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Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Docket No. 2005P-0458
Comments of Cardinal Health Inc.

These comments are submitted on behalf of Cardinal Health Medical Products and Services ("Cardinal") in response to a Citizen Petition and a Petition for Stay of Agency Action filed by Medi-Flex, Inc. ("Medi-Flex"). In its Petitions, Medi-Flex requests that FDA require changes to, and impose an unwarranted delay in approval of, Cardinal's Abbreviated New Drug Application ("ANDA") No. 77-271 for a pre-surgical antiseptic skin preparation product that will compete in the market with Medi-Flex's ChloroPrep® line of products. The Petitions are based on two premises: (1) that the 3-year regulatory exclusivity granted to Medi-Flex's ChloroPrep® With Tint product precludes FDA approval of Cardinal's ANDA until May 2008; and (2) that Cardinal's ANDA references an incorrect Reference Listed Drug ("RLD"), specifically, Medi-Flex's ChloroPrep® One Step product. As shown below, Medi-Flex's Petitions are without merit, are blatantly and frivolously anticompetitive, and should promptly be denied.

BACKGROUND

On September 9, 2004 Cardinal submitted an ANDA for an antiseptic pre-surgical skin preparation product containing chlorhexidine gluconate 2% and isopropyl alcohol 70% in a 10.5 ml applicator. This product is identical to ChloroPrep® One Step in all material respects except that Cardinal's product is formulated with an additional inactive ingredient, FD&C Red No. 40, which makes the otherwise clear product solution more visible, both in the applicator tube and when applied to the skin. Cardinal's ANDA product is pharmaceutically and therapeutically equivalent to ChloroPrep® One Step, and at the time of Cardinal's ANDA submission ChloroPrep® One Step was the only RLD to which Cardinal's ANDA could possibly have referenced.¹

¹ As Medi-Flex notes in its Petition, Cardinal did submit a Suitability Petition seeking FDA permission to file an ANDA for a 26 ml product, but contrary to Medi-Flex's supposition, Cardinal is not currently pursuing approval of such a product.

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At the time of the submission of Cardinal's ANDA, there were no patents listed in the Orange Book in connection with ChloroPrep® One Step, and thus Cardinal's ANDA contained a Paragraph I Certification, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(I), stating that no patent information had been submitted to FDA by Medi-Flex in connection with that product. In fact, however, at the time of Cardinal's ANDA submission, there were patents that Medi-Flex had not submitted to FDA, but which Medi-Flex now claims cover ChloroPrep® One Step. *See* Cit. Pet. at 10. When those patents were belatedly submitted to FDA for listing in the Orange Book, Cardinal amended its ANDA to include Paragraph IV Certifications alleging that its product does not infringe the listed patents. Cardinal also submitted Paragraph IV Notifications to Medi-Flex pursuant to 21 U.S.C. § 355(j)(2)(B). Medi-Flex never filed any patent infringement action against Cardinal in response to the Paragraph IV Notifications. Because the patents were "late listed" by Medi-Flex (more than 30 days after the NDA was approved and the patents were issued), Cardinal subsequently withdrew its Paragraph IV Certifications pursuant to 21 C.F.R. § 314.94(a)(12)(viii).

On May 3, 2005, well after the filing of Cardinal's ANDA, Medi-Flex received FDA approval of a supplement to its ChloroPrep® One Step NDA (NDA No. 20-832/S-008) for a new higher volume (26 ml) product configuration, containing FD&C green No. 3 as a tint. This product is branded as ChloroPrep® with Tint. Medi-Flex submitted four (4) patents which are now listed in the Orange Book in connection with ChloroPrep® with Tint (but not in connection with ChloroPrep® One Step). FDA granted a 3-year "New Product" exclusivity to ChloroPrep® with Tint. Cardinal's product is neither pharmaceutically equivalent, nor therapeutically equivalent, to ChloroPrep® with Tint. *See* 21 C.F.R. § 320.1(c).

On November 14, 2005, Medi-Flex, through its attorneys, filed a Citizen Petition with FDA, accusing Cardinal of "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." Cit. Pet. at 1. Thus, Medi-Flex requests (1) that FDA refrain from approving Cardinal's ANDA until May 3, 2008, when the three-year exclusivity for ChloroPrep® with Tint expires, and (2) that FDA require Cardinal to amend its ANDA to refer to ChloroPrep® with Tint, instead of ChloroPrep® One Step, as the relevant RLD for the ANDA. On December 23, 2005, Medi-Flex filed a Petition for Stay of Agency Action (the "Stay Petition") that repeated the substantive arguments of the Citizen Petition and requested that FDA stay approval of Cardinal's ANDA until the Agency rules on the Citizen Petition. Medi-Flex requested a decision on the Stay Petition by January 20, 2006, and has threatened to sue FDA if such a decision is not granted. These comments respond to both the Citizen Petition and the Stay Petition, and demonstrate why both Petitions should be denied.

ANALYSIS

Medi-Flex makes two arguments against approval of Cardinal's ANDA: (1) that the 3-year exclusivity granted to ChloroPrep® with Tint prevents approval of an ANDA for any tinted chlorhexidine gluconate/isopropyl alcohol skin preparation product until May 2008, even if such product uses a different tint than ChloroPrep® with Tint; and (2) that Cardinal's ANDA is

required to make reference to ChloroPrep® with Tint, and not to ChloroPrep® One Step. Both of Medi-Flex's arguments are unsustainable.

I. THE 3-YEAR EXCLUSIVITY GRANTED FOR CHLORAPREP® WITH TINT DOES NOT BLOCK APPROVAL OF CARDINAL'S ANDA

Medi-Flex argues that FDA may not approve Cardinal's ANDA until the 3-year exclusivity granted for ChloroPrep® with Tint expires on May 3, 2008. Medi-Flex's position is based, at least expressly, on the erroneous assumption that Cardinal's ANDA seeks approval of a tinted 26 ml product. Because Cardinal's product does not seek approval of such a product, the only way Medi-Flex's exclusivity could block approval of Cardinal's ANDA is if the exclusivity covers *any size* product that contains *any tint* (not just FD&C Green No. 3, as studied by Medi-Flex). As shown below, because such a position has no legal or factual support, Medi-Flex's exclusivity does not block immediate FDA approval of Cardinal's ANDA.

A. The Governing Statutory and Regulatory Provisions

The FDCA provides for a 3-year period of market exclusivity for certain drug products under certain conditions. Specifically relevant here, section 505(j)(5)(F)(iv) provides a 3-year exclusivity that protects a specific change to a previously approved drug, where that change required new clinical studies as a condition of approval:

If a supplement to an [NDA]...contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement...the Secretary may not make the approval of an [ANDA]...for a change approved in the supplement effective before the expiration of three years from the date of the approval of the [NDA] supplement....

21 U.S.C. § 355(j)(5)(F)(iv) (emphasis added). FDA has implemented this provision by regulation as follows:

If a supplemental application...contained reports of new clinical investigations (other than bioavailability studies)...that were essential to the approval of the supplemental application, the agency will not make effective for a period of 3 years after the date of approval of the supplemental application the approval of...an [ANDA] for a change...approved in the supplemental new drug application.

21 C.F.R. § 314.108(b)(5) (emphasis added).

**B. The ChloroPrep® with Tint Studies,
Approval, and FDA Exclusivity Award**

Medi-Flex received approval of an sNDA for two contemporaneous changes to its ChloroPrep® One Step product – an increase in volume from 10.5 ml to 26 ml, and the addition of FD&C Green No. 3 as a tinting agent. Medi-Flex conducted a safety study to support the increased volume, and a separate study to demonstrate that the use of FD&C Green No. 3, embedded in the applicator sponge (pledget) did not reduce the efficacy of the product. FDA subsequently granted a 3-year “new product” exclusivity to ChloroPrep® with Tint. The scope of that exclusivity is not made clear in the FDA’s Orange Book, but there are four possible interpretations:

- The exclusivity could be interpreted to apply to ANDAs for a product that *combines both* a 26 ml applicator volume and FD&C Green No. 3 as a tinting agent. As such, the exclusivity would not prevent immediate FDA approval of Cardinal’s ANDA, which does not incorporate both (indeed includes neither) a 26 ml volume or an FD&C Green No. 3 tint.
- Alternatively, the exclusivity could apply to ANDAs for products that *combine both* a 26 ml volume and the use of *any* tinting agent. Here again, Cardinal’s ANDA would not be affected, since it does not incorporate the 26 ml volume element.
- Third, the exclusivity could be interpreted to apply separately to ANDAs for any 26 ml product, or the use of FD&C Green No. 3 as a tint in any size product. Again, since Cardinal’s product has neither a 26 ml volume, nor FD&C Green No. 3 tint, it would not be affected by exclusivity.
- Finally, Medi-Flex advocates that the exclusivity separately covers any 26 ml product, or any product size that uses any tint whatsoever.

Not surprisingly, Medi-Flex latches onto and advocates for the only (and arguably least plausible) of the four possible exclusivity interpretations that would protect it from market competition from Cardinal. Under no scenario can any exclusivity on a 26 ml product block Cardinal’s 10.5 ml product, so the only way for Medi-Flex to receive any exclusivity against Cardinal’s ANDA is if Medi-Flex’s exclusivity covers the use of any tinting agent in any size product. Thus, the remainder of this section addresses why Medi-Flex’s exclusivity with respect to tinting (if it properly exists at all²) must be limited to products that use FD&C Green No. 3, and why Cardinal’s FD&C Red No. 40 product is not blocked by Medi-Flex’s exclusivity.

² In fact, as discussed below, based on the study conducted to evaluate Medi-Flex’s use of green tint, Medi-Flex is ineligible for exclusivity for the use of a green, or any other color, tint in ChloroPrep® with Tint.

C. **Any Tint-Based Exclusivity Does Not Block Approval of Cardinal's ANDA**

1. **Cardinal's ANDA Does Not Seek Approval of A Change Approved For ChloroPrep® with Tint**

Medi-Flex conducted a 20-subject study of ChloroPrep® with Tint versus an untinted version to confirm that the addition of FD&C Green No. 3 as a tinting agent created a product with equivalent efficacy to an untinted product. Thus, assuming, *arguendo*, that this study qualifies as a new “clinical trial” and that it was properly deemed “essential to the approval” of ChloroPrep® with Tint, a 3-year exclusivity period may apply so that FDA must delay approval of any ANDA product that seeks approval of the same change – i.e., the addition of FD&C Green No. 3 as a tint. Medi-Flex, however, argues for a much broader applicability of any such exclusivity by claiming that FDA must delay approval of ANDAs for competing skin preparation products that use *any* other tinting agent(s). Specifically, Medi-Flex claims that

Medi-Flex's studies [sic: study] 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.

Petition at 6.

Medi-Flex's position is unfounded because it appears to proceed from the mistaken premise that the efficacy question posed and answered by its study was whether the *functional tinting effect* of any inactive ingredient alters the clinical efficacy of the product.³ That is simply not the case. First, nothing in the ChloroPrep® with Tint approved labeling describes the function of the green tint, nor any clinical advantage of the tint *vis á vis* an untinted product. Indeed, no clinical benefit has ever been proven for the tint in ChloroPrep® with Tint. Moreover, if Medi-Flex's study had been designed to test whether the *function* of tinting its product altered its efficacy, the study would have had to test whether a tinted product aided surgeons in assuring more complete skin coverage than an untinted product, thus reducing the risk of infection due to undetected untreated areas of the patient's skin. Such a study would require testing of multiple skin sites per patient (and the inclusion of far more than 20 test subjects to achieve statistical significance) to determine whether some sites were missed with untinted product that were not missed as a result of using a tinted product. However, that is not the study Medi-Flex conducted.

Rather, FDA requested a study designed in accordance with the procedures for dry surgical sites as outlined in the Tentative Final Monograph for Health Care Antiseptic Drug Products. *See* FDA Comments to NDA No. 20-832/S-008 (September 3, 2004) (at Tab 2 of Citizen Petition); 59 Fed. Reg. 31402 (Tentative Final Monograph, June 17, 1994). Thus, Medi-

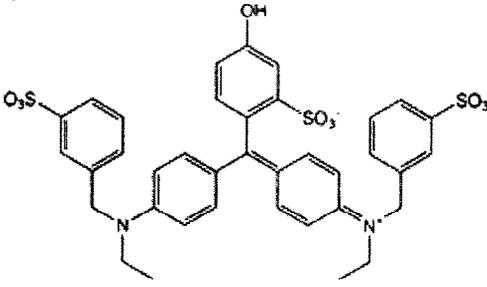
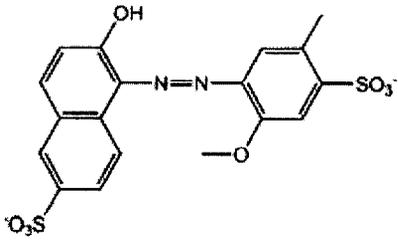
³ *See, e.g.*, Declaration of James R. Majerle, accompanying Medi-Flex's Stay Petition, at ¶ 4 (stating that “This tint colors the product so that the user may quickly determine previously treated areas.”).

Flex was asked to study whether the addition of the specific tint FD&C Green No. 3 altered the physiological bacterial reductions in a single skin test site for each patient. *See* 59 Fed. Reg. 31402 at 31451 (proposed 21 C.F.R. § 333.470(b)(3)(I)(1) (specifying sampling procedure). Under the design of the requested Medi-Flex study, the most that could possibly have been evaluated was whether the specific chemical properties of FD&C Green No. 3 altered the antiseptic properties of chlorhexidine gluconate and isopropyl alcohol compared to an untinted ChloroPrep® product. Because this – the specific addition of FD&C Green No. 3 – is the “change” for which Medi-Flex was asked to conduct its study, Cardinal’s use of FD&C Red No. 40 cannot be considered the “same change” for purposes of applying a 3-year exclusivity period to delay approval of Cardinal’s ANDA.

Moreover, Medi-Flex’s position that its approval covers the use of *any* tint is discredited by the express terms of FDA’s approval letter for ChloroPrep® with Tint, which states, “This supplemental new drug application proposes a newly-designed applicator with a sponge-tip (pledget) applicator impregnated with FD&C Green No. 3 dye for preoperative skin preparation.” ChloroPrep® with Tint Approval Letter, available at <http://www.fda.gov/cder/foi/appletter/2005/020832s008ltr.pdf> (emphasis added). If Medi-Flex’s sNDA and associated exclusivity actually covered products that used any tint (including as in Cardinal’s case an alternative tint in the drug solution itself, as opposed to impregnated in the pledget), FDA’s approval letter certainly would not have been so narrowly tailored as to describe approval only for the use of FD&C Green No. 3 in Medi-Flex’s unique sponge-tip applicator.

Medi-Flex’s position is also unfounded because it presumes, without any medical or legal bases, that proving the efficacy of one inactive ingredient in a general class (e.g., tints) automatically proves the efficacy of all other members of that class. Chemically different inactive ingredients can have significantly different effects on the efficacy (or safety) of a product in which they are used, even where the chemical differences are seemingly small. Medi-Flex and FDA agree on this point. *See* Cit. Pet. at 5-6, n. 5 (citing 21 C.F.R. § 314.127(a)(8) for the well-founded proposition that individual inactive ingredients can pose unique efficacy and safety concerns). Thus, there is no scientifically sound basis to extrapolate the efficacy of one ingredient to the efficacy of a different ingredient.

In this case, there are in fact substantial chemical differences between FD&C Green No. 3 and FD&C Red No. 40 that could impact the efficacy of a product. These differences disprove Medi-Flex’s theory that the efficacy of FD&C Red No. 40 was proven by Medi-Flex’s study, and that use of Red No. 40 should therefore be considered to be the “same change” as Medi-Flex’s use of FD&C Green No. 3 for exclusivity purposes. Several chemical differences between the two tints are summarized in the table below:

	FD&C Green No. 3	FD&C Red No. 40
Chemical Structure	<p>a disodium salt of <i>N</i>-ethyl-<i>N</i>-[4-[[4-ethyl[(3-sulfophenyl)methyl]amino]phenyl](4-hydroxy-2-sulfophenyl)methylene]-2,5-cyclohexadien-1-ylidene]-3-sulfobenzenemethanaminium hydroxide.</p>  <p>The structure shows a central cyclohexadiene ring with a double bond to a methanaminium group (N-ethyl-N-(4-sulfophenyl)methyl) and a double bond to a methylene group. This methylene group is further substituted with a 4-hydroxy-2-sulfophenyl group and a 4-ethylamino group (via a 4-ethylaminophenyl ring).</p>	<p>a disodium salt of 6-hydroxy-5-[(2-methoxy-5-methyl-4-sulfophenyl)azo]-2-naphthalenesulfonic acid.</p>  <p>The structure shows a naphthalene ring system with a hydroxyl group at position 6 and a sulfonate group at position 2. At position 5, there is an azo group (-N=N-) connected to a 2-methoxy-5-methyl-4-sulfophenyl ring.</p>
Acid or base?	Basic	Acidic
Molecular weight	808.85 g/mole	496.42 g/mole

Thus, notwithstanding Medi-Flex's absurd "all tints are the same" argument, the differential effects of FD&C Green No. 3 and FD&C Red No. 40 on the efficacy of a chlorhexidine/alcohol skin preparation product were not established by Medi-Flex's study. While Cardinal expects that these and any other differences between FD&C Green No. 3 and FD&C Red No. 40 will not ultimately affect the efficacy of Cardinal's product, the answer to that question cannot in any way be determined based upon Medi-Flex's studies on FD&C Green No. 3. Indeed, the narrow nature of the question presented and answered by the Medi-Flex tint study is reflected by the fact that FDA required Cardinal to conduct its own comparative bioequivalence tests as between its tinted product and the untinted RLD, ChlorPrep® One Step, to specifically confirm that the addition of FD&C Red No. 40 does not alter the antiseptic efficacy of Cardinal's product. If Medi-Flex's "all tints are the same" theory was correct, FDA would not and could not require such a study by Cardinal.⁴

Furthermore, it is significant to note that FD&C Red No. 40 has been used for many years in approved topical antiseptic chlorhexidine products, including Hibiclens (chlorhexidine gluconate 4%). Despite this long-term approved effective use of Red No. 40 in a similar product, FDA did not consider that use to prove the efficacy of FD&C Green No. 3 in

⁴ Moreover, the absurdity of Medi-Flex's theory is that it has no logical or scientific bounds, and would require FDA to accept Medi-Flex's study as proving the efficacy of any and all other tinting agents including, for example, human or animal blood, and banned color additives such as lead chromate, copper sulfate, or coal tar dyes.

ChloroPrep® with Tint. Thus, FDA required Medi-Flex to conduct its study on FD&C Green No. 3 prior to approval of ChloroPrep® with Tint. This further disproves Medi-Flex's "all tints are the same" theory, because if (as Medi-Flex erroneously claims) a study on Green No. 3 was sufficient to prove the efficacy of Red No. 40, then the proven efficacy of Red No. 40 in Hibiclens would have made Medi-Flex's Green No. 3 studies not "essential" to approval of ChloroPrep® with Tint.

It is also worth noting that any grant of 3-year exclusivity that covers Medi-Flex's use of FD&C Green No. 3 tint (or any tint, under Medi-Flex's expansive interpretation) is of doubtful validity. The study conducted by Medi-Flex, while characterized as a new clinical study, in fact is nothing more than a comparative bioequivalence study with an efficacy endpoint. *See* 21 C.F.R. § 320.24(b)(4). Bioequivalence and bioavailability studies do not qualify a product for 3-year exclusivity. 21 C.F.R. § 314.108(a). Thus, Cardinal respectfully requests that FDA clarify that the scope of Medi-Flex's exclusivity is, at most, limited to products containing 26 ml of the active ingredients in the ChloroPrep® line of products.

2. Zeneca v. Shalala Does Not Preclude Immediate Approval of Cardinal's ANDA

In light of the foregoing, Medi-Flex's tortured effort to distinguish the facts and result in *Zeneca v. Shalala* falls flat. In that case, Zeneca obtained sNDA approval and 3-year exclusivity for a new version of Diprivan® (propofol), an injectable anesthetic drug, that included the preservative EDTA. FDA required Zeneca to conduct clinical studies on the *safety* of this EDTA-preserved product. As Medi-Flex notes in its Petition, FDA did identify specific concerns about the use of EDTA in this product – specifically, concerns related to EDTA's known effects on essential minerals in the body – that precipitated the request for clinical safety studies. Zeneca's studies thus were only required to address this safety concern. Zeneca did not study whether the general use of preservatives in propofol, as a functional matter, posed a safety concern. Thus, when a generic competitor, Gensia Sicor, successfully developed a competing propofol product using sodium metabisulfite as a preservative, FDA did not consider Gensia Sicor's product to fall within the scope of Zeneca's exclusivity. Because Zeneca's EDTA studies were irrelevant to the safety and efficacy of Gensia Sicor's sodium metabisulfite product, the "change approved" in Zeneca's sNDA and for which it was entitled to exclusivity, was only the addition of the specific preservative EDTA. The court upheld this determination. *See Zeneca v. Shalala*, 1999 U.S. Dist. LEXIS 12327 at *38 (D. Md. Aug. 11, 1999).

The same analysis must apply here, even if, as Medi-Flex argues, FDA did not specifically *identify* a particular efficacy concern with FD&C Green No. 3. Because FDA required an *efficacy-endpoint* study for the addition of FD&C Green No. 3, the Agency obviously had some concern, even if based on the lack of specific information, that this ingredient could alter the efficacy of the drug product. Indeed, all efficacy-based studies for new drugs are based on a generalized, non-specific concern that a particular product's efficacy cannot be assumed but must be proven through appropriate trials. Because Cardinal is proposing the use of a different tinting agent, Medi-Flex's study on FD&C Green No. 3 does not demonstrate the

efficacy of FD&C Red No. 40, and its exclusivity cannot apply generally to all tints, or to FD&C Red No. 40 in particular.

In summary, any ChloroPrep® with Tint exclusivity covering the 26 ml strength cannot apply to delay approval of Cardinal's 10.5 ml product. Moreover, any exclusivity that may apply to the tint aspect of ChloroPrep® with Tint must be narrowly construed to apply only to the use of FD&C Green No. 3, and therefore cannot delay approval of Cardinal's product with FD&C Red. No. 40.

II. CARDINAL'S ANDA PROPERLY REFERENCES CHLORAPREP® ONE STEP

Medi-Flex also argues that Cardinal's ANDA must identify ChloroPrep® with Tint (26 ml applicator), and not ChloroPrep® One Step, as the Reference Listed Drug. Here too, Medi-Flex is incorrect, as FDA itself specifically determined in accepting Cardinal's ANDA for review.

A. The Governing Statutory and Regulatory Provisions

Under the FDCA, an ANDA must include "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new [generic] drug have been previously approved for a drug listed" in the Orange Book. 21 U.S.C. § 355(j)(2)(A)(i) (emphasis added). FDA identifies certain NDA-approved drugs as "Reference Listed Drugs" for purposes of ANDA reference. There may be multiple similar RLDs that could be referenced in an ANDA, and indeed each strength (volume) of ChloroPrep® One Step and ChloroPrep® with Tint are listed as separate RLDs in FDA's Orange Book. However, when Cardinal submitted its ANDA, ChloroPrep® with Tint had not yet been approved, and thus the only possible RLD to which Cardinal's ANDA could have referred was ChloroPrep® One Step. As shown below, Cardinal's reference to ChloroPrep® One Step was not only proper at the time it was made, it remains proper notwithstanding the intervening approval of ChloroPrep® with Tint.⁵

An ANDA not only must identify an RLD for which the proposed conditions of use of its generic product have previously been approved, the ANDA must also demonstrate that the proposed generic drug is "pharmaceutically equivalent" to the RLD – i.e. that it is the "same" as the chosen RLD with respect to active ingredient(s), strength, dosage form, and route of administration. 21 U.S.C. § 355(j)(2)(A)(ii)-(iii). Generic drugs generally may use different inactive ingredients (such as tints). In addition, an ANDA must show that the generic drug is bioequivalent to, and has the same labeling as, the reference listed drug referred to in the ANDA.

⁵ The timing of Cardinal's ANDA – prior to the approval and listing of ChloroPrep® with Tint – demonstrates the falsity of Medi-Flex's hyperbolic charges that Cardinal "seems to be trying to game the system" and "trying to end-run Medi-Flex's exclusivity and patent protection by referencing the wrong RLD and by certifying to the wrong patents." Pet. at 8. Medi-Flex claims ignorance as to the date of Cardinal's ANDA submission, but argues, in a footnote necessarily devoid of legal substantiation, that "even if ChloroPrep® 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." Pet at 9, n. 10.

21 U.S.C. § 355(j)(2)(A)(iv)-(v). By demonstrating “sameness” in these respects, FDA is able to conclude, without new duplicative clinical safety and efficacy data (but possibly based on bioequivalence studies), that the proposed generic product will be as safe and effective as the identified RLD for its intended use.

B. The Differences Between ChloraPrep® With Tint and Cardinal’s Product Preclude Use of ChloraPrep® With Tint as an RLD for Cardinal’s ANDA

The foregoing sameness requirements as between an RLD and a proposed generic drug are important here because Cardinal’s product is the same as ChloraPrep® One Step in all respects relevant to the filing of an ANDA, but is materially different than ChloraPrep® with Tint in several respects. The differences between the three products at issue are illustrated in the following table.

	Strength (Volume)	Tint	Location of tint
Cardinal Product	10.5 ml	FD&C Red No. 40	In the active ingredient solution
ChloraPrep® One Step	10.5 ml	None	n/a
ChloraPrep® with Tint	26 ml	FD&C Green No. 3	Embedded in applicator assembly; solution tinted during use

1. Cardinal’s Product Is Pharmaceutically Equivalent To ChloraPrep® One Step But Is Not Pharmaceutically Equivalent to ChloraPrep® With Tint.

As Medi-Flex acknowledges, an ANDA should reference an RLD that is a pharmaceutical equivalent to the proposed generic drug. Pet. at 9. Here, the only pharmaceutically equivalent RLD that Cardinal can possibly refer to is ChloraPrep® One Step. “Pharmaceutical equivalents” are defined in FDA regulations as “drug products in identical dosage forms that contain the same amounts of the identical active drug ingredient, i.e.,...that deliver identical amounts of the active drug ingredient over the identical dosing period; [and] do not necessarily contain the same inactive ingredients....” 21 C.F.R. § 320.1(c) (emphases added). The Orange Book defines pharmaceutical equivalents as follows:

Pharmaceutically equivalent drug products are formulated to contain the same amount of active ingredient in the same dosage form and to meet the

same compendial or other applicable standards (i.e., strength, quality, purity, and identity), but they may differ in characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and, within certain limits, labeling.

APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, at vii (25th Ed., 2005) (emphasis added).

Here, Cardinal's product is pharmaceutically equivalent to ChloroPrep® One Step, but is not pharmaceutically equivalent to ChloroPrep® with Tint. This is because Cardinal's 10.5 ml product does *not* contain or deliver identical amounts of the active ingredients as Medi-Flex's 26 ml ChloroPrep® with Tint product, but does contain and deliver the same amount of drug as ChloroPrep® One Step. Moreover, the fact that Cardinal's product includes an inactive tint ingredient does *not* render it pharmaceutically *inequivalent* to ChloroPrep® One Step, nor does it make it pharmaceutically equivalent to ChloroPrep® with Tint. *See Id.* Thus, Cardinal's ANDA did, and does, reference the only proper RLD.

2. Cardinal's Product Will Have Materially Identical Labeling As ChloroPrep® One Step But Significantly Different Labeling Than ChloroPrep® With Tint

In addition, as noted above, a generic ANDA product is required to use the "same" labeling as the RLD identified in the ANDA, 21 U.S.C. § 355(j)(2)(A)(v), except for changes required because the drugs are produced or distributed by different manufacturers. 21 C.F.R. § 314.94(a)(8)(iv). Such labeling differences may include those required by different expiration dates, formulation, bioavailability or other pharmacokinetic properties, labeling changes necessary to comply with FDA labeling or other guidance, and labeling changes to omit labeling protected by patent(s) or exclusivity. *Id.* Here, the labeling for ChloroPrep® with Tint includes several elements that are not included in the labeling for ChloroPrep® One Step and which could not be included in Cardinal's labeling once approved. These additional labeling statements for ChloroPrep® with Tint include:

- The warning: "Solution contains alcohol and gives off flammable vapors while drying – allow to dry 3 minutes on skin." (Emphasis added) (ChloroPrep® One Step and Cardinal's product have no drying time warning).
- The bolded Direction: "**Maximal treatment area for one applicator is approximately 1126 cm² (approx. 13.2 in. x 13.2 in.)**." (ChloroPrep® One Step and Cardinal's product have a maximal treatment area of 457 cm²).
- The bolded Direction: "Allow the area to air dry for approximately **three (3) minutes**." This statement is repeated in the Directions for both dry and wet surgical site procedures. (ChloroPrep® One Step and Cardinal's product instruct to allow drying for 30 seconds).

Thus, if Cardinal were to use ChloroPrep® with Tint as the RLD, it would be required to modify its labeling substantially (although it would be permissible to do so, absent a more appropriate RLD). In contrast, using ChloroPrep® One Step as the RLD does not require any substantive changes to the Cardinal labeling – the only changes would be to the manufacturer information, and to list FD&C Red. No. 40 as an inactive ingredient. As FDA explained in the preamble to the original proposed regulations implementing the ANDA provisions of Hatch-Waxman, an ANDA must “show that the conditions of use, which include, among other things, indications and dosage instructions for which the applicant is seeking approval, have been previously approved for the reference listed drug.” 54 Fed. Reg. 28872, 28881 (Proposed Rule, July 10, 1989) (emphasis added). The fact that the dosage instructions (e.g. maximal coverage area and drying time warning and directions) for ChloroPrep® One Step are identical to Cardinal’s labeling, and that the ChloroPrep® with Tint dosage instructions are not the same as those for Cardinal’s product, further supports that ChloroPrep® One Step is the only proper RLD for Cardinal’s ANDA.

3. The Intervening Approval Of ChloroPrep® With Tint Does Not Make ChloroPrep® One Step An Inappropriate RLD For Cardinal’s ANDA

Even if ChloroPrep® with Tint 26 ml had been approved as an RLD at the time of Cardinal’s ANDA filing (which it was not), Cardinal would have been, and would remain, perfectly justified in referencing only ChloroPrep® One Step. FDA’s governing regulation, 21 C.F.R. § 314.101(d)(3) makes clear that where there is more than one RLD to which an ANDA may refer, the ANDA may properly refer to either of two (or more) RLDs. Specifically, the regulation states that an ANDA “must refer to a listed drug. Ordinarily, that listed drug will be the drug product selected by the agency as the reference standard for conducting bioequivalence testing.” 21 C.F.R. § 314.94(a)(3) (emphasis added).⁶ By its terms, this regulation contemplates and permits the filing of an ANDA that refers to “a” listed drug, not any particular listed drug, and thus permits reference to one RLD, even if reference to a different RLD might also be possible. Moreover, there is no legal basis for FDA to require an applicant to change the RLD identified in its ANDA at the time of submission, even if other potential RLD products are approved after submission of the ANDA.

In addition, FDA has recognized that in some situations, there may be multiple RLDs that differ only by strength. “In these circumstances, FDA considers each strength to represent a different drug product and will require an ANDA applicant to demonstrate that each proposed drug product is bioequivalent to its corresponding reference listed drug.” 57 Fed. Reg. 17950, 17954 (Final Rule, April 28, 1992). For these purposes, the term “strength” “refers to the amount of the product’s active ingredient. . . .” *Id* at 17956 (emphasis added). Here, ChloroPrep® with Tint is approved only in a 26 ml strength, whereas ChloroPrep® One Step and

⁶ In the preamble to the original proposed regulations implementing the ANDA provisions of Hatch-Waxman, FDA explained that “an applicant may submit an ANDA for a drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug, so long as its submission is not precluded by exclusivity.” 54 Fed. Reg. 28872, 28877 (July 10, 1989) (emphasis added).

Cardinal's product are 10.5 ml strength products. Each is listed as an RLD, and thus the only legal and logical choice for Cardinal's 10.5 ml ANDA was, and is, to reference ChloroPrep® One Step due to the more complete identity of those two products.⁷

For the foregoing reasons, Medi-Flex's exclusivity does not block immediate approval of Cardinal's ANDA, and that ANDA properly references ChloroPrep® One Step as the Reference Listed Drug. Accordingly, Medi-Flex's Citizen petition must be denied.

III. MEDI-FLEX'S STAY PETITION SHOULD BE DENIED

On December 23, 2005, as a follow-on to its Citizen Petition, Medi-Flex filed a Petition for Stay of Agency Action in which it requested that FDA stay approval of Cardinal's ANDA No. 77-271 until FDA rules on Medi-Flex's Citizen Petition. Medi-Flex requested a decision on its Stay Petition by January 20, 2006, based upon the belief that FDA might approve Cardinal's ANDA before issuing a response to Medi-Flex's Citizen Petition. As discussed below, Medi-Flex's Stay Petition should also be denied.

Medi-Flex's Stay Petition includes sections tracking each of the regulatory criteria for a Stay of Action, arguing (1) that Medi-Flex will suffer irreparable harm without a stay, (2) that its Petition is not frivolous and was filed in good faith, (3) that the requested stay is supported by sound public policy grounds, and (4) that the public interest would not be outweighed by a stay. However, Medi-Flex's boilerplate arguments under each of those criteria are fatally flawed for the basic reason that Medi-Flex is simply and completely wrong on the merits of its Citizen Petition. Because there is no substantive basis for FDA to delay or deny the approval of Cardinal's ANDA, as requested in the Citizen Petition, there is no procedural basis for FDA to stay such approval under the Stay Petition. More specifically,

- Medi-Flex has no exclusivity or patent rights as against Cardinal, and thus has no right to be protected from the rigors of free-market competition with Cardinal; Any amount of lost sales from such lawful competition is not "irreparable harm" for purposes of a stay of approval;
- Regardless of whether the Stay Petition is frivolous or was filed in good faith, it is, in fact, based on erroneous assumptions of fact and incorrect theories of law, and thus may not be granted;

⁷ We note that Medi-Flex is marketing a tinted ChloroPrep® product in a 10.5 ml strength, even though neither the electronic Orange Book, nor FDA's drug approval web site, "Drugs@FDA," reflects that such a product has ever received approval. See <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchDrugDetails> www.drugs@FDA.gov (January 20, 2006). Even if such a 10.5 ml product were to eventually receive approval, there would be no basis at this late date to require Cardinal to change the RLD identified in its ANDA, because Cardinal obviously did not need to rely upon approval of such a product in support of its ANDA.

- There is no legal or public policy basis for granting Medi-Flex's Citizen Petition, and thus there is no sound basis for granting the Stay Petition; and
- The public interest in prompt access to Cardinal's product far outweighs Medi-Flex's self-serving, anti-competitive, and legally baseless interest in obtaining a stay of approval of Cardinal's ANDA.

In addition, Cardinal takes umbrage at Medi-Flex's "David and Goliath" metaphor for why a stay is appropriate, and particularly Medi-Flex's apparent belief that Cardinal's role as a distributor of Medi-Flex products somehow precludes Cardinal from participating fully in this country's free market economy. *See* Stay Pet. At 5-7. Indeed, as a self-described "entrepreneurial" company, (Stay Petition at 2, n. 1), one would think Medi-Flex would abhor the type of anti-competitive "corporate welfare" policy it advocates in its petitions. Neither the fact that Cardinal is relatively larger than Medi-Flex, nor anything in the Medi-Flex-Cardinal business relationship, disqualifies Cardinal from developing and selling competing products that differ from, and are not covered by the exclusivity for, the ChloroPrep® line of products, regardless of the alleged free-market economic impact on Medi-Flex. Such competition does not qualify as "irreparable harm."

It should also be noted that Medi-Flex's hypotheses as to the market impact of a Cardinal launch are wholly speculative and overstated in the extreme. Perhaps there will be price pressures on both Medi-Flex and Cardinal (which would benefit the public), but perhaps there will be continued demand for a green-tinted product as opposed to a red-tinted product, and Medi-Flex's sales will remain strong. There is also no basis to assume that Cardinal will discontinue distribution of the Medi-Flex product upon approval of the Cardinal ANDA. Such decisions are based on sound business considerations, including market conditions and product demand, and not on whether Cardinal offers a competing product. Indeed, Medi-Flex's doom-and-gloom hypothesis reflects ignorance of Cardinal's business model, which is based on providing customers with a wide variety of options in all product classes. This is reflected by the fact that Cardinal distributes thousands of different medical/surgical products from at least 2,600 other manufacturers,⁸ including the concomitant distribution of many products from other companies even where Cardinal itself offers its own version of the same product. In fact, for almost every product Cardinal self-manufactures, it continues to distribute competing products from other companies. Thus, approval of Cardinal's ANDA is not nearly the threat that Medi-Flex makes it out to be.

Finally, it is hypocritical for Medi-Flex to allege irreparable personal and public harm when the mere filing of its Petitions has already damaged Cardinal and harmed the public interest in free-market competition for this class of products, by introducing an additional delay-inducing layer of administrative burden on FDA. Rather than waste time answering Medi-Flex's baseless Petitions, FDA staff could (and should) be spending time addressing the many real crises facing

⁸ *See* <http://www.cardinal.com/businesses/mps/>.

American consumers, such as drug safety issues, enforcement against unapproved and fraudulent products, and review and approval of other life-saving innovative drugs and money-saving generic equivalents.

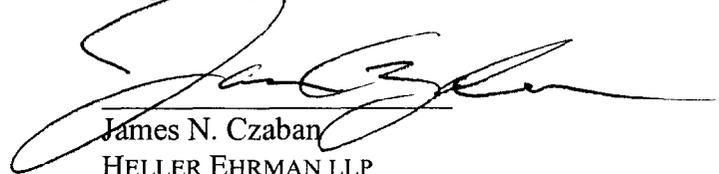
If Medi-Flex has any real concern for the public interest, it would withdraw its frivolous anti-competitive petitions, and we call upon Medi-Flex to do so immediately.

* * *

CONCLUSION

For the reasons discussed hereinabove, Medi-Flex's Citizen Petition and Stay Petition should both be denied, and Cardinal's ANDA should be approved without delay.

Respectfully submitted,



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