IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

Hospira, Inc. 275 N. Field Drive Lake Forest, IL 60045,	*	
Plaintiff,	*	
v.	*	CIVIL ACTION NO.
Sylvia Mathews Burwell, Secretary U.S. Department of Health and Human Services 200 Independence Ave., SW Washington, D.C. 20201, and	*	
Dr. Margaret Hamburg, Commissioner U.S. Food and Drug Administration 10903 New Hampshire Ave. Silver Spring, MD 20993,	*	
U.S. Food and Drug Administration 10903 New Hampshire Ave. Silver Spring, MD 20993,	*	
Defendants.		

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MEMORANDUM IN SUPPORT OF MOTION FOR TEMPORARY RESTRAINING ORDER AND/OR PRELIMINARY INJUNCTION

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Introduction

Plaintiff Hospira, Inc. ("Hospira") seeks a temporary restraining order and/or preliminary injunction staying the decision of the U.S. Food and Drug Administration ("FDA") in Docket No. FDA-2014-N-0087 (Aug. 18, 2014) (the "FDA August 18 Decision" or "FDA Decision") (Ex. A), rescinding *ab initio* any generic-drug approval action which FDA has taken predicated upon that Decision, ordering FDA to recall any product sold or distributed under such an approval, and enjoining FDA from granting any further or additional approvals predicated upon the August 18 Decision in Docket No. FDA-2014-N-0087.

Hospira will suffer irreparable harm if FDA's decision goes unchecked. Generic versions of Hospira's brand drug Precedex will flood the market and Hospira will be without a full and adequate remedy even if it prevails on the merits of this action. This harm will occur at the moment of generic product launch; the harm will be irreparable; and this irreparable harm can be avoided only by the Court's granting Hospira's request for temporary and/or preliminary injunctive relief. *See* Ex. B (Declaration of Thomas Moore). This case calls out for emergency injunctive relief.

In this action, Hospira challenges the lawfulness of FDA's final decision in Docket No. FDA-2014-N-0087 issued on August 18, 2014, in which FDA violated well-established statutory and regulatory requirements in connection with its review of a generic version of Precedex. Instead of complying with statutory and regulatory requirements, FDA adopted an unauthorized procedure (the opening of Docket No. FDA-2014-N-0087) and then relied upon that unauthorized procedure to make a decision which is contrary to law. Absent injunctive relief, FDA's unauthorized approach will allow generic versions of Precedex on the market without those generics' first establishing, as the law requires, that they do not infringe Hospira's rights under its method-of-use patent, and FDA will have applied a "rule" within the meaning of the Administrative Procedure Act which rule FDA adopted without complying with any of the rulemaking requirements of the Act.

Patent protection is essential to encourage the development of new and innovative drugs. Accordingly, patent protection is central to the generic-drug approval statutory scheme under the Hatch-Waxman Amendments to the federal Food, Drug & Cosmetic Act ("FDCA"). To assure that patent rights are protected, the standard process by which a generic drug company seeks FDA approval for a generic version of a brand drug requires the generic to certify that the brand's patent is invalid, unenforceable, or will not be infringed by the generic product while also affording the brand company notice and an opportunity to challenge the generic's non-infringement certification (a "paragraph IV certification"). FDA has exceedingly limited authority to deviate from this procedure. As the Supreme Court has recognized, FDA may approve a generic without the paragraph IV certification only when there is no "overlap" between the brand's patent "use code" (*i.e.*, the brand's description of the method of use protected by the patent) and the generic's proposed labeling (which must "carve-out" the brand's

use code). *See Caraco Pharm. Labs. Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1677 (2012). Here, in the face of demonstrable and FDA admitted overlap between the indications included in the generic's labeling and Hospira's patent use code, FDA has acted unlawfully in issuing a decision which allows approval of generic versions of Precedex.

In addition, FDA has not adopted a regulation, pursuant to the notice and comment rulemaking requirements of the Administrative Procedure Act ("APA"), to modify its prior rule and authorize the agency to approve a generic version in an "overlap case" such as this (assuming, without conceding, that FDA would have statutory authority to adopt such a rule). In its review and approval of applications for generic versions of Precedex, FDA has unlawfully applied a new substantive rule without FDA's complying with the rulemaking requirements of the APA. Because FDA's past or imminent approvals of generic versions of Precedex rests entirely on this unauthorized, unlawfully adopted new rule, any resulting generic drug approval decisions are invalid.

Hospira's motion for temporary and/or preliminary injunctive relief should be granted because Hospira is likely to succeed on the merits of its claims; Hospira will suffer irreparable harm in the absence of injunctive relief; the balance of hardships tips in Hospira's favor; and granting the requested injunctive relief is in the public interest. *See Pashby v. Delia*, 709 F.3d 307, 320-21 (4th Cir. 2013).

Statement of Facts

A. Brand-Name Drug Development, Review, and Approval

Hospira is the New Drug Application ("NDA") holder for dexmedetomidine hydrochloride, which it markets under the brand name Precedex. Hospira obtained FDA's approval for two indications (*i.e.*, FDA-approved uses) for Precedex: (1) "sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting,

[administered] by continuous infusion not to exceed 24 hours," and (2) "sedation of non-intubated patients prior to and/or during surgical and other procedures." Ex. B, ¶ 3.

Hospira is an owner of U.S. Patent No. 6,716,867 ("the '867 patent"). The '867 patent gives Hospira exclusive rights over the claimed "method of use" of Precedex. The '867 patent contains two independent use claims directed to methods of "sedating a patient in an intensive care unit." *Id.* ¶ 4, Att. A.[1] Hospira timely filed the '867 patent with FDA on May 6, 2004, along with the patent's expiration date and a description of the method-of-use protected by the patent (the patent "use code"). *Id.* ¶ 5. In line with FDA's self-described "ministerial" role with respect to patent matters, FDA published Hospira's use code, "intensive care unit sedation," in FDA's comprehensive listing of all drug products (commonly referred to as the "Orange Book"). *Id.*

B. FDA's Authority to Approve Generic Versions of Brand Name Drugs and FDA's Limited Section viii Authority

Companies seeking to bring a generic version of a brand drug product to market may submit an Abbreviated New Drug Application ("ANDA"). ANDA applicants may rely on the safety and efficacy studies contained in the NDA (in this case, Hospira's NDA for Precedex), as long as the generic version of the drug has the same active ingredients and routes of administration as, and is "bioequivalent" to, the innovator (brand) drug. *See* § 21 U.S.C. 355(j)(2)(A)(ii)-(v).

The FDCA requires that an ANDA file one of four certifications with respect to each patent listed in the Orange Book: (i) patent information has not been submitted; (ii) the patent

[1] Claim 1 states, "A method of ***sedating a patient in an intensive care unit***, which comprises administering to the patient an affective amount of dexmedetomidine of a pharmaceutically acceptable salt thereof, wherein the patient remains arousable and oriented." (emphasis added). Claim 3 likewise states, "A method of ***sedating a patient in an intensive care unit***, comprising administering a pharmaceutical composition to the patient, wherein the pharmaceutical composition comprises an active agent and an inactive agent, wherein the active agent consists of dexmedtomidine or a pharmaceutically acceptable salt thereof, an[d] wherein the patient remains arousable and oriented." (emphasis added).

has expired; (iii) the ANDA applicant will not seek final FDA approval before the date the patent expires; or (iv) the brand's patent is invalid, unenforceable, or will not be infringed by the ANDA applicant's product ("paragraph IV"). 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV). The FDCA and FDA regulations provide clear mechanisms for timely and expeditious judicial review and resolution of any patent disputes if an ANDA files a paragraph IV certification. An ANDA applicant that submits a paragraph IV certification must give notice to the holder of the patent, which then has a 45-day period in which to bring an action for patent infringement, and the bringing of this action automatically stays final FDA approval of the ANDA application until the court rules that the patent is not infringed, or until 30 months have passed, whichever occurs first. *See* 21 U.S.C. § 355(j)(5)(B).

In very limited circumstances, an ANDA applicant is permitted to bypass the paragraph IV certification and notice requirements and seek immediate review and then approval for its generic drug. An ANDA applicant seeking to bypass the paragraph IV certification procedure must state in its application that it is not seeking approval for an approved indication (an FDA approved use for the drug) covered by the patented method of use, but, instead, is seeking approval only for an approved indication that is *not* covered by any unexpired method-of-use patent. 21 U.S.C. § 355(j)(2)(A)(viii). This statement is commonly referred to as a "section viii statement." FDA, for its part, can approve an ANDA that relies on a section viii statement *only* when (a) FDA has approved more than one indication for the particular drug, *and* (b) at least one of those indications is not covered by any of the brand's patents. *See id.*; 21 C.F.R. § 314.94(a)(12)(iii)(A); *Caraco*, 132 S. Ct. at 1677.

In that limited situation, a generic applicant will propose labeling (proposed use) for the generic drug that redacts or "carves-out" from the brand drug's approved labeling the patented

methods of use. *See* 21 C.F.R. § 314.94(a)(8)(iv). This, too, is at variance from the norm because the labeling for generic drugs must be the "same" as the brand drug's labeling. *See* 21 U.S.C. § 355(j)(2)(A)(v), (j)(4)(G); 21 C.F.R. § 314.92(a)(1) (a generic product's labeling must be "identical in . . . conditions of use" to the branded label, "except that the conditions of use for which approval cannot be granted because of . . . an existing patent may be omitted"). Section viii statements are thus very much the exception, and FDA may approve a modified "carve-out" label only if the applicant satisfies the section viii conditions. *See* 21 C.F.R. § 314.127(a)(7). A carve-out to support a section viii statement may only be accomplished, however, by the "omission[s] of an indication or other aspect of labeling protected by [a] patent." *Id.* § 314.94(a)(8)(iv).

As required, FDA's clear policy and practice for years has been that it would not approve an ANDA that relies on a section viii statement if that statement overlaps *in any way* with the brand's use code as published in the Orange Book. *See* 68 Fed. Reg. 36676, 36682-36683 (2003). As the Supreme Court has noted, "whether section viii is available to a generic manufacturer depends on how the brand describes its patent. Only if the [innovator's] use code provides sufficient space for the generic's proposed label will the FDA approve an ANDA with a section viii statement." *Caraco*, 132 S. Ct. at 1677.

Thus, if the NDA holder's use code and related narrative for its method-of-use patent overlaps "at all" with all approved indications, the FDA has to reject a section viii statement. *See id.* ("[T]he FDA will not approve such an ANDA if the generic's proposed carve-out label *overlaps at all* with the brand's use code." (emphasis added)). Therefore, when, as here, the NDA holder's use-code statement asserts that its method-of use patent overlaps with all approved indications, FDA must reject an ANDA application based upon a section viii statement

and require the ANDA applicant to proceed according to the standard paragraph IV patent certification and notice procedure. That is the case here; generic companies cannot make a section viii certification to the FDA because they cannot say that the procedural indication is not encompassed by the '867 patent.

C. FDA's Unlawful and Unorthodox "Rulemaking Lite" Approach to Approving Generic Versions of Precedex Via Section viii Statements

A number of ANDAs seeking approval for a generic version of Precedex have been filed with and are pending before FDA. In recognition of the factual and legal impossibility of their obtaining approval via the section viii statement route, seven of those applicants, all sophisticated pharmaceutical companies, followed the proper patent certification and notice procedure. Ex. B, ¶ 6. One of those applicants, Sandoz, followed this process, initiated litigation, and is now, pursuant to a negotiated settlement with Hospira, scheduled to come to market in December 2014, five years before Hospira's patent expires. *Id.* ¶¶ 6, 17.

At least two other ANDA applicants, however, relied instead on a section viii statement. *Id.* ¶ 7. Hospira became aware of these applications and was concerned that the applicants or FDA failed to recognize the overlap between Hospira's existing use code and both of the approved indications for use contained in Precedex's labeling. Hospira thus filed with FDA a non-substantive clarifying amendment of its use code. *Id.* ¶ 8. As amended, the use code for Precedex reads "intensive care unit sedation, including sedation of non-intubated patients prior to and/or during surgical and other procedures." *Id.* This amendment made crystal clear what should have been abundantly clear previously, namely that Hospira's use code overlaps both approved indications and, therefore, FDA cannot approve a generic version of Precedex via a section viii statement. *See Caraco*, 132 S. Ct. at 1677 (the use code provides no "space for the generic's proposed label").

The approved indications for Precedex are (a) "sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting, [administered] by continuous infusion not to exceed 24 hours," and (b) "sedation of non-intubated patients prior to and/or during surgical and other procedures." There is an obvious overlap between the approved indications and Hospira's '867 patent; the use code description ("intensive care unit sedation, including sedation of non-intubated patients prior to and/or during surgical and other procedures") plainly overlaps with both of the labeled indications: (a) for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting, and (b) for sedation of non-intubated patients prior to and/or during surgical and other procedures where those procedures take place in an intensive care unit ("ICU").

The use code totally overlaps Precedex's first FDA approved indication ("sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting"). The use code partially overlaps the second indication ("sedation of non-intubated patients prior to and/or during surgical and other procedures"). Doctors routinely use Precedex to sedate non-intubated patients prior to or during surgical and other procedures *in ICUs*. Ex. B, ¶ 3. Indeed, the Co-Director and Critical Care Director of the largest and busiest burn center in the United States, Dr. Bruce Friedman, testifies in his declaration (submitted to FDA) that he "very frequently use[s] PRECEDEX™ for [its] second indication" on patients in the ICU prior to and/or during surgical and other procedures. Ex. C, ¶¶ 1, 5-7, 10. At his burn center, on average, "twice every week" such procedures are performed on non-intubated ICU patients; the procedures include wound or burn debridement and dressing changes, which are typically performed in the ICU and "very frequently" on non-intubated patients. *Id.* ¶¶ 10-11.

Studies confirm Dr. Friedman's first-hand testimony. Ex. B, ¶ 15, Att. E (citing Maxime

Madhere et al., *Dexmedetomidine as Sole Agent for Awake Fiberoptic Intubation in a Patient with Local Anesthetic Allergy*, 25 J. Anesthesia 592-94 (2011) (case report demonstrating the successful use of dexmedetomidine to sedate an ICU patient for awake fiberoptic intubation, a procedure specifically referenced in the labeling for the second indication); Julin F. Tang et al., *Dexmedetomidine Controls Agitation and Facilitates Reliable, Serial Neurological Examinations in a Non-Intubated Patient with Traumatic Brain Injury*, 15 Neurocritical Care 175-81 (2011) (dexmedetomidine has been used in the ICU for a non-intubated patient with a traumatic brain injury); Shinji Akada et al., *The Efficacy of Dexmedetomidine in Patients with Noninvasive Ventilation: A Preliminary Study*, 107 Anesthesia & Analgesia 167-70 (July 2008) (clinical study successfully used dexmedetomidine to sedate non-intubated patients in the ICU who were being treated for respiratory failure)).

On January 6, 2014, Hospira wrote to FDA's Chief Counsel requesting that FDA confirm that it would not grant final approval to any ANDA for generic Precedex based on a section viii statement. *Id.* ¶ 9, Att. B. FDA declined to do so. *Id.* ¶ 10, Att. C. Instead, on January 15, 2014, FDA sent a letter to Hospira (as the NDA holder) and a limited pool of others ("all applicants who submitted Abbreviated New Drug Applications (ANDAs) to the [FDA] referencing Precedex") soliciting comments in a public online docket (Docket No. FDA-2014-N-0087). *Id.* ¶ 11, Att. D. FDA sought comments "on certain legal and regulatory issues that pertain to Precedex." *Id.* In issuing this letter, FDA did not follow the notice and comment requirements of the APA, including the requirement that this request for comments on important issues of drug application review and approval be published in the *Federal Register*. *Id.* ¶ 13.

In its Dear Applicant letter, FDA at least indirectly acknowledged the overlap between Hospira's use code and both of Precedex's approved indications, based on the "breadth of the

new use code description." *Id.* ¶ 11, Att. D ("Does the breadth of the new use code description for the '867 patent foreclose ANDA applicants from gaining approval for any of the approved indications (or for any subset of those indications) before the '867 patent expires?"). Nevertheless, FDA sought comments from ANDA applicants about the legality of a section viii carve-out notwithstanding that this would amend the existing regulations (*see* § 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7)), and allow an applicant "to add new words" to the approved label and thereby bring its application within the scope of section viii. *Id.*

In response to the Dear Applicant letter, FDA received a variety of comments (some quite lengthy). *Id.* ¶ 14. One commenter noted that "[t]he issues raised by the FDA have created a firestorm of controversy, and a tangled web of conflicting legal interpretations," illustrating with a matrix that documented the utter lack of any consensus to FDA's many questions. Some commenters advocated that FDA apply its existing policies and rules and deny section viii carve-outs. Others supported the proposed section viii approach, although they took inconsistent approaches. Two commenters objected to the "limited" and "narrow request for commentary." The comments are available online at http://www.regulations.gov/#!docketDetail;D=FDA-2014-N-0087.

On August 18, 2014, FDA issued its decision on Docket No. FDA-2014-N-0087. Ex. A. In its decision, FDA stated that "the agency can approve an ANDA that submits a 'section viii' statement and omits labeling that discloses the protected use (as identified by Hospira.)" *Id.* at 1. FDA acknowledged the overlap between the use code and the procedural indication. *Id.* at 12. FDA's Decision is the predicate for FDA to grant final approval of one or more generic versions of Precedex based upon a section viii statement, and in fact, FDA approved one or more generic

versions on the same day it issued its decision. But for the August 18 Decision, no section viii approvals would or could be granted.

D. Hospira Will Suffer Irreparable Harm if FDA Authorizes Generics to Enter the Market

Absent this Court's immediate intervention, FDA's decision in Docket No. FDA-2014-N-0087 will cause irreparable harm to Hospira. Hospira has planned for a generic version of Precedex (offered by Sandoz) to enter the market in December 2014, almost five years prior to the expiration of Hospira's '867 patent. Ex. B, ¶ 17. A premature generic launch, as authorized by FDA here, will result in the placement of multiple months of generic product into the wholesale distribution channel, effectively eliminating Hospira's remaining period as the exclusive supplier of Precedex. *Id.* ¶ 22.

Immediately upon FDA's final approval of an ANDA for a generic version of Precedex, generic supplier(s) will flood the market, placing at least six months' worth of generic product into the wholesale distribution channel within days of final approval. *Id.* ¶ 18. At least two prospective companies have already contacted product wholesalers and hospital providers regarding a generic version of Precedex; indeed, one of those companies entered into a contract with Novation, a large group purchasing organization, to provide generic Precedex, and offered its product at a unit price 45% lower than that of the current Precedex brand price. *Id.* ¶ 19. The company was promising to launch on "day one" following FDA approval. *Id.* ¶ 19. In August 2014, another large group purchasing organization was approached with an offer to purchase a generic version of Precedex at a 25% discount with an expected approval and launch date of September 1, 2014. *Id.*

As an almost immediate consequence of generic entry, Hospira will be forced to terminate its U.S. brand drug sales force of approximately 130 persons. *Id.* ¶ 20. With this new,

unexpected competition, customers will purchase product through drug wholesalers at the lowest available price and regardless of brand; Hospira will have neither reason nor need to continue to have a sales force to visit prescribers and hospital providers. *Id.* This loss of sales force will cause further harm by eliminating the expected growth in Precedex sales, which is directly dependent on the education efforts of the sales force. *Id.* Given the importance of Precedex, Hospira will likely be caused to reduce additional corporate staff, as well. *Id.* If Hospira is denied temporary and/or preliminary injunctive relief but ultimately prevails on the merits, these employees will be lost as they will move on to other jobs. *Id.*

The premature entry of a generic version of Precedex will cause loss of market share and the rapid and immediate sales and price erosion. *Id.* ¶ 21. These harms are irreparable. One generic is proposing to sell its product at a 45% reduction on Hospira's unit price; once a number of generics are on the market, it can be expected that this price reduction will become even steeper. *Id.* Hospira would have to significantly drop its price to compete with the generic competitors' drug. *Id.* Even if Hospira is successful on the merits here and thus is ultimately able to prevent generics from further sales beyond what occurs in the first days after approval, the market would not return to pre-generic prices as customers typically enter into two- to three-year contracts to purchase drugs. *Id.* Further, Hospira has no monetary damages remedy against FDA for wrongfully allowing generics to launch.

A premature generic launch, with the effective loss of the remaining period of exclusivity, would cost Hospira tens of millions of dollars, if not more than a hundred million dollars, in profits even if Hospira is ultimately successful in preventing further generic sales beyond those which would occur in the first days after FDA approval. *Id.* ¶ 22. Premature generic entry will cause Hospira to lose revenue and profit from otherwise reasonably anticipated

sales, including the anticipated growth in product sales. *Id.* The loss would be significant and cannot be quantified exactly. *Id.* The loss of these profits will hinder Hospira's ability to fund research and development on new drug products that Hospira would like to bring to market in the future. *Id.* ¶ 23. Revenue from Precedex has allowed Hospira to commit enormous resources toward the research and development of multiple generic and biosimilar drug programs, products which are crucial to FDA's mission of providing safe, effective, and affordable drugs to the public at large. *Id.* Reduced funding of those programs due to a premature generic entry for Precedex will likely delay or eliminate some of those programs. *Id.*

Hospira would also be forced to stop funding, to the extent possible, clinical trials for Precedex. *Id.* ¶ 24. The public would face a significant loss as a result. *Id.* Hospira has conducted or supported extremely important, breakthrough clinical trials that have greatly impacted the healthcare and patient communities. *Id.* The growth of Precedex – and its potential new uses – will be stopped as a result of premature generic entry. *Id.*

Argument

I. Standard for Temporary or Preliminary Injunctive Relief

Parties seeking preliminary injunctions must demonstrate that (1) "they are likely to succeed on the merits"; (2) "they are likely to suffer irreparable harm"; (3) "the balance of hardships tips in their favor"; and (4) "the injunction is in the public interest." *Pashby v. Delia*, 709 F.3d 307, 320-21 (4th Cir. 2013). Hospira's present motion should be granted because it satisfies all four factors.

II. Hospira Is Entitled to Temporary or Preliminary Injunctive Relief.

A. Hospira Is Likely To Succeed on the Merits.

1. FDA Violated the FDCA by Making a Decision that Authorizes Immediate Approval of an ANDA for a Generic Version of Precedex Based Upon a Section viii Statement.

The core legal question presented in this case is this: Has FDA violated its limited authority to approve a generic drug pursuant to a section viii statement? Because the answer to that question is "yes," Hospira is likely to prevail on the merits.[2]

"Where the 'intent of Congress is clear . . . the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress.'" *Chevron U.S.A., Inc. v. Nat. Res. Def. Council*, 467 U.S. 837, 842-43 (1984). Here, the plain meaning of the statute and regulations are clear. *See United States v. Lehman*, 225 F.3d 426, 428 (4th Cir. 2000) ("A fundamental canon of statutory construction requires that 'unless otherwise defined, words will be interpreted as taking their ordinary, contemporary, common meaning.'"); *Air Line Pilots Assoc., Int'l v. US Airways Group, Inc.*, 609 F.3d 338 (4th Cir. 2010) ("[We] must assume that the legislative purpose is expressed by the ordinary meaning of the words used."). FDA is authorized to approve a generic drug pursuant to a section viii statement only when at least one of the approved indications for use for the branded drug is not covered by any of the brand's patented methods of use as described by the use code. *See* 21 U.S.C. § 355(j)(2)(A)(viii).

[2] On August 18, 2014, the FDA decided that "the agency can approve an ANDA that submits a 'section viii' statement and omits labeling that discloses the protected use (as identified by Hospira.)." Ex. A at 1. That final decision is final agency action. *See, e.g., Novartis Pharms. Corp. v. Leavitt*, 435 F.3d 344 (D.C. Cir. 2006) (reviewing challenge to FDA's disposition of plaintiff's citizen petition involving ANDA dosage form and labeling issues despite revocation of ANDA approval); *AstraZeneca Pharms. LP v. FDA*, 850 F. Supp. 2d 230, 242 (D.D.C. 2012) ("[T]he FDA's denial of [AstraZeneca's] citizen petitions constitutes final agency action."); *Mylan Pharms., Inc. v. FDA*, No. 1:04-cv-242, 2005 U.S. Dist. LEXIS 22269, at *11 (D. W.Va. Sept. 29, 2005) (denial of citizen petition is final agency action because it was based on interpretations of a statute); *Estee Lauder, Inc. v. FDA*, 727 F. Supp. 1, 6 (D.D.C. 1989) ("The Commissioner's determination on a citizen petition is final agency action subject to judicial review."). In addition, this matter is ripe for judicial resolution. In determining ripeness, the Court considers (1) "the fitness of the issues for judicial decision" and (2) "the hardship to the parties of withholding court consideration." *Cooksey v. Futrell*, 721 F.3d 226, 239-40 (4th Cir. 2013). All those factors are satisfied here.

Hospira is likely to succeed on the merits of its claim that FDA acted unlawfully because, contrary to law, the generic's proposed carve-out does *overlap* with Hospira's use code – a fact which FDA acknowledges in its decision. *See* Ex. A at 12. As the Supreme Court has noted, FDA is barred from approving an ANDA which relies upon a section viii statement where "the generic's proposed carve-out label *overlaps at all* with the brand's use code." *Caraco*, 132 S. Ct. at 1677 (emphasis added). That is what FDA has done here and that is unlawful agency action. *See* 5 U.S.C. § 706(2)(a).

Hospira's use code ("intensive care unit sedation, including sedation of non-intubated patients prior to and/or during surgical and other procedures")[3] covers *both* of Precedex's approved indications. The use code completely overlaps the first indication ("sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting") and partially overlaps the second ("sedation of non-intubated patients prior to and/or during surgical and other procedures") when such sedation occurs in an intensive care unit. *See also* Ex. C, ¶¶ 1, 5-7, 10 (declaration of Dr. Friedman testifying that he "very frequently use[s] PRECEDEX™ for [its] second indication" on patients in the ICU prior to and/or during surgical and other procedures). As both a matter of fact and as a matter of law, the section viii statement route is unavailable here because *there are no approved uses of the drug which are not covered by, or do not overlap with, Hospira's patented methods of use*.

The Supreme Court has made clear that Hospira's description of its patent controls the analysis and the conclusion here. *See Caraco*, 132 S. Ct. at 1677 ("[W]hether section viii is available to a generic manufacturer depends on how the brand describes its patent."). FDA has no proper or lawful role in the determination or approval of the proper use code for a patented

[3] Hospira clarified its use code in January 2014; however, both the analysis and the result are the same under the original use code and the clarified use code. "Intensive care unit sedation," the original use code, covers both approved indications of use.

drug. *Id.* ("The FDA takes that [use] code as a given: It does not independently assess the patent's scope or otherwise look behind the description authored by the brand."). FDA's role is limited strictly to the question of whether Hospira's "use code provides sufficient space for the generic's proposed label." *Id.*; *see also aaiPharma Inc. v. Thompson*, 296 F.3d 227, 241, 243 (4th Cir. 2002) ("[T]he FDA's conception of its role in Orange Book listings as purely ministerial rests on a permissible construction of [21 U.S.C.] § 355."); *Watson Pharms. v. Henney*, 194 F. Supp. 2d 442, 445-46 (D. Md. 2001) ("In fact, the legislation clearly reflects that Congress recognized that the FDA had a very limited, ministerial role in patent fights between patentees and generic marketers – that of taking information from the patentee, publishing that information in the Orange Book, and awaiting the institution and/or outcome of patent litigation.").

Here, there is no "space" between Hospira's use code and any approved use for the drug. Notwithstanding the Supreme Court's recent interpretation of the text of the statute, FDA unlawfully made a decision that authorizes approval of "an ANDA [where] the generic's carve-out label overlaps . . . with [Hospira's] use code." FDA decided that "ANDAs omitting references to the protected use in an intensive care unit may be approved for the procedural indication." Ex. A at 13.

FDA's action in this matter is unlawful because the agency has acted beyond and in violation of its statutory and regulatory authority. Courts, including the Supreme Court, have not hesitated to reject FDA's actions when, as here, FDA had no authority to take them. *See, e.g.*, *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120 (2000) (FDA has no statutory authority to regulate tobacco products); *Cook v. FDA*, 733 F.3d 1 (D.C. Cir. 2013) (FDA has no authority to exercise enforcement discretion not to review shipments of drug used in lethal

injections and allow processing of them for importation because the statute required FDA to refuse admission to misbranded or unapproved drugs); *Pac. Legal Found. v. Goyan*, 664 F.2d 1221 (4th Cir. 1981) (FDA has no statutory authority to spend public funds to reimburse qualified participants in its proceedings).

FDA is limited to acting in a ministerial role with respect to a patent, taking the use code as given, "not independently assess[ing] the patent's scope or otherwise look[ing] behind the description authored by the brand." *Caraco*, 132 S. Ct. at 1677 (citing 68 Fed. Reg. at 36682-83). The agency has neither the "expertise" nor the "authority" to do so. *Id.* FDA acted unlawfully when it made the decision in Docket No. FDA-2014-N-0087 which then provides the basis for "authorizing" approval of one or more generic versions of Precedex based upon section viii statements. Hospira is highly likely to prevail on the merits of its claim that FDA acted contrary to law.

2. FDA's Decision on the Docket Is Unlawful Under the APA Because the Revision of the Regulation on Which It is Based Was Not Subject to Notice and Comment Rulemaking.

Hospira is also likely to succeed on the merits of its claim that FDA acted unlawfully when it made a decision allowing approval of generic versions of Precedex based upon an unauthorized revision of its rules. An ANDA application that relies on a section viii statement is permissible *only* when (a) FDA has approved more than one indication for the particular drug, *and* (b) at least one of those indications is not covered by any of the brand's patents. *See id.*; 21 C.F.R. § 314.94(a)(12)(iii)(A); *Caraco*, 132 S. Ct. 1677. In that limited situation, generic applicants may propose labeling for the generic drug that redacts, or "carves-out" from the brand drug's approved labeling the patented methods of use. *See* 21 C.F.R. § 314.94(a)(8)(iv). FDA may approve a modified "carve-out" label in this instance. *See* 21 C.F.R. § 314.127(a)(7). But,

a carve-out to support a section viii statement may only be accomplished by the "omission[s] of an indication or other aspect of labeling protected by [a] patent." 21 C.F.R. § 314.94(a)(8)(iv).

FDA's decision here amends, effectively rewrites, that rule by allowing approval of an ANDA where there is conceded overlap between a patent protected use and the as approved ANDA's use. FDA, however, failed to follow the statutorily required notice and comment procedures, including publication in the *Federal Register*, in purporting to promulgate a "rule" that FDA can approve an ANDA if the applicant's section viii statement "overlaps at all" with Hospira's use code. *See Caraco,* 132 S. Ct. at 1677.

FDA is, of course, obliged to comply with the requirements of the APA, including those governing rulemaking. *See* 5 U.S.C. § 702. As a result, FDA cannot, for example, simply decide to apply a "rule" to a matter if the purported new "rule" was not properly adopted in accordance with the APA. *See Morton v. Ruiz*, 415 U.S. 199, 231-36 (1974). That is what FDA has done here. FDA's decision to authorize approval of an ANDA in the face of clear overlap between the generic's proposed carve-out label and Hospira's use code is an invalid, new and not properly adopted rule or regulation. That rule, therefore, is invalid, and any generic product approval decision based upon that rule is equally and necessarily invalid. *See* 5 U.S.C. § 706(2)(a).

The APA defines a rule as "an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency." 5 U.S.C. § 551(4). That precisely describes FDA's new approach, challenged here, of making a decision that authorizes approval of an ANDA in the face of clear overlap with Hospira's use code. FDA's decision is "an agency statement of general or particular applicability" "designed to implement . . . or prescribe law," notably rights and obligations which are unauthorized, unprecedented, and

directly contrary to the statute and the Supreme Court's directive. While Hospira does not concede that FDA has statutory authority to lawfully promulgate the rule applied in this matter, that issue is not present here; rather, the issue here is whether FDA can lawfully apply the rule it applied given the undeniable complete absence of any proper rulemaking process to adopt the rule.

Agency rules that "affect[] individual rights and obligations," such as the purported "rule" at issue in this case, are invalid if they are not adopted in accordance with the rulemaking requirements of the APA. *Morton*, 415 U.S. at 232; *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 95-96 (D.C. Cir. 1997) (FDA notice/guidance was an invalid substantive rule); *Comm. Nutrition Inst. v. Young*, 818 F.2d 943, 946-49 (D.C. Cir. 1987) (holding that FDA's action levels informing food producers of allowable levels of unavoidable contaminants were legislative rules subject to notice and comment because they had a present, binding effect and cabined FDA's discretion); *United States v. Articles of Drug*, 634 F. Supp. 435, 454-60 (N.D. Ill. 1985) (holding that FDA's failure to "adopt its unwritten, varying, and highly intrusive 'policies' as written, published regulations" prohibited FDA from enforcing the policies against a company), *vacated as moot*, 818 F.2d 569 (7th Cir. 1987); *Bellarno Int'l Ltd. v. FDA*, 678 F. Supp. 410, 413-15 (E.D.N.Y. 1988) (holding that an import alert was invalid because of the requirements it imposed, which mandated automatic detention and re-export of all imports of certain pharmaceuticals and removed all enforcement discretion); *see also United States v. Bioclinical Sys., Inc.*, 666 F. Supp. 82, 83 (D. Md. 1987) (holding that FDA's sterility assurance levels must be established according to formal procedures and not as "a *de facto* requirement"). Further, an agency cannot "amend" an existing rule (*see* 21 C.F.R. § 314.94(a)(8)(iv)) without notice and comment. *See, e.g., Jerri's Ceramic Arts, Inc. v. Cons. Prod. Safety Comm'n*, 874 F.2d 205, 206

(4th Cir. 1989) ("Because we believe this 'interpretation' is actually a substantive amendment to the [Rule], and because the [agency] did not comply with the statutory procedures of notice and comment required for such amendments, we grant appellant's petition to set the [agency's] statement aside."); *N.C. Growers' Ass'n, Inc. v. United Farm Workers*, 702 F.3d 755, 765-66 (4th Cir. 2012) (agency engaged in rulemaking when it reinstated superseded and void regulations because "their reinstatement would have put in place a set of regulations that were new and different [from existing regulations]").

The APA requires an agency engaged in rulemaking to: (1) provide adequate advance notice and publication of the proposed rule in the Federal Register, 5 U.S.C. § 553(b); (2) afford all interested persons (including members of the public) an opportunity to participate through the submission of written data, views, or arguments, *id.* (c); and (3) publish the final rule in the *Federal Register* with a statement of basis and purpose not less than thirty days before its effective date, *id.* (c), (d). FDA did none of this.

Strikingly, FDA's docket purports to be a "Rulemaking" docket. Under "Docket Details," "Rulemaking" is listed as the "Type" of docket. *See* http://www.regulations.gov/#!docketDetail;D=FDA-2014-N-0087. FDA's use of an unauthorized "regulation lite" process (Docket No. FDA-2014-N-0087) further demonstrates that FDA understood that it was formulating a rule. *See N.C. Growers'*, 702 F.3d at 765 ("The Department's own conduct, however, is highly relevant and shows that the Department viewed the reinstatement of the 1987 regulations as 'rule making.'"). The docket, indeed, purports to be a "rulemaking" docket. Ex. B, ¶ 12. FDA's January 9, 2014 letter to Hospira also admits to opening a docket to "establish an administrative record on which the Agency may base future decisions." *Id.* ¶ 10, Att. C. FDA's process fell far short, however, of what the APA requires.

FDA did not publish any notice or request for comments in the *Federal Register* in connection with the January 15 letter, *id.* ¶ 13; FDA only requested comments from an agency-selected and limited pool of commenters (as distinguished from all "interested persons"), *Id.* ¶ 11, Att. D; FDA provided only a short period in which to comment (as distinguished from adequate advance notice and publication in the *Federal Register*), *id.*; and FDA failed to publish in the *Federal Register* a final rule that adequately discussed the many divergent comments (indeed, FDA did not discuss many of the comments in its unpublished final rule), *see* Ex. A.

FDA has no authority to develop or adopt rules pursuant to some process of its invention which the agency "makes up on the fly," and rules so developed, like the one here, without the procedures required by the APA are invalid. *See, e.g.*, *id.* at 769-70 (agency acted arbitrarily and capriciously where it did not provide a meaningful opportunity for comment and allowed only a 10-day comment period); *Am. Radio Relay League, Inc. v. FCC*, 524 F.3d 227 (D.C. Cir. 2008) (agency failed to comply with APA when it did not provide a reasoned explanation for dismissal of data submitted at its invitation); *Owner-Operators Indep. Drivers Ass'n v. Fed. Motor Carriers Safety Admin.*, 494 F.3d 188 (D.C. Cir. 2007) (vacating provisions of rule where agency failed to give interested parties opportunity to comment on methodology used to justify increase in the maximum number of hours truck drivers may drive and work and failed to provide an explanation that would confirm action was the product of reasoned decisionmaking); *Nw. Tissue Ctr. v. Shalala*, 1 F.3d 522 (7th Cir. 1993) (agency's "back door procedure" denied plaintiff the right to notice and comment on the regulation of allografts which the FDA Act and APA guarantee); *United States v. Nova Scotia Food Prods. Corp.*, 568 F.2d 240 (2d Cir. 1977) (regulation invalid because interested persons were not informed of scientific data so that

comments could address the data and agency failed to discuss or answer "vital" questions in its concise general statement).

Hospira thus is likely to prevail on the merits of its claim that FDA's decision on the docket is based on or creates a purported "rule" which FDA "adopted" without compliance with the rulemaking requirements of the APA. FDA's decision which authorizes approval of generic versions of Precedex based on section viii statements cannot stand because the "rule" upon which that action rests is invalid.

B. Absent Emergency Relief, Hospira Will Be Irreparably Harmed Without Any Adequate Remedy.

The harms Hospira will suffer as a result of FDA's decision are clear. Without judicial intervention, Hospira will suffer immediate, irreparable harm caused by FDA's approval of generics (and FDA has already approved one or more generic versions of Precedex) and the generics' immediate flooding of the market. In the absence of emergency injunctive relief, Hospira has no adequate remedy for the harms it will suffer. *See* Ex. B (Declaration of Mr. Moore); pp. 11-13, *supra*; *see also AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010) (affirming grant of preliminary injunction barring Apotex from launching generic version of a drug made by AstraZeneca where Apotex relied on a section viii statement).

Injunctive relief is appropriate because Hospira will suffer actual and imminent harm which cannot be remedied at a later time. *See Senior Execs. Ass'n v. United States*, 891 F. Supp. 2d 745, 755 (D. Md. 2012). Irreparable harm is demonstrated where any calculation of damages is "'difficult to ascertain or are inadequate'" or where "the failure to grant preliminary relief creates the possibility of permanent loss of customers to a competitor or the loss of goodwill." *Multi-Channel TV Cable Co. v. Charlottesville Quality Cable Operating Co.*, 22 F.3d 546, 551-52 (4th Cir. 1994). Price erosion and diminished market share also constitute irreparable harm,

particularly in the context of generic drug entry. *Bayer Healthcare, LLC v. FDA*, 942 F. Supp. 2d 17, 26 (D.D.C. 2013). The entry of a generic to market inevitably results in a decline in the brand's price and a loss of good will to customers, who will buy the less expensive drug. *Id.*; *see also Allergan, Inc. v. Apotex Inc.*, No. 1:10-cv-681 et al., 2013 U.S. Dist. LEXIS 57656, at *19-21 (M.D.N.C. Apr. 23, 2013) ("Plaintiffs [Allergan] will suffer irreparable harm if Defendants launch their generic versions of Latisse® [by losing market share and loss of revenue and where Allergan would not recoup its expenditures].").

The harm here is imminent; it will continue to increase with every day that passes following FDA's decision. Following FDA's approval of one or more generic versions of Precedex, and FDA has already approved one or more generic versions of Precedex, the approved generic manufacturers will likely flood the market with as much generic Precedex as they can manufacture (which is likely to be at least six months' worth), and their market penetration will increase with each passing day. *See* Ex. B, ¶ 18. Indeed, Hospira has learned from product wholesalers and hospital providers that they have been contacted by at least two prospective companies regarding a generic version of Precedex. *Id.* ¶ 19. This information includes the fact that one of those companies has entered into a contract with Novation, a large group purchasing organization, to provide generic Precedex, and is offering its product at a unit price 45% lower than that of the current Precedex brand price and is promising to launch on "day one" following FDA approval. *Id.* In August 2014, another large purchasing organization was approached by another company offering a 25% discount to the current Precedex brand price with an expected approval and launch date of September 1, 2014.

With the immediate introduction of a less expensive generic version to market in large quantities, Hospira will be forced to terminate its U.S. brand drug sales force of

approximately130 persons. *Id.* ¶ 20; *AstraZeneca LP*, 633 F.3d at 1063 (affirming grant of injunctive relief where damage from layoffs caused by generic entry would be significant and unquantifiable). Customers will purchase product through drug wholesalers at the lowest available price and regardless of brand, and Hospira will have neither reason nor need to continue to have a sales force to visit prescribers and hospital providers. Ex. B, ¶ 20. This sales force will move on, and rehiring them at a later date will be impossible. *Id.* The loss of the sales force will further harm the Company by eliminating the expected growth in the sales of Precedex, which is directly dependent on the education efforts of the sales force. *Id.* Precedex is a "detail sensitive" drug because of its unique effects on the patient, and education and training are critical to drive adoption and growth in the market. *Id.* The loss of the sales force will further harm the Company by eliminating the expected growth in the sales of Precedex. *Id.* Given the importance of Precedex, Hospira will likely be caused to reduce and/or reorganize additional corporate staff, in addition to its sales force, in the event of a premature generic entry. *Id.*

Sandoz's generic launch is expected in December 2014. *Id.* ¶ 17. A premature generic launch in advance of that of Sandoz will effectively eliminate Hospira's remaining period as the exclusive supplier of Precedex. *Id.* ¶ 22; *AstraZeneca LP*, 633 F.3d at 1061-62 (affirming grant of injunctive relief where confidential settlement agreement giving Teva an exclusive license to sell a generic drug would make calculating economic harm from premature entry impossible). Multiple months of generic product will be placed into the wholesale distribution channel immediately following generic approval. Ex. B, ¶ 18 , 22. With a premature generic entry, Hospira would lose tens of millions of dollars, if not more than a hundred million dollars, in profits even if it is successful in preventing further generic sales beyond what occurs in the first days after approval, and ultimately successful in this matter. *Id.* ¶ 22. Further, Hospira will

suffer rapid and immediate sales and price erosion that is not recoverable once generics come onto the market. *Id.* ¶ 21. As mentioned above, one generic is proposing to sell its product at a 45% reduction on Hospira's unit price; once a number of generics are on the market, this price reduction will become even steeper. *Id.* As a result, Hospira would have to significantly drop its price to compete with the generic competitors' drug. *Id.*

Hospira's ability to fund research and development on new drug products that Hospira would like to bring to market in the future would be hindered with this lost profit. *Id.* ¶ 23. Revenue from Precedex has allowed Hospira to commit enormous resources toward the research and development of multiple generic and biosimilar drug programs, products which are crucial to FDA's mission of providing safe, effective, and affordable drugs to the public at large. *Id.* Reduced funding of those programs due to a premature generic entry for Precedex will likely delay or eliminate some of those programs. *Id.* Hospira would also be forced to stop funding, to the extent possible, clinical trials for Precedex, which would significantly and adversely impact the public who has benefitted from these trials. *Id.* ¶ 24.

These harms are real but impossible to quantify and can never fully be remedied. *Multi-Channel TV*, 22 F.3d at 552 ("Irreparability of harm includes the impossibility of ascertaining *with any accuracy* the extent of the loss." (quoting *Blackwelder Furn. Co. v. Seilig Mfg., Inc.*, 550 F.2d 189, 197 (4th Cir. 1977))). Even if Hospira is successful and ultimately able to prevent generics from further sales beyond what occurs in the first days after approval, the market would not return to pre-generic prices as customers typically enter into two- to three-year contracts to purchase drugs. *Id.* ¶ 21. This constitutes irreparable loss. Moreover, premature generic entry will cause Hospira to lose revenue and profit from otherwise reasonably anticipated sales, including the anticipated growth in product sales; this loss would be significant and cannot be

quantified exactly. *Id.* ¶ 22; *see also AstraZeneca LP*, 633 F.3d at 1062-63 (affirming grant of injunctive relief where AstraZeneca would suffer unquantifiable harm if the generic began distribution only to later be forced to remove the drug from market, causing confusion among patients and physicians and price changes).

Furthermore, Hospira will have no means to recover its losses because FDA's sovereign immunity would preclude Hospira from recovering money damages. *See, e.g.*, *Smoking Everywhere, Inc. v. FDA*, 680 F. Supp. 2d 62, 77 n.19 (D.D.C. 2010) (claimed economic injury is irreparable because plaintiffs cannot recover damages against FDA because it is shielded by sovereign immunity), *aff'd*, 627 F.3d 891 (D.C. Cir. 2010); *Senior Execs.*, 891 F. Supp. 2d at 755 (explaining that monetary damages are an inadequate remedy because "they are unavailable" (citing *United States v. Mitchell*, 445 U.S. 535, 538-39 (1980); *Smoking Everywhere*, 680 F. Supp. 2d at 77 n.19)).

C. The Balance of Hardships Tips Strongly in Hospira's Favor.

The balance of hardships here tips heavily in favor of Hospira. Absent action by this Court, Hospira will be severely and irreparably prejudiced. Hospira will lose the advantages it enjoys from the rights it has in the '867 patent while it waits for a resolution of the underlying question of the illegality of FDA's action. On the other hand, granting the limited interim relief requested will not prejudice FDA. It will only maintain the status quo while this Court reviews the agency's actions. *Bayer*, 942 F. Supp. 2d at 26 (issuing temporary restraining order where brand drug owner challenged approval of generic; hardship tipped in favor of brand owner rather than FDA and generic company).

Hospira fully supports expediting proceedings on the merits of this case. This matter should proceed very quickly to the merits, with the parties' filing cross-motions for judgment. There is no discovery to be conducted here. This matter is to be decided on the record of FDA's

August 18 Decision. Hospira would be harmed seriously, however, if FDA's decision were to go unstayed in the meantime and if approvals were not withdrawn and products not recalled; FDA, by contrast, would suffer no harm as a result of having its decision stayed pending a full hearing and decision on the merits.

D. The Public Interest Favors Granting the Limited Relief Requested.

Hospira's request for relief is in the public interest. "The public interest is best served by ensuring [agency] compliance with [its governing] statute." *Bayer*, 942 F. Supp. 2d at 27. Here, for example, Sandoz followed the law, litigated the patent issues, and obtained the right to come on the market five years prior to patent expiration. The process worked exactly as Congress intended. A generic provided the required notice and certification and as a result of a settlement following litigation, obtained the right to enter the market prior to the expiration of the patent. The public interest is not served by undermining that process or that outcome. That, however, is the consequence of FDA's action.

Similarly, the public interest is served by requiring FDA to comply with the law, not by allowing it to act outside the bounds of its authority and without the notice and full public participation the APA requires for promulgating rules. *See N.C. Growers*, 702 F.3d at 763 (notice and comment procedures ensure the agency "benefits from the experience and input of comments by the public" and are "designed to encourage public participation in the administrative process"). The ANDA applicants will not be irreparably harmed if this Court takes action. Once this Court reviews FDA's final agency action, then FDA can take the lawful, appropriate next steps. If the Court rules in FDA's favor, then FDA can authorize the ANDA applicants to carve-out their labels and they will come to market, just at a slightly later time.

Conclusion

Hospira satisfies the requirements to warrant the grant of temporary and/or preliminary injunctive relief for the short period of time necessary to determine the legality of FDA's August 18 Decision. Accordingly, Hospira respectfully requests that the Court grant its motion for a temporary restraining order and/or preliminary injunction, and order that FDA withdraw and rescind any approvals already granted, recall any product sold or distributed under such an approval, and stay the application of FDA's August 18 Decision pending resolution on the merits of the legal issues raised in Hospira's complaint.

Respectfully submitted,

Dated: August 19, 2014

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that the above motion for temporary restraining order and/or preliminary injunction and memorandum in support was served this 19th day of August, 2014, by hand delivery, as follows:

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