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Efficacy. Experience. Excellence.

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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

Re: Docket No. FDA-2020-P-1421

CITIZEN PETITION SUPPLEMENT

Encore Dermatology, Inc. (Encore) respectfully submits this supplement to the above-referenced citizen petition. As described in the citizen petition, Glenmark Pharmaceuticals Limited (Glenmark) has submitted an abbreviated new drug application (ANDA) for a generic version of Encore's Impoyz® (clobetasol propionate) 0.025% topical cream that Glenmark claims has significantly different excipients than Impoyz. Impoyz is a novel formulation that uses half the clobetasol propionate as other approved products and relies on Transcutol® (diethylene glycol monoethyl ether or DEGEE), rather than propylene glycol, to increase cutaneous retention of clobetasol propionate while limiting systemic and local safety risks. According to Glenmark, it has developed its own 0.025% clobetasol propionate formulation by changing the key ingredients in Impoyz. Glenmark asserts that its proposed generic product contains more than 10% propylene glycol, a well-known penetration enhancer associated with certain safety issues.

Despite the claimed formulation differences, Glenmark is seeking approval for its proposed product under an ANDA. Glenmark's apparent formulation changes raise questions of safety and effectiveness that cannot be answered by relying on the clinical data for Impoyz. Not only do the claimed changes violate FDA requirements governing sameness for generic topical products, they require independent clinical data to establish safety and effectiveness that should be submitted under a new drug application (NDA). Furthermore, the asserted changes make FDA's typical reliance on the vasoconstrictor assay to establish bioequivalence of generic corticosteroid products insufficient in this situation.

To investigate the potential formulation differences, an independent contract provider of topical product testing services, MedPharm Ltd. (MedPharm), performed a series of *in vitro* permeation testing (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. Encore submits this supplement to provide FDA with the new IVPT results.

I. 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 cornea) 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 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."[1] 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."[2] Consistent with the research, FDA has incorporated IVPT into numerous product-specific bioequivalence guidance documents for generic topical products.[3]

II. 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

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[1] FDA, FY2018 GDUFA Science and Research Report: Topical Dermatological Drug Products at 2, https://www.fda.gov/media/130622/download (Tab 1).

[2] 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 2).

[3] *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).

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.[4]

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.[5] Furthermore, Glenmark has not asserted that its formulation contains any Transcutol.[6]

The composition of the three 0.025% test formulations believed to be representative of Glenmark's asserted formulation were based on the deformulation 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] 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]

[4] *See* Prof. Marc Brown *Curriculum Vitae* (Tab 3).

[5] Letter from J. Reisman to R. Moccia (January 24, 2020) (excerpt, Citizen Petition 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.

[6] *See id*.

[redacted]

[redacted]

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

[8] *See* Study No. 370-1701-02 Slides (confidential) (excerpt, Tab 5); *see also* MedPharm Study Plan, *In Vitro* Permeation Testing of Clobetasol Propionate Creams (confidential) (Tab 6). Study reports and Standard Operating Procedures are on file with MedPharm.

[redacted]

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.

III. The IVPT Results Show a Significant Difference in the Permeation of Clobetasol Propionate

The clobetasol propionate IVPT results are striking. The testing measured two key parameters: (1) cumulative amount of clobetasol propionate (ng/cm^2) delivered to the receptor solution at 24 hours; and (2) flux ($ng/cm^2/hr$). 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.

A. Results

1. Total Cumulative Amount of Clobetasol Propionate Permeated into the 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 (ng/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. [redacted]

[redacted]

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® 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).[9]

Importantly, the results show that all of the formulations with propylene glycol delivered significantly more clobetasol propionate to the receptor solution than Impoyz.[10] [redacted]

[9] *See* Clobetasol Propionate IVPT Study Data (confidential) (excerpt, Tab 4) at slide 6 ([redacted]).

[10] *See id.* at slide 18 (table showing [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.[12] 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^2/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]

[11] *See id.* at slides 15, 16 ([redacted]).

[12] *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.") (Citizen Petition Tab 13).

[redacted]

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.[13]

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^2/hr) of clobetasol propionate over 24 hours following application than Impoyz.[14] 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.

[13] *See* Clobetasol Propionate IVPT Study Data (confidential) (excerpt, Tab 4) at slide 10 ([redacted]).

[14] *See id.* at slide 19 ([redacted]).

[redacted]

B. 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.[15] 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.[16]

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

[15] 21 USC 355(j)(8)(B)(i); 21 CFR 320.21(e).

[16] FDA, *Draft Product-Specific Bioequivalence Guidance for Acyclovir Topical Cream* at 15-16 (Dec. 2016) (Tab 7); *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 8).

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.

In its citizen petition, Encore explains that FDA should refuse to approve Glenmark's claimed formulation under an ANDA because Glenmark's asserted formulation change exceeds the types of changes permitted under FDA regulations governing the sameness of generic topical products. In particular, FDA regulations provide that FDA will refuse to approve an ANDA if "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."[17] Furthermore, FDA regulations provide that one example of a change that may be prohibited is "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…."[18] The IVPT results show that Glenmark's claimed formulation change falls squarely within FDA's regulation and should not be allowed under an ANDA.

The IVPT results also show that FDA's typical reliance on the vasoconstrictor assay is not sufficient in this case, where the formulations are qualitatively different and one formulation is designed to have a depot effect. 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."[19] 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.[20] The results show "a striking disparity in the sensitivity of the two tests,"[21] 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

[17] 21 CFR 314.127(8)(ii)(A).

[18] 21 CFR 314.127(8)(ii)(A)(7).

[19] 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 2).

[20] The five products were Temovate ointment, cream, emollient cream, gel, and scalp application.

[21] 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 9).

> 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.[22]

The difference in sensitivity between IVPT and the vasoconstrictor assay is also 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."[23] 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.[24] 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."[25]

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.[26] Although FDA typically relies on the vasoconstrictor assay to establish the bioequivalence of generic topical corticosteroid products, the vasoconstrictor assay is not sufficiently sensitive in this situation to distinguish important formulation differences. Glenmark's claimed formulation changes raise new questions of safety and effectiveness that cannot be answered by relying on the clinical data for Impoyz. Accordingly, Glenmark must submit its claimed formulation of clobetasol propionate under a new drug application with independent clinical data showing that its formulation is safe and effective.

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[22] *Id.* at 3536-37.

[23] *Id*. at 3536.

[24] *See id*.

[25] *Id.*

[26] 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® (aciclovir) cream were not bioequivalent to Zovirax® because they contained different amounts of propylene glycol) (Tab 10).

IV. 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]

[redacted]

The analysis included the cumulative amount of propylene glycol permeated into the receptor solution at 24 and 48 hours ($\mu g/cm^2$), and the flux ($\mu g/cm^2/hr$) of propylene glycol.

A. Results

1. Total Cumulative Amount of Propylene Glycol Permeated into the 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]

[27] Propylene Glycol IVPT Study Data (confidential) (excerpt, Tab 11) at slide 4; *see also* MedPharm Study Plan, *In Vitro* Permeation Testing of Propylene Glycol Creams (confidential) (Tab 12).

[28] Propylene Glycol IVPT Study Data (confidential) (excerpt, Tab 11) at slide 8.

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 ($p < 0.05$).[29] As expected, the Impoyz formulations did not deliver any propylene glycol to the receptor solution because Impoyz does not contain propylene glycol. [redacted]

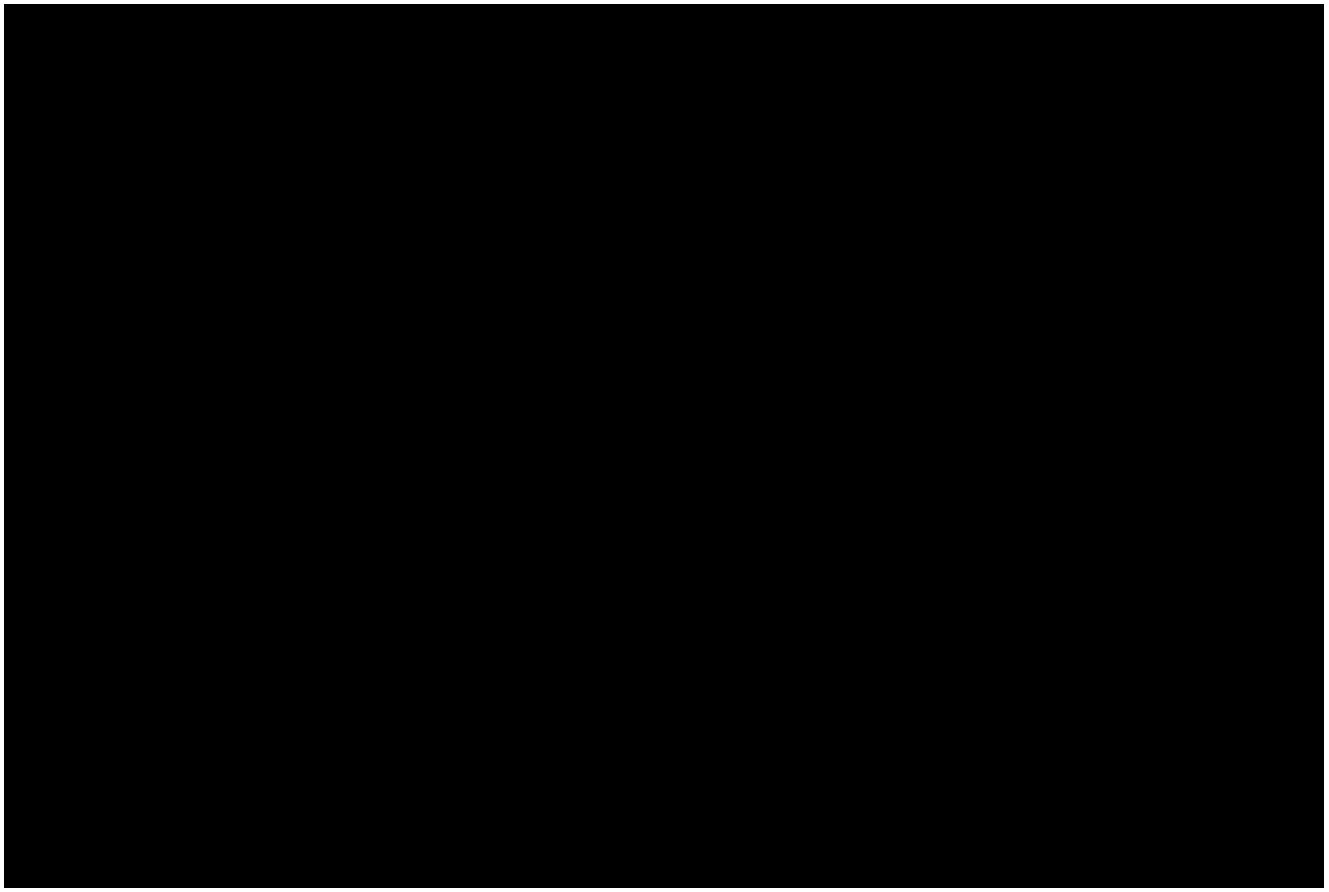
[redacted]

[redacted]

[29] *Id.* at slide 31.

[30] *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.[31] 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 ($\mu g/cm^2/hr$) were the same as the results for cumulative propylene glycol delivered to the receptor solution at 24 hours ($\mu g/cm^2$) (Figure 5).[32] Additionally, as a trend, the propylene glycol flux ($\mu g/cm^2/hr$) appeared to continuously increase over most of the 24-hour period. In contrast, in a previous IVPT study

[31] *Id.* at slide 16.

[32] *Id.* at slide 10.

conducted by MedPharm and described in the citizen petition, [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.

B. 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 III). 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.[34] Propylene glycol allergies are not

[33] *Id.* at slides 34, 35.

[34] *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 (Citizen Petition Tab 31); Lessmann, H., *et al*., Skin-sensitizing and irritant properties of propylene glycol, CONTACT

uncommon. Propylene glycol has been included as part of the series of the North American Contact Dermatitis Group for patch testing since 1992 and in the Mayo Clinic's standard patch test series since 1997.[35] In one retrospective analysis spanning almost twenty years of data and more than 11,000 patients, 0.85% of patients who underwent patch testing to 5%, 10%, or 20% propylene glycol tested positive and 0.35% had irritant reactions.[36] Moreover, increased concentrations of propylene glycol were associated with increased reactions. In another epidemiologic study, propylene glycol 100% had a reaction rate of 2.8% in nearly 5,000 patients who were patch tested, ranking it among the top 25 screening allergens.[37] The potential risks of a propylene glycol allergy are not speculative.

Propylene glycol was named the American Contact Dermatitis Society's Allergen of the Year for 2018.[38] According to one article, propylene glycol was one of two "most commonly present potential allergens."[39] Transcutol® (the key excipient in Impoyz), is not associated with significant irritancy, allergenicity, or toxicity.[40] Moreover, Impoyz was supported with three dermal safety studies that FDA determined "did not demonstrate a potential for phototoxicity, photoallergenicity, or cumulative irritancy/contact sensitization . . ."[41] Those dermal studies would not support the approval or labeling of Glenmark's claimed formulation.

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 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

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

[35] Lalla, S.C., *et al.*, Patch testing to propylene glycol: The Mayo Clinic experience, DERMATITIS. 2018;29(4):200-205 at 200 (Tab 13).

[36] *Id.* at 201.

[37] *See* DeKoven, J.G., *et al.*, North American Contact Dermatitis Group Patch Test Results 2013-2014, DERMATITIS. 2017;28(1):33-46 (Tab 14).

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

[39] *See* Coloe, J. & Zirwas, M.J., Allergens in corticosteroid vehicles, DERMATITIS. 2008;19(1):38-42 at 38 (Citizen Petition Tab 34).

[40] 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 at 27 (Citizen Petition Tab 1).

[41] 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 (Citizen Petition Tab 16).

> 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.[42]

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,"[43] and some states have automatic generic drug substitution laws. Even putting aside the bioequivalence issues raised in this petition and supplement, 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.

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."[44] In contrast, propylene glycol solvates the α–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.[45]

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

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

[43] FDA, Facts About Generic Drugs at 2, *available at* https://www.fda.gov/media/79301/download (Tab 15).

[44] 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 (Citizen Petition Tab 11).

[45] *See id.*

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 and in the citizen petition, Encore respectfully requests that FDA grant the actions requested in the citizen petition.

VERIFICATION

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about 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); and July 1, 2020 (propylene glycol permeation testing results). 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