



SIDLEY AUSTIN LLP
 1501 K STREET, N.W.
 WASHINGTON, D.C. 20005
 (202) 736 8000
 (202) 736 8711 FAX

Direct: (202) 736 8304
 E-mail: dtroy@sidley.com

BEIJING	GENEVA	SAN FRANCISCO
BRUSSELS	HONG KONG	SHANGHAI
CHICAGO	LONDON	SINGAPORE
DALLAS	LOS ANGELES	TOKYO
FRANKFURT	NEW YORK	WASHINGTON, DC

FOUNDED 1866

September 13, 2006

By Hand Delivery

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

Re: Docket No. 2005P-0458: Refrain from Approving ANDA No. 77-271 Until the
 Three-Year Period of Market Exclusivity for the Product has Expired

1 4 8 0 '06 SEP 13 P 2 039

SUPPLEMENT TO MEDI-FLEX'S CITIZEN PETITION

Medi-Flex, Inc. ("Medi-Flex") submits this supplement to its Citizen Petition in response to several issues that were raised during Medi-Flex's meeting with FDA. First, FDA discussed the issue of whether Medi-Flex's study demonstrates anything over the previously approved product Hibiclens®. Medi-Flex's exclusivity is based on the determination that its tint study was new and essential to approval. Applying Hibiclens® to ChloroPrep® with Tint would undercut that exclusivity. In this supplement, Medi-Flex details the differences between Hibiclens® and ChloroPrep® with Tint and explains why Hibiclens® is not relevant to the ChloroPrep® with Tint formulation.¹ Second, FDA raised an issue at the meeting regarding the scope of Medi-Flex's exclusivity with respect to a product that contains a different quantity of tint than ChloroPrep® with Tint. Medi-Flex confirms in this supplement that its three-year exclusivity covers such a product. Finally, Medi-Flex provides information regarding several examples that were discussed where FDA required a pending ANDA to rely on a new and more appropriate Reference Listed Drug.

I. Hibiclens® is Not Relevant

Importantly, FDA has previously acknowledged that the Hibiclens® formulation is not relevant to ChloroPrep® with Tint. In particular, FDA required Medi-Flex to conduct a new efficacy study regarding the ChloroPrep® with Tint formulation despite the availability of Hibiclens® information. It seems that FDA would not have required Medi-Flex to perform a new clinical trial if the teachings of Hibiclens® were applicable to the ChloroPrep® with Tint formulation. Any knowledge gained from Hibiclens® is limited to similar formulations. Additionally, FDA's Exclusivity Summary for ChloroPrep® with Tint provides that Medi-Flex's efficacy study of the ChloroPrep® with Tint formulation does not duplicate the results of any

¹ Medi-Flex previously provided a brief analysis of Hibiclens® in Medi-Flex's response to comments by Cardinal Health, Inc. Medi-Flex's Response at 6-7.

2005P-0458

SUP 1

prior investigation relied on by FDA to support the efficacy of a previously approved product, including Hibiclens®. FDA Exclusivity Summary for NDA 20-832/S-08 (April 13, 2005) at 5. It is clear that the teachings of Hibiclens® are not relevant to ChloroPrep® with Tint.

Although both Hibiclens® and ChloroPrep® with Tint contain chlorhexidine gluconate, isopropyl alcohol, and tint, the products otherwise have very different formulations and can not be compared. The performance of a pharmaceutical product is the result of the interaction of all of the ingredients of the formulation. There is no scientific basis to conclude that the ingredients contained in Hibiclens® would also work in ChloroPrep® with Tint, which has a very different overall formulation. As FDA has recognized, formulation changes to Hibiclens® could “dramatically change its activity.” Medical Officer’s Review and Microbiologist’s Review of NDA 17-768 (June 1, 1976) at 32. Furthermore, topical products are particularly sensitive to formulation changes. According to FDA’s regulations, generic topical products must generally contain the same inactive ingredients as the listed drug. 21 C.F.R. § 314.94(a)(9)(v).

Medi-Flex’s unique formulation for ChloroPrep® with Tint comprises chlorhexidine gluconate, isopropyl alcohol, tint, and water. *See* Table of Ingredients (attached). The Hibiclens® formulation contains almost twice as many ingredients as the ChloroPrep® with Tint formulation. In addition to the ingredients in ChloroPrep® with Tint, Hibiclens® contains: (1) a mild sudsing nonalkaline base, *i.e.*, a surfactant; (2) unidentified “other ingredients”; and (3) fragrance. None of those ingredients are contained in the ChloroPrep® with Tint formulation.

The additional ingredients contained in Hibiclens® affect the performance of the product. Importantly, Hibiclens® contains a surfactant that is not contained in ChloroPrep® with Tint.² Surfactants are wetting agents that lower the surface tension of the formulation, thus affecting the delivery of chlorhexidine to the skin. Furthermore, surfactants adhere to the skin and may strip the lipid layer of the skin or otherwise affect permeability. The surfactant contained in Hibiclens® produces a sudsing effect on the skin surface. By affecting the skin surface, the surfactant in Hibiclens® affects the local interaction of chlorhexidine and bacteria on the skin.

Additionally, surfactants generally are comprised of hydrophilic and hydrophobic regions, and many are charged. Chlorhexidine is a cationic compound. Its formulations are governed by ionic interactions. The ionic forces in Hibiclens® are likely different than the ionic forces in ChloroPrep® with Tint. Removing the surfactant ingredient from Hibiclens® may change the balance of ionic interactions and affect the stability of the final product.

Due to the significant formulation differences, there is no basis to apply the teachings of Hibiclens® to the ChloroPrep® with Tint formulation used by Medi-Flex and Cardinal Health, Inc. (“Cardinal”). The surfactant in Hibiclens® seems to play an important functional role in the delivery, action, and stability of Hibiclens®. Without the surfactant, there is no basis to conclude that the interaction of the remaining ingredients would result in a successful product. At the very least, eliminating the surfactant would have an unpredictable effect on the product. Similarly, altering the Hibiclens® formulation by removing other ingredients, such as the

² The specific surfactant is not disclosed in the Hibiclens® label.

fragrance and unidentified ingredients, would also affect the product. The formulation for ChloroPrep® with Tint does not contain the critical surfactant ingredient or the fragrance and other unidentified ingredients contained in Hibiclens®. These significant formulation differences between the products prevent the application of Hibiclens® to ChloroPrep® with Tint.³ As described above, if Hibiclens® had been applicable, FDA would not have required Medi-Flex to conduct a new clinical trial on the ChloroPrep® with Tint formulation, and would not have granted Medi-Flex exclusivity for that study.

Furthermore, there is no basis to compare Hibiclens® and ChloroPrep® with Tint because the products have different active ingredients. ChloroPrep® with Tint contains a combination of chlorhexidine gluconate 2% and isopropyl alcohol 70% as its active ingredients. In contrast, Hibiclens® contains only chlorhexidine gluconate 4% as its active ingredient, which is twice as strong as ChloroPrep® with Tint. Hibiclens® does contain isopropyl alcohol, but it is at a 4% concentration (versus 70% for ChloroPrep® with Tint) and is not an active ingredient. Importantly, FDA has recognized that the isopropyl alcohol contained in the ChloroPrep® with Tint formulation directly contributes to the antimicrobial properties of the product. Hibiclens® and ChloroPrep® with Tint are simply different products that contain different active and inactive ingredients. The differences between the products are underscored by the fact that, due to the different active ingredients, Medi-Flex could not have submitted ChloroPrep® with Tint under an ANDA referencing Hibiclens®. As FDA has implicitly recognized, the products have different active ingredients and can not be compared.

II. Medi-Flex's Exclusivity is Not Limited to a Specific Quantitative Formulation

At the meeting, FDA also discussed the scope of Medi-Flex's exclusivity with respect to a product that is qualitatively (Q1) the same, but quantitatively (Q2) different, than ChloroPrep® with Tint. In other words, a product that contains a tint ingredient like ChloroPrep® with Tint, but at a different concentration. As indicated in *Zeneca Inc. v. Shalala*, Medi-Flex's exclusivity covers such products. *Zeneca Inc. v. Shalala*, 1999 U.S. Dist. LEXIS 12327 (D. Md. 1999), *aff'd on other grounds*, 213 F.3d 161 (4th Cir. 2000) (attached at Citizen Petition, Tab 6).

In *Zeneca*, the court indicated that the scope of three-year exclusivity is commensurate with the scope of the underlying study and covers products that share the same efficacy concern that was studied. *Id.* at 38. Medi-Flex has previously explained in great detail that the scope of its tint study is not limited to the specific color tint contained in ChloroPrep® with Tint, FD&C Green No. 3. Rather, Medi-Flex's study covers other tint ingredients, such as the color used in

³ In Cardinal's comments to Medi-Flex's Citizen Petition, Cardinal also provides that Hibiclens® is not applicable to ChloroPrep® with Tint. Comments of Cardinal Health, Inc. at 7-8 (January 20, 2006). However, Cardinal states that Hibiclens® is not relevant because it contains a different color tint than ChloroPrep® with Tint. Hibiclens® contains FD&C Red No. 40, and ChloroPrep® with Tint contains FD&C Green No. 3. The red and green tints are both anionic FD&C dyes. They have the same empirical behavior and do not prevent the application of Hibiclens® to ChloroPrep® with Tint. Rather, it is the significant formulation differences described above that prevent any comparison between Hibiclens® and ChloroPrep® with Tint.

Cardinal's generic version of ChloraPrep® with Tint, FD&C Red No. 40. See Citizen Petition at 5-8; Medi-Flex's Response to Cardinal at 4-6; and Medi-Flex's Meeting Slides at 12-20.

The *Zeneca* case also demonstrates that three-year exclusivity is not limited to the specific concentration of new ingredient. In that case, Zeneca reformulated its propofol product to include a new preservative ingredient, EDTA, at a 0.005% concentration. FDA required Zeneca to conduct new clinical trials concerning a safety issue specific to EDTA. As the scope of Zeneca's studies were limited to the EDTA ingredient, FDA awarded three-year exclusivity only for EDTA and not other preservatives. Importantly, Zeneca's exclusivity was not limited to the addition of EDTA at a 0.005% concentration. Zeneca's exclusivity broadly covered any propofol product containing EDTA. As stated by the court, the exclusivity "applies to propofol products including EDTA." *Zeneca* at *38.

Consistent with *Zeneca*, Medi-Flex's three-year exclusivity is not limited to the specific concentration of tint used in the ChloraPrep® with Tint formulation. The innovative change deserving exclusivity and supported by Medi-Flex's clinical study broadly covers other tinted product formulations, including Cardinal's generic ChloraPrep® with Tint product.

III. FDA has Previously Required Pending ANDAs to Change RLDs

As detailed in Medi-Flex's Citizen Petition material, Cardinal has submitted an ANDA for a generic ChloraPrep® with Tint product and should be required to reference ChloraPrep® with Tint as the Reference Listed Drug ("RLD") instead of the untinted ChloraPrep® One-Step.⁴ See Medi-Flex's Citizen Petition at 8-11; Medi-Flex's Response to Cardinal at 9-12; and Medi-Flex's Meeting Slides at 21-26. At the meeting, Medi-Flex detailed several examples where FDA has required an unapproved ANDA to change its RLD.

For example, FDA required all unapproved ANDAs for Cytoxan® (cyclophosphamide) to reference a new formulation of Cytoxan® as the RLD. 69 Fed. Reg. 9630 (March 1, 2004). Although the old Cytoxan® formulation had been voluntarily withdrawn from the market, it was not withdrawn for reasons of safety or effectiveness and was therefore still available as an RLD. (A product is a listed drug and may serve as the basis for an ANDA unless it is withdrawn from sale for safety or efficacy reasons. See 21 C.F.R. § 314.3(b)). Despite the availability of both formulations as RLDs, FDA required all unapproved ANDAs, including pending applications, to reference the new formulation. According to FDA, "Because Bristol has supplemented its CYTOXAN NDA and obtained approval for a new formulation . . . any *unapproved* ANDAs seeking to reference CYTOXAN as a reference listed drug must reference the currently approved formulation" 69 Fed. Reg. 9630 (emphasis added).

⁴ Alternatively, FDA should require Cardinal to submit a 505(b)(2) application with its own clinical data. Cardinal's ANDA is for a generic product with tint. However, Cardinal's ANDA uses the untinted ChloraPrep® One-Step as the RLD. The addition of a tint ingredient must be supported by clinical data, as evidenced by FDA's requirement that Medi-Flex conduct a clinical trial with respect to ChloraPrep® with Tint. Thus, Cardinal must either rely on ChloraPrep® with Tint as its RLD or submit a 505(b)(2) application with clinical data. To apply a higher standard of approval to Medi-Flex would be arbitrary and capricious. See Citizen Petition at 7.

Similarly, FDA required Watson Labs. ("Watson") to reference a new RLD with respect to Watson's ANDA for hydrocodone bitartrate and acetaminophen tablets (10 mg/500 mg). In that situation, a new and more relevant RLD became available after Watson had submitted its ANDA. Consequently, FDA required Watson to conduct tests against the new RLD. As explained in FDA's review of Watson's ANDA:

Subsequently, the D.M. Graham Laboratories product (Lortab®) became the reference listed product (1/26/96) for the 10 mg/500 mg strength tablet. The Division of Chemistry, therefore requested that the sponsor conduct dissolution testing between their 10 mg/500 mg test product vs the new RLD.

Approval Package for Watson's ANDA 40-148, Review of a Waiver Request (Amendment) (February 13, 1997).

Importantly, the examples above demonstrate that FDA has required pending ANDAs to change RLDs when a new and more relevant RLD formulation is available. This is exactly the situation with Cardinal. Cardinal submitted its ANDA for a tinted product. As ChloraPrep® with Tint was not available when Cardinal submitted its ANDA, Cardinal relied on the untinted ChloraPrep® One-Step as its RLD. Now, however, a new and more relevant RLD formulation (*i.e.*, ChloraPrep® with Tint) is available. ChloraPrep® with Tint is the product that Cardinal has duplicated. As with Cytosan® and Watson's hydrocodone tablets, Cardinal should reference the new RLD.⁵

IV. Conclusion

In sum, there is no basis to apply Hibiclens® to ChloraPrep® with Tint because the products are very different. In addition to having different active ingredients, Hibiclens® also contains almost twice as many ingredients as ChloraPrep® with Tint. In particular, Hibiclens® contains a critical surfactant ingredient that is not in ChloraPrep® with Tint. These formulation differences prevent any comparison between the products. Even FDA has previously acknowledged that Hibiclens® is not relevant. If Hibiclens® were relevant, FDA would not have required Medi-Flex to conduct a new clinical trial regarding the ChloraPrep® with Tint formulation, and would not have granted Medi-Flex exclusivity for that study, which it did.

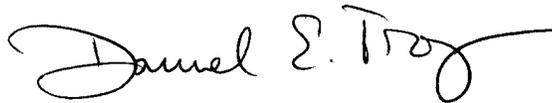
Furthermore, Medi-Flex's exclusivity is not limited to a specific quantitative formulation. As indicated in *Zeneca*, three-year exclusivity is based on the scope of the underlying study. It is not limited to a specific concentration of ingredient. Medi-Flex developed an innovative tinted chlorhexidine product and conducted a required clinical trial to obtain approval. Cardinal now seeks approval for a generic version of that product, except that Cardinal uses a different color tint. The scope of Medi-Flex's study and exclusivity is not limited to the exact ChloraPrep® with Tint formulation, but broadly covers Cardinal's generic tinted formulation.

⁵ Cardinal has previously argued that it can not reference ChloraPrep® with Tint as the RLD because ChloraPrep® with Tint has a 26 ml applicator volume, while Cardinal is seeking approval for a 10.5 ml applicator volume. Medi-Flex recently received approval for a 10.5 ml volume ChloraPrep® with Tint, which is the same volume as Cardinal's ANDA product. Cardinal's argument is now moot.

In addition, Cardinal should be required to rely on ChloroPrep® with Tint as the RLD for Cardinal's tinted generic product. As demonstrated by the Cytosan® and hydrocodone examples, FDA has previously required pending ANDAs to reference new and more appropriate RLDs.

If you have any questions, please do not hesitate to contact the undersigned.

Respectfully submitted,



Daniel E. Troy
Gary L. Veron
Sidley Austin LLP
1501 K Street, N.W.
Washington, D.C. 20005
(202) 736-8000
Attorneys for Medi-Flex, Inc.

cc: Linda McBride, R.Ph.
Senior Director, Regulatory Affairs
Medi-Flex, Inc.

TABLE OF INGREDIENTS

Hibiclens®	ChloraPrep® with Tint
Chlorhexidine gluconate 4% (active ingredient)	Chlorhexidine gluconate 2% (active ingredient)
Isopropyl alcohol 4% (not an active ingredient)	Isopropyl alcohol 70% (active ingredient)
FD&C Red No. 40 (anionic tint)	FD&C Green No. 3 (anionic tint)
Purified water	Purified water
Fragrance	None
"Other ingredients"	None
Mild sudsing nonalkaline base (i.e., surfactant)	None
Adjusted pH 5.0-6.5	Adjusted pH about 6.5