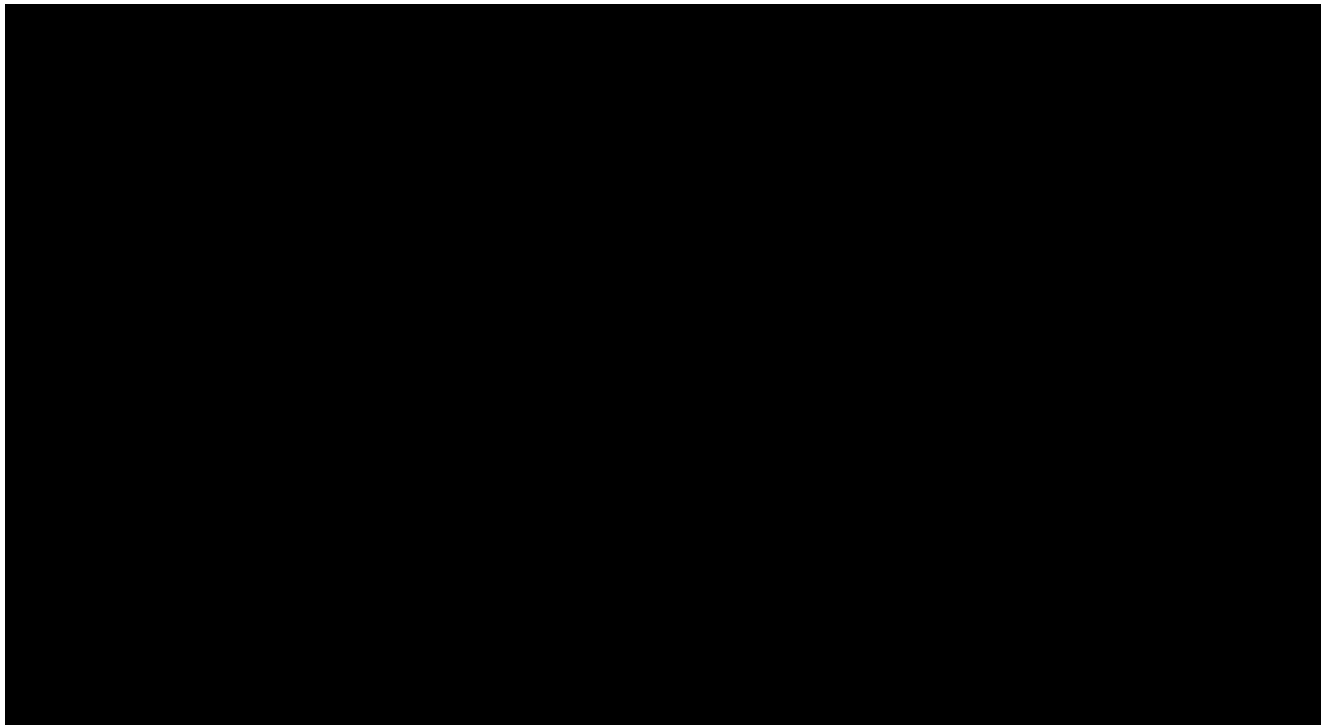
<sup>97</sup> 21 USC 355(j)(8)(B)(i); 21 CFR 320.21(e).

<sup>98</sup> FDA, *Draft Product-Specific Bioequivalence Guidance for Acyclovir Topical Cream* at 15-16 (Dec. 2016) (Tab 44); see also FDA, *Draft Guidance for Industry: Transdermal and Topical Delivery Systems - Product Development and Quality Considerations* (Nov. 2019) ("In vitro permeation testing (IVPT) with the use of excised human skin may be utilized to characterize the rate and extent of transdermal or topical drug delivery.") (Tab 45).

receptor solution. The results correlated with increasing amounts of propylene glycol and were consistent across 0.025% and 0.05% clobetasol propionate strengths. The results show that formulations with higher amounts of propylene glycol have higher permeation. Glenmark claims that its formulation contains a significant amount of propylene glycol, and the IVPT results indicate that Glenmark's asserted formulation is not bioequivalent to Impoyz.

**E. The IVPT Results Show Substantial Permeation of Propylene Glycol**

The IVPT studies conducted by MedPharm also assessed the delivery of the excipient propylene glycol to the receptor solution from the same seven formulations described above with respect to the clobetasol propionate IVPT studies (Section II). The test formulations included three 0.025% clobetasol propionate formulations (CR04, CR03, and CR02) designed to be representative of Glenmark's purported proposed product, and containing 60%, 48%, and 36% propylene glycol, respectively. The basic parameters and protocols for the propylene glycol IVPT studies were similar to those used for the clobetasol propionate IVPT studies, [REDACTED]



**1. Total Cumulative Amount of Propylene Glycol Permeated into Receptor Solution**

The IVPT results show that propylene glycol is highly permeable and that the permeation amount generally correlates to the amount contained in the formulation. [REDACTED]

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<sup>99</sup> Propylene Glycol IVPT Study Data (confidential) (excerpt, Tab 46) at slide 4; *see also* MedPharm Study Plan, *In Vitro* Permeation Testing of Propylene Glycol Creams (confidential) (Tab 47).

[REDACTED]

[REDACTED] The amount delivered by the formulation containing 60% propylene glycol was approximately 2-fold and 1.7-fold more than the 36% and 48% formulations, respectively, differences that were statistically significant ( $p < 0.05$ ).<sup>101</sup> As expected, the Impoyz formulations did not deliver any propylene glycol to the receptor solution because Impoyz does not contain propylene glycol. [REDACTED]

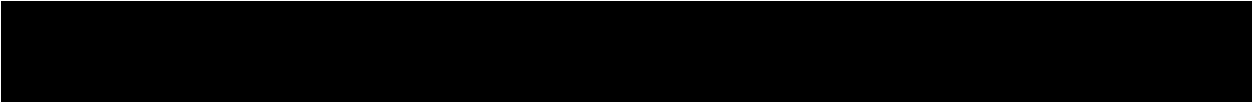
[REDACTED]

[REDACTED]

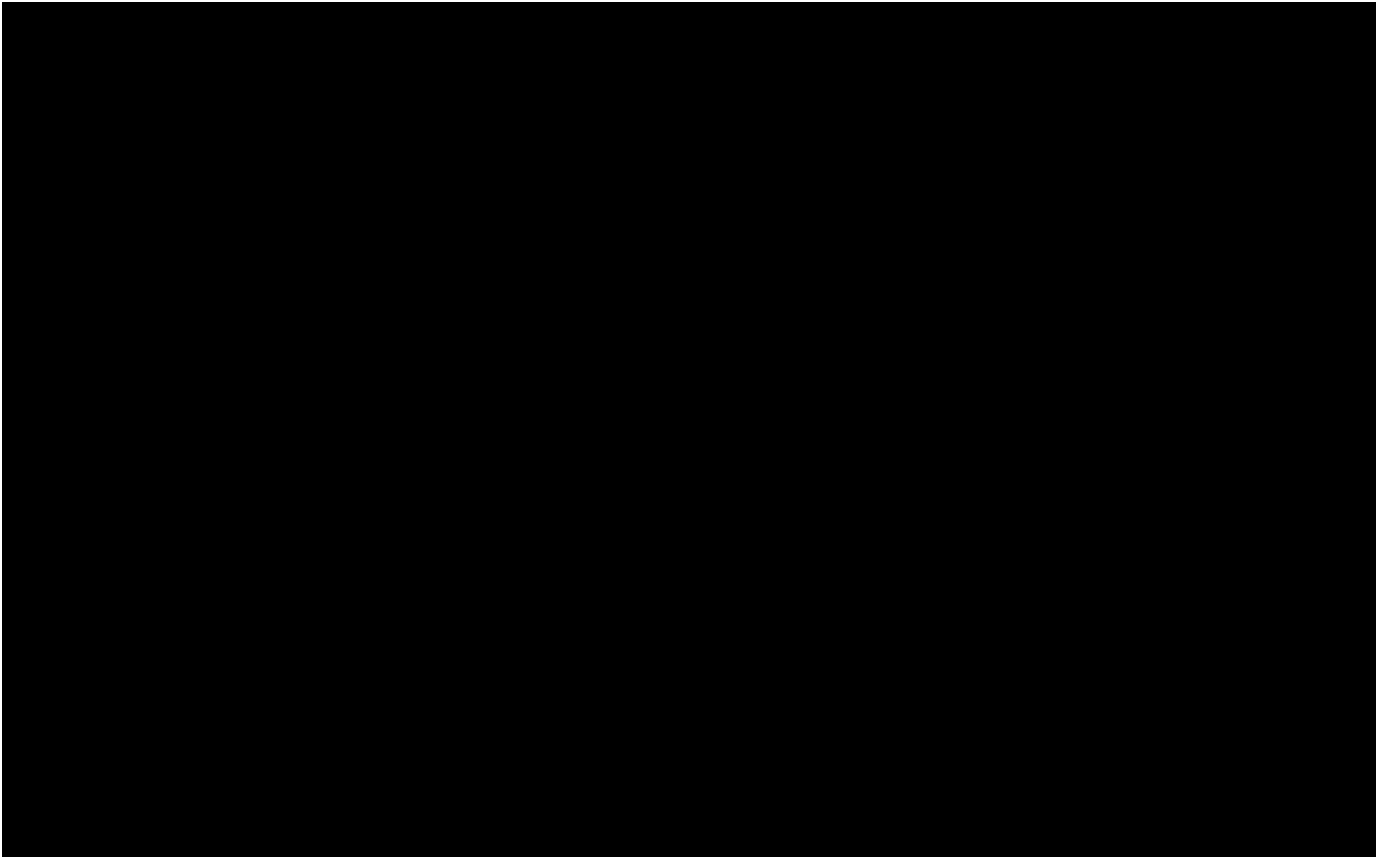
<sup>100</sup> Propylene Glycol IVPT Study Data (confidential) (excerpt, Tab 46) at slide 8.

<sup>101</sup> *Id.* at slide 31.

<sup>102</sup> *Id.* at slide 5.



The studies also measured the cumulative amount of propylene glycol permeation through 48 hours post-application, as represented in Figure 4.<sup>103</sup> The rank order results of the mean cumulative amount delivered at 48 hours were consistent with the results at 24 hours.



As noted with regard to the clobetasol propionate results, these amounts resulted from testing permeation of propylene glycol through healthy skin. Permeation may be higher where the skin is damaged or diseased.

## **2. Flux**

Across all seven formulations, the rank order results for flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ ) were the same as the results for cumulative propylene glycol delivered to the receptor solution at 24 hours ( $\mu\text{g}/\text{cm}^2$ ) (Figure 5).<sup>104</sup> Additionally, as a trend, the propylene glycol flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ ) appeared to continuously increase over most of the 24-hour period. In contrast, in a previous IVPT study

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<sup>103</sup> *Id.* at slide 16.

<sup>104</sup> *Id.* at slide 10.

conducted by MedPharm, [REDACTED] [REDACTED]  
[REDACTED]



The IVPT results show the permeability of propylene glycol and highlight the effect of adding propylene glycol to a topical formulation. In addition to bioavailability issues, the use of propylene glycol in a topical formulation raises distinct safety issues. By purportedly adding propylene glycol, Glenmark's claimed product has changed the nature of the Impoyz formulation and created a new formulation that must be supported with independent clinical data.

**F. The Claimed Use of Propylene Glycol in Glenmark's Product Creates a New Formulation with a Potentially Distinct Clinical Profile**

Although Glenmark has submitted an ANDA, Glenmark's claimed formulation is fundamentally different than Impoyz. The results of the propylene glycol IVPT show that Glenmark's claimed formulation likely delivers significant amounts of propylene glycol, in addition to the increased delivery of clobetasol propionate (Section IV.C). Glenmark's claimed formulation raises safety issues that are not raised with Impoyz because propylene glycol is known to produce allergic and irritant contact dermatitis and systemic cutaneous reactions, including in patients using topical corticosteroids.<sup>106</sup>

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<sup>105</sup> *Id.* at slides 34, 35.

<sup>106</sup> *See id.*; Al Jasser, M., *et al.*, Propylene glycol: An often unrecognized cause of allergic contact dermatitis in patients using topical corticosteroids, *SKIN THERAPY LETT.* 2011 16(5):5-7 (Tab 31); Lessmann, H., *et al.*, Skin-sensitizing and irritant properties of propylene glycol, *CONTACT DERMATITIS*.



Approval of a propylene glycol-based formulation as a generic version of Impoyz would indicate that the products are freely interchangeable for patients. FDA's public education material actively promotes the idea that generic drugs "have the same risks and benefits as the brand-name drugs,"<sup>107</sup> and some states have automatic generic drug substitution laws. Even putting aside the bioequivalence issues raised in this petition, the products would not be the same for patients with propylene glycol allergies. The formulation differences could cause confusion among health-care providers and patients, resulting in unnecessary adverse events and delay of treatment while the problem is being addressed.

For patients with propylene glycol allergies and prescribers trying to manage those patients, the difference between Impoyz and a formulation based on propylene glycol is significant. One well-known advantage of Impoyz is that it is free of propylene glycol:

One advantage of Impoyz Cream is that it is propylene glycol-free, according to Dr. Vlahovic, a Clinical Professor in the Department of Podiatric Medicine at the Temple University School of Podiatric Medicine. As she notes, the American Contact Dermatitis Society named propylene glycol, found in many topical substances, the 2018 Allergen of the Year. Dr. Vlahovic adds the Impoyz Cream's vehicle contains a stabilizer that keeps the active ingredient in and around the epidermis.<sup>108</sup>

In addition to safety issues, the propylene glycol IVPT results highlight the difference in how Transcutol and propylene glycol work and impact the delivery of clobetasol. Transcutol is a hydrophilic solvent with a "unique ability to swell the intercellular path of the skin's barrier" that can result in skin retention - a depot effect - and skin penetration enhancement.<sup>109</sup> In contrast, propylene glycol solvates the  $\alpha$ -keratin and acts as a hydrophilic penetration enhancer that alters the skin structure by disrupting the intercellular lipid bilayer and proteins, increasing skin partitioning, and increasing transepidermal water loss and protease activity in the skin, further disrupting the barrier property of the stratum corneum.<sup>110</sup>

The different mechanisms of action of Transcutol and propylene glycol result in different permeation profiles. The propylene glycol-based formulations (CRO2, CRO3, and CRO4) delivered a significant amount of propylene glycol to receptor solution at 24 hours after

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2005 ;53(5):247-59 (Tab 32); Catanzaro, J., *et al.*, Propylene glycol dermatitis, J. AM. ACAD. DERMATOL. 1991 ;24(1):90-5 (Tab 33).

<sup>107</sup> FDA, Facts About Generic Drugs at 2, available at <https://www.fda.gov/media/79301/download> (Tab 48).

<sup>108</sup> McCurdy, B., Top ten innovations in podiatry, PODIATRY TODAY. 2018;31(7):26-34 (Tab 2).

<sup>109</sup> Osborne, D.W. & Musakhanian, J., Skin penetration and permeation properties of Transcutol® – Neat or diluted mixtures, AAPS PHARMSCITECH. 2018;19(8):3512-3533 at 3518 (Tab 11).

<sup>110</sup> See *id.*

application [REDACTED] Furthermore, the propylene glycol flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ ) appeared to continuously increase over most of the 24-hour period. In contrast, a different IVPT study of Impoyz showed that [REDACTED]  
[REDACTED]

In sum, the data confirm the mechanistic and functional differences between a propylene glycol-based and a Transcutol-based clobetasol propionate topical cream. Each may be safe and effective on its own, with labeling calibrated to the individual product, but the two are not the same within the meaning of the generic drug statute and regulations, and cannot be considered therapeutically equivalent.

## **V. 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.

### **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 (information regarding Glenmark's ANDA submission and the composition of Glenmark's claimed product); June 19, 2020 (clobetasol propionate permeation testing results); July 1, 2020 (propylene glycol permeation testing results); October 16, 2020 (response from FDA to Encore's May 22, 2020 citizen petition). 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,

A handwritten signature in black ink, appearing to read "Robert J. Moccia". The signature is fluid and cursive, with the first name "Robert" being more prominent and the last name "Moccia" following in a similar style.

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Enclosures