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## **CITIZEN PETITION**

Medi-Flex, Inc. has recently obtained information indicating that Cardinal Health, Inc. is seeking to circumvent Medi-Flex's three-year exclusivity and patents associated with ChloroPrep® with Tint by relying on the wrong RLD and by certifying to the wrong patents. Accordingly, Medi-Flex, Inc. ("Medi-Flex") submits this petition under Section 505 of the Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. § 10.30. The petition asks that the Commissioner of Food and Drugs (the "Commissioner") refrain from approving Abbreviated New Drug Application ("ANDA") No. 77-271 filed by Cardinal Health, Inc. ("Cardinal") until the applicable three-year exclusivity for the product has expired. (The ANDA is for a generic chlorhexidine gluconate 2% and isopropyl alcohol 70% product with tint.) Additionally, Medi-Flex asks that the Commissioner require ANDA 77-271 to rely on the appropriate reference listed drug ("RLD"), ChloroPrep® with Tint, and to provide certifications for the patents listed with respect to that RLD.

As detailed in this Citizen Petition, Medi-Flex only recently became aware of Cardinal's ANDA and the related issues underlying this Citizen Petition. Immediately upon learning about Cardinal's ANDA, Medi-Flex contacted Cardinal to obtain more details about the facts and to obtain a resolution to the issues. Unfortunately, Cardinal has been unwilling to provide Medi-Flex with any additional information. Nor has Cardinal made any effort to resolve these important issues. Consequently, Medi-Flex believes that it has no choice but to submit this Citizen Petition seeking the action requested below.

## **A. ACTION REQUESTED**

Medi-Flex respectfully requests that the Commissioner: (1) refrain from approving ANDA 77-271 until the three-year period of market exclusivity granted with the approval of ChloroPrep® with Tint (NDA 20-832/S008) has expired on May 3, 2008; and (2) require ANDA 77-271 to rely on ChloroPrep® with Tint as the reference listed drug and to provide certifications for the patents listed for ChloroPrep® with Tint.

## **B. STATEMENT OF GROUNDS**

### **1. BACKGROUND**

Medi-Flex owns New Drug Application (“NDA”) 20-832. That NDA covers several over-the-counter products containing the combination of active ingredients chlorhexidine gluconate 2% and isopropyl alcohol 70%. These products, which are delivered by a topical sponge, are broad spectrum antiseptics used for preparing a patient’s skin before surgery. The first product, ChloroPrep® One-Step (chlorhexidine gluconate 2%, isopropyl alcohol 70%) was approved on July 14, 2000. It was designated by the U.S. Food and Drug Administration (“FDA”) as the RLD for generic applications. ChloroPrep® One-Step is now available in the following applicator volumes: 1.5 ml; 3.0 ml; and 10.5 ml. There are no Hatch-Waxman Act market exclusivity periods associated with this product; however, there are several patents listed for the product in FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations 25<sup>th</sup> Ed.* (2005) (the “Orange Book”).<sup>1</sup>

Although ChloroPrep® One-Step is already a very effective product, Medi-Flex developed several important innovations to further improve it. Specifically, ChloroPrep® One-Step is applied as a clear liquid. Consequently, users of the product occasionally had difficulty distinguishing treated skin from untreated skin. Additionally, the largest volume for ChloroPrep® One-Step is 10.5 ml. The area of skin needing treatment is typically much larger than the area covered by 10.5 ml of product. Medi-Flex therefore developed a second product, ChloroPrep® with Tint (chlorhexidine gluconate 2%, isopropyl alcohol 70%) in a 26 ml applicator volume. Importantly, ChloroPrep® 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, ChloroPrep® with Tint has an applicator volume of 26 ml, more than double the volume of the previous applicator. Medi-Flex submitted the new tint product to FDA for approval under supplemental NDA 20-832/S-008.

FDA required numerous clinical trials over several years to prove that the changes were safe and effective. Medi-Flex first attempted to increase its applicator volume to 26 ml in a supplement filed on March 11, 2003 (NDA 20-832/S-005). FDA refused to file the supplement. It stated that “[c]linical data is required to support the safety of this product in perioperative

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<sup>1</sup> Although the product was approved in July 2000, through inadvertance on the part of a regulatory consultant, these patents were not submitted for listing in the Orange Book until May 2005.

environments.” Letter from David Hilfiker to Beckloff Associates, Inc. (April 9, 2003) (Tab 1). Medi-Flex then met with FDA on June 11, 2003 to discuss what FDA wanted Medi-Flex to do to demonstrate the safety of the increased applicator volume.

In light of the meeting with FDA, Medi-Flex performed a clinical trial. It submitted supplemental NDA 20-832/S-008 on July 6, 2004 for a product with a 26 ml applicator volume and a tint ingredient. On November 5, 2004, FDA issued an “unapprovable” letter for those changes. It stated that the new tint product would not be approved until two additional clinical trials, one directed to safety and one directed to efficacy, had been completed. Letter from Curtis Rosebraugh, M.D., M.P.H., to Medi-Flex, Inc. (Nov. 5, 2004) (with related faxes) (Tab 2). In particular, FDA was concerned that the tint ingredient could affect efficacy. Although the tint ingredient had been used in other approved products, FDA was concerned that the dye might adversely affect the efficacy of chlorhexidine gluconate and isopropyl alcohol. Consequently, FDA required Medi-Flex to conduct a clinical trial examining bacterial reductions achieved with the new tinted product against the old, untinted product. Medi-Flex invested about \$120,000 to perform this clinical trial, which involved approximately 60 subjects. Medi-Flex’s clinical trial conclusively demonstrated to FDA that the addition of a tint ingredient does not affect efficacy.

FDA also required Medi-Flex to conduct another clinical trial establishing that the 26 ml volume is safe. Specifically, FDA was concerned that the increased volume contains a sufficient amount of alcohol that could cause harm to a patient if accidentally ignited. FDA manifested this concern even though, as in the case of the tint, there were other products on the market with large volumes of alcohol.<sup>2</sup> Nonetheless, FDA required Medi-Flex to conduct a safety study that involved applying the product for the maximum allowed period of time in accordance with the labeling to determine the approximate area of skin that the product covered.

FDA was particularly strict in requiring this clinical trial data from Medi-Flex. Medi-Flex had previously performed such a study using artificial skin, but FDA had required a clinical trial on the grounds that it would be both practical and more informative. Furthermore, FDA rejected Medi-Flex’s first clinical study regarding this issue. FDA was unhappy that Medi-Flex had applied the product for 30 seconds instead of two minutes.

So, as required, Medi-Flex conducted another clinical trial evaluating skin coverage and safety. Medi-Flex’s studies cost approximately \$75,000 and involved approximately 60 patients. Ultimately, the trials demonstrated that the 26 ml volume is safe.

In light of Medi-Flex’s successful clinical trials supporting the new tinted product, FDA approved ChloroPrep® with Tint in a 26 ml applicator volume on May 3, 2005. FDA designated ChloroPrep® with Tint as the RLD for generic products containing tint and a 26 ml volume. Due to the essential clinical trials involving the tint ingredient and increased applicator volume, ChloroPrep® with Tint received three-years of Hatch-Waxman market exclusivity. In addition to three-year exclusivity, there are four patents listed in the Orange Book for ChloroPrep® with Tint. These patents were submitted for listing with the application and were listed in the Orange

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<sup>2</sup> For example, Cardinal marketed Prevail® (providine iodine and alcohol) products in 59 ml and 40 ml volumes.

Book when the product was approved. Three of these listed patents are also listed with respect to ChloroPrep® One-Step. However, one patent is specifically directed to the tint ingredient (the "Tint Patent") and is listed only with respect to ChloroPrep® with Tint.<sup>3</sup>

Medi-Flex recently obtained information indicating that Cardinal is seeking approval of a generic ChloroPrep® with Tint product despite the three-year exclusivity and without certifying to the appropriate patents, including the Tint Patent. Specifically, Medi-Flex believes that Cardinal is deliberately using the untinted ChloroPrep® One-Step as the RLD for its tinted generic product, instead of the appropriate ChloroPrep® with Tint, to avoid the three-year exclusivity and patents associated with ChloroPrep® with Tint.

On November 18, 2004, Cardinal submitted a Suitability Petition to the FDA seeking permission to file an ANDA for a generic product containing chlorhexidine gluconate 2% and isopropyl alcohol 70% with tint, FD&C Red No. 40, in a 26 ml applicator volume. Letter from Michael L. Groesbeck to Gary Buehler (Nov. 18, 2004) (Tab 3). The Suitability Petition, which was filed before ChloroPrep® with Tint had been approved, states that Cardinal's ANDA for the generic tint product would use the untinted ChloroPrep® One-Step as the RLD. Furthermore, the Suitability Petition states that the generic tint product would be based on Cardinal's ANDA 77-271. It is unclear whether FDA granted Cardinal's Suitability Petition for a generic tint product.

On September 13, 2005, well after ChloroPrep® with Tint had been approved and was available as an RLD, Cardinal sent Medi-Flex a letter. The letter reported that Cardinal had filed ANDA 77-271 for a generic chlorhexidine gluconate and isopropyl alcohol product using ChloroPrep® One-Step as the RLD.<sup>4</sup> Letter from Andrew G. Rozycki to Medi-Flex Hospital Products, Inc. (Sept. 13, 2005). The letter also indicated that Cardinal had filed paragraph IV certifications for all of the patents listed with respect to ChloroPrep® One-Step. Cardinal did not provide a certification for the Tint Patent, which is listed only for ChloroPrep® with Tint.

Medi-Flex replied to Cardinal on September 19, 2005. Letter from Daniel E. Troy to Andrew G. Rozycki (Sept. 19, 2005) (Tab 4). That letter was followed by several telephone calls, all of which sought to determine whether Cardinal's ANDA covers a generic product with tint and which sought to resolve any outstanding exclusivity and patent issues. Unfortunately, Cardinal has not cooperated and has provided no additional information. Rather, Cardinal simply sent a letter to Medi-Flex stating that Cardinal now withdrew its paragraph IV certifications. Letter from Robert P. Giacalone to Medi-Flex Hospital Products, Inc. (Oct. 6, 2005) (Tab 5). The letter provided no other information.

Based on the available facts, Medi-Flex believes that Cardinal's ANDA 77-271 seeks approval of a generic product with tint in a 26 ml applicator, and that Cardinal's ANDA inappropriately relies on the untinted ChloroPrep® One-Step in a 10.5 ml applicator as the RLD to circumvent the three-year exclusivity and patents associated with the appropriate RLD,

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<sup>3</sup> U.S. Patent No. 6,729,786 is directed to the approved dosage form containing a tint ingredient.

<sup>4</sup> Cardinal previously attempted to send that letter to Medi-Flex on August 29, 2005; however, the letter was sent to the wrong address.

ChloroPrep® with Tint. As such, FDA should not approve Cardinal's ANDA until the exclusivity for ChloroPrep® with Tint expires. Cardinal must reference ChloroPrep® with Tint as the RLD and must certify to the patents listed for that RLD.

## 2. ARGUMENT

### **(a) FDA May Not Approve Cardinal's ANDA 77-271 Until the Three-Year Exclusivity for ChloroPrep® With Tint Expires on May 3, 2008**

To reward innovation and investment in new clinical studies, the FDCA grants three-years of market exclusivity to a change submitted in a supplemental NDA that is based on new clinical studies for approval. As the statute says:

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). Similarly, FDA's regulations prohibit FDA from approving an ANDA for a change contained in a supplemental NDA until three years after the supplemental NDA has been approved if two conditions, met here, are met. First the supplemental NDA must have contained reports of new clinical investigations that were conducted or sponsored by the applicant. Second, the studies must have been essential to the approval of the supplement. 21 C.F.R. § 314.108(b)(5). Furthermore, the regulations provide that the three-year exclusivity applies to an ANDA submitted pursuant to a suitability petition that relies on the information supporting the change approved in the supplemental NDA. *Id.*

As such, under the statute and FDA's implementing regulations, FDA may not approve Cardinal's ANDA 77-271 until Medi-Flex's three-year market exclusivity for such a product has expired on May 3, 2008. Medi-Flex substantially improved its first generation product, ChloroPrep® One-Step, by adding a tint ingredient and increasing the applicator volume to 26 ml. On May 3, 2005, Medi-Flex became the first company to receive FDA marketing approval for a chlorhexidine gluconate 2% and isopropyl alcohol 70% with tint product in a 26 ml applicator. To obtain approval, Medi-Flex invested significant resources to perform several essential clinical trials addressing serious safety and efficacy issues.

Importantly, FDA required Medi-Flex to conduct a clinical trial establishing that the addition of a tint ingredient does not affect the efficacy of the active ingredients.<sup>5</sup> This

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<sup>5</sup> Although the tint ingredient is an inactive ingredient, FDA has recognized that an inactive ingredient may seriously affect the safety and efficacy of a product, particularly with respect to topical products. 21 C.F.R. § 314.127(a)(8) (FDA may not approve an ANDA if "on the basis of information available to the agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the

requirement was more than limited confirmatory testing of an inactive ingredient. It was a significant undertaking essential to approval. The efficacy issue raised by FDA and studied by Medi-Flex was not a specific concern regarding Medi-Flex's dye, FD&C Green No. 3. Rather, it was a general concern regarding the addition of a tint ingredient. There is no substantive difference between Medi-Flex's FD&C Green No. 3 and Cardinal's FD&C Red No. 40. The same efficacy issues that were raised about Medi-Flex's product would apply to Cardinal's product. The results of Medi-Flex's study are generally applicable to the use of a tint ingredient in such products. Thus, the exclusivity that Medi-Flex earned for its tint study applies to Cardinal's use of a tint ingredient.

Applying Medi-Flex's exclusivity to Cardinal's product is consistent with the holding in *Zeneca Inc. v. Shalala*, 1999 U.S. Dist. LEXIS 12327 (D. Md. 1999), *aff'd on other grounds*, 213 F.3d 161 (4<sup>th</sup> Cir. 2000) (Tab 6). In that case, the court indicated that the scope of exclusivity was consistent with the scope of the underlying studies. Specifically, Zeneca had performed studies on the preservative EDTA to address safety concerns specifically related to EDTA. Recognizing that Zeneca's studies related only to EDTA, the court applied exclusivity only to EDTA, and not to preservatives in general. As the court stated, "The clinical investigations it submitted to the FDA with that supplement were necessitated by specific concerns related to EDTA, not to preservatives in general. Thus, the exclusivity applies to propofol products including EDTA, not to propofol products with other preservatives." *Id.* at \*38 (quoting Letter Order dated June 8, 1999). In contrast to the facts of *Zeneca*, Medi-Flex's studies were not necessitated by specific concerns relating to FD&C Green No. 3, but rather to the addition of a tint ingredient in general. As such, Medi-Flex's exclusivity extends to Cardinal's product, which contains the tint ingredient FD&C Red No. 40.

Furthermore, Medi-Flex conducted another clinical trial FDA required to prove that the new 26 ml volume is safe. Specifically, FDA was concerned that the large volume of alcohol could pose a fire hazard. Although there were other products on the market with large volumes of alcohol, those products had not been approved by FDA under an NDA or ANDA, and FDA had received reports of flammability problems with those products.<sup>6</sup> Memorandum of Meeting Minutes for June 11, 2003 Meeting between Medi-Flex and FDA (July 2, 2003) at 4 (Tab 7). Thus, FDA was particularly strict with respect to this clinical requirement. It required Medi-Flex to conduct a clinical study to determine the skin coverage provided by the new volume so that users could minimize spillage and pooling. Medi-Flex first conducted a study on artificial skin. FDA rejected that study because it had not been a clinical trial involving human skin. Medi-Flex then performed a clinical trial where the product was applied for 30 seconds. However, FDA

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proposed drug or its composition raises serious questions or safety or efficacy."); *see also* 21 C.F.R. § 314.94(a)(9)(v) ("Generally, a drug product intended for topical use . . . shall contain the same inactive ingredients as the reference listed drug . . .")

<sup>6</sup> Although Cardinal marketed Prevail® (providine iodine and alcohol) products in 59 ml and 40 ml volumes, these products are not in the relevant volume, 26 ml. Moreover, they do not contain the relevant ingredient combination, chlorhexidine gluconate and isopropyl alcohol. Importantly, these products were never evaluated or approved by FDA through the NDA or ANDA process. Rather, such products appear to be on the market through the over-the-counter monograph scheme, which does not require pre-approval.

deemed that study deficient as well because FDA believed the product should be applied for two minutes in accordance with the maximum time recommended by the label. As a result, Medi-Flex performed a second clinical trial supporting the safety of the new 26 ml volume. The exclusivity earned for this essential study applies to Cardinal's use of a 26 ml volume.

As described above, Medi-Flex earned three years of market exclusivity for the addition of a tint ingredient and use of a 26 ml volume applicator, which expires on May 3, 2008. Cardinal now seeks approval of a generic version of ChloroPrep® with Tint. However, FDA may not approve any ANDA for such a generic product, including Cardinal's ANDA 77-271, until the three-year exclusivity period has expired on May 3, 2008.

Through its investment and clinical trials, Medi-Flex cleared the way for other companies to develop generic products with tint and 26 ml volumes. Undoubtedly, Cardinal (and FDA) will have to rely on Medi-Flex's safety and efficacy studies for approval of its generic product. The innovations that Medi-Flex was required to study, i.e., the addition of a tint ingredient and an increased applicator volume, are the same innovations that Cardinal now seeks in its generic product. Cardinal's generic product faces the same safety and efficacy issues that Medi-Flex encountered, and Cardinal's ANDA will need to be supported with essential clinical data.<sup>7</sup> See 21 C.F.R. § 314.94(a)(9)(v) ("an abbreviated application may include different inactive ingredients provided that the applicant . . . provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product"). As Cardinal filed an ANDA rather than an NDA, it is evident that Cardinal has not conducted its own clinical trials.<sup>8</sup> Furthermore, as described below, FDA should rely, to the maximum extent possible, on the studies already conducted by Medi-Flex and information already reviewed by FDA. See Guidance for Industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (May 2005) at 2 (FDA will "consider factors such as use in previously approved products" when analyzing inactive ingredients). Thus, Medi-Flex's successful safety and efficacy studies for the addition of a tint ingredient and use of a 26 ml applicator support the approval of Cardinal's ANDA.

The three-year exclusivity earned by Medi-Flex for conducting its safety and efficacy studies applies to any ANDA that relies on those same studies for approval. See 21 C.F.R. § 314.108(b)(5) (applying three-year exclusivity to an ANDA that "relies on the information supporting a change approved in the supplemental new drug application") (emphasis added); and 21 U.S.C. § 355(c)(3)(E) (applying three-year exclusivity to 505(b)(2) applications that "relied

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<sup>7</sup> It would be arbitrary and capricious for FDA to hold Medi-Flex to a higher standard of approval than Cardinal by requiring Medi-Flex to provide clinical trial data for approval of a tint product in a 26 ml volume but not require Cardinal to provide such data, whether through original studies or by relying on Medi-Flex's studies. See 5 U.S.C. § 706(2)(A); *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 28 (D.D.C. 1997) ("The disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious.").

<sup>8</sup> It is also evident that other companies have not studied these essential issues. The statute grants exclusivity only to a "new" study, which means that the results of the study do not duplicate the results of previous studies relied on by FDA. 21 C.F.R. § 314.108(a). Medi-Flex received exclusivity for its "new" studies, indicating that there are no similar studies by other companies.

upon” the studies underlying the exclusivity). Although Cardinal improperly failed to designate ChloroPrep® with Tint as the RLD, Cardinal’s ANDA must rely on the essential clinical trial data supporting the changes approved in ChloroPrep® with Tint. Cardinal’s ANDA thus should be blocked from approval until the relevant exclusivity period has expired on May 3, 2008.

Furthermore, the three-year exclusivity associated with ChloroPrep® with Tint is not limited to those ANDAs that use ChloroPrep® with Tint as the RLD. The statutory provision governing three-year exclusivity does not limit the scope of exclusivity to an ANDA that references a specific RLD. Rather, the statute broadly prohibits the approval of those ANDAs that have been submitted for the change subject to exclusivity. Additionally, FDA stated that exclusivity should be interpreted broadly without respect to the specific RLD referenced in the ANDA. Abbreviated New Drug Application Regulations (Proposed Rule), 54 Fed. Reg. 28872, 28897 (July 10, 1989). According to that proposed rule, exclusivity delays the effective date of approval of any ANDA for the change subject to exclusivity “regardless of the specific listed drug product to which the ANDA or 505(b)(2) application refers.” *Id.* Thus, the three-year exclusivity associated with ChloroPrep® with Tint applies to Cardinal’s ANDA even though that ANDA relies on ChloroPrep® One-Step as the RLD.<sup>9</sup>

**(b) FDA Should Require Cardinal’s ANDA 77-271 to Rely on ChloroPrep® with Tint as the Reference Listed Drug and to Include Certifications to the Patents Listed for ChloroPrep® with Tint**

Cardinal appears to be trying to end-run Medi-Flex’s exclusivity and patent protection by referencing the wrong RLD and by certifying to the wrong patents. As detailed below, Cardinal seeks approval of a generic product with tint. Yet its ANDA uses the untinted ChloroPrep® One-Step as the RLD, instead of ChloroPrep® with Tint. By improperly using ChloroPrep® One-Step as the RLD, Cardinal certainly seems to be trying to game the system to avoid the exclusivity and patents listed with ChloroPrep® with Tint, specifically the Tint Patent.<sup>10</sup>

<sup>9</sup> The three-year exclusivity would apply to Cardinal’s ANDA even if the ANDA was submitted before exclusivity had been granted. Three-year exclusivity is not limited to those ANDAs submitted after exclusivity was awarded. Rather, it blocks any ANDA pending at the time exclusivity is granted. As explained by FDA with respect to 505(b)(2) applications, “Consequently, if two 505(b)(2) applications are under review at the same time and one is approved before the other, the effective date of approval of the second application to be approved will be delayed, regardless of the date of submission, if the first contained new clinical investigations essential for approval and thereby qualified for exclusivity.” Abbreviated New Drug Application Regulations (Proposed Rule), 54 Fed. Reg. 28872, 28901 (July 10, 1989). It is unclear when Cardinal submitted its ANDA for a tinted product in a 26 ml applicator. However, as in the case of FDA’s example, even if Cardinal had submitted its ANDA before exclusivity had been granted, Cardinal’s ANDA would still be blocked by the exclusivity because the ANDA is still pending.

<sup>10</sup> As Cardinal has been unwilling to share any information with Medi-Flex, it is unclear to us exactly when Cardinal submitted its ANDA for a generic tint product in a 26 ml applicator. Cardinal had not submitted its ANDA covering such a generic product by November 18, 2004, the date Cardinal submitted its Suitability Petition, because the Petition sought permission to file such an ANDA in the future. However, we know that the ANDA had been filed by August 29, 2005, the date on which Cardinal sent its first paragraph IV notification letter to Medi-Flex. The statute requires that letter to be sent within 20

The regulations define a “reference listed drug” or RLD as “the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application.” 21 C.F.R. § 314.3. Typically, there is one designated RLD for each product. FDA requires each generic version of a product to use the designated RLD for that product. *See* Orange Book at xi. As FDA has stated, “By designating a single reference listed drug as the standard . . . FDA hopes to avoid possible significant variations among generic drugs and their brand name counterpart.” *Id.*

In a recent letter, FDA explained the requirements for choosing a listed drug. 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) (“Letter”) (Tab 8). Although the letter concerned 505(b)(2) applications, the requirements are equally applicable to ANDAs. Letter at 8 (“This interpretation also treats ANDAs and 505(b)(2) applications comparably.”). Specifically, the letter states that the listed drug should be a pharmaceutical equivalent and, if there are none, that the “applicant should choose the listed drug or drugs that are most similar to the drug for which approval is sought.” Letter at 9. As indicated in the letter, an ANDA should choose the RLD that most closely matches its generic product.<sup>11</sup> According to FDA, this requirement ensures that the applicant and the FDA can rely, to the maximum extent possible, on information that is already known about a drug without having to re-prove and re-review information that has already been demonstrated. Letter at 9. Such a requirement also avoids ethical concerns associated with unnecessary duplicative testing. Furthermore, FDA stated that its requirement governing choosing a listed drug prevents an applicant from making an end-run around otherwise applicable patents. *Id.* As the patents most likely to cover a generic product are listed with the RLD that is most similar to the generic product, requiring an ANDA to reference the closest RLD prevents the ANDA applicant from circumventing the most relevant patents.<sup>12</sup>

Cardinal seeks approval of a generic chlorhexidine gluconate 2% and isopropyl alcohol 70% with tint product in a 26 ml applicator. As such, it should have chosen the RLD specifically designated for such a product. Medi-Flex’s Chloraprep® with Tint is the single RLD specifically designated by FDA for those products. Medi-Flex conducted several clinical trials to

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days of filing of the ANDA (21 U.S.C. § 355(j)(2)(B)(ii)). This indicates that the relevant ANDA covering Cardinal’s tint product in a 26 ml applicator was submitted after Chloraprep® with Tint had been approved. However, even if Chloraprep® with Tint was not available as an RLD at the time Cardinal’s ANDA was submitted, it became available soon after and should have been referenced by Cardinal. At the very least, Cardinal should have resolved the exclusivity and patent issues presented by the approval of Chloraprep® with Tint. Cardinal’s failure to resolve these important issues and, even now, failure to cooperate indicates an intent to circumvent the exclusivity and patents.

<sup>11</sup> Although a generic product is intended to be the same as the RLD product, a generic product may contain certain variations. For example, a generic product may vary inactive ingredients or incorporate changes approved through a suitability petition. *See* 21 C.F.R. §§ 314.93 and 314.94(a)(9). For the reasons explained in this Citizen Petition, it is particularly important that an ANDA for a generic product that varies from an RLD use the RLD that most closely matches the generic product.

<sup>12</sup> An ANDA applicant has a strong incentive to circumvent the most relevant patents because those patents are likely to delay approval of the ANDA by resulting in patent infringement litigation and potentially a 30-month stay of approval of the ANDA. *See* 21 U.S.C. § 355(j)(5)(B)(iii).

obtain approval of a product containing a tint ingredient and use of a 26 ml volume. Both Medi-Flex and FDA have already put forth the effort to demonstrate that the use of a tint ingredient does not affect efficacy and that the 26 ml volume is safe. As indicated in FDA's Letter, FDA and Cardinal should rely upon the studies conducted for ChloroPrep® with Tint to the maximum extent possible, and Cardinal should use ChloroPrep® with Tint as the RLD. Instead, Cardinal uses the untinted ChloroPrep® One-Step in a 10.5 ml applicator as its RLD and makes an end-run around the Tint Patent and exclusivity listed with ChloroPrep® with Tint.

Importantly, FDA stated that an ANDA applicant may not choose an RLD to circumvent patent protection. As explained by FDA:

[I]f a tablet and a capsule are approved for the same moiety with patents listed for the tablet and none listed for the capsule, an ANDA applicant seeking approval for a tablet should cite the approved tablet as the reference listed drug. It should not circumvent the patents on the tablet by citing the capsule as the reference listed drug and filing a suitability petition under section 505(j)(2)(C) of the Act and 21 CFR 314.93 seeking to change to a tablet dosage form.

Letter at 9 fn 13 (emphasis added).

Yet, like FDA's example, Cardinal has submitted an ANDA and a suitability petition for a generic product with tint in a 26 ml volume applicator, and appears to be trying to circumvent patent protection through its choice of RLD. Pursuant to FDA's patent listing requirements, Medi-Flex listed the Tint Patent only with respect to ChloroPrep® with Tint and not with respect to ChloroPrep® One-Step.<sup>13</sup> Cardinal certified only to those patents listed for its RLD, ChloroPrep® One-Step.<sup>14</sup> Thus, Cardinal has effectively avoided certifying to the one patent specifically directed to its generic tint product. To allow Cardinal to rely on ChloroPrep® One-Step as the RLD for its generic tint product while prohibiting Medi-Flex from listing the Tint Patent with that RLD would grossly distort the balance sought by the Hatch-Waxman Act and would thwart the Act's goal of creating a process for resolving patent disputes before marketing begins. *See Applications for FDA Approval to Market a New Drug; Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug is Invalid or Will Not be Infringed (Proposed Rule)*, 67 Fed. Reg. 65448 (Oct. 24, 2002) ("The act promotes competition by creating a process . . . for resolving challenges to patents before marketing begins."); *see also Marion Merrell Dow, Inc. v. Hoechst-Roussel Pharms., Inc.*, Civ. No. 93-5074, 1994 U.S. Dist. LEXIS 10024, 32 U.S.P.Q. 2d 1156 (D.N.J. 1994) (prohibiting a 505(b)(2) applicant for an extended release drug from circumventing patents by relying on the immediate release listed drug instead of the more appropriate extended release listed drug) (Tab 9).

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<sup>13</sup> See 21 C.F.R. § 314.53 (requiring an NDA applicant to list patents that claim the drug product for which the applicant submitted the NDA).

<sup>14</sup> See 21 C.F.R. § 314.94(a)(12) (requiring an ANDA applicant to certify each patent that claims the RLD).

Even if Cardinal were not required to use ChloroPrep® with Tint as its RLD, Cardinal should still be required to certify the Tint Patent.<sup>15</sup> As explained in FDA's Letter regarding 505(b)(2) applications, the statute requires certifications to patents listed "for the drug product relied on for approval" and that the regulations "reinforce this relationship between reliance and certification." Letter at 7. The same principle applies here, where the ANDA has avoided the appropriate RLD. *See id.* at 8. Medi-Flex conducted essential clinical trials for the approval of ChloroPrep® with Tint proving that the addition of a tint ingredient and use of a 26 ml volume do not affect safety or efficacy. Although Cardinal improperly failed to use ChloroPrep® with Tint as the RLD, and thus did not certify to the patents listed for that RLD, Cardinal's ANDA (and/or FDA's approval thereof) will undoubtedly rely on ChloroPrep® with Tint's clinical data. In light of FDA's recognition of the relationship between reliance and certification, Cardinal should be required to certify the patents listed for ChloroPrep® with Tint. In particular, Cardinal should certify to the Tint Patent, which is the patent that most likely covers its generic product.

Cardinal's choice of RLD also attempts to circumvent Medi-Flex's three-year exclusivity. Pursuant to FDA's regulations, Cardinal's ANDA must include a statement as to whether its choice of RLD is entitled to a period of market exclusivity, which FDA presumably relies upon in determining the date of approval for the ANDA. 21 C.F.R. § 314.94(a)(3)(ii). Cardinal improperly used ChloroPrep® One-Step, rather than ChloroPrep® with Tint, as its RLD. ChloroPrep® One-Step does not have any market exclusivity period, while ChloroPrep® with Tint earned a three-year period of market exclusivity. Thus, even though Cardinal's ANDA is for a generic version of ChloroPrep® with Tint and is blocked by the associated exclusivity period, Cardinal's ANDA did not identify that applicable exclusivity period to FDA. Without receiving such information, FDA may not be aware of the applicable exclusivity period and may make an approval decision contrary to that exclusivity.<sup>16</sup> Thus, Cardinal's choice of RLD seems designed to keep FDA in the dark about the applicable exclusivity period and to facilitate an approval contrary to that exclusivity period.

### 3. CONCLUSION

Cardinal's ANDA 77-271 may not receive approval until Medi-Flex's three-year exclusivity has expired on May 3, 2008. Medi-Flex invested significant resources to bring to market ChloroPrep® with Tint (chlorhexidine gluconate 2%, isopropyl alcohol 70%) in a 26 ml volume applicator. To obtain approval, FDA required Medi-Flex to conduct essential clinical studies demonstrating that the tint ingredient does not affect efficacy and that the 26 ml volume applicator is safe. Medi-Flex successfully completed those trials proving that its innovations were safe and effective. As a result, ChloroPrep® with Tint earned three-years of exclusivity. Medi-Flex believes that Cardinal is currently seeking approval of a generic version of

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<sup>15</sup> The other patents listed with ChloroPrep® with Tint are also listed with ChloroPrep® One-Step, and Medi-Flex received certifications for those patents in Cardinal's September 13, 2005 letter.

<sup>16</sup> If an ANDA were to fail to disclose applicable exclusivity due to its strategic choice of RLD and is subsequently approved, it would cause significant regulatory issues, as FDA would be required to withdraw approval for that ANDA.

ChloroPrep® with Tint. However, FDA may not approve any ANDA, including Cardinal's ANDA 77-271, for a generic version of ChloroPrep® with Tint until its exclusivity expires.

Furthermore, FDA should require Cardinal to use the proper RLD and to certify the proper patents. Cardinal's ANDA for a generic tinted product in a 26 ml applicator relies on ChloroPrep® One-Step, which is untinted and uses a 10.5 ml applicator, as its RLD. The FDA has designated ChloroPrep® with Tint as the RLD for generic products containing tint and a 26 ml volume. As such, FDA should require Cardinal to use ChloroPrep® with Tint as its RLD. By relying on ChloroPrep® One-Step as its RLD, Cardinal is circumventing those patents listed with ChloroPrep® with Tint. In particular, Cardinal should be required to certify to the Tint Patent, which is listed only with respect to ChloroPrep® with Tint. So far, Cardinal appears to be trying to make an end-run around the Tint Patent, which is the patent most likely to cover its generic product. FDA should not allow such a tactic to succeed.

### **C. ENVIRONMENTAL IMPACT**

The actions requested in this petition are subject to categorical exclusions under 21 C.F.R. § 25.31.

### **D. ECONOMIC IMPACT**

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

**E. CERTIFICATION**

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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