



May 18, 2007

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### **CITIZEN PETITION**

The undersigned, Sandoz, Inc. (“Sandoz”), submits this petition under Section 505A of the Federal Food, Drug, and Cosmetic Act (“FDC Act”), 21 U.S.C. § 355a, to request the Commissioner of Food and Drugs to grant the relief set forth in Section A below regarding the interplay between pediatric exclusivity and the approval of Abbreviated New Drug Applications (“ANDA”).

#### **A. Action Requested**

This petition requests that the Food and Drug Administration (“FDA”) not grant final ANDA approval for any generic versions of Toprol-XL®, metoprolol succinate extended-release tablets (“metoprolol”), 50 mg, until the expiration of pediatric exclusivity on March 18, 2008.

#### **B. Statement Of Grounds**

1. Factual Background

AstraZeneca, Inc. (“AstraZeneca”) is the holder of the approved New Drug Application (“NDA”) for metoprolol, which is sold under the trade name Toprol-XL. The Orange Book lists the following four patents for Toprol-XL, and also shows that AstraZeneca has been awarded pediatric exclusivity in connection with each patent:

<u>U.S. Patent No.</u>	<u>Patent Expiration Date</u>	<u>Pediatric Exclusivity Expiration Date</u>
4,927,640 (“the ’640 patent”)	May 22, 2007	November 22, 2007
4,957,745 (“the ’745 patent”)	September 18, 2007	March 18, 2008
5,001,161 (“the ’161 patent”)	September 18, 2007	March 18, 2008
5,081,154 (“the ’154 patent”)	September 18, 2007	March 18, 2008

In December 2003, Andrx Pharmaceuticals, LLC (“Andrx”) submitted ANDA 76-862 to market metoprolol in the 50 mg strength.<sup>1</sup> Andrx’s ANDA contained a paragraph IV certification to each of the four patents listed in the Orange Book. Within 45 days of receiving notice of Andrx’s paragraph IV certifications, AstraZeneca sued Andrx for alleged infringement of the ’154 patent and the ’161 patent.<sup>2</sup> AstraZeneca did not sue Andrx on the ’640 or ’745 patents. By being the first paragraph IV ANDA sponsor for 50 mg metoprolol, Andrx was entitled to 180-day exclusivity. Andrx subsequently relinquished that exclusivity.

Sandoz submitted ANDA 76-969 for 50 mg metoprolol. Sandoz also submitted paragraph IV certifications to each of the four Orange Book patents and notified AstraZeneca.<sup>3</sup> AstraZeneca did not sue Sandoz for infringement of either the ’640 patent or the ’745 patent. Sandoz received final ANDA approval on May 21, 2007.

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<sup>1</sup> Andrx has since become a wholly owned subsidiary of Watson Pharmaceuticals, Inc.

<sup>2</sup> The District Court held that these patents are invalid. AstraZeneca appealed to the Federal Circuit and a decision is expected in the next several months.

<sup>3</sup> The ANDA was submitted by Eon Labs, Inc., which was acquired by Sandoz.

To the best of our knowledge, KV Pharmaceutical Company (“KV”) also has a pending paragraph IV ANDA for 50 mg metoprolol. AstraZeneca did not sue KV for infringement of either the ’640 patent or the ’745 patent. KV has not yet received final ANDA approval for 50 mg metoprolol.

2. Discussion

Now that the ’640 patent has expired (on May 22, 2007), FDA may have to decide whether AstraZeneca’s pediatric exclusivity bars the approval of ANDAs during the period of pediatric exclusivity. The issue also will arise when the ’745 patent (among other patents) expires on September 18, 2007. For the reasons explained below, AstraZeneca’s pediatric exclusivity does bar ANDA approvals during these periods. In other words, FDA cannot issue final approval for any 50 mg metoprolol ANDAs until March 18, 2008 at the earliest.

- a. A Decision That Pediatric Exclusivity Does Not Bar ANDA Final Approvals If The Innovator Has Not Sued The ANDA Applicant Would Be Contrary To The Clear Language Of The Statute And Relevant Precedent

The clear and unambiguous language of the FDC Act conditions eligibility for pediatric exclusivity on the type of patent certification submitted for each patent. Under Section 505A(c)(2) of the FDC Act:

- (A) if the drug is the subject of –
- (i) a listed patent for which a certification has been submitted under [paragraph II] . . . and for which pediatric studies were submitted prior to the expiration of the patent (including any patent extensions); or
  - (ii) a listed patent for which a certification has been submitted under [paragraph III],

the period during which an application may not be approved under...or section 505(j)(5)(B) shall be extended by a period of six months after the patent expires (including any patent extension) or

- (B) if the drug is the subject of a listed patent for which a certification has been submitted under [paragraph IV] . . . , and in the patent infringement litigation resulting from the certification the court determines that the patent is valid and would be infringed, the period during which an application may not be approved under section...or section 505(j)(5)(B) shall be extended by a period of six months after the date the patent expires (including any patent extensions).

21 U.S.C. § 355a(c)(2).

The statute expressly addresses pediatric exclusivity in three situations: (1) when the ANDA contains a paragraph II certification; (2) when the ANDA contains a paragraph III certification; and (3) when the ANDA contains a paragraph IV certification but a court has determined that the patent is valid and would be infringed. In interpreting this statutory provision, FDA has applied its long-held policy and its regulations to convert all paragraph IV certifications to paragraph II certifications upon patent expiry. Under the clear language of the statute, pediatric exclusivity must be given effect at patent expiration, because the ANDA will contain a paragraph II certification (the original paragraph IV certification that automatically converts to a paragraph II certification). The courts have agreed with this interpretation.

The courts interpreted these pediatric exclusivity provisions in Ranbaxy v. FDA, 307 F. Supp. 2d 15 (D.D.C.), aff'd 96 Fed. Appx. 1 (D.C. Cir. 2004) (the “Ranbaxy case”). In that case, which involved an ANDA for fluconazole, the ANDA applicant filed a paragraph IV certification, and successfully defended a patent infringement suit, even to the extent of surviving a motion for summary judgment. Through no fault of the applicant, the patent expired before the court could issue a decision on the merits of the patent infringement case. The patent

holder, therefore, stipulated to the dismissal of the suit because the patent infringement suit necessarily would be dismissed as moot upon expiry of the patent. 307 F. Supp. 2d at 17.

In deciding whether pediatric exclusivity should attach, FDA concluded that the statute was ambiguous because it only expressly addressed pediatric exclusivity when there is a finding of validity and infringement. 307 F. Supp. 2d at 20. In light of this ambiguity, FDA decided to read the statute in conjunction with its regulation and policy governing amendments to patent certifications, which require an ANDA applicant to amend its patent certification to reflect a change in a patent's status. 307 F. Supp. 2d at 18; see 21 C.F.R. § 314.94(a)(12)(viii)(C)(1).

Although the ANDA applicant had validly maintained a paragraph IV certification up to and including the date of expiry, FDA concluded that the applicant's paragraph IV certification could not remain in effect past the expiration of the patent. "Instead, the FDA decided that upon patent expiry, the Paragraph IV certification became a Paragraph II certification (irrespective of [the applicant's] failure to amend its certification to reflect the change in each patent's status under 21 C.F.R. § 314.92(a)(12)(viii)(C)(1)) and that under a Paragraph II certification, the statute provides for a delayed ANDA approval for six months beyond expiration of the patent." 307 F. Supp. 2d at 18.

The district court upheld FDA's decision, holding that whether pediatric exclusivity attached turned on FDA's policy requiring paragraph IV certifications to convert to paragraph II certifications upon expiration of the patent:

The Court concludes that under the FDCA final approval of Ranbaxy's ANDA's did not automatically take place upon the dismissal of the underlying patent litigation, the expiration of the patent and the lifting of the "30 month" stay. Nor is *nunc pro tunc* approval available to Ranbaxy under the statute. Rather, at that "magic moment," midnight on January 29, 2004, the Paragraph IV

certifications became invalid, and either converted as a matter of law to Paragraph II certifications or became inaccurate, thereby creating both an obligation on Ranbaxy's part to amend its ANDAs to reflect patent expiry and an inability on the part of the FDA to approve the ANDAs in their inaccurate form. Under either scenario, the applicable provision of Section 505a(c)(2)(A)(i), and, under that provision, approval of Ranbaxy's ANDAs is delayed six months until July 29, 2004.

307 F. Supp. 2d at 21. The D.C. Circuit Court of Appeals, in an unpublished decision, expressly agreed that, upon expiration of the patent, the paragraph IV certification became invalid and exclusivity was governed by the provision pertaining to paragraph II certifications. Ranbaxy v. FDA, 2004 U.S. App. LEXIS 8311 (D.C. Cir. 2004).

FDA also applied the same long-standing policy in Mylan Labs, Inc. v. Thompson, 332 F. Supp. 2d 106 (D.D.C.), aff'd 389 F.3d 1272 (D.C. Cir. 2004) (the "Mylan case"). There, FDA also determined that Mylan's application must contain a paragraph II certification upon expiry of the patent, and both the district court and the D.C. Circuit adopted that reasoning. 332 F. Supp. 2d at 123; 389 F. 3d at 1278.

An ANDA applicant that has submitted a paragraph IV certification sufficiently before the expiration of the patent to allow the innovator to sue, but that has not been sued, is in precisely the same position as the ANDA applicant in the fluconazole case. In both situations, the ANDA applicant validly maintained a paragraph IV certification; in both cases the patent holder had the opportunity to sue prior to expiry; in both cases the patent holder failed to secure a court decision "that the patent is valid and would be infringed," the statutory prerequisite for pediatric exclusivity for those applications containing a paragraph IV certification under 21 U.S.C. § 355a(c)(2)(B). Accordingly, both situations must be treated similarly under the statute.

The holdings of the courts in the Ranbaxy and Mylan cases compel the conclusion that pediatric exclusivity attaches when an ANDA contains a paragraph IV certification at the time the patent expires, and the patent has not been determined invalid or not infringed in a patent suit brought against the ANDA applicant. By operation of FDA's policy, a paragraph IV certification must be amended, or deemed to have been amended, to a paragraph II certification at that time and pediatric exclusivity must attach. Application of this policy to KV (and any other applicant that may have submitted a paragraph IV certification to the '640 patent and to the '745 patent) is required by agency and court precedent.

Most recently, in the amlodipine litigation, Teva Pharmaceuticals USA, Inc. ("Teva") was a later ANDA applicant that was not sued for patent infringement pursuant to its paragraph IV certification. Teva contended that it was not blocked by pediatric exclusivity. FDA rejected that contention, and FDA's decision was upheld by the district court, which stated: "Until Teva succeeds in its own patent litigation with Pfizer or until administrative or legal action completely de-lists Pfizer's patent from the Orange Book, the FDA's decision to withhold market approval for Teva's generic drug remains in effect." Mylan Pharmaceuticals, Inc. v. Leavitt, 2007 U.S. Dist. LEXIS 31170 (D.D.C. Apr. 30, 2007), appeals pending (D.C. Cir.).

Like Teva, KV was a paragraph IV sponsor that was not sued for patent infringement. If Teva had no right to bypass pediatric exclusivity because it had not received final approval as of patent expiration, then it follows that the same result must apply to KV.<sup>4</sup> Any other result would

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<sup>4</sup> If anything, Teva had a stronger case for bypassing pediatric exclusivity than KV would have. In the amlodipine matter, Apotex Inc. ("Apotex"), another later ANDA sponsor, had obtained, before patent expiration, a decision from the Federal Circuit that the claims of the patent asserted against Apotex were invalid; however, the Federal Circuit's mandate had not issued by the time of patent expiration. Here, there would be no judicial decision (whether at the district court or Federal Circuit level) of invalidity or non-infringement with regard to any

be unlawful agency action, as it would result in the disparate treatment of similarly situated persons. See, e.g., Bracco Diagnostics, Inc. v. Shalala, 923 F. Supp. 20, 27-28 (D.D.C. 1997) (granting injunctive relief against FDA based on FDA's disparate treatment of one product as a device and another product as a drug).

- b. **A Decision To Ignore Pediatric Exclusivity When The ANDA Applicant Has Not Been Sued Would Contravene Congressional Intent, Create Opportunities To Manipulate The System, And Result In An Irrational Set Of Rules That Bear No Relation To The Statute**

The pediatric exclusivity statute was intended as a reward for applicants that conduct pediatric studies. That policy objective is unquestionably important because, for most drugs, there is otherwise no great incentive for applicants to conduct the expensive clinical studies necessary to determine whether and how their drugs affect children. As FDA has recognized in the past, “[b]y giving NDA sponsors an additional six-month period without generic competition, Congress elevated the goal of obtaining pediatric labeling information over the goal of approving generic copies of brand name drugs at the earliest possible time.” Letter from Gary Buehler to Mylan Technologies, Inc. and ALZA Corporation, June 22, 2004, p. 7. In fact, Congress was so desirous of making sure that pediatric exclusivity blocked ANDAs that it provided for a delay in ANDA approvals for up to 90 days where, at patent expiration, FDA is determining whether the eligibility conditions for pediatric exclusivity have been fulfilled. 21 U.S.C. § 355a(e). In multiple ways Congress expressed its intention that pediatric exclusivity confer a meaningful benefit on applicants that earn it.

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applicant and the '640 patent or the '745 patent. Thus, unlike amlodipine, there is no possible basis for the de-listing of either patent.

In addition, giving effect to pediatric exclusivity only if the patent holder has sued the ANDA applicant would be unfair to generic companies. Allowing later generic applicants less likely to be sued to receive ANDA approval while earlier applicants might not be approved because their lawsuits have not been resolved would be manifestly unfair, and create a distinction that could not be justified under any reasonable interpretation of the statute. Further, it would allow innovators to influence whether an ANDA would or would not be delayed by pediatric exclusivity. An NDA sponsor/patent holder could decide either not to sue or to sue and quickly resolve the suit to control whether its pediatric exclusivity would bar the ANDA approval for six months after patent expiration.

Finally, a solution that requires litigation to obtain effective pediatric exclusivity would be an enormous incentive for innovators to file unnecessary lawsuits, delaying generic competition, clogging the courts, and forcing branded and generic companies to spend millions of dollars on litigation filed for the purpose of perfecting pediatric exclusivity.

c. FDA Should Not Change Its Position Without Advance Notice to the Affected Companies

It has been commonly understood, based on FDA's previous decision and the Ranbaxy and Mylan cases, that, upon patent expiration, paragraph IV certifications convert to paragraph II certifications, and those ANDAs that have not received final approval will be blocked by pediatric exclusivity.

Where the application of a statute is commonly understood to be interpreted in a particular way, it is simply unfair for FDA to change that interpretation without an opportunity for the companies that make decisions representing millions of dollars based on their reasonable

understanding of the law to be heard. This is particularly true in a situation like this one, where the consequences for both the innovator and generic pharmaceutical industry are so large.<sup>5</sup>

**C. Environmental Impact**

The requested relief is entitled to a categorical exclusion under 21 C.F.R. § 25.31(a).

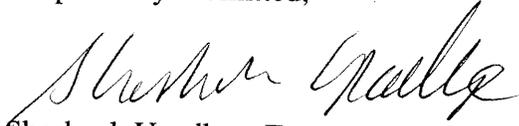
**D. Economic Impact**

Information on economic impact will be submitted upon request.

**E. Certification**

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

Respectfully submitted,

  
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<sup>5</sup> Moreover, while an agency may change its position, it must be able to present an adequate basis and explanation for doing so. Motor Vehicle Manufacturers Association of the United States v. State Farm Mutual Automobile Insurance Company, 463 U.S. 29, 57 (1983). Here, we are not aware of any reasonable basis that could support a change in agency position.

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