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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

MEDI-FLEX'S RESPONSE TO CARDINAL'S COMMENTS

Medi-Flex, Inc. ("Medi-Flex") submits this response to the comments filed by Cardinal Health, Inc. ("Cardinal") opposing Medi-Flex's Citizen Petition and Petition for Stay of Action. As a preliminary matter, Medi-Flex underscores the fact that it contacted Cardinal several times before filing its Petitions to obtain more details about the facts and to promptly resolve these issues. However, as explained in the Petitions, Cardinal did not give Medi-Flex any additional information and made no effort to resolve the issues. Thus, Medi-Flex had no choice but to file its Petitions. Only through the petition process has Medi-Flex learned of several important facts affecting Medi-Flex's rights and the underlying issues. It is unfortunate that Cardinal waited so long to participate in this matter and has caused Medi-Flex and FDA to waste time on incorrect premises. Cardinal's statement that Medi-Flex seeks an unwarranted delay is completely baseless. Any undue delay is, ultimately, Cardinal's doing.

Medi-Flex's Citizen Petition raises serious issues regarding the scope of three-year exclusivity for Medi-Flex's product, ChloraPrep® with Tint. This product manifests several innovations over the first generation product, including the addition of a tint ingredient to facilitate the safe and effective administration of the product. To get FDA's approval, FDA made Medi-Flex perform an efficacy study regarding the tint ingredient. Medi-Flex successfully completed the study. It thus earned three years of market exclusivity. Now, despite Medi-Flex's exclusivity, Cardinal seeks approval of a generic product containing the same innovation. Although Cardinal has changed the color of the tint in its generic product, Medi-Flex's exclusivity is not limited to a specific color. As indicated in the trade name ChloraPrep® with Tint, the important innovation was the addition of a tint ingredient -- not the specific color. Furthermore, Cardinal's dye and Medi-Flex's dye contain the same anionic chemical group that could neutralize the active ingredient, chlorhexidine. Medi-Flex specifically studied the effect of this problematic group, and the results of the study are applicable to Cardinal's product. Cardinal should not be allowed to circumvent Medi-Flex's exclusivity simply by using a different color than Medi-Flex, as that would render Medi-Flex's three-year exclusivity essentially meaningless.

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Additionally, Medi-Flex's Citizen Petition raises serious issues regarding ANDA approval requirements. Cardinal's ANDA is for a generic product with tint. However, Cardinal's ANDA does not use ChloraPrep® with Tint as the Reference Listed Drug ("RLD"). Rather, Cardinal references the untinted ChloraPrep® One-Step. Cardinal's use of the untinted RLD has allowed Cardinal to avoid certifying to Medi-Flex's patent specifically directed to a tinted product. Pursuant to FDA regulations, Medi-Flex listed that patent only for ChloraPrep® with Tint and not ChloraPrep® One-Step. Consistent with the Hatch-Waxman Act, FDA should require Cardinal to use ChloraPrep® with Tint as the RLD and, at the very least, provide a certification to Medi-Flex's patent.

Background

As detailed in the Citizen Petition, Medi-Flex was the first company to receive approval for several over-the-counter antiseptic products containing the combination of active ingredients chlorhexidine gluconate 2% and isopropyl alcohol 70%. These products are delivered by topical sponge and are used for the preparation of a patient's skin before surgery. Medi-Flex's first generation product is ChloraPrep® One-Step, which was approved under NDA 20-832 on July 14, 2000. Medi-Flex's second generation product is ChloraPrep® with Tint, which was approved under supplemental NDA 20-832/S-008 on May 3, 2005. FDA designated both of these products as RLD's for generic applications.

ChloraPrep® with Tint embodies several improvements over ChloraPrep® One-Step. Importantly, ChloraPrep® with Tint contains an additional tint ingredient, FD&C Green No. 3. This tint colors the product so that the user may quickly determine previously treated areas. Furthermore, ChloraPrep® with Tint was originally approved with a 26 ml applicator volume, more than double the volume of ChloraPrep® One-Step's applicator volume of 10.5 ml. In addition to the 26 ml volume, ChloraPrep® with Tint is also now available in a 10.5 ml applicator volume. Medi-Flex is marketing that product under a "changes being effected" supplement (NDA 20-832/S-010). FDA issued an approvable letter on November 7, 2005 for the 10.5 ml applicator volume, which simply requested minor labeling revisions. Letter from Andrea Segal to Medi-Flex, Inc. (November 7, 2005). On November 16, 2005, Medi-Flex complied with the approvable letter, and final approval for the product is expected shortly.[1]

FDA required Medi-Flex to conduct numerous clinical trials over several years to prove that ChloraPrep® with Tint is safe and effective. In particular, FDA required Medi-Flex to conduct an efficacy study concerning the tint ingredient, as well as several safety studies concerning the increased applicator volume. In light of the successful clinical trials, ChloraPrep® with Tint earned three years of market exclusivity, which expires May 3, 2008. Additionally, ChloraPrep® with Tint is protected by U.S. Patent No. 6,729,786 (the "Tint Patent"). The Tint Patent is specifically directed to a product containing a tint ingredient and is listed only for ChloraPrep® with Tint in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations 26th Ed.* (2006) (the "*Orange Book*").

[1] It should be noted that the electronic *Orange Book* incorrectly indicates that ChloraPrep® with Tint in a 10.5 ml applicator volume was approved on December 27, 2005. However, this listing is incorrect. FDA has not yet issued an approval letter for that product.

In September 2005, well after ChloraPrep® with Tint had been approved, Medi-Flex learned that Cardinal was seeking approval of a generic product containing chlorhexidine gluconate 2% and isopropyl alcohol 70%. Based on the available facts, Medi-Flex believed that Cardinal had submitted ANDA No. 77-271 for a generic version of ChloraPrep® with Tint containing the tint ingredient FD&C Red No. 40 and using a 26 ml volume applicator. Additionally, Medi-Flex believed that Cardinal's ANDA relied on ChloraPrep® One-Step, not ChloraPrep® with Tint, as the RLD. Consistent with Medi-Flex's belief, Cardinal did not provide a patent certification with respect to the Tint Patent.

Despite repeated attempts by Medi-Flex and its counsel to obtain more information from Cardinal, and to talk to and with Cardinal and/or its counsel, Cardinal supplied no additional information. Indeed, Cardinal showed no interest in seeking a resolution to the underlying exclusivity and patent issues. Consequently, on November 14, 2005, Medi-Flex submitted its Citizen Petition requesting that FDA: (1) refrain from approving Cardinal's ANDA 77-271 until the applicable three-year exclusivity for ChloraPrep® with Tint expires on May 3, 2008; and (2) require ANDA 77-271 to rely on ChloraPrep® with Tint as the RLD and to provide certifications for the patents listed with respect to ChloraPrep® with Tint. Medi-Flex later learned that final approval of Cardinal's ANDA may be imminent. Thus, Medi-Flex submitted a Petition for Stay of Action on December 23, 2005 asking FDA to stay approval of the ANDA until FDA rules on the Citizen Petition.

Only after Medi-Flex's promise of further action has Cardinal finally deigned to respond to Medi-Flex's reasonable concerns. On January 20, 2006, Cardinal responded to Medi-Flex's Petitions ("Cardinal's Response"). Importantly, Cardinal's Response clarified several key facts. Contrary to Medi-Flex's belief, Cardinal stated that its product uses a 10.5 ml applicator volume, as opposed to a 26 ml applicator volume. Cardinal also stated that its ANDA had been submitted on September 9, 2004, which is before ChloraPrep® with Tint had received approval. Furthermore, Cardinal confirmed that its product contains a tint ingredient, FD&C Red No. 40.

In addition to providing important factual information, Cardinal's response details several arguments as to why its ANDA should be approved despite ChloraPrep® with Tint's exclusivity and despite the fact that the ANDA uses ChloraPrep® One-Step as the RLD and does not certify to the Tint Patent. For the reasons detailed below and in the Citizen Petition, Cardinal's Response is not persuasive. Medi-Flex renews its request that FDA refrain from approving Cardinal's ANDA for a generic ChloraPrep® with Tint product.

I. Cardinal Seeks Approval of a Generic Product Incorporating Medi-Flex's Innovation

To encourage drug development, the Hatch-Waxman Act extends three years of market exclusivity for innovations to existing products. Specifically, the statute provides:

> If a supplement to an application approved under subsection (b) is approved . . . and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection [ANDA] for

> a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

21 U.S.C. § 355(j)(5)(F)(iv). ChloraPrep® with Tint embodies two innovations: (1) the addition of a tint ingredient; and (2) an increased applicator volume. FDA required Medi-Flex to conduct several essential clinical trials to support approval of each of these innovations. As a result, each of these innovations deserves three-year market exclusivity.

A. Medi-Flex's Study Covers Cardinal's Product

First, Cardinal argues that any exclusivity Medi-Flex earned with respect to the addition of a tint ingredient does not extend to Cardinal's tinted product because Cardinal uses FD&C Red No. 40 instead of FD&C Green No. 3. Specifically, Cardinal argues that Medi-Flex's study is not relevant to Cardinal's product, and therefore Medi-Flex's exclusivity should not apply to Cardinal's product. Cardinal's Response at 5-8. This argument slices the baloney too fine. Medi-Flex's study covers Cardinal's product because Cardinal's dye contains the same problematic chemical group that was specifically studied by Medi-Flex.

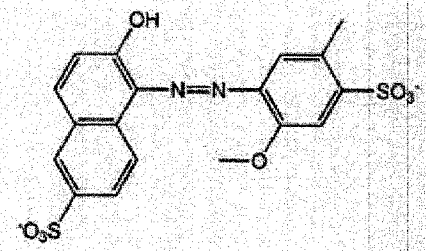
FDA made Medi-Flex conduct an efficacy study concerning the tint ingredient. Specifically, Medi-Flex studied the bacterial reduction achieved with a tinted product, untinted product, and povidone-iodine product as measured against the efficacy standards provided in FDA's Tentative Final Monograph for Health-Care Antiseptic Drug Products, 59 Fed. Reg. 31402 (June, 17, 1994). In essence, this study measured the function and effect of the addition of the tint ingredient. Medi-Flex's efficacy study involved FD&C Green No. 3 because this happened to be the dye used in Medi-Flex's formulation. However, the results of Medi-Flex's study are also applicable to Cardinal's dye, FD&C Red No. 40. Importantly, both dyes contain the same negatively charged chemical structure that is known to react with chlorhexidine and potentially affect its efficacy.

Chlorhexidine is a positively charged, or cationic, compound. *See* Jones; "Chlorhexidine: Is it Still the Gold Standard?"; *Periodontology* 2000, 15:55-62 (1997) at 55 (Tab 1). Chlorhexidine's efficacy is believed to be due to its positive charge. As stated by Jones:

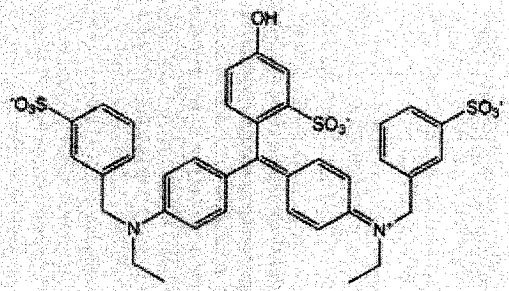
> The antibacterial mode of action of chlorhexidine is thought to be as follows. The bacterial cell is characteristically negatively charged. The cationic chlorhexidine molecule is rapidly attracted to the negatively charged bacterial cell surface, with specific and strong adsorption to phosphate-containing compounds.

Id.; *see also* Leard et al.; "The Propensity of Different Brands of Tea and Coffee to Cause Staining Associated with Chlorhexidine"; *J. Clin. Periodontal.*; 24:115-18 (1997) at 115 (Tab 2) ("The activity of chlorhexidine appears derived from the dicationic nature of the antiseptic molecule . . . .").

As indicated below in the chemical structures, the dye in Cardinal's generic product, FD&C Red No. 40, and the dye in ChloraPrep® with Tint, FD&C Green No. 3, have the same negatively charged sulfonic acid (SO^3) end groups.



FD&C Red No. 40
[contains two SO^3 Groups]



FD&C Green No. 3
[contains three SO^3 Groups]

This negatively charged, or anionic, SO^3 group has the potential to bind with the positively charged chlorhexidine and neutralize its efficacy. In fact, Jensen specifically confirmed that FD&C dyes containing anionic sulfonic acid SO^3 groups bind to chlorhexidine. According to Jensen:

> A common molecular feature of the investigated dyes exhibiting a selective binding to chlorhexidine-treated apatite is the presence of two or three acidic groups. Indigo carmine and sunset yellow have two sulfonic acid groups . . . and brilliant blue, amaranth and azocarmine B have three sulfonic acid groups. It can therefore be suggested that the increased binding of these dyes mediated by chlorhexidine is caused by an interaction between the cationic groups of the adsorbed chlorhexidine molecules and the anionic groups of the dyes.

Jensen; "Binding of Dyes to Chlorhexidine-Treated Hydroxyapatite"; *Scand. J. Dent. Res.*; 85: 334-340 (1977) (Tab 3) at 339; *see also* Leard et al. at 115 ("it is certain that chlorhexidine can precipitate or bind to . . . dyes in vitro to produce complexes identical in colour to those seen clinically" (citations omitted)).

Although the studies described above did not examine how dyes affect chlorhexidine's efficacy, other studies have confirmed that anionic compounds neutralize chlorhexidine. *See* Walsh et al.; "The Effect of Handcream on the Antibacterial Activity of Chlorhexidine Gluconate"; *J. Hosp. Infect.*; 9:30-33 (1987) (Tab 4). As stated by Walsh et al., "It is known that chlorhexidine is inactivated by anionic substances (Senior, 1972) and this study confirms that a handcream containing an anionic emulsifying agent reduces the residual antibacterial effect of chlorhexidine in routine practice." *Id.* at 32. Although Walsh et al. conducted their study using the anionic ingredient triethanolamine, the article's conclusion is not limited to triethanolamine. Rather, the authors apply their results generally to handcreams containing anionic emulsifying agents. *Id.* Similarly, Medi-Flex's study is not limited to FD&C Green No. 3. Rather, it provides important information concerning other dyes, such as FD&C Red No. 40, that contain the same anionic property.

Importantly, Cardinal's dye and Medi-Flex's dye share the same anionic group that is known to bind with chlorhexidine. The anionic group contained in the dyes creates an efficacy concern because chlorhexidine is a cationic compound that could be inactivated by the anionic

structure. Medi-Flex specifically studied the effect of the anionic group on chlorhexidine's efficacy. The results are applicable to Cardinal's product. Consistent with the holding in *Zeneca v. Shalala*, Medi-Flex's exclusivity is also applicable to Cardinal's product. *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). In *Zeneca*, the court indicated that three-year exclusivity covers products that share the same efficacy concern that was studied. *Id.* at *38. As detailed below, that Cardinal performed its own bioequivalence tests does not negate the fact that Medi-Flex's study and exclusivity cover Cardinal's product.

B. Cardinal's Bioequivalence Tests Are Not Determinative of Medi-Flex's Exclusivity

Cardinal argues that Medi-Flex's study is not applicable to Cardinal's product because FDA required Cardinal to perform its own comparative bioequivalence tests. Specifically, Cardinal states that, if Medi-Flex's theory were correct, then FDA "would not and could not" have required Cardinal to perform its own bioequivalence tests. Cardinal's Response at 7. Unfortunately, Cardinal provides no details regarding its tests. It is unclear to Medi-Flex whether Cardinal even performed a clinical study or whether Cardinal was simply required to perform less rigorous tests, such as *in vitro* comparative tests.

In any event, Cardinal would have been required to conduct such tests even if Cardinal had used the same dye as Medi-Flex. The statute requires every ANDA to conduct bioequivalence tests concerning the ANDA formulation. With respect to topical products, an ANDA applicant may show bioequivalence through clinical data. *See* 21 C.F.R. § 320.24. Although Medi-Flex does not know Cardinal's exact formulation, there are at least inherent (and likely significant) manufacturing and formulation variations in Cardinal's product that could affect its safety and efficacy. Thus, the fact that FDA required Cardinal to perform additional bioequivalence tests is not determinative of Medi-Flex's exclusivity. There is no statutory requirement that Medi-Flex's study be sufficient for Cardinal's approval for it to qualify for exclusivity that would preclude Cardinal from entering the market with a product that manifests the same innovation as Medi-Flex's earlier product.

Cardinal's theory would render three-year exclusivity meaningless. As noted above, every ANDA must conduct bioequivalence tests. If such tests negated three-year new product exclusivity, then no ANDA would ever be subject to that exclusivity. This is particularly true with respect to ANDAs for topical products, such as Cardinal's ANDA, which may include clinical bioequivalence data. *See* Abbreviated New Drug Application Regulations (Proposed Rule), 54 Fed. Reg. 28872, 28891 (1989) ("Proposed Rule") ("If exclusivity could easily be avoided by an application containing only minimal data generated or purchased by the applicant, the incentive created by the availability of such exclusivity would decrease considerably."); *id.* at 28897 (rejecting a narrow interpretation of exclusivity because it would "seriously undermine its value, reducing the incentives for research and innovation in the pharmaceutical industry").

C. Hibiclens® Is Not Relevant

Additionally, Cardinal notes that Hibiclens® (chlorhexidine gluconate 4%) contains FD&C Red No. 40 and has been on the market for years. According to Cardinal, FDA did not

rely on this product to prove the efficacy of FD&C Green No. 3.[2] Therefore, Cardinal maintains, Medi-Flex's study involving FD&C Green No. 3 is not applicable to FD&C Red No. 40. Cardinal's Response at 7-8. Cardinal's analogy, however, falls flat. There are major differences between Hibiclens® and ChloraPrep® with Tint that are not present between Cardinal's product and ChloraPrep® with Tint. Importantly, Hibiclens® does not contain the same active ingredients as ChloraPrep® with Tint. ChloraPrep® with Tint contains the combination of active ingredients chlorhexidine gluconate and isopropyl alcohol. In contrast, Hibiclens® contains Hibitane® chlorhexidine gluconate, but does not contain the active ingredient isopropyl alcohol. Additionally, Hibiclens® is a different strength than ChloraPrep® with Tint. Hibiclens® contains chlorhexidine gluconate 4%. It is twice as strong as ChloraPrep® with Tint, which contains chlorhexidine gluconate 2%. Furthermore, Hibiclens® contains surfactants that are not contained in ChloraPrep® with Tint. In contrast to Hibiclens®, Cardinal's generic product is the same as ChloraPrep® with Tint with respect to the characteristics described above.

D. ChloraPrep® with Tint's Labeling and Approval Letter Support Exclusivity

Cardinal also relies on the labeling for ChloraPrep® with Tint to support its argument that Medi-Flex's exclusivity is limited to FD&C Green No. 3. In particular, Cardinal argues that there is nothing in the labeling for ChloraPrep® with Tint that describes the function or advantage of a tint ingredient. Cardinal's Response at 5. Medi-Flex disagrees. The important function of the tint ingredient is prominently displayed in the most visible portion of the label -- the trade name. Specifically, the trade name for the product includes the phrase "with Tint." The tint ingredient facilitates the administration of the product in a safe and effective manner. As the tint is an inactive ingredient, FDA would not have permitted Medi-Flex to prominently display the tint ingredient if it did not provide an important functional role in the formulation. According to FDA's regulations, labeling may be misleading due to "[t]he featuring in the labeling of inert or inactive ingredients in a manner that creates an impression of value greater than their true functional role in the formulation." 21 C.F.R. § 201.10(c)(4).

In addition to the labeling, Cardinal relies on the approval letter for ChloraPrep® with Tint, which mentions FD&C Green No. 3. Cardinal's Response at 6. An NDA covers a specific product formulation, which is reflected in the approval letter. However, the innovative change developed by Medi-Flex was the addition of a tint. The approved name for ChloraPrep® with Tint clearly indicates that FDA recognized that the important change from the marketed product was the addition of a tint ingredient, and not the specific dye. Despite the language of the approval letter, FDA did not require Medi-Flex to name the product ChloraPrep® with FD&C Green No. 3. Rather, the name incorporates the generic word "tint" because that word accurately describes the change approved to the existing product. Cardinal should not be permitted to circumvent Medi-Flex's exclusivity simply by using a different color in its formulation.

[2] It is interesting to note that Cardinal purports to know what FDA relied on to approve ChloraPrep® with Tint even though the approval package for that product does not appear to have been publicly released. In any event, contrary to Cardinal's statement, it seems that FDA could have considered both Hibiclens' marketing history and other essential information.

Consistent with this approach, FDA has indicated that three-year exclusivity is not limited to specific product formulations. *See* Proposed Rule, 54 Fed. Reg. at 28897 (rejecting a narrow interpretation of three-year exclusivity that would have covered "only specific drug products").

E. Medi-Flex's Study was an Efficacy Study and Deserved Exclusivity

Cardinal states that Medi-Flex does not even deserve three-year exclusivity with respect to the tint. Cardinal's Response at 8. According to Cardinal, Medi-Flex's tint study was a comparative bioequivalence study that is excluded from three-year exclusivity under the statute. *See* 21 U.S.C. § 355(j)(5)(F)(iv) (providing that the supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement"). Cardinal's conclusion, however, is premised on incorrect facts. Based on FDA's November 5, 2004 not approvable letter for ChloraPrep® with Tint (Citizen Petition at Tab 2), Cardinal states that Medi-Flex conducted a 20-subject study of ChloraPrep® with Tint versus an untinted product, using a single skin test site for each subject. Furthermore, Cardinal surmises that the purpose of Medi-Flex's study was to confirm that the tinted product had equivalent efficacy to the untinted product. Cardinal's Response at 5-6. However, the scope of the study outlined in the not approvable letter changed after Medi-Flex discussed that letter with FDA.

Contrary to Cardinal's assertions, Medi-Flex's study actually involved approximately 60 subjects, who were tested over their groin and abdomen areas. The study evaluated two test products, ChloraPrep® with Tint and ChloraPrep® in 26 ml applicator volumes, and included one povidone-iodine control product, Scrub Care® Preoperative Skin Prep Tray. Each subject had two treatment areas for the groin (left and right) and two treatment areas for the abdomen (left and right). These treatment areas were further divided into four sub-areas, which varied by contact time. Overall, Medi-Flex's study created 16 test sites per subject and resulted in approximately 750 evaluated sites.

The study was designed to measure the reduction in bacteria levels achieved with a product containing tint. The protocol specifically provides that "[t]his evaluation will measure the antimicrobial effectiveness of a preoperative skin product as specified by the Food and Drug Administration Tentative Final Monograph (TFM) for *Effectiveness Testing of a Patient Preoperative Skin Preparation* . . . ." Test for Pre Operative Skin Preparations (September 7, 2004) at 4. This is a direct measurement of efficacy. As noted in the protocol and by Cardinal, FDA required Medi-Flex to perform the study in accordance with the testing procedures of the Tentative Final Monograph for Health-Care Antiseptic Drug Products, 59 Fed. Reg. 31402 (June 17, 1994) ("TFM"). Cardinal's Response at 5. According to the TFM, the study performed by Medi-Flex was an efficacy study. For example, the TFM describes the testing as "[e]ffectiveness testing of a patient preoperative skin preparation" and provides that the TFM clarifies "the effectiveness criteria for health-care antiseptics." *Id.* at 31450, 31431 (emphasis added).

Additionally, the results of Medi-Flex's study were compared against the efficacy standards of the TFM, which require a certain log reduction of bacteria. As stated in the final report regarding the study:

> The $\log_{10}$ reductions in CFU/cm^2 of skin on the groin sites achieved by the test and the reference products met and exceeded the FDA's proposed 3.0 $\log_{10}$ reduction criteria for groin at the 2 and 10-minute sampling intervals.
>
> The $\log_{10}$ reductions in CFU/cm^2 of skin on the abdomen sites achieved by the test and the reference products, met and exceeded the FDA's proposed 2.0 $\log_{10}$ reduction criteria for abdomen at the 30-second and 10-minute sampling interval.

Final Report: Test for the Pre-Operative Skin Prep, Project No. 371-109 (December 29, 2004) at 4. Use of the objective TFM efficacy criteria clearly indicates that the study was not a comparative bioequivalence study between ChloraPrep® with Tint and ChloraPrep®, but rather a direct measure of efficacy. In fact, ChloraPrep® was itself a test product, with the povidone-iodine product serving as the control product.

Furthermore, FDA specifically refers to the study as an efficacy study, not a bioavailability study. According to the not approvable letter, FDA required Medi-Flex to "[c]onduct the Patient Pre-operative Skin Preparation (efficacy) study . . . ." Letter from Curtis Rosebraugh, M.D., M.P.H., to Medi-Flex, Inc. (November 5, 2004) (Citizen Petition at Tab 2) (emphasis added).

Importantly, FDA has previously recognized that the studies described in the TFM are efficacy studies deserving of exclusivity. In particular, Medi-Flex performed studies based on the TFM to prove the effectiveness of the original NDA product, ChloraPrep® One-Step.[3] As FDA stated in its Microbiology Review for that product:

> The assessment of a product as an effective preoperative skin prep is described in the Tentative Final Monograph, which states that a preoperative skin prep study must be performed and meet the efficacy requirements as described therein . . . . Efficacy is demonstrated by reduction of the microbial flora at each site from a predetermined baseline at specified intervals.

Microbiology Review of NDA 20-832 (June 6, 2000) at 10. In response to a not approvable letter, Medi-Flex conducted two pivotal efficacy tests using TFM methodology and was awarded three-year exclusivity for ChloraPrep® One-Step, which expired July 14, 2003. Similarly, ChloraPrep® with Tint was awarded three-year exclusivity for its efficacy study based on the TFM, which must be respected and enforced.

II. Cardinal's ANDA Should Not Be Approved Because It Uses an Inappropriate RLD

As Cardinal refused to share information with Medi-Flex before the Citizen Petition was filed, Medi-Flex believed that Cardinal had filed an ANDA for a generic product containing tint in a 26 ml volume applicator. Furthermore, it was unclear to Medi-Flex when Cardinal had filed

[3] *See* FDA's Approval Package for ChloraPrep® One-Step accessible on FDA's website at http://www.fda.gov/cder/foi/nda/2000/20-832_CHLORAPREP.htm.

its ANDA, although it seemed to be after the approval of ChloraPrep® with Tint. Accordingly, Medi-Flex argued in its Citizen Petition that Cardinal appeared to be trying to circumvent ChloraPrep® with Tint's three-year exclusivity and patent protection by referencing the wrong RLD and by certifying to the wrong patents.

Cardinal has now clarified several key facts affecting Medi-Flex's Citizen Petition. Importantly, Cardinal has now clarified that its ANDA was submitted on September 9, 2004, before the approval of ChloraPrep® with Tint. Additionally, Cardinal stated that its generic product uses a 10.5 ml applicator volume and not a 26 ml applicator. Again, it is unfortunate that Cardinal waited so long to share this information and caused Medi-Flex and FDA to focus on incorrect premises. However, even in light of these new facts, Medi-Flex believes that FDA should refrain from approving Cardinal's ANDA on the grounds that it uses ChloraPrep® One-Step as the RLD and fails to provide a patent certification to Medi-Flex's Tint Patent.

A. FDA has Authority to Require Cardinal to Change Its RLD

Cardinal's generic product contains tint, but Cardinal's ANDA relies on the untinted ChloraPrep® One-Step, and not ChloraPrep® with Tint, as the RLD. Cardinal argues that it submitted the ANDA before ChloraPrep® with Tint was approved, and FDA lacks authority to require Cardinal to amend its ANDA to rely on ChloraPrep® with Tint as the RLD. Cardinal's Response at 12. Contrary to Cardinal's argument, FDA has acknowledged that it has broad authority to require an ANDA applicant to amend its application to reference another RLD. Specifically, FDA stated:

> Currently, the agency uses one product as a reference standard against which the bioequivalence of the applicant's product is compared . . . . However, if the listed drug chosen by the applicant is different from that chosen by the agency as the standard for bioequivalence determinations, the agency will require the applicant to amend its application to refer to the agency's bioequivalence reference standard as its listed drug.

Proposed Rule, 54 Fed. Reg. at 28882. Similarly, FDA may require Cardinal to amend its ANDA to reference ChloraPrep® with Tint as the RLD instead of the untinted ChloraPrep® One-Step.

B. Labeling Concerns Support the Use of ChloraPrep® with Tint as the RLD

Cardinal also argues that a generic product must have the same labeling, with minor exceptions, as the RLD, and Cardinal's product will have the same labeling as the untinted ChloraPrep® One-Step but different labeling than ChloraPrep® with Tint. Cardinal's Response at 11-12. According to Cardinal, its labeling would be the same as ChloraPrep® One-Step's labeling except for the manufacturer information and the list of inactive ingredients, which would identify FD&C Red No. 40. A review of Cardinal's draft label provided in Cardinal's Suitability Petition also indicates that the phrase "One Step" will be prominently displayed just below the trade name, Prevail CHG™. *See* Citizen Petition at Tab 3. Furthermore, Cardinal

notes that its labeling would differ from ChloraPrep® with Tint's labeling with respect to drying time and treatment area information, which are dependent on applicator volume.

Cardinal's argument, however, does not hold weight. Cardinal admits that, if ChloraPrep® with Tint were the RLD, Cardinal would be permitted to modify its labeling accordingly. Cardinal's Response at 12. Thus, there appear to be no labeling issues that would prevent FDA from requiring Cardinal to use ChloraPrep® with Tint as the RLD.

However, there are labeling issues that should prevent Cardinal from using ChloraPrep® One-Step as the RLD. Although Cardinal's product is similar to ChloraPrep® with Tint, its labeling will be similar to ChloraPrep® One-Step. This could cause confusion in the marketplace. Indeed, Medi-Flex believes that Cardinal's labeling would be misleading. Unlike ChloraPrep® with Tint's labeling, Cardinal's labeling will not prominently display the fact that the product contains a tint ingredient, which provides an important functional role in the formulation. Medi-Flex's labeling prominently displays the tint ingredient in the proprietary name, which contains the phrase "with Tint." FDA has approved names with similar phrases to indicate an important aspect of the product, such as the addition of an active ingredient. For example, FDA has approved names such as "Phrenilin with Caffeine and Codeine" and "Promethazine with Codeine Syrup." Cardinal's labeling apparently not only fails to prominently display important information about the product, but it seems to display misleading information. Specifically, it appears that Cardinal's labeling will contain the phrase "One Step," which is likely to add to the confusion between these products. Cardinal submitted its ANDA for a generic ChloraPrep® with Tint product. Cardinal should not be allowed to use ChloraPrep® One-Step as the RLD.

C. Cardinal's Product is Not Pharmaceutically Equivalent to ChloraPrep® One-Step

Additionally, Cardinal's product should not be considered pharmaceutically equivalent to ChloraPrep® One-Step. Pharmaceutically equivalent products may differ in labeling "only within certain limits." *Orange Book* at vi. For the reasons described above, Cardinal's generic product should have labeling similar to ChloraPrep® with Tint, and not ChloraPrep® One-Step. The differences in labeling between these products should not be considered to be within the acceptable limits for pharmaceutically equivalent products. In essence, Cardinal's generic tinted product and the untinted ChloraPrep® One-Step are different products. The tint ingredient plays an important functional role by facilitating administration of the product in a safe and effective manner. These products should not be considered interchangeable in a clinical setting. A health care worker accustomed to applying a tinted formulation may have difficulty applying an untinted formulation, which raises safety and efficacy issues. In contrast, Cardinal's generic product is similar to ChloraPrep® with Tint.

Cardinal argues, however, that its generic product is not pharmaceutically equivalent to ChloraPrep® with Tint because Cardinal's generic product uses a 10.5 ml applicator volume, while ChloraPrep® with Tint uses a 26 ml volume applicator. Of course, as noted above, ChloraPrep® with Tint is now available in a 10.5 ml applicator volume. Medi-Flex recently received an approvable letter from FDA for ChloraPrep® with Tint in a 10.5 ml applicator volume, and is currently marketing that product under a "changes being effected" submission

(NDA No. 20-832/S-010). Medi-Flex complied with FDA's approvable letter on November 16, 2005 and expects that product to receive final approval shortly. Accordingly, Cardinal's argument that its generic product is not pharmaceutically equivalent to ChloraPrep® with Tint is no longer relevant.

Even if FDA were not to consider Medi-Flex's 10.5 ml ChloraPrep® with Tint, it seems that Cardinal's product incorporates important features from two RLD products, i.e., the tint from ChloraPrep® with Tint and the 10.5 ml applicator volume from ChloraPrep® One-Step. Similar to a 505(b)(2) application that relies on several RLDs, the patents for both ChloraPrep® with Tint and ChloraPrep® One-Step are relevant to Cardinal's application. Thus, Cardinal should be required to provide a certification to Medi-Flex's Tint Patent. *See* Letter from Steven K. Galson, M.D., M.P.H., to Donald O. Beers and William F. Cavanaugh, Jr., Docket No. 2004P-0386/CP1 & RC1 (Nov. 30, 2004) (Citizen Petition at Tab 8) at 7 ("505(b)(2) applicant must identify in its application the drug product or products on which it relies and certify to any relevant patents for those drug products.").

D. Cardinal is Circumventing Medi-Flex's Patent Contrary to the Hatch-Waxman Act

Cardinal's use of ChloraPrep® One-Step as the RLD allows Cardinal to circumvent Medi-Flex's Tint Patent. Although Cardinal finally clarified that its ANDA was filed before ChloraPrep® with Tint was approved, the continued use by Cardinal of ChloraPrep® One-Step as the RLD effectively circumvents the Tint Patent. Pursuant to FDA's patent listing requirements, Medi-Flex listed the Tint Patent, which is specifically directed to a product containing tint, only with ChloraPrep® with Tint and not with ChloraPrep® One-Step. Cardinal's generic product contains tint. But Cardinal's use of the untinted ChloraPrep® One-Step as the RLD has allowed Cardinal to avoid certifying to the Tint Patent. Contrary to the balance sought by the Hatch-Waxman Act, Cardinal is benefiting from Medi-Flex's hard-earned data but is avoiding the patent that most likely covers Cardinal's generic product. FDA should require Cardinal's ANDA for a tinted product to use ChloraPrep® with Tint as the RLD, or at the very least, to include a certification with respect to the Tint Patent. As the same underlying safety and efficacy data that supports ChloraPrep® One-Step also supports ChloraPrep® with Tint, the use of ChloraPrep® with Tint as the RLD would not require any additional analysis. It would simply group similar products together so that patent issues may be resolved before the generic product receives approval as intended by the Hatch-Waxman Act.

III. Medi-Flex's Exclusivity Earned for the Increased Applicator Volume

Due to Cardinal's refusal to cooperate with Medi-Flex before Medi-Flex filed its Citizen Petition, Medi-Flex mistakenly believed that Cardinal was seeking approval of a generic product with a 26 ml applicator volume. Consequently, Medi-Flex's Citizen Petition provides that Cardinal's ANDA should not be approved based on Medi-Flex's exclusivity earned as a result of increasing the applicator volume from 10.5 ml to 26 ml.

Cardinal has now disclosed that its product uses a 10.5 ml applicator and not a 26 ml applicator. It is unfortunate that Cardinal waited until after Medi-Flex submitted its Citizen Petition to disclose this important information. In light of Cardinal's belated disclosure, Medi-

Flex believes that the exclusivity Medi-Flex earned due to its 26 ml applicator volume is not applicable to Cardinal's product.

IV. Medi-Flex's Petition for Stay of Action Should Be Granted

Cardinal opposes Medi-Flex's Petition for Stay of Action mainly because Cardinal believes that Medi-Flex's substantive case is frivolous. Cardinal's Response at 13. As detailed above and in Medi-Flex's Petitions, Cardinal's ANDA raises serious issues regarding the scope of Medi-Flex's three-year exclusivity and ANDA approval requirements. Medi-Flex firmly believes that FDA should refrain from approving Cardinal's ANDA and is prepared to vigorously defend its position. The Petition for Stay of Action simply requests that FDA stay approval of Cardinal's ANDA until FDA has fully evaluated these complicated issues. Importantly, Medi-Flex has earned a period of market exclusivity, and courts have consistently held that such exclusivity periods should be protected until underlying substantive issues are resolved. *See* Petition for Stay of Action at 5-7.

Additionally, Cardinal argues that its large size is not relevant to the stay decision. Cardinal's Response at 14. Although Cardinal attempts to gloss over this important fact, courts routinely consider a company's size and competitive advantage when determining irreparable injury. Cardinal is the leading provider of health care products and services. It was recently ranked No. 16 on the Fortune 500 list with $75 billion of revenue. In fact, Cardinal is a major distributor of ChloraPrep® with Tint. *See* Petition for Stay of Action at 5. Cardinal's strategic position and deep pockets will likely combine to provide Cardinal with a significant market share within a very short period of time from approval.

Cardinal claims that Medi-Flex's market prediction is overstated and "reflects an ignorance of Cardinal's business model," but offers no specific information to the contrary. Cardinal's Response at 14. Undoubtedly, Cardinal has extensively analyzed the market for its generic product, the expected revenue from its product, and the impact on sales of ChloraPrep® with Tint. (Cardinal does not provide any of this information.) It seems that if Cardinal really believed that its generic product would not substantially impact the market for ChloraPrep® with Tint, then Cardinal would have provided supporting information. The mere fact that Cardinal, which did not have to invest in underlying safety and efficacy tests, will almost certainly price its generic product below ChloraPrep® with Tint creates a significant market impact for Medi-Flex. Cardinal, however, disingenuously implies that there will be a market utopia where Cardinal markets its generic product equally with ChloraPrep® with Tint. Medi-Flex does not believe this will be the situation, and Cardinal's lack of cooperation to date serves to confirm Medi-Flex's belief.

Finally, Cardinal ironically criticizes Medi-Flex for filing its Petitions because of the potential delay and administrative burden. As previously described, Medi-Flex attempted to avoid filing the Petitions by repeatedly contacting Cardinal to obtain more factual detail and a resolution to these issues. Unfortunately, Cardinal did not cooperate and simply ignored Medi-Flex's overtures. Cardinal provided no additional information to Medi-Flex and made no attempt to resolve these important issues. As such, Medi-Flex had no choice but to file its

Petitions. Indeed, only through the petition process has Medi-Flex learned of important facts affecting its rights and persuaded Cardinal to engage in these issues.

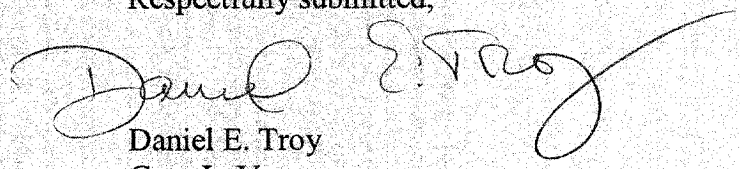
V. Conclusion

In sum, Medi-Flex's ChloraPrep® with Tint embodies several innovations over the first generation product, ChloraPrep® One-Step. Importantly, Medi-Flex added a tint ingredient to improve application of the product. As indicated in the trade name, the addition of a tint ingredient was an important innovation. To obtain approval, FDA required Medi-Flex to complete an efficacy study regarding the tint ingredient. Consequently Medi-Flex earned three-years of market exclusivity. Despite Medi-Flex's exclusivity, Cardinal now seeks approval for a generic product containing tint. Although Cardinal's tint is a different color than Medi-Flex's color, both tints share the same anionic property that was studied in Medi-Flex's clinical trial. Cardinal's generic product incorporates Medi-Flex's innovation. As such, Cardinal should not be allowed to circumvent Medi-Flex's exclusivity simply by using a different color dye than Medi-Flex. Otherwise, three-year new product exclusivity would be rendered meaningless.

Although Cardinal's ANDA is for a generic product with tint, Cardinal uses the untinted ChloraPrep® One-Step as the RLD. This will lead to misleading labeling and potential confusion in the marketplace. Moreover, Cardinal's use of ChloraPrep® One-Step has allowed Cardinal to avoid certifying to the patent that most likely covers its generic product, the Tint Patent. The Tint Patent is specifically directed to a product containing tint, such as Cardinal's product, and is listed only with respect to ChloraPrep® with Tint. In fact, Medi-Flex is prohibited under FDA's regulations from listing the Tint Patent with ChloraPrep® One-Step. To allow Cardinal to use ChloraPrep® One-Step as the RLD for its generic product with tint while prohibiting Medi-Flex from listing the Tint Patent with that RLD is contrary to the intent of the Hatch-Waxman Act. FDA should require Cardinal's ANDA to use ChloraPrep® with Tint as the RLD and, at the very least, provide a certification to the Tint Patent.

If you have any questions, please do not hesitate to contact the undersigned. We will be contacting the Chief Counsel's office to request a meeting on this matter.

Respectfully submitted,



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