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CITIZEN PETITION

ACTION REQUESTED

Teva Pharmaceuticals USA, Inc. ("Teva") respectfully submits this Citizen Petition pursuant to section 505 of the Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 355, and section 10.30 of the Agency's implementing regulations, 21 C.F.R. § 10.30. This petition requests that the Agency:

(1) Relist U.S. Patent No. 5,158,952 ("the '952 patent") in *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") for 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg Risperdal® (risperidone) tablets, all approved products of Janssen Pharmaceutica Inc. as the holder of NDA No. 20-272;

(2) Confirm that Teva's right to 180-day exclusivity with regard to ANDA No. 76-228 has not been affected by FDA's erroneous delisting of the '952 patent from the Orange Book; and

(3) Refrain from approving any Abbreviated New Drug Application ("ANDA") for 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg risperidone tablets until Teva's 180-day exclusivity period expires.

STATEMENT OF GROUNDS

INTRODUCTION

The plain text, structure, and history of 21 U.S.C. § 355(j)(5)(B)(iv) establish that Teva is entitled to 180 days of marketing exclusivity for its generic risperidone tablets as a result of Teva's August 28, 2001 paragraph IV certification to the '952 patent. That is so because the '952 patent appeared in the official Orange Book on the day Teva submitted its paragraph IV certification; because Teva thus was required to submit a certification to that patent at the time it

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submitted its ANDA for generic risperidone drug products; and because Teva then became the first company to submit a paragraph IV certification to any of the listed patents claiming Risperdal®. FDA's purported "delisting" of the '952 patent in no way undermines Teva's entitlement to 180-day exclusivity, because the Agency failed to provide official notice of the "delisting" for several months following the submission of Teva's ANDA. As the D.C. Circuit recently recognized in the *Ranbaxy* (simvastatin) case, the adoption of a rule that would divest the first generic applicant of its exclusivity after that applicant has assumed the very risks 180-day exclusivity is designed to reward—the expense of formulating a non-infringing product and preparing a legal defense to a potential action for patent infringement, and then the submission of an infringing paragraph IV certification to the Agency—would fundamentally "change the incentive structure adopted by Congress," in clear violation of the plain text and structure of the Hatch-Waxman Act. *Ranbaxy Laboratories Ltd. v. Leavitt*, 469 F.3d 120, 125-26 (D.C. Cir. 2006).

At bottom, given that the '952 patent remained listed in the official Orange Book on the date Teva submitted its paragraph IV certification to the Agency, and in view of the plain language of section 355(j)(5)(B)(iv), court precedent compelling FDA to preserve Teva's exclusivity by relisting the '952 patent, and the Agency's own practice regarding patent relisting, Teva thus petitions FDA to relist the '952 patent for Risperdal®, maintain Teva's exclusivity against subsequently filed ANDAs, and confirm Teva's right to its 180-day exclusivity period.

BACKGROUND

Risperidone is an atypical antipsychotic medication sold by Janssen Pharmaceutica ("Janssen") under the trade-name Risperdal®. Janssen holds NDA No. 20-272, for risperidone tablets. As of August 2001, FDA's official *Approved Drug Products with Therapeutic Equivalence Evaluations* (known as the "Orange Book") listed two patents as claiming Risperdal® tablets: U.S. Patent No. 4,804,663 ("the '663 patent"), which is set to expire on December 29, 2007, and U.S. Patent No. 5,158,952 ("the '952 patent"), which will expire on October 27, 2009. *See* Orange Book (2001 ed.), at ADA 57 (Exhibit 1).

On August 28, 2001, Teva submitted an original Abbreviated New Drug Application ("ANDA"), No. 76-228, seeking approval to market generic risperidone tablets in 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg strengths. *See* Patent Certification for Risperdal® ANDA ("Original Patent Certification") (Exhibit 2). In accordance with 21 U.S.C. § 355(j)(2)(A)(vii), Teva's ANDA contained a certification with respect to each patent listed as claiming Risperdal® tablets. *Id.* Because the official Orange Book listed both the '663 and '952 patents for Risperdal® tablets, Teva was required to certify as to both patents, and it did so. *See* 21 C.F.R. 314.53(f). Teva filed a certification under § 355(j)(2)(A)(vii)(III) ("Paragraph III certification") as to the '663 patent, which is set to expire on December 29, 2007, and a certification under § 355(j)(2)(A)(vii)(IV) ("Paragraph IV certification") as to the '952 patent, asserting that the patent was invalid or would not be infringed by Teva's generic risperidone tablets. *See* Original Patent Certification.

On October 12, 2001, FDA notified Teva that it had "delisted" the '952 patent from the Orange Book (even though it continued to appear in the official Orange Book at that time). *See* Letter from Deborah Jaskot to Gary Buehler (Oct. 22, 2001) ("Jaskot Letter") (Exhibit 3). It also informed Teva that it would not accept Teva's ANDA for filing unless Teva modified its patent certification to reflect that the '952 patent was no longer listed as claiming the reference drug product. *Id.* Thus, even though FDA had not informed Teva of the putative delisting prior to the submission of Teva's paragraph IV certification; even though the official Orange Book continued to list the '952 patent as claiming Risperdal® tablets; and even though Teva had assumed the very risks 180-day exclusivity is designed to reward, Teva was forced to follow the agency's directive and amend its ANDA.

In January 2002, FDA released a revised Orange Book, which for the first time noted the official delisting of the '952 patent, and listed only the '663 patent as claiming Risperdal® tablets. *See* Orange Book (2002 ed.), at ADA 65 (Exhibit 4).

In November 2006, the D.C. Circuit ruled that the plain text of the FDCA prevented FDA from effectuating the delisting of a patent following the submission of a paragraph IV certification as to that patent. *Ranbaxy Laboratories Ltd. v. Leavitt*, 469 F.3d 120, 125-26 (D.C. Cir. 2006). The court struck down FDA's practice because it "change[d] the incentive structure adopted by Congress," by "depriv[ing] the generic applicant of a period of marketing exclusivity" after the generic manufacturer had expended significant resources in developing a non-infringing generic substitute and undertaken the risk of infringing the patent by filing a paragraph IV certification. *Id.* at 126. The D.C. Circuit thus held that FDA's approach to delisting contravened the plain meaning of the FDCA, and invalidated FDA's practice under *Chevron* step one. *Id.*

Following the D.C. Circuit's decision, Teva began reviewing its portfolio of pending ANDAs to determine whether FDA's unlawful delisting practices had deprived Teva of its entitlement to 180-day exclusivity for any other generic product. As with respect to Ivax's ANDA for olanzapine drug products, this case presents such a situation.

ARGUMENT

The plain language of the FDCA entitles Teva to a 180-day period of first-filer exclusivity for generic Risperdal® tablets. Teva was the first generic manufacturer to file an ANDA for generic risperidone tablets containing a paragraph IV certification as to the '952 patent. Under 21 U.S.C. § 355(j)(5)(B)(iv) (2002), the earliest any subsequently-filed paragraph IV ANDA can be approved is "one hundred and eighty days after" Teva first commercially markets its generic risperidone tablets or the date of a court decision holding the '952 patent to be invalid or not infringed. *Id.*[1] To date, neither of these events has occurred—there has been no

[1] Because Teva filed its ANDA in August 2001, its claims are governed by the version of the FDCA that existed prior to the amendments made in the Medicare Modernization Act of 2003 ("MMA"). *See* MMA, Pub. L. No. 108-173, 117 Stat. 2006, § 1102(b)(1) (Dec. 8, 2003). All citations in this petition are to the pre-MMA version of the statute.

litigation concerning the '952 patent, and Teva will not begin commercial marketing of its generic risperidone products until the patent term of (and any subsequent period of pediatric exclusivity with respect to) the '663 patent expires. At that time Teva will be entitled to 180 days of sole marketing exclusivity under the plain terms of § 355(j)(5)(B)(iv).[2]

Teva's entitlement to generic exclusivity may not be denied on the basis of FDA's putative "delisting" of the '952 patent prior to the submission of Teva's paragraph IV certification to the Agency. At the time Teva submitted its original ANDA for generic risperidone products (which contained a paragraph IV certification to the '952 patent), it had no choice but to certify as to the '952 patent. After all, the official Orange Book continued to list the '952 patent as claiming Risperdal® tablets. Both FDA regulations and longstanding case law make clear that the agency does not adjudicate questions of patent law; instead, it plays only a ministerial role in maintaining the Orange Book. *See, e.g.*, *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1349-50 (Fed. Cir. 2003); *Alphapharm Pty Ltd. v. Thompson*, 330 F. Supp. 2d 1, 7 (D.D.C. 2004); *see also* 21 C.F.R. § 314.53(f). As a result, where a patent remains listed for a particular drug in the official Orange Book, a generic applicant has no choice but to believe that the NDA holder is continuing to assert that patent as claiming the listed drug. In that situation, both the statute and agency regulations require the generic applicant to submit a certification with respect to the disputed patent. *Apotex*, 347 F.3d at 1350 ("The statutory language shows a clear congressional intention to require certification whenever an ANDA applicant seeks approval of a drug that is claimed by a patent *that is listed in the Orange Book.*") (emphasis added); *Sandoz, Inc. v. FDA*, 439 F. Supp. 2d 26, 31 (D.D.C. 2006) (same); 21 C.F.R. § 314.53(f).

Thus, at the time of its ANDA submission in August 2001, Teva was required to submit a certification to the '952 patent. FDA's putative delisting of the '952 patent did not become effective until January 2002, when the official Orange Book reflected the delisting of that patent. Absent any change in the Orange Book listings that reasonably would have put Teva on notice of the '952 delisting, it had no choice but to certify to the '952 patent on the date that it submitted its paragraph IV certification to the Agency. *See Apotex*, 347 F.3d at 1350 (noting that certification is "require[d]" for any patent listed in the Orange Book as claiming a drug). Teva thus did precisely what it was obligated to do under the plain text of the governing statute and Agency regulations, and it therefore earned its exclusivity as the first applicant to file a paragraph IV certification to a patent listed as claiming the reference listed drug.

Divesting Teva of its 180-day exclusivity under these circumstances would fundamentally undermine the incentive scheme established by the Hatch-Waxman Act, and expose the exclusivity reward to manipulation by brand manufacturers. Courts, including the D.C. Circuit in its recent *Ranbaxy* decision, routinely reject such an approach to the statutory

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2 Because the Federal Circuit recently held that the '663 patent is valid and enforceable, *see Janssen Pharmaceutica v. Mylan Pharms.*, No. 07-1021 (Fed. Cir. May 11, 2007), no manufacturer is entitled to exclusivity based on its first-to-file status with respect to that patent. Thus, under FDA's pre-MMA, patent-by-patent approach to exclusivity, Teva's exclusivity based on its first-filer status with respect to the '952 patent will not be shared with the first applicant that filed a paragraph IV certification with respect to the '663 patent. Teva alone is entitled to exclusivity for these drug products.

scheme. Thus, a brand manufacturer may not delist a patent in order to eliminate generic exclusivity after an ANDA applicant wins its paragraph IV litigation on a patent. *See, e.g.*, 21 CFR § 314.94(a)(12)(viii)(B); *Torpharm v. Thompson*, 260 F. Supp. 69, 83 n.15 (D.D.C. 2003). By the same token, as the *Ranbaxy* Court recognized, FDA may not effectuate the delisting of a patent for a referenced drug after a generic manufacturer submits a paragraph IV certification. 469 F.3d at 125-26.

The reasoning behind these decisions is straightforward. The primary purpose of the Hatch-Waxman Act is to promote generic competition in the pharmaceutical market and prevent brand manufacturers from using inapplicable patents to block generic applicants from entering the market. A policy that permits a brand manufacturer to effectuate the delisting of a patent after the submission of a paragraph IV certification and without notice to the pharmaceutical community allows brand manufacturers to manipulate the generic approval process by forcing generic manufacturers to invest significant resources and assume the risk of patent litigation without any guarantee of the 180-day exclusivity reward. By thereby decreasing the incentives for generic manufacturers to develop competing products for listed drugs, such an approach is fundamentally inconsistent with the Hatch-Waxman Act. *Id.*

That is precisely the case here. On the date Teva filed its ANDA for generic risperidone drug products, Teva was obligated to rely on the official Orange Book's indication that its generic risperidone product would have to be designed so as not to infringe the '952 patent, or that Teva otherwise would have to invest significant sums in preparing a legal challenge to the validity or enforceability of the '952 patent. As a result, Teva invested substantial resources to engineer a non-infringing drug product and prepare a legal challenge to the '952 patent. Most important, Teva then assumed the very risk 180-day exclusivity is designed to reward, by deliberately exposing itself to patent litigation with the submission of a paragraph IV certification to the '952 patent in its original ANDA. *See* 35 U.S.C. § 271(e)(2); *see also Purepac Pharmaceutical Co. v. Thompson*, 354 F.3d 877, 889 (D.C. Cir. 2004); Brief of the Federal Defendants, *Purepac Pharmaceutical Co. v. Thompson*, 354 F.3d 877 (D.C. Cir. 2004) ("An original ANDA which includes a paragraph IV certification is considered effectively submitted on the date it is received by FDA, provided that FDA finds, after conducting a threshold review, that the application is substantially complete.").

Thus, even though Teva did precisely what the statute is designed to reward, FDA's putative "delisting" of the patent—despite the fact that the '952 continued to appear in the official Orange Book—has deprived Teva of the reward Congress guaranteed in the Hatch-Waxman Act.

At bottom, FDA's decision to effectuate the delisting of the '952 patent without prior notice rendered Teva's substantial investment in generic risperidone a nullity. Just as in *Ranbaxy*, the adoption of such a policy clearly "diminishes the incentive for a manufacturer of generic drugs to challenge a patent listed in the Orange Book." *Ranbaxy*, 469 F.3d at 126. Ultimately, such a rule will act as an overall disincentive for companies to even attempt to produce generic drug alternatives, lest their significant investment in the design of a non-infringing product and preparation of a legal defense to an infringement action turn out to have been wasted. Such a policy directly contradicts the policies behind the Hatch-Waxman Act, and cannot be sustained. *See Ranbaxy*, 469 F.3d at 125-26.

Indeed, FDA itself has acknowledged as much. On May 15, 2007, the Agency relisted eight patents for Zyprexa® (olanzapine) that had been delisted several years earlier at the request of the brand manufacturer. That decision only underscores FDA's understanding that *Ranbaxy* requires not only a prospective change in agency practice, but also remedial action to restore to generic manufacturers any statutory rights wrongly denied by previous delistings. Patents that have been wrongly removed from the Orange Book must be relisted, and any exclusivity owed generic companies on those patents must be restored--even if several years have passed since the original delisting. As it did with the olanzapine patents, FDA must relist the '952 patent to protect the policies behind the Hatch-Waxman Act.

The fact that FDA never accepted Teva's paragraph IV ANDA for filing thus has no bearing on the fact that FDA must relist the '952 patent. FDA's refusal to file Teva's paragraph IV certification as to the '952 patent was based on its since-overturned delisting policy. At that time, the Agency gave Teva no choice but to amend its patent certification for its risperidone ANDA. And as in the olanzapine case, FDA now has no choice but to relist the '952 patent and restore Teva's exclusivity.

CONCLUSION

This case rises and falls on one fact: on the date Teva submitted its original ANDA containing a paragraph IV certification in August 2001, the '952 patent continued to appear in the official Orange Book. Teva thus did everything it was required to do under the plain text of the statutes and governing regulations in order to secure the statutory reward of 180-day exclusivity: it had engineered a non-infringing pathway around the '952 patent, it had prepared a legal challenge to that patent, and most critically, it filed the very first paragraph IV certification to the '952 patent. As the first filer, Teva thus earned its 180-day period of exclusivity under the Hatch-Waxman Act, and FDA may not lawfully deprive Teva of this right.

Teva thus respectfully requests that FDA relist the '952 patent, confirm Teva's status as the first generic applicant to file a paragraph IV certification as to that patent, and acknowledge Teva's entitlement to a 180-day period of exclusivity on generic risperidone tablets.

ENVIRONMENTAL IMPACT

The relief requested by this petition would result in the recognition of a 180-day period of exclusivity for an ANDA applicant. Because the grant of the petition would not have an effect on the environment, no environmental assessment is required. *See* 21 C.F.R. § 25.31(a).

ECONOMIC IMPACT

Information on the economic impact of the action will be submitted if requested by the Commissioner.

CERTIFICATION

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

Sincerely,

DAJ