**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

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| ROXANE LABORATORIES, INC.,<br><br>Plaintiff,<br><br>v.<br><br>UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*,<br><br>Defendants. | Civil Action No. ___-_____ |

**PLAINTIFF ROXANE'S MEMORANDUM IN SUPPORT OF MOTION FOR PRELIMINARY INJUNCTION**

Pursuant to Fed. R. Civ. P. 65, Roxane Laboratories, Inc. ("Roxane") has moved the Court to enter a preliminary injunction ordering the Food and Drug Administration ("FDA") to deny Teva Pharmaceuticals USA, Inc. ("Teva") 180-day exclusivity and to approve Roxane's Abbreviated New Drug Applications ("ANDAs") to market generic losartan on April 6, 2010.[1] Roxane's claim here is straightforward. The only patent on which Teva bases its claim to 180-day marketing exclusivity has expired. Under the plain language of the Federal Food Drug and Cosmetics Act ("FFDCA"), 180-day exclusivity cannot be awarded based on an expired patent. FDA, however, in a March 26, 2010, decision, admittedly ignored the plain language of the statute and determined that Teva had not forfeited its 180-day exclusivity. FDA's sole support for its position is the D.C. Circuit's decision in *Teva Pharm. USA, Inc. v. Sebelius*, a case that does not apply here. *Teva* not only involved a different provision of the statute, but the

[1] Although FDA has not announced that Teva was the first to file an ANDA with a "paragraph IV" certification (the prerequisite to obtaining 180-day exclusivity), as noted by the D.C. Circuit, "Teva has every reason to believe" that it was the first filer for Cozaar and Hyzaar. *Teva Pharm. USA, Inc. v. Sebelius*, 595 F.3d 1303, 1307 (D.C. Cir.

reasoning behind the Court's decision, on which FDA relies, is inapplicable to the patent expiration forfeiture provision at issue in this case. FDA's March 26, 2010, decision violates the FFDCA and the Administrative Procedure Act ("APA").

Absent the immediate issuance of a preliminary injunction, Roxane will suffer irreparable harm, in the form of lost net sales of approximately $18 million for the twelve-month period between April 2010 and April 2011 – which translates to a 20 percent loss to Roxane's projected bottom line for that period. *See* Exhibit A (Declaration of Randy Wilson ("Wilson Decl.")) at ¶¶ 27-31. An exclusivity award would also cause Roxane to lose $3.3 million in fixed costs associated with preparing to launch its losartan products on April 6, 2010. *Id.* at ¶¶ 32-34. Moreover, awarding exclusivity to Teva would also significantly – and perhaps irretrievably – harm Roxane's ability to compete in other generic drug markets. *Id.* at ¶¶ 36-40. Finally, Roxane would also face non-monetary loss from an exclusivity award, in the form of a loss of goodwill and reputation within the generic drug industry. *Id.* at ¶ 41.

In a case such as this, where the benefit to Teva of the 180-day exclusivity is contrary to law, and the harm resulting to Roxane would be irreparable, the Court should enter a preliminary injunction ordering FDA to deny Teva 180-day exclusivity and to approve Roxane's ANDAs for generic losartan on April 6, 2010. The approval date of April 6, 2010 is fast approaching, and if that date were to come and go without approval for Roxane, the damage could not be undone.

## FACTUAL BACKGROUND

### A. The FFDCA and The Hatch-Waxman Amendments

The Hatch-Waxman Amendments ("Hatch-Waxman") to the FFDCA establish the regime for generic drug approvals in the United States. These provisions strike a balance

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2010). Accordingly, throughout this memorandum, Teva will be referred to as the applicant claiming rights to 180-day exclusivity for generic losartan.

between protecting the incentives for pharmaceutical innovation and encouraging generic competition to provide lower cost versions of branded drugs as early as possible. *See, e.g., Abbott Labs, Inc. v. Young*, 920 F.2d 984 (D.C. Cir. 1990) *citing* H.R. Rep. No. 98-857 (Pt. 1), at 14, 15, *as reprinted in* 1984 U.S.C.C.A.N. 2647, 2648; *see also* 54 Fed. Reg. 28872, 28874 (July 10, 1989). Hatch-Waxman contains certain requirements regarding the listing and certification of patents, and in certain cases provides for a 180-day period of generic exclusivity to encourage generic companies to challenge unenforceable, uninfringed, or invalid patents.

**1. New Drugs and Patent Information Requirements**

Before marketing a new drug in the United States, a manufacturer must submit a New Drug Application ("NDA") to FDA, and FDA must approve it. 21 U.S.C. § 355(a). Once approved, new drugs generally are referred to as "brand name drugs" because they are marketed under a trade name or trademark for the drug product.

An NDA must contain technical information to show that the product proposed for approval is safe and effective for its intended uses. 21 U.S.C. § 355(b)(1). In addition, an NDA applicant is required to submit to FDA information on each patent that claims the drug or a method of using the drug that is the subject of the NDA. *Id.*

Once FDA approves an NDA, it publishes the patent information submitted by the brand name drug manufacturer in the agency's "Approved Drug Products with Therapeutic Equivalence Evaluations," known as the Orange Book. 21 U.S.C. § 355(b)(1). The Orange Book includes an index of drug products by trade or established name as well as drug patent and exclusivity information. 21 C.F.R. § 314.53.

## 2. Generic Drugs and Patent Certification Requirements

A generic drug is a version of a brand name drug that is generally sold without a trade name or trademark for the drug product. Generic drugs are frequently prescribed in an effort to control healthcare costs. *See, e.g.,* Federal Trade Commission, *Generic Drug Entry Prior to Patent Expiration: An FTC Study* (July 2002) at 9 (citing Congressional Budget Office studies to show, *inter alia*, that in 1994 the availability of generic drugs saved consumers $8-$10 billion). Generic drugs represent an increasing portion of the medicines used in the United States. The introduction of a generic drug as an alternative to a brand name drug typically results in a dramatic reduction in the brand name drug's market share, particularly within the first six months. *See* Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry" (July 1998), *available at* http://www.cbo.gov/doc.cfm?index=655&type=0.

Before marketing a generic drug in the United States a manufacturer must receive approval from the FDA of an Abbreviated New Drug Application ("ANDA"). 21 U.S.C. § 355(a). An ANDA applicant must show that its generic drug is bioequivalent to the previously approved brand name drug. 21 U.S.C. § 355(j)(8)(B). FDA has established regulations and scientific guidance on how an applicant can demonstrate bioequivalence. *See, e.g.,* 21 C.F.R. § 320.1; FDA's Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (March 2003); FDA's Draft Guidance for Industry – Bioequivalence Recommendations for Specific Products (May 2007).

A generic drug manufacturer seeking FDA approval for a generic version of an approved brand name drug product must file one of four certifications with FDA for each patent listed in the Orange Book as claiming the brand name drug. These certifications are described as

paragraph I, II, III or IV certifications. A paragraph I certification states that no patent information has been filed; a paragraph II certification states that the patent has expired; and a paragraph III states the date on which the patent will expire. 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(III). A paragraph IV certification states that the patent claiming the brand name drug is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of the generic drug for which the ANDA is submitted. 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.50(i). Paragraph II and paragraph IV certifications are both relevant to the issues in this case.

If an ANDA applicant submits a paragraph IV certification to FDA, it is required to notify the patent owner and the holder of the approved NDA of its intent to seek approval of its ANDA and to compete with the brand name drug manufacturer before expiration of the listed patent. 21 U.S.C. § 355(j)(2)(B); 21 C.F.R. § 314.52(a). The filing of an ANDA with a paragraph IV certification is deemed to be an act of infringement, and if the brand name drug manufacturer does not sue for patent infringement within 45 days of receiving notice of the paragraph IV certification and if the ANDA meets the statutory requirements, approval of the ANDA "shall be made effective immediately." 35 U.S.C. § 271(e)(2); 21 U.S.C. § 355(j)(5)(B)(iii).

In order to encourage generic market entry, the first ANDA applicant to file an ANDA with a paragraph IV certification is eligible for a 180-day period in which it is the only ANDA applicant allowed to market a generic version of the brand name product. This is commonly referred to as "the 180-day exclusivity period." Specifically, if an ANDA with a paragraph IV certification "is for a drug for which a first applicant has submitted an application containing such a certification," the later-filed ANDA "shall be made effective on the date that is 180 days after" the first applicant has commenced marketing. 21 U.S.C. § 355(j)(5)(B)(iv).

### 3. Forfeiture of Generic Exclusivity

In 2003, Congress passed the Medicare Prescription Drug Improvement and Modernization Act of 2003 ("MMA"), which substantially amended the provisions of Hatch-Waxman pertaining to generic exclusivity. *See* Pub. L. 108-173, 117 Stat. 2066. Congress added section 505(j)(5)(D) to the FFDCA, providing six "forfeiture events" by which an ANDA applicant that might otherwise qualify for 180 days of protection from competition by other generic manufacturers could lose its eligibility for such exclusivity. The loss of 180-day exclusivity is triggered when any one of the forfeiture events occurs. One such "forfeiture event" occurs when "[a]ll of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period [have] *expired.*" 21 U.S.C. § 355(j)(5)(D)(i)(VI) (emphasis added).

## B. The Facts Leading Up To FDA's March 26, 2010, Decision

Merck & Co., Inc. ("Merck") is the holder of approved NDAs for losartan potassium tablets (sold under the brand name Cozaar®) and for losartan potassium hydrochlorothiazide tablets (sold under the brand name Hyzaar®). Cozaar® and Hyzaar® are prescribed to treat hypertension. As part of its NDAs, Merck submitted to the FDA information about the following patents for inclusion in the Orange Book: (1) U.S. Patent No. 5,138,069 ("the '069 patent"); (2) U.S. Patent No. 5,153,197 ("the '197 patent); and (3) U.S. Patent No. 5,608,075 ("the '075 patent"). The only patent at issue in this case is the '075 patent. Prior to March 15, 2010, the expiration date for the '075 patent was listed in the Orange Book as March 4, 2014.

On December 22, 2004 and May 31, 2005, Roxane filed Abbreviated New Drug Applications for generic losartan potassium tablets and losartan potassium hydrochlorothiazide tablets, respectively. Roxane's ANDAs contained paragraph IV certifications to the '075 patent.

Roxane received tentative FDA approval of its ANDA for losartan potassium tablets on May 25, 2006, and tentative approval of its ANDA for losartan potassium hydrochlorothiazide tablets on August 16, 2006. *See* Exhibit B (Letters from FDA granting Roxane tentative approvals). Teva, however, was the first generic manufacturer to file ANDAs for generic losartan products that contained a paragraph IV certification for the '075 patent, thereby making it eligible for a period of 180-day marketing exclusivity. After receiving notice of Teva's paragraph IV certification, Merck did not sue Teva within 45 days, and, as a result, the provision in the statute for a 30-month stay of Teva's approval was not triggered.

In lieu of suing Teva, Merck had, in March 2005, asked FDA to remove or "delist" the '075 patent from the Orange Book, and on April 28, 2005, it disclaimed the '075 patent. In response to Merck's request, FDA delisted the patent (but did not make it publicly known until April 18, 2008). *Teva,* 595 F.3d at 1307. Under similar circumstances involving other products, FDA had interpreted the delisting of a patent to constitute a forfeiture event under the MMA and had determined that the first filer of a paragraph IV certification was not eligible for 180-day exclusivity for a delisted patent. *E.g.*, Dorzolamide Hydrochloride-Timolo Maleate Ophthalmic Soluction, Dear ANDA Applicant Letter (Oct. 28, 2008).

Teva, in an effort to protect its 180-day exclusivity, sued FDA and filed a motion for a preliminary injunction. The Court consolidated the motion with trial on the merits, held that FDA's interpretation of the forfeiture provision was reasonable under the APA and entered judgment for FDA. *Teva Pharm. USA, Inc. v. Sebelius*, 638 F. Supp. 2d 42 (D.D.C. 2010). Teva appealed. On March 2, 2010, the D.C. Circuit ruled in Teva's favor, held that FDA's interpretation of Merck's delisting of the '075 patent as a forfeiture event violated the FFDCA,

and remanded the case "for further proceedings not inconsistent with this opinion." *Teva Pharm. USA, Inc. v. Sebelius*, 595 F.3d 1303, 1319 (D.C. Cir. 2010).

Shortly after the D.C. Circuit issued its opinion, FDA became aware that the '075 patent had expired on March 4, 2009 due to Merck's failure to pay maintenance fees. The United States Patent and Trademark Office ("USPTO") published this information regarding expiration of the '075 patent. *See* Exhibit C (USPTO, Official Gazette, 1341 OG 121 (Apr. 21, 2009)). After receiving confirmation from Merck that the '075 patent had expired, on or about March 15, 2010, FDA updated the Orange Book to reflect an expiration date of March 4, 2009 for the '075 patent. Roxane has since changed its paragraph IV certifications to paragraph II certifications, the certification reserved for patents that have expired. *See* Exhibit D (Amendments to Roxane's ANDA certifications). The expiration of the '075 patent raised new issues, none of which were previously litigated before the district court or the D.C. Circuit in *Teva*. That case concerned the discrete issue of whether the delisting of the '075 patent was a forfeiture event under 21 U.S.C. § 355(j)(5)(D)(i)(I) that would deprive Teva of 180-day exclusivity.

On March 16, 2010, upon remand from the D.C. Circuit and after hearing oral argument from the parties, the Court in *Teva* issued an Order: (1) declaring that "Teva has not forfeited its right to 180-day marketing exclusivity for generic losartan potassium products under 21 U.S.C. § 355(j)(5)(D)(i)(I)"; and (2) enjoining FDA from approving ANDAs for specific dosage forms of Cozaar® and Hyzaar® prior to the conclusion of Teva's 180-day period of marketing exclusivity. *See* Exhibit E (*Teva*, No. 09-1111 (RMC), March 16, 2010 Order). At FDA's request, the Court clarified that its Order extended only to the delisting provision, 21 U.S.C. § 355(j)(5)(D)(i)(I). *See* Exhibit F (*Teva*, No. 09-1111 (RMC), Order, March 26, 2010).

Later that day, FDA issued its decision on whether Teva's 180-day exclusivity survived expiration of the '075 patent. Although it conceded that the plain language of the statute required FDA to deny Teva 180-day exclusivity, FDA determined, based solely on its interpretation of the reasoning in the D.C. Circuit's decision in *Teva*, that Teva had not forfeited or otherwise lost its 180-day exclusivity. *See* Exhibit G (FDA letter to ANDA Applicants, Docket No. FDA-2010-N-0134 (March 26, 2010) ("FDA Decision") at 7); *id.* at 8 (stating "consistent with the reasoning of the Court of Appeals in *Teva*, despite having been delisted by the patent owner and having expired, the '075 patent nevertheless must be considered to remain a basis for 180-day exclusivity").

## ARGUMENT

Courts weigh four factors in deciding whether to grant a preliminary injunction: (1) whether there is a substantial likelihood that the movant will succeed on the merits; (2) whether the movant will suffer irreparable harm if the injunction is not granted; (3) whether the injunction will substantially injure other interested parties; and (4) whether the public interest would be furthered by the injunction. *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1066 (D.C. Cir. 1998); *Mylan Pharms., Inc. v. Shalala*, 81 F. Supp. 2d 30, 36 (D.D.C. 2000); *accord Mylan Pharms., Inc. v. Thompson,* 207 F. Supp. 2d 476, 483-84 (N.D. W. Va. 2001). These four factors "interrelate on a sliding scale and must be balanced against each other." *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1318 (D.C. Cir. 1998). As demonstrated below, Roxane has met each of these factors, and the Court should issue a preliminary injunction.

### I. There Is A Substantial Likelihood That Roxane Will Succeed On The Merits Of Its Claims.

Pursuant to Section 706(2)(A) of the APA, this Court "shall hold unlawful and set aside agency action . . . found to be arbitrary, capricious, an abuse of discretion, or otherwise not is

accordance with law." 5 U.S.C. § 706(2)(A). FDA's March 26, 2010, decision is contrary to the plain language of the Hatch-Waxman Amendments' 180-day exclusivity provisions and is not in accordance with law. The D.C. Circuit opinion in *Teva*, on which FDA bases its decision, does not apply to the effect of patent expiration on a first's applicant's claim to 180-day exclusivity, and, as explained below, there are sound reasons for treating the patent expiration issue here differently from the delisting issue that the Court addressed in *Teva*. As also explained below, Roxane is likely to prevail on its claims that FDA violated the FFDCA and the APA.

### A. The Plain Language of FFDCA Requires That FDA Deny Teva 180-Day Exclusivity.

#### 1. The Plain Language Of The 180-Day Exclusivity Provision Conditions The Exclusivity Period On ANDAs Containing Paragraph IV Certifications.

The 180-day exclusivity provision is found at 21 U.S.C. § 355(j)(5)(B)(iv) and provides:

> Subject to subparagraph (D), if the application contains a certification described in paragraph (2)(A)(vii)(IV) [a paragraph IV certification] and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

The central requirement in Section 355(j)(5)(B)(iv) is that the application must contain a "certification described in paragraph (2)(A)(vii)(IV)." Subclause IV provides "that such patent is invalid or will not be infringed by the manufacture, use, or sale for the new drug for which the application is submitted." 21 U.S.C. § 355(j)(2)(A)(vii)(IV). This type of certification is known as a paragraph IV certification.

Thus, based on the plain language of Section 355(j)(5)(B)(iv), in order for FDA to determine whether the first filer of an application for a drug containing a paragraph IV certification is entitled to 180-day exclusivity, it must determine initially whether a subsequent

application for the same drug also contains a paragraph IV certification. If a particular application does not contain a paragraph IV certification, then approval of that ANDA is not blocked by the 180-day exclusivity. Here, Roxane's application, which was filed after Teva's, contains a paragraph II certification, not a paragraph IV certification.[2] For this reason alone, based on the plain language of the statute, the 180-day exclusivity may not block approval of Roxane's ANDA.

In addition, Teva's application no longer contains a valid paragraph IV certification. Upon expiration of a patent, a paragraph IV certification becomes invalid as a matter of law. *See* 21 C.F.R. § 314.94(a)(12)(viii)(C)(1) (stating "an applicant *shall* amend a submitted certification if, at any time before the effective date of the approval of the application, the applicant learns that the submitted certification is no longer accurate") (emphasis added); *Ranbaxy Labs Ltd. v. FDA*, 96 Fed. Appx. 1 (D.C. Cir. 2004) (unpublished). Therefore, Teva's ANDA did not contain a valid paragraph IV certification after the '075 patent expired on March 4, 2009. Under the plain language of Section 355(j)(5)(B)(iv), FDA may not award Teva 180-day exclusivity because its application no longer contains a paragraph IV certification on which to base such exclusivity. FDA concedes in blunt terms that the foregoing is a correct statement of the law: "permitting the first applicant to retain exclusivity as to an expired patent requires FDA to take an action that is not sanctioned by the words of the statute." FDA Decision at 6.

[2] As explained below, upon expiration of a patent, a paragraph IV certification is invalid as a matter of law. Therefore, even if other applicants who also filed applications with paragraph IV certifications after Teva have not changed their certifications to paragraph II certifications, their paragraph IV certifications are invalid and are not subsequent applications containing paragraph IV certifications.

### 2. The Plain Language Of The Expired Patent Forfeiture Provision States That 180-Day Exclusivity Is Forfeited When The Patent For Which There Are Paragraph IV Certifications Expires.

There is a second reason why Teva is not entitled to a 180-day stay. The Hatch-Waxman Amendments, as modified by the MMA, 21 U.S.C. § 355(j)(5)(D)(ii), provides that "[t]he 180-day exclusivity period described in subparagraph (B)(iv) shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant." One "forfeiture event" occurs when "[a]ll of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period [] *expired.*" 21 U.S.C. § 355(j)(5)(D)(i)(VI) (emphasis added). The plain language of Section 355(j)(5)(D)(i) states that a forfeiture event occurs when the patent(s) for which there are paragraph IV certificates has expired.[3] Thus, even if somehow Roxane were forced to retain its paragraph IV certification and Teva were permitted to retain its paragraph IV certification, Teva would be require to forfeit its 180-day exclusivity because its patent has expired.

There is no basis in the statute for FDA to look behind the fact of expiration to the reason for such expiration. Nor is there any exception in the section for patents that have expired due to non-payment of maintenance fees. Under the clear and unambiguous language of the statute, if a patent has expired – for any reason – 180-day exclusivity has been forfeited. Accordingly, on March 4, 2009, when the '075 patent expired, a forfeiture event under 355(j)(5)(D)(i)(VI) occurred, and Teva forfeited its right to 180-day exclusivity. Again, FDA concurs. FDA Decision at 5 ("[T]here is no apparent statutory basis for the Agency to conclude that only some patent expirations result in forfeiture.").

## B. The D.C. Circuit's Decision In *Teva* Does Not Apply To This Case.

In *Teva*, the D.C. Circuit addressed whether a "forfeiture event" had occurred under Section 355(j)(5)(D)(i) as a result of FDA's decision to delist the '075 patent at Merck's request. The expiration of the '075 patent was not known to FDA or the Court until after the *Teva* decision, and the potential effect of the patent's expiration on Teva's claim to 180-day exclusivity was not before the Court. Accordingly, as this Court held in its March 26 Order (see p. 9, *supra*), the holding in *Teva*, which pertained solely to the "forfeiture event" of delisting, does not apply to this case. Moreover, as explained below, nor does the Court's "reasoning" in *Teva*.

The Court in *Teva* relied heavily on its decision in *Ranbaxy Labs. Ltd. v. Leavitt*, a case that was decided prior to the enactment of the MMA exclusivity provisions. In *Ranbaxy*, the Court invalidated an FDA policy that allowed brand manufacturers to deprive generic manufacturers of 180-day marketing exclusivity by delisting their patents. The Court held that the FDA delisting policy "'diminishe[d] the incentive for a manufacturer of generic drugs to challenge a patent . . . in the hope of bringing to market a generic competitor for an approved drug without waiting for the patent to expire.'" *Teva,* 595 F.3d at 1316 (quoting *Ranbaxy Labs. Ltd. v. Leavitt*, 469 F.3d 120, 126 (D.C. Cir. 2006)). And further that "FDA may not, however, change the incentive structure adopted by Congress." *Id.*

In *Teva*, FDA argued that it was free to allow brand manufacturers to delist patents under any circumstances, based on the plain language of the forfeiture provision and policy considerations underlying the Hatch Waxman Amendments. *Id.* at 1315-16. The Court rejected these arguments in favor of a "structural" argument. The Court held that even though the statute had been amended in 2003, the structure of the statute had not changed so as to allow a brand

[3] In this case, the '075 patent is the only patent for which Teva submitted a paragraph IV certification.

company to cause a generic company to forfeit its 180-day exclusivity by asking FDA to delist the patent. Accordingly, the Court rejected FDA's interpretation of the statute and remanded the case to the district court. *Id.* at 1318-19.

The reasoning articulated by the Court in *Teva* does not apply to the separate and distinct forfeiture event based on patent expiration. The plain language of that provision states that 180-day exclusivity is forfeited when the patent has expired. Thus, the correctness of FDA's decision to grant Teva the 180-day exclusivity for losartan depends entirely on whether the FDA may determine that the '075 patent has not "expired" within the meaning of the applicable provisions in the FFDCA. Unlike delisting, there is no action for FDA to take and no issue about whether the agency has the authority to take that action. Instead the lawfulness of FDA's decision turns solely on whether it correctly interpreted the term "expired" in the Act.

Congress did not provide a definition for the meaning of expired under Section 355(j)(5)(D)(i)(VI). FDA, however, does not monitor or administer patent law. It does not process patent applications, oversee adjudications related to patent issues or apply the patent law provisions on patent expiration. Indeed, FDA has "no expertise in making patent law judgments." *aaiPharma Inc. v. Thompson*, 296 F. 3d 227, 241 (4th Cir. 2002); *see also Watson Pharms., Inc. v. Henney*, 194 F. Supp. 2d 442, 445 (D. Md. 2001) ("[FDA] has no expertise – much less any statutory franchise – to determine matters of substantive patent law."); *see also* 59 Fed. Reg. 50338, 50345 (Oct. 3, 1994) ("FDA does not have the resources or the expertise to review patent information for its accuracy and relevance to an NDA."); *Id.* at 50350 ("[FDA] . . . reiterates that the agency does not have the expertise or the desire to become involved in issues concerning patent law . . . .").

In fact, since the enactment of Hatch-Waxman FDA has consistently stated that it cannot adjudicate patent issues in determining the appropriateness of the 180-day exclusivity, and, importantly, the courts have upheld the agency. *See Teva Pharms., USA, Inc. v. Leavitt*, 548 F. 3d 103, 106 (D.C. Cir. 2008) ("When it comes to the veracity of the patent information supplied by NDA holders, FDA operates in a purely ministerial role, relying on the NDA holders to provide the Agency with accurate patent information"); *Apotex, Inc. v. Thompson*, 347 F.3d 1335, 1349 (Fed. Cir. 2003) (finding "nothing in the Hatch-Waxman Act [] supports [the] argument that the FDA has a duty to screen Orange Book submissions by NDA applicants and to refuse to list those that do not satisfy the statutory requirements for listing . . . .").

As FDA and the courts have recognized, Congress delegated those responsibilities and all others related to patents to the USPTO. In this case, the issue concerns the meaning of "expiration" in the FFDCA. But patent expiration is a concept embedded in patent law and appropriately interpreted by the USPTO, and not FDA. In *Teva*, the Court was reviewing the agency's interpretation of the concept of delisting a patent from the Orange Book, which is a concept applicable only in the context of Hatch-Waxman, and which the Court determined could be adjusted to accommodate certain policies advanced by Hatch-Waxman. In this case, significantly, the FDA and now this Court, must interpret the term "expiration" which is fundamentally a concept of patent law and not of Hatch-Waxman or the FFDCA. Thus, in contrast to the *Teva* case, FDA and this Court's interpretation of "expiration" should reflect the use of that term in patent law and by the USPTO.

As applicable to this case, Congress stated in 35 U.S.C. § 41(b) that: "Unless payment of the applicable maintenance fee is received in the Patent and Trademark Office on or before the date the fee is due or within a grace period of 6 months thereafter, the patent will *expire* as of the

end of such grace period." (Emphasis added.) The USPTO lists the '075 patent as having expired on March 4, 2009 for failure to pay maintenance fees. *See* Exhibit C (USPTO, Official Gazette, 1341 OG 121 (Apr. 21, 2009)). Therefore, under the applicable patent law, and USPTO's application of that law to the '075 patent, the '075 patent has expired and Teva has forfeited its 180-day exclusivity.

In this case, FDA and the Court's duty is to determine the intent of Congress when it stated that all patents that have expired are forfeited (and that the 180-day exclusivity is available only when a second applicant has essentially certified under paragraph IV that the patent has not expired). The natural, straight forward and plain language reading of "expired" in the FFDCA is that it has the same meaning as "expired" in patent law. There is no basis in the FFDCA for concluding that "expired" has a different meaning. The term is not ambiguous and FDA had no authority to give it a different meaning than given explicitly in U.S. patent law.

If the reasoning in *Teva* were to be applied to the patent expiration forfeiture provision, FDA would be required, based on the incentive structure for 180-day exclusivity designed by Congress, to interpret the term expired in the forfeiture provision as not including expiration of a patent for failure to pay maintenance fees. To do otherwise would allow the brand manufacturer to unilaterally deprive the generic manufacturer of 180-day exclusivity in contravention of the incentive structure. This would mean that the term expired, as interpreted by FDA, would be in direct conflict with the very same term in the patent code. There is no basis in patent law, in the FFDCA, or insofar as we can determine in the legislative history of either statute, for concluding that Congress intended FDA, without any expertise whatsoever in patent law, to define expire in a manner that directly conflicts with the meaning of that term under patent law, and even FDA has indicated that it does not support such an interpretation.

The Court's decision in *Teva* involved a different forfeiture provision and different circumstances surrounding that provision. The delisting forfeiture provision did not implicate any statutory schemes involving other agencies. It also did not depend on a term that was given meaning elsewhere in the law. Instead, the delisting forfeiture provision involved withdrawal by the brand manufacturer of its patent information from the Orange Book. FDA has exclusive responsibility for that process, which is essential to the functioning of the 180-day exclusivity provisions. It is against the patents listed in the Orange Book that the generic manufacturers provide the certifications in their ANDAs. The same cannot be said of patent expiration. It is incidental to the 180-day exclusivity scheme designed by Congress, yet essential to the patent law. Unlike in *Teva*, where the Court stated that "the agency, however, offers not a single cogent reason why Congress might have permitted brand manufacturers to trigger subsection (CC) by withdrawing a challenged patent, outside the counterclaim scenario identified by Teva," such a cogent reason exists here. In order to maintain consistency between the FFDCA and the patent code, Congress must have intended for the same meaning of expired to apply in both statutory schemes. A necessary bi-product of Congress's intent to maintain uniformity would have been that a brand manufacturer, by not paying maintenance fees on his patents could unilaterally strip a generic manufacturer of 180-day exclusivity.

## II. Roxane Will Suffer Irreparable Harm If Teva Is Awarded 180-Day Exclusivity.

The second factor for this Court to consider is whether Roxane, absent the entry of a preliminary injunction, will suffer irreparable harm. Irreparable harm is an injury that cannot be redressed by a legal or equitable remedy at a later date. *See City of Moundridge v. Exxon Mobile Corp.*, 429 F. Supp. 2d 117, 127 (D.D.C. 2006).

As set forth in the attached declaration of Randy Wilson, Roxane would suffer substantial and irreparable harm by virtue of FDA's decision to deny Roxane approval of its ANDA for generic losartan on April 6, and instead to award Teva generic exclusivity for losartan on that date. Such harm would take the form, first, of approximately $18 million in reduced net sales for Roxane's generic losartan, which would translate to $15 million – or 20 percent – reduction in Roxane's projected annual profits for the period between April 2010 and April 2011. *See* Exhibit A (Wilson Decl.) at ¶¶ 27-31. Roxane would also lose as a result of FDA's expected award of exclusivity over $3 million in fixed costs associated with Roxane's efforts to plan to launch generic losartan in April 2010. *Id.* at ¶¶ 32-34.

This overall $18 million loss would significantly impair the company's ability to invest in new products and to compete in the overall generic marketplace in the future. *Id.* FDA's decision to grant Teva exclusivity and to deny Roxane approval of its ANDA on April 6 would also confer on Teva significant "first-to-market" advantages that extend beyond the generic losartan market itself, and would allow Teva to potentially capture Roxane's customers in other product areas. *Id.* at ¶¶ 36-40. Finally, FDA's decision would cost Roxane – a relatively small subsidiary of Boehringer-Ingelheim seeking to establish itself as a significant force in the generic drug industry – dearly in terms of loss of reputation and goodwill. *Id.* at ¶ 41.

While generally, courts have held that economic harm, standing alone, does not constitute irreparable injury sufficient to meet the preliminary injunction standard,[4] there are three factors present in this case that compel the conclusion that Roxane will suffer irreparable harm here, absent a preliminary injunction.

First, FDA's denial of approval to Roxane on April 6 would cause Roxane to lose a statutory entitlement to approval. *See Hi-Tech Pharm. Co., Inc. v. FDA*, 587 F. Supp. 2d 1, 11

(D.D.C. 2008) (collecting cases). As noted above, Roxane has received tentative approval from FDA to market generic losartan – that is, FDA has determined that Roxane's generic product is safe and effective and has met all the requirements for approval of an ANDA under the FFDCA. The *only* obstacle blocking its approval is FDA's anticipated – and, in Roxane's view, legally baseless – award of exclusivity to Teva on that date. Delayed approval of Roxane's ANDA for generic losartan would operate to deny the company for six critical months an approval to which FDA has acknowledged it is entitled, and which the law affords no basis for denying. This loss, added to the size of the economic harms suffered by the company as a result of the delayed approval, constitutes irreparable harm. *See Mylan*, 81 F. Supp. 2d at 43 (noting that generic drug makers "face continued harm" when their products are wrongfully kept off the market, but finding no irreparable harm because of financial health of generic manufacturer and its delay in moving for a temporary restraining order) (citations omitted).

Second, the losses that Roxane would suffer if FDA grants Teva exclusivity cannot be recovered from FDA (which enjoys sovereign immunity against a damages award in this case) or anyone else: in other words, there is no "adequate compensatory or other corrective relief . . . available at a later date, in the ordinary course of litigation" to Roxane to recover its anticipated losses. *Wis. Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985) (distinguishing between recoverable and unrecoverable loss and *quoting Virginia Petroleum Jobbers Ass'n v. FPC*, 259 F.2d 921, 925 (D.C. Cir. 1958)). *See also Alf v. Donley*, 666 F. Supp. 2d 60, 70 (D.D.C. 2009) (recognizing that inability to recoup lost income, due to sovereign immunity, can constitute irreparable harm); *Feinerman v. Bernardi*, 558 F. Supp. 2d 36, 51 (D.D.C. 2008) ("[W]here, as here, the plaintiff . . . cannot recover damages from the defendant due to the defendant's sovereign immunity . . ., any loss of income suffered by a plaintiff is irreparable *per se*") (*citing*

[4] *E.g., Mylan Pharm., Inc. v. Shalala*, 81 F. Supp. 2d 30, 42 (D.D.C. 2000).

*United States v. New York,* 708 F.2d 92, 93-94 (2d Cir. 1983)); *Clarke v. Office of Fed. Hous. Enter. and Oversight*, 355 F. Supp. 2d 56, 65-66 (D.D.C. 2004) ('[C]ourts have recognized that economic loss may constitute 'irreparable harm' where a plaintiff's alleged damages are unrecoverable." (citations omitted)).

Third, much of the harm that would be caused to Roxane by FDA's grant of exclusivity is difficult to quantify in monetary terms and therefore constitutes irreparable injury. *See Multi-Chanel TV Cable Co. v. Charlottesville Quality Cable Operating Co.*, 22 F.3d 546, 552 (4th Cir. 1994) ("[W]hen the failure to grant preliminary relief creates the possibility of permanent loss of customers to a competitor or the loss of goodwill, the irreparable injury prong is satisfied." (citation omitted)); *Alf*, 666 F. Supp. 2d at 70 (D.D.C. 2009) (damage to business reputation resulting in loss of customers can constitute irreparable harm); *see also* 11A Wright, Miller & Kane, Fed. Prac. & Proc. § 2948.1 (stating that "[i]njury to reputation or goodwill is not easily measurable in monetary terms, and so often is viewed as irreparable"). In particular, the "first-to-market" advantages that Roxane would be deprived of if it were not able to sell generic losartan at the same time as its competitors are very difficult to quantify, but are nonetheless likely significant, as they affect not only the losartan market itself, but also other current and future generic product markets. Wilson Decl. at ¶¶ 36-40. Additionally, by not being among the "first-to-market," Roxane will lose overall prestige and goodwill among potential customers and in the industry (*id.* at ¶ 41), losses that traditionally have been determined to be impossible to quantify and therefore a basis for a finding of irreparable harm. *Multi-Chanel TV Cable Co.*, 22 F.3d at 552; *Patriot, Inc.* v. *U.S. Dep't of Hous. & Urban Dev.*, 963 F. Supp. 1, 5 (D.D.C. 1997) (noting that "plaintiffs have demonstrated irreparable harm in damage to their business reputation") (citation omitted).

In short, this is a case in which Roxane, by virtue of FDA's award of exclusivity to Teva, will be deprived for six critical months of that to which FDA has essentially conceded Roxane is entitled under the FFDCA, and as a result will suffer substantial, and in certain cases unquantifiable harms, that it cannot recover in the ordinary course of litigation. Roxane has therefore satisfied the irreparable harm prong, especially given the "sliding scale" employed in this court on motions for a preliminary injunction, and the strength of Roxane's case on the merits. *Alf*, 666 F. Supp.2d at 70-71 (finding "some degree of irreparable harm" and, in combination with movant's likelihood of success on the merits, granting preliminary injunction).

## III. No Other Interested Party Will Be Substantially Harmed By The Preliminary Injunction Requested In This Case.

The other interested parties in this case are: (1) other generic companies with tentative approvals for their ANDAs who also want to go to market immediately without waiting for Teva to enjoy 180 days of exclusivity; (2) FDA; and (3) Teva, the recipient of the 180-day exclusivity. Neither the other generic companies similarly situated to Roxane, nor FDA will suffer any injury if FDA is enjoined from granting Teva 180-day exclusivity and is ordered to approve Roxane's ANDAs. Although FDA interpreted the statute as permitting exclusivity to survive expiration of the '075 patent, FDA believed it was not the right result, but instead was the result that was "consistent with the reasoning of the Court of Appeals." FDA Decision at 8 ("The Agency makes this finding even though it is not the result that FDA, as the agency that administers the statute, believes is appropriate given the relevant statutory language or the policies underlying the statute."). Accordingly, there is no injury to FDA. If Roxane prevails, FDA will be ordered to take the action that it believes to be the most appropriate.

Teva is the only interested party that will suffer any injury, but that injury is less substantial than the injury Roxane will suffer if it is kept off the market for 180 days while Teva

markets its losartan products free from any competition. Under no circumstances will Teva be excluded from the market entirely, as Roxane will be for 180 days if the Court does not grant this motion. Instead, Teva will go to market on April 6, 2010, along with Roxane and others. Teva's injury of having to compete with other generic companies on day one, instead of on day one hundred eighty-one pales in comparison to Roxane being denied access to the market for a full 180 days while Teva markets its products without any competition.

## IV. The Public Interest Supports Granting Roxane's Motion For Preliminary Injunction.

As this Court has recognized, the public benefits when agencies correctly apply the law. *Boehringer Ingelheim Corp. v. Shalala*, 993 F. Supp. 1, 2 (D.D.C. 1997) ("[T]he public interest is served by the lawful application of statutes and requiring an agency to act lawfully and within its obligations under the APA."); *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 30 (D.D.C. 1997) (recognizing that "there is [] a strong public interest in requiring an agency to act lawfully, consistent with its obligations under the APA"); *Fund for Animals, Inc. v. Espy*, 814 F. Supp. 142, 152 (D.D.C. 1993) ("'[T]here is a strong public interest in meticulous compliance with the law by public officials."). For the reasons explained above in Section I, the law will be applied correctly in this case if FDA is enjoined from granting Teva 180-day exclusivity and is ordered to approve Roxane's ANDA.

In addition, the correct application of the law will serve the purpose of the Hatch-Waxman Amendments – namely, to introduce quickly generic drugs to the marketplace, which will result in increased competition and reduced drug prices. *Serano Laboratories, Inc. v. Shalala*, 158 F.3d 1313, 1326 (D.C. Cir. 1998) ("The purpose of the Hatch-Waxman Amendments was, after all, 'to increase competition in the drug industry by facilitating the

approval of generic copies of drugs.'") (quoting *Mead Johnson Pharm. Group v. Bowen*, 838 F.2d 1332, 1333 (D.C. Cir. 1988)).

## CONCLUSION

For the foregoing reasons, Roxane's motion for a preliminary injunction should be granted.

Dated: March 30, 2010

Respectfully submitted,

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Carlos T. Angulo (DC Bar No. 466257)
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*Attorneys for Roxane Laboratories, Inc.*

# EXHIBIT A

**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

| | | |
|---|---|---|
| ROXANE LABORATORIES, INC.,<br><br>Plaintiff,<br><br>v.<br><br>UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*<br><br>Defendants. | ) | Civil Action No. ___-_____ |

DECLARATION OF RANDY WILSON IN SUPPORT OF PLAINTIFF'S MOTION FOR A PRELIMINARY INJUNCTION

I, Randy Wilson, declare as follows:

1. I am the Vice President of Scientific, Regulatory and Medical Affairs for Roxane Laboratories, Inc. ("Roxane"). Roxane is a Nevada corporation that is headquartered in Ohio. Roxane is a wholly-owned subsidiary of Boehringer Ingelheim, a German-based pharmaceutical company that develops and manufactures generic and brand-name drugs for sale in the United States and around the world.

2. I am submitting this declaration as Exhibit A to Roxane's motion for a preliminary injunction in the above case.

3. Roxane is the sponsor of Abbreviated Drug Application Nos. 77-732 and 77-459 for generic versions of Hyzaar® (losartan potassium/HCTZ tablets) and Cozaar® (losartan potassium tablets), respectively (collectively, "generic losartan"). Losartan is used to treat hypertension.

4. I have personal knowledge of the facts set forth herein, or believe them to be true based on my experience in the pharmaceutical industry, or on information I have received in the course of my employment. I am competent to testify on these matters.

5. I have been employed by Roxane for over nine years and have worked in the pharmaceutical industry for 27 years. My current responsibilities include developing and overseeing multisource portfolio business strategies, product selection, active pharmaceutical ingredient ("API") sourcing, API partnership contracts, intellectual property management and regulatory and medical activities. I serve on the committee that is responsible for developing multisource portfolio market assumptions for budgeting purposes and strategic pre-launch assessments. I am a member of the Leadership Team that is responsible for overseeing Roxane's ANDA filings.

6. I have been substantially involved at Roxane with the marketing of new generic drug products, including involvement with meeting the relevant statutory and regulatory requirements, the market impact of the launch of a new generic product, and the financial benefits that a company obtains from being the first to launch a generic product.

7. I have regularly participated in the formulation of market projections relating to the introduction of new generic drug products on the market, including for generic losartan. Such projections typically utilize standard industry formulas to project the price, market share, net sales, and profits that can be expected upon the launch of a new generic product.

8. I am also familiar with Roxane's generic losartan drug products, Roxane's marketing plans for these products, and the regulatory history of these products.

Brief Factual Background

9. Merck & Co., Inc. ("Merck"), the holder of FDA approvals for brand-name Hyzaar® and Cozaar®, caused three patents to be listed in FDA's Orange Book in connection with these products: U.S. Patent Nos. 5,138,069 ("the '069 patent"); 5,153,197 ("the '197 patent"); and 5,608,075 ("the '075 patent"). The '069 patent expired on February 11, 2010, and is not relevant here.

10. The '197 patent expired on October 6, 2009, but Merck is currently enjoying an additional statutory pediatric exclusivity award under that patent which expires on April 6, 2010.

11. The '075 patent was originally scheduled to expire in 2014. In March 2005, Merck requested that FDA delist the '075 patent from the Orange Book. In response to Merck's request, the FDA delisted the '075 patent (but did not make it publicly known until April 18, 2008). On March 4, 2009, the '075 patent expired because of Merck's failure to pay maintenance fees. Merck confirmed the expiration of the '075 patent on March 12, 2010, and the Orange Book reference to the '075 patent was then changed to reflect that expiration.

12. Roxane filed its ANDA for generic losartan potassium tablets on December 22, 2004, and for Losartan potassium/HCTZ tablets (50mg/12.5mg and 100mg/25mg) on May 31, 2005. Roxane's ANDAs each initially included "Paragraph IV" certifications regarding the '075 patent. On March 22, 2010, in light of the expiration of that patent, Roxane changed these Paragraph IV certifications to Paragraph II certifications. Exhibit D to Roxane's motion for a preliminary injunction.

13. Teva has asserted that it too has filed an ANDA for generic losartan and claims that it is entitled to 180-day exclusivity, under which it would be allowed to market and sell its

product free from other generic competition for 180 days, because it claims it was the first to file an ANDA for generic losartan containing a Paragraph IV certification to the '075 patent.

14. Because Merck's pediatric exclusivity under the '197 patent expires on April 6, 2010, it is anticipated that on that date, FDA will be in the position to approve, and will approve, ANDAs for generic losartan.

15. Roxane received tentative FDA approval of its ANDA for losartan potassium tablets on May 25, 2006, and tentative approval of its ANDA for losartan potassium/HCTZ tablets (150 mg/12.5mg and 100 mg/25mg) on August 16, 2006. Exhibit B to Roxane's motion for a preliminary injunction.

16. To the best of Roxane's knowledge, there is no obstacle standing in the way of FDA's final approval of Roxane's generic losartan ANDAs other than an award of generic exclusivity to another ANDA applicant for generic losartan, and Roxane is prepared to launch its generic losartan products on April 6, 2010.

17. In a letter to all ANDA applicants for generic losartan dated March 26, 2010, FDA indicated that a generic company otherwise entitled to 180-day exclusivity for generic losartan will not be found to have lost that exclusivity by virtue of the expiration of the '075 patent. Exhibit G to Roxane's motion for a preliminary injunction.

18. Roxane believes that FDA intends to award exclusivity to Teva for generic losartan on April 6, 2010, at which time it can first approve ANDAs for generic losartan. My understanding is that Teva, if approved and awarded exclusivity on that date, will immediately launch its generic losartan product.

19. FDA's award of generic exclusivity for losartan to Teva would block Roxane from receiving FDA approval and from marketing its generic losartan products until at least October 2010 - six months after the expected April 2010 launch by the exclusivity recipient.

20. In this action, Roxane takes the position that it is entitled to FDA approval of its generic losartan ANDAs on April 6, 2010, the first date such ANDAs are eligible for approval, because the expiration of the '075 patent requires, as a matter of law, all Paragraph IV certifications to that patent to be changed to Paragraph II certifications, and deprives FDA of any legal basis for awarding exclusivity for generic losartan to Teva or any other generic manufacturer. In addition, Roxane takes the position that no 180-day exclusivity period is warranted because the expiration of the '075 patent causes any exclusivity claimed on the basis of a certification to that patent to be forfeited as a matter of law.

21. Roxane seeks a preliminary injunction that would prevent FDA from delaying approval of Roxane's ANDA through an award of 180-day exclusivity for generic losartan.

Irreparable Harm to Roxane from a Grant of 180-Day Exclusivity

22. Roxane will suffer substantial and irreparable harm if this Court denies its request for a preliminary injunction, and FDA denies Roxane approval of its ANDA for generic losartan on April 6, 2010, on the basis of an award of generic exclusivity to Teva or any other generic losartan ANDA applicant.

23. My experience is that a grant of 180-exclusivity brings with it enormous benefits to the recipient, and causes substantial, corresponding harm to the generic companies that are forced to refrain from marketing and selling their products for 180 days because of the exclusivity.

24. The first and most obvious impact of exclusivity is that an ANDA applicant other than the exclusivity recipient could not market or sell its product for at least six months. If Roxane were excluded from the market for six months because of another company's generic exclusivity, Roxane would obviously lose 100 percent of its net sales for that period.

25. The second, less obvious impact of exclusivity is that it allows the recipient to establish market dominance that persists even after the exclusivity expires. In the generic drug industry, profits lost in the first six months due to a competitor's exclusivity are rarely recovered. The first generic entrant usually gains customers because it is the sole supplier of the generic drug. This often means that it can enter into advantageous long-term contracts that make it difficult for other generic manufacturers to do business even after the exclusivity has expired. Moreover, once a generic company establishes a relationship with a buyer (*i.e.*, becomes the "incumbent" supplier), that buyer will give the company the opportunity to continue to be the supplier of the new product – even after other companies are on the market. For example, if a new company enters the market and offers the buyer a better price on the generic drug, the buyer typically will give the incumbent supplier the right of first refusal – *i.e.*, the opportunity to meet that better price.

26. Roxane uses standard projections routinely utilized in the industry to estimate sales and profits from 180-day generic exclusivity on generic products, as well as to estimate the corresponding losses that occur when companies are blocked from marketing and selling their products due to the grant of exclusivity to another generic company. Additionally, Roxane has experiences from past generic launches to guide its estimates.

27. Based on its experience and industry practice in this area, Roxane has estimated that if it were to be able to receive FDA approval on or before April 6, 2010, and to launch and

begin marketing its generic losartan product on that date, it can expect a 15 percent share of the generic market for losartan. Assuming this market share, Roxane would expect to earn approximately $2 million per month in net sales of generic losartan for the first year it was on the market – or approximately $24 million.

28. If Roxane were to be blocked by Teva's generic exclusivity from marketing its product for six months, Roxane estimates that it would be able to maintain a 15 percent market share during the six months following the expiration of the exclusivity, but that to do so, it would have to make significant reductions in the pricing of its product - reductions that it would not have to make if it were to go on the market on the first marketing date for any generic losartan products. As a result of these reductions, Roxane estimates it would earn approximately $1 million in net sales per month, rather than the approximately $2 million in net sales per month Roxane estimates it would enjoy if it entered the market on April 6, 2010.

29. Thus, assuming an award of generic exclusivity in this case, Roxane would not only earn $0 per month in sales for the first six month exclusivity period; it would also earn only approximately $1 million in net sales per month for the first six months after the expiration of such exclusivity – or approximately $6 million. Thus, in this scenario, Roxane's lost net sales for the first 12 months arising out of the award of exclusivity for generic losartan would be approximately $18 million.

30. If Roxane were unwilling or unable to adjust its pricing in that second six month period, I believe it would lose all its projected net sales for that period. These projected sales relate to a single large retail customer that would likely choose to purchase generic losartan from another manufacturer unless Roxane gave it a substantial price discount to keep its business.

31. Even assuming that Roxane did adjust its price for generic losartan and earned some profits during the first six months its generic losartan products were on the market, the $18 million of lost net sales would translate into a loss of profits for Roxane in the amount of approximately $15 million between April 2010 and April 2011. This $15 million loss would amount to a loss of approximately 20 percent of the profits Roxane anticipates earning in that period if there were no exclusivity for generic losartan. The loss of these substantial profits will make it more difficult for Roxane to invest in the development of other products and will significantly impair its growth and wellbeing as a company.

32. In addition to the above-mentioned harms caused to Roxane by a grant of generic exclusivity in this case, the grant of exclusivity would also cause irretrievable loss to Roxane in the form of lost fixed costs associated with preparing to launch its product on April 6, 2010.

33. In order not to lose the above-described market advantages that would accompany being the one of the first generic entrants into the generic losartan market, Roxane, consistent with industry practice, has committed substantial resources to ensure that adequate quantities of its generic losartan products will be ready on time for approval and marketing on April 6, 2010. Many of these costs cannot be recovered.

34. Roxane has manufactured 30 commercial lots of losartan ("the active pharmaceutical ingredient," or "API") in anticipation of an April 2010 launch. Some of this API has already been converted to finished product, some of it is in the process of being converted to finished product ("product in process"), and some of it remains in raw form. Both the API and the finished product have expiration dates, after which they may not be sold. I estimate that Roxane will lose up to $3.3 million from the six-month delay in its launch of generic losartan, because of the amount of API (worth approximately $400,000), product in process (worth

approximately $2.4 million), and finished product (worth approximately $500,000) that will either have to be destroyed as a result of the delay, or will lose value because of shorter expiration dates.

35. A grant of exclusivity for generic losartan to Teva would also have important, harmful indirect effects on Roxane, in addition to the lost profits and fixed costs described above.

36. It is commonly recognized in the industry that the first drug company to offer a generic version of particular drug enjoys other important "first-to-market" advantages.

37. Purchasers of generic drugs, such as wholesalers and large retailers, want to purchase a new generic drug from the first company that is able to put its product on the market, so that they can make the new generic available immediately to their customers.

38. Access to major customers provides not only the opportunity to sell the new generic product exclusively, but also the opportunity to supply to these purchasers other, non-exclusive products that are part of the purchasers' portfolios. This is because wholesalers and large retailers prefer to order from a manufacturer who is in a position to offer a full product portfolio. When a manufacturer is blocked from selling one product by FDA's grant of generic exclusivity for that product, and therefore cannot meet the buyer's demand for a full line, a buyer may well shift to a competitor that can offer a full line rather than deal with multiple suppliers.

39. The advantages associated with being able to offer a group of products that includes a new generic drug, such as generic losartan, in a portfolio therefore extend well beyond the 180-day exclusivity period. Customers who shift to competitors that as a result of exclusivity can offer a full product line may never return.

40. The value of these selling opportunities differs vastly from customer to customer because each has a unique portfolio of products. Accordingly, the loss of these opportunities from being deprived exclusivity is extremely difficult to quantify.

41. Granting the 180-day exclusivity to Teva for generic losartan also would negatively impact Roxane's prestige and goodwill in the market. Being first to market and achieving 180-day exclusivity on generic products is a critical component of establishing and maintaining a reputation as a top-tier generic company. Customers expect that Roxane will be at the forefront of a product like generic losartan and if FDA's mistaken award of exclusivity prevents Roxane from being among the first to market that product, its reputation will suffer.

42. There would be no way to compensate Roxane for these losses, both monetary and otherwise, associated with the improper award of exclusivity for generic losartan.

I declare under penalty of perjury that the foregoing is true and correct.

Date: March 29, 2010

Randall S Wilson

Randy Wilson

# EXHIBIT B

DEPARTMENT OF HEALTH & HUMAN SERVICES

ANDA 77-459

Food and Drug Administration
Rockville MD 20857

MAY 25 2006

Roxane Laboratories, Inc.
Attention: Elizabeth A. Ernst
Associate Director, DRA-Multisource
1809 Wilson Road
Columbus, OH 43228

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 21, 2004, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Losartan Potassium Tablets, 25 mg, 50 mg, and 100 mg.

Reference is also made to your amendments dated June 30, and December 13, 2005; and January 31, February 16, and March 10, 2006.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the unresolved patent issues discussed below. Therefore, the ANDA is **tentatively approved.** This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices of the facilities used in the manufacture and testing of the drug product. This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Cozaar Tablets, 25 mg, 50 mg, and 100 mg, of Merck Research Laboratories, is subject to periods of patent protection. The following patents with their expiration dates (pediatric exclusivity added) are currently listed in the

agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

| Patent Number | Expiration Date |
|---|---|
| 5,138,069 (the '069 patent) | February 11, 2010 |
| 5,153,197 (the '197 patent) | April 6, 2010 |
| 5,210,079 (the '079 patent) | November 11, 2010 |
| 5,608,075 (the '075 patent) | September 4, 2014 |

With respect to the '079 patent, your ANDA contains a statement under section 505(j)(2)(A)(viii) of the Act indicating that the '079 patent is a method of use patent, and that this patent does not claim any indication for which you are seeking approval under your ANDA.

With respect to the '075 patent, your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that '075 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Losartan Potassium Tablets, 25 mg, 50 mg, and 100 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the act provides that approval of this ANDA shall be made effective immediately unless action was brought against Roxane Laboratories, Inc. (Roxane) for infringement of the '075 patent which was the subject of the paragraph IV certification. You have notified the agency that Roxane complied with the requirements of Section 505(j)(2)(B) of the Act, and that no action for infringement of the '075 patent was brought against Roxane within the statutory 45-day period, which action would have resulted in a 30-month stay under section 505(j)(5)(B)(111) of the Act.

Finally, with respect to the '069 and '197 patents, your ANDA contains a paragraph III certification under section 505(j)(2)(A)(vii)(III) of the Act to each of these patents stating that you will not market this drug product prior to the expiration of both patents, the later of which expires (with pediatric exclusivity added) on April 6, 2010. Therefore, final approval cannot be granted until (1) these patents have expired, and (2) the agency is assured there is no new information that would affect whether final approval should be granted.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval, and it should also identify changes, if any, in the conditions under which the ANDA was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the ANDA will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 501 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed to be approved for marketing under section 505 of the Act, and will not be listed in the "Orange Book." Should you believe that there are grounds for issuing the final approval letter prior to April 6, 2010, you should amend your ANDA accordingly.

For further information on the status of this ANDA, or prior to submitting additional amendments, please contact Simon Eng, PharmD, Project Manager, at (310) 827-5848, for further instructions.

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 77-732

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs
1809 Wilson Road
Columbus, OH 43228

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated May 31, 2005, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Losartan Potassium and Hydrochlorothiazide Tablets, 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg.

Reference is also made to our tentative approval letter issued on August 16, 2006, and to your amendments dated November 20, 2007; February 15, 2008; February 18, March 2, March 31, April 8, and April 17, 2009.

We have completed the review of this ANDA, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your ANDA at this time because of the patent issues noted below. Therefore, the ANDA remains **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your ANDA and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. This letter does not address issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The reference listed drug (RLD) upon which you have based your ANDA, Hyzaar Tablets, 50 mg/12.5 mg, 100 mg/12.5 mg and 100 mg/25 mg, of Merck and Co., Inc., is currently subject to periods of patent protection. The following patents with their expiration dates (with pediatric exclusivity added) are currently listed in the agency's publication titled Approved

Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

| U.S. Patent Number | Expiration Date |
|---|---|
| 5,138,069 (the '069 patent) | February 11, 2010 |
| 5,153,197 (the '197 patent) | April 6, 2010 |
| 5,608,075 (the '075 patent) | September 4, 2014 |

With respect to the '075 patent, your ANDA contains a paragraph IV certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that this patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Losartan Potassium and Hydrochlorothiazide Tablets, 50 mg/12.5 mg and 100 mg/25 mg, under this ANDA. You have notified the agency that Roxane Laboratories, Inc. (Roxane) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of the '075 patent was brought against Roxane within the statutory 45-day period, which action would have resulted in a 30-month stay of approval under section 505(j)(5)(B)(iii).

With respect to the '069 and '197 patents, your ANDA contains paragraph III certifications under section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market these drug products prior to the expiration of each of these patents. Therefore, final approval cannot be granted until the '197 patent expires, with pediatric exclusivity added, on April 6, 2010.

To reactivate your ANDA prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made. This amendment should be designated clearly in your cover letter as a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED".

In addition to the amendment requested above, the agency may request at any time prior to the date of final approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both

amendments may result in rescission of the tentative approval status of your ANDA, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this ANDA as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (cGMPs) are subject to agency review before final approval of the ANDA will be made. Such changes should be submitted as an amendment to the ANDA and categorized as representing either "major" or "minor" changes. The amendment will be reviewed according to OGD policy in effect at the time of receipt. Your submission of multiple amendments prior to final approval may also lead to a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under section 501 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under section 505 of the Act, and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final approval letter prior to April 6, 2010, you should amend your ANDA accordingly.

For further information on the status of this ANDA or upon submitting an amendment to the ANDA, please contact Dat Doan, RPh, Project Manager, at 240-276-8573.

Sincerely yours,

(See appended electronic signature page)

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

/s/
---
Robert L. West
5/14/2009 10:10:02 AM
Deputy Director, for Gary Buehler

# EXHIBIT C

# Notice of Expiration of Patents Due to Failure to Pay Maintenance Fee

## Notice of Expiration of Patents Due to Failure to Pay Maintenance Fee

35 U.S.C. 41 and 37 CFR 1.362(g) provide that if the required maintenance fee and any applicable surcharge are not paid in a patent requiring such payment, the patent will expire at the end of the 4th, 8th or 12th anniversary of the grant of the patent depending on the first maintenance fee which was not paid.

According to the records of the Office, the patents listed below have expired due to failure to pay the required maintenance fee and any applicable surcharge.

### PATENTS WHICH EXPIRED ON March 4, 2009 DUE TO FAILURE TO PAY MAINTENANCE FEES

| Patent Number | Application Number | Issue Date |
|---|---|---|
| 5,606,745 | 08/589,803 | 03/04/97 |
| 5,606,747 | 08/490,421 | 03/04/97 |
| 5,606,755 | 08/417,518 | 03/04/97 |
| 5,606,765 | 08/523,166 | 03/04/97 |
| 5,606,772 | 08/382,694 | 03/04/97 |
| 5,606,782 | 08/424,715 | 03/04/97 |
| 5,606,783 | 08/527,030 | 03/04/97 |
| 5,606,784 | 08/472,112 | 03/04/97 |
| 5,606,791 | 08/123,428 | 03/04/97 |
| 5,606,796 | 08/335,794 | 03/04/97 |
| 5,606,797 | 08/494,368 | 03/04/97 |
| 5,606,811 | 08/432,427 | 03/04/97 |
| 5,606,815 | 08/557,674 | 03/04/97 |
| 5,606,833 | 08/295,939 | 03/04/97 |
| 5,606,834 | 08/509,148 | 03/04/97 |
| 5,606,835 | 08/285,320 | 03/04/97 |
| 5,606,838 | 08/448,260 | 03/04/97 |
| 5,606,840 | 08/582,620 | 03/04/97 |
| 5,606,841 | 08/428,712 | 03/04/97 |
| 5,606,842 | 08/625,676 | 03/04/97 |
| 5,606,846 | 08/304,226 | 03/04/97 |
| 5,606,848 | 08/238,167 | 03/04/97 |
| 5,606,855 | 08/448,397 | 03/04/97 |
| 5,606,860 | 08/422,547 | 03/04/97 |
| 5,606,877 | 08/423,757 | 03/04/97 |
| 5,606,895 | 08/287,390 | 03/04/97 |
| 5,606,897 | 08/577,332 | 03/04/97 |
| 5,606,898 | 08/447,616 | 03/04/97 |
| 5,606,906 | 08/590,271 | 03/04/97 |
| 5,606,915 | 08/418,214 | 03/04/97 |
| 5,606,923 | 08/371,818 | 03/04/97 |
| 5,606,940 | 08/576,277 | 03/04/97 |
| 5,606,944 | 08/618,316 | 03/04/97 |
| 5,606,953 | 08/392,885 | 03/04/97 |
| 5,606,955 | 08/516,053 | 03/04/97 |

| | | |
|---|---|---|
| 5,607,816 | 08/531,853 | 03/04/97 |
| 5,607,824 | 08/281,398 | 03/04/97 |
| 5,607,827 | 08/531,714 | 03/04/97 |
| 5,607,834 | 08/420,443 | 03/04/97 |
| 5,607,835 | 08/473,589 | 03/04/97 |
| 5,607,847 | 08/275,053 | 03/04/97 |
| 5,607,857 | 08/489,859 | 03/04/97 |
| 5,607,862 | 08/497,731 | 03/04/97 |
| 5,607,863 | 08/163,860 | 03/04/97 |
| 5,607,865 | 08/381,425 | 03/04/97 |
| 5,607,869 | 08/595,369 | 03/04/97 |
| 5,607,885 | 08/636,970 | 03/04/97 |
| 5,607,887 | 08/367,265 | 03/04/97 |
| 5,607,888 | 08/452,939 | 03/04/97 |
| 5,607,894 | 08/487,847 | 03/04/97 |
| 5,607,904 | 08/421,224 | 03/04/97 |
| 5,607,911 | 08/635,630 | 03/04/97 |
| 5,607,920 | 08/278,617 | 03/04/97 |
| 5,607,924 | 08/469,177 | 03/04/97 |
| 5,607,925 | 08/333,017 | 03/04/97 |
| 5,607,935 | 08/232,029 | 03/04/97 |
| 5,607,955 | 08/431,425 | 03/04/97 |
| 5,607,958 | 08/394,757 | 03/04/97 |
| 5,607,959 | 08/495,509 | 03/04/97 |
| 5,607,960 | 08/532,573 | 03/04/97 |
| 5,607,961 | 08/517,999 | 03/04/97 |
| 5,607,962 | 08/591,329 | 03/04/97 |
| 5,607,967 | 08/330,518 | 03/04/97 |
| 5,607,971 | 08/413,797 | 03/04/97 |
| 5,607,995 | 08/583,218 | 03/04/97 |
| 5,607,996 | 08/318,395 | 03/04/97 |
| 5,608,017 | 08/449,250 | 03/04/97 |
| 5,608,028 | 08/189,984 | 03/04/97 |
| 5,608,029 | 08/402,067 | 03/04/97 |
| 5,608,035 | 08/190,788 | 03/04/97 |
| 5,608,041 | 08/591,565 | 03/04/97 |
| 5,608,042 | 08/594,487 | 03/04/97 |
| 5,608,057 | 08/518,303 | 03/04/97 |
| 5,608,058 | 08/189,700 | 03/04/97 |
| 5,608,059 | 08/356,187 | 03/04/97 |
| 5,608,060 | 08/351,469 | 03/04/97 |
| 5,608,063 | 08/412,409 | 03/04/97 |
| 5,608,075 | 08/371,937 | 03/04/97 |
| 5,608,079 | 08/473,509 | 03/04/97 |
| 5,608,080 | 08/424,504 | 03/04/97 |



| | | |
|---|---|---|
| 5,608,082 | 08/281,639 | 03/04/97 |
| 5,608,095 | 08/637,968 | 03/04/97 |
| 5,608,096 | 08/580,417 | 03/04/97 |
| 5,608,109 | 08/350,462 | 03/04/97 |
| 5,608,119 | 08/463,896 | 03/04/97 |
| 5,608,128 | 08/495,662 | 03/04/97 |
| 5,608,154 | 08/397,969 | 03/04/97 |
| 5,608,157 | 08/544,591 | 03/04/97 |
| 5,608,160 | 08/627,740 | 03/04/97 |
| 5,608,167 | 08/390,980 | 03/04/97 |

# EXHIBIT D

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

March 22, 2010

**Attention: Dat Doan**
**Martin Shimer**

**ANDA 77-459**
**Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg**

**Patent Amendment**

**Elizabeth A. Ernst,**
**Director,**
**Drug Regulatory Affairs and Medical Affairs**

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail
elizabeth.ernst@boehringer-ingelheim.com

Dear Mr. Doan:

We wish to amend ANDA 77-459, Losartan Potassium Tablets, 25 mg, 50 mg and 100 mg. Please find enclosed a revised patent certification.

Correspondence concerning this application should be directed to Elizabeth Ernst, Director, Drug Regulatory Affairs and Medical Affairs, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Sarah Smith, Associate, Drug Regulatory Affairs at (614) 241-4122.

Respectfully,

Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

# APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

*(Title 21, Code of Federal Regulations, Parts 314 & 601)*

*Form Approved: OMB No. 0910-0430*
*Expiration Date: April 30, 2009*
*See OMB Statement on page 2.*

**FOR FDA USE ONLY**

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Roxane Laboratories, Inc | March 22, 2010 |
| TELEPHONE NO. *(Include Area Code)* | FACSIMILE *(FAX)* Number *(Include Area Code)* |
| (614) 272-4785 | (614) 276-2470 |
| APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* | AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |
| Roxane Laboratories, Inc.<br>1809 Wilson Road<br>Columbus, Ohio 43228 | |

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 77-459

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
| Losartan Potassium | |

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt

CODE NAME *(If any)*

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Tablet | 25, 50 mg and 100 mg | Oral |

(PROPOSED) INDICATION(S) FOR USE:
1.) Treatment of hypertension 2.) Reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy
3.) Treatment of diabetic nephropathy

## APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug COZAAR® (losartan potassium) Tablets Holder of Approved Application Merck & Co., Inc.

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Patent Amendment

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED N/A THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

**ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)**
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attached.

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)**

| This application contains the following items: *(Check all that apply)* | |
|---|---|
| ☐ | 1. Index |
| ☐ | 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling |
| ☐ | 3. Summary (21 CFR 314.50 (c)) |
| ☐ | 4. Chemistry section |
| ☐ | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) |
| ☐ | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| ☐ | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) |
| ☐ | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) |
| ☐ | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) |
| ☐ | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) |
| ☐ | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) |
| ☐ | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) |
| ☐ | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) |
| ☐ | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) |
| ☐ | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) |
| ☐ | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) |
| ☒ | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |
| ☐ | 15. Establishment description (21 CFR Part 600, if applicable) |
| ☐ | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| ☐ | 17. Field copy certification (21 CFR 314.50 (l)(3)) |
| ☐ | 18. User Fee Cover Sheet (Form FDA 3397) |
| ☐ | 19. Financial Information (21 CFR Part 54) |
| ☐ | 20. OTHER *(Specify)* |

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE: |
|---|---|---|
| | Elizabeth A. Ernst, Director<br>Drug Regulatory Affairs and Medical Affairs | March 22, 2010 |

| ADDRESS *(Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| 1809 Wilson Road, Columbus, OH 43228 | ( 614 ) 272-4785 |

**Public reporting burden for this collection of information** is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Roxane Laboratories, Inc.
ANDA – Losartan Potassium Tablets 25, 50 and 100 mg
Module 1: Administrative Information and Prescribing Information

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Paragraph II Certification [21 CFR 314.94(a)(12)(i)(A)(2)]

In accordance with the Federal Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our Abbreviated New Drug Application for Losartan Potassium Tablets 25, 50 and 100 mg. Roxane Laboratories, Inc. certifies that in its opinion and to the best of its knowledge the following U.S. Patents as listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book, 30th Edition and supplements) for the drug Cozaar® Tablets, 25, 50 and 100 mg have expired as follows:

U.S. Patent No. 5,608,075 expired on September 4, 2009 with pediatric exclusivity
U.S. Patent No. 5,138,069 expired on February 11, 2010 with pediatric exclusivity

Paragraph III Certification [21 CFR 314.94(a)(12)(i)(A)(3)]

In accordance with the Federal Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our Abbreviated New Drug Application for Losartan Potassium Tablets 25, 50 and 100 mg. Roxane Laboratories, Inc. certifies that in its opinion and to the best of its knowledge U.S. Patent No. 5,153,197 as listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book, 30th Edition and supplements) for the drug Cozaar® will expire on April 6, 2010 with pediatric exclusivity. Roxane Laboratories, Inc. agrees not to market Losartan Potassium Tablets 25, 50 and 100 mg before April 6, 2010.

Statement of Method of Use [21 CFR 314.94(a)(12)(iii)]

In accordance with 505(j)(2)(A)(viii) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.94(a)(12)(iii) of the regulations the following statement is made: U.S. Patent No. 5,210,079 expiring on November 11, 2010 with pediatric exclusivity as listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book, 30th Edition and supplements), claims a method of use for the reference listed drug Cozaar®. Roxane Laboratories, Inc. states that the labeling for the drug product for which it is seeking approval does not include the indication that is covered by this method of use patent.

Roxane Laboratories, Inc.
ANDA – Losartan Potassium Tablets 25, 50 and 100 mg
Module 1: Administrative Information and Prescribing Information

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Statement of Exclusivity [21 CFR 314.94(a)(3)(ii)]

In the opinion of Roxane Laboratories, Inc., in accordance with the list published in the Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book, 30th Edition and supplements), there are no unexpired exclusivities for the listed drug, Cozaar® Tablets 25, 50 and 100 mg.

Prepared by: _____ 3/15/10
Elizabeth Ernst
Director, Drug Regulatory and Medical Affairs - Multisource Products
Date

Reviewed by: _____ 3/15/10
Julia Economou
Director, Product Development Strategy
Date

Approved by: _____ 3/15/10
Randall S. Wilson
Vice President, Scientific, Medical and Regulatory Affairs
Date

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

March 22, 2010

**Attention: Dat Doan**
**Martin Shimer**

**ANDA 77-732**
**Losartan Potassium Hydrochlorothiazide Tablets, 50/12.5 mg, 100/25 mg and 100/12.5 mg**

**Elizabeth A. Ernst,**
**Director,**
**Drug Regulatory Affairs and Medical Affairs**

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail
elizabeth.ernst@boehringer-ingelheim.com

**Patent Amendment**

Dear Mr. Doan:

We wish to amend ANDA 77-732, Losartan Potassium Hydrochlorothiazide Tablets, 50/12.5mg, 100/25mg and 100/12.5mg. Please find enclosed a revised patent certification.

Correspondence concerning this application should be directed to Elizabeth Ernst, Director, Drug Regulatory Affairs and Medical Affairs, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Sarah Smith, Associate, Drug Regulatory Affairs at (614) 241-4122.

Respectfully,

Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs

Boehringer Ingelheim
Roxane Laboratories

Ms. Kathleen D. Culver
Pre-Approval Manager
FDA District Office
6751 Steger Drive
Cincinnati, Ohio 45237-3097

March 22, 2010

**Elizabeth A. Ernst,**
**Director,**
**Drug Regulatory Affairs and Medical Affairs**

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail
elizabeth.ernst@boehringer-ingelheim.com

**Patent Amendment**
**ANDA # 77-732**
**Losartan Potassium - Hydrochlorothiazide Tablets, 50/12.5, 100/25 and 100/12.5 mg**

Dear Ms. Culver:

Enclosed please find the Certified True Copy of the Patent Amendment to the ANDA for Losartan Potassium - Hydrochlorothiazide Tablets, 50/12.5 mg, 100/25 and 100 mg/12.5 mg.

The archival and review copies have been submitted to the Office of Generic Drugs, CDER, FDA, Metro Park North II, 7500 Standish Place, Room 150, Rockville, Maryland 20855-2773.

Correspondence concerning this application should be directed to Elizabeth Ernst, Director, Drug Regulatory Affairs and Medical Affairs, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by fax at (614) 276-2470.

Respectfully,

Elizabeth Ernst,
Director, Drug Regulatory Affairs and Medical Affairs

**Certification of Submission to the District Office**

Roxane Laboratories, Inc. hereby certifies that a third (field) copy of the patent amendment for Losartan Potassium Hydrochlorothiazide Tablets, 50/12.5 mg, 100/25 mg and 100/12.5 mg has been submitted to the Cincinnati, Ohio District Office in accordance with 21 CFR 314.94(d)(5) and that the field copy is a "true copy" of the technical sections contained in the archival and review copies of the original application.

Elizabeth Ernst
Director, Drug Regulatory Affairs and Medical Affairs

3/22/10
Date

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

# APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

*(Title 21, Code of Federal Regulations, Parts 314 & 601)*

*Form Approved: OMB No. 0910-0338*
*Expiration Date: September 30, 2008*
*See OMB Statement on page 2.*

**FOR FDA USE ONLY**

APPLICATION NUMBER

**APPLICANT INFORMATION**

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Roxane Laboratories, Inc. | March 22, 2010 |
| TELEPHONE NO. *(Include Area Code)* | FACSIMILE *(FAX)* Number *(Include Area Code)* |
| 614-272-4785 | 614-276-2470 |
| APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* | AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |
| 1809 Wilson Rd.<br>Columbus, OH 43228 | NA |

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
| Losartan Potassium – Hydrochlorothiazide | NA |

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
Losartan Potassium, USP - 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl-phenyl)benzyl]-imidazole-5-methanol monopotassium salt

Hydrochlorothiazide, USP - 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide

CODE NAME *(If any)*
NA

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Tablet | 50mg-12.5mg, 100mg-12.5mg, 100mg-25mg | Oral |

(PROPOSED) INDICATION(S) FOR USE:
Indicated for the treatment of hypertension.

**APPLICATION DESCRIPTION**

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☒ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug: Hyzaar® (Losartan Potassium, USP – Hydrochlorothiazide, USP) Tablets — Holder of Approved Application: Merck & Co. Inc.

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Patent Amendment

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED N/A — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

**ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)**
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attachment.

**Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)**

Drug Master File References: Type II DMF 16996 – Teva Pharmaceuticals; Type II DMF 2115 – Teva Pharmaceuticals; Type III DMFs 1186 – Exxon Mobil Chemical; 1362 – Ineos Oelfins & Polymers; 1933 – Drug Plastics & Glass; 3782 – Unipac; 4837 – Owens-Illinois; 9869 – Owens-Illinois Closure Inc.; 10562 – Phillips-Sumika Polypropylene;

| This application contains the following items: *(Check all that apply)* | |
|---|---|
| ☐ | 1. Index |
| ☐ | 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling |
| ☐ | 3. Summary (21 CFR 314.50 (c)) |
| ☐ | 4. Chemistry section |
| ☐ | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) |
| ☐ | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| ☐ | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) |
| ☐ | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) |
| ☐ | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) |
| ☐ | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) |
| ☐ | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) |
| ☐ | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) |
| ☐ | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) |
| ☐ | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) |
| ☐ | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) |
| ☐ | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) |
| ☒ | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |
| ☐ | 15. Establishment description (21 CFR Part 600, if applicable) |
| ☐ | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| ☒ | 17. Field copy certification (21 CFR 314.50 (l)(3)) |
| ☐ | 18. User Fee Cover Sheet (Form FDA 3397) |
| ☐ | 19. Financial Information (21 CFR Part 54) |
| ☐ | 20. OTHER *(Specify)* |

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE: |
|---|---|---|
| | Elizabeth Ernst, Director,<br>Drug Regulatory Affairs and Medical Affairs | March 22, 2010 |

| ADDRESS *(Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| Roxane Laboratories, 1809 Wilson Rd., Columbus, OH 43228 | ( 614 ) 272-4785 |

**Public reporting burden for this collection of information** is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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Roxane Laboratories, Inc.
ANDA – Losartan Potassium-Hydrochlorothiazide Tablets, 50-12.5mg and 100-25mg
Module 1: Administrative Information and Prescribing Information

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Paragraph II Certification [21 CFR 314.94(a)(12)(i)(A)(2)]

In accordance with the Federal Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our Abbreviated New Drug Application for Losartan Potassium-Hydrochlorothiazide Tablets, 50-12.5mg and 100-25mg. Roxane Laboratories, Inc. certifies that in its opinion and to the best of its knowledge the following U.S. Patents as listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book, 30th Edition and supplements) for the drug Hyzaar® Tablets, 50-12.5mg and 100-25mg have expired as follows:

U.S. Patent No. 5,608,075 expired on September 4, 2009 with pediatric exclusivity
U.S. Patent No. 5,138,069 expired on February 11, 2010 with pediatric exclusivity

Paragraph III Certification [21 CFR 314.94(a)(12)(i)(A)(3)]

In accordance with the Federal Food, Drug and Cosmetic Act, Patent Certification is hereby provided for our Abbreviated New Drug Application for Losartan Potassium-Hydrochlorothiazide Tablets, 50-12.5mg and 100-25mg. Roxane Laboratories, Inc. certifies that in its opinion and to the best of its knowledge U.S. Patent 5,153,197 as listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book, 30th Edition and supplements) for the drug Hyzaar® 50-12.5mg and 100-25mg will expire on April 6, 2010 with pediatric exclusivity. Roxane Laboratories, Inc. agrees not to market Losartan Potassium-Hydrochlorothiazide Tablets, 50-12.5mg and 100-25mg tablets before April 6, 2010.

Statement of Exclusivity [21 CFR 314.94(a)(3)(ii)]

In the opinion of Roxane Laboratories, Inc., in accordance with the list published in the Approved Drug Products with Therapeutic Equivalence Evaluations (Electronic Orange Book, 30th Edition and supplements), there are no unexpired exclusivities for the listed drug, Hyzaar® Tablets, 50-12.5mg and 100-25mg.

Prepared by: _____ 3/15/10
Elizabeth Ernst
Director, Drug Regulatory and Medical Affairs - Multisource Products
Date

Reviewed by: _____ 3/15/10
Julia Economou
Director, Product Development Strategy
Date

Approved by: _____ 3/15/10
Randall S. Wilson
Vice President, Scientific, Medical and Regulatory Affairs
Date

# EXHIBIT E

**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

| | | |
|---|---|---|
| **TEVA PHARMACEUTICALS USA, INC.,** | ) | |
| **Plaintiff,** | ) | |
| **v.** | ) | **Civil Action No. 09-1111 (RMC)** |
| **KATHLEEN SEBELIUS, Secretary of Health and Human Services, *et al.*,** | ) | |
| **Defendants.** | ) | |

**ORDER**

On March 2, 2010, the U.S. Circuit Court of Appeals for the D.C. Circuit reversed the judgment of this Court. *See Teva Pharmaceuticals USA, Inc. v. Sebelius*, 638 F. Supp. 2d 42 (D.D.C. 2009), *rev'd* Nos. 09-5281 & 09-5308, 2010 WL 695446 (D.C. Cir. Mar. 2, 2010).[1] Noting that the district court had not yet addressed the appropriateness of each form of relief that Teva Pharmaceuticals USA, Inc. ("Teva") sought, the Circuit remanded for further proceedings not inconsistent with its Opinion. *See Teva*, 2010 WL 695446 at *15.

On remand and upon consideration of oral argument presented at a March 15, 2010, status conference, it is hereby

**ORDERED AND DECLARED** that Teva has not forfeited its right to 180-day marketing exclusivity for generic losartan potassium products under 21 U.S.C. § 355(j)(5)(D)(i)(I); and it is

[1] The Circuit issued the mandate in this case on March 12, 2010.

**FURTHER ORDERED** that the Food and Drug Administration ("FDA") is **ENJOINED** from approving any Abbreviated New Drug Application ("ANDA"), *see* 21 U.S.C. § 355(j), for a generic version of Cozaar®[2] 25mg, 50mg, and 100mg tablets other than Teva's ANDA No. 07-6958 prior to the conclusion of Teva's 180-day period of marketing exclusivity; and it is

**FURTHER ORDERED** that the FDA is **ENJOINED** from approving any ANDA for a generic version of Hyzaar® 50mg/12.5mg and 100mg/25mg tablets other than Teva's ANDA No. 07-7157 prior to the conclusion of Teva's 180-day period of marketing exclusivity.

Accordingly, this case is closed. This is a final appealable order. *See* Fed. R. App. P. 4(a).

**SO ORDERED.**

Date: March 16, 2010

/s/
ROSEMARY M. COLLYER
United States District Judge

[2] Merck and Co., Inc., holds two approved New Drug Applications, *see* 21 U.S.C. § 355(a) & (b), relating to losartan potassium/hydrochlorothiazide tablets, which it commercially markets under the brand name Cozaar® and Hyzaar®.

# EXHIBIT F

**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF COLUMBIA**

| | |
|---|---|
| **TEVA PHARMACEUTICALS USA, INC.,** | |
| **Plaintiff,** | |
| **v.** | **Civil Action No. 09-1111 (RMC)** |
| **KATHLEEN SEBELIUS, Secretary of Health and Human Services, *et al.*,** | |
| **Defendants.** | |

**ORDER**

On March 16, 2010, this Court ordered as follows:

It is hereby

ORDERED AND DECLARED that Teva has not forfeited its right to 180-day marketing exclusivity for generic losartan potassium products under 21 U.S.C. § 355(j)(5)(D)(i)(I); and it is

FURTHER ORDERED that the Food and Drug Administration ("FDA") is ENJOINED from approving any Abbreviated New Drug Application ("ANDA"), *see* 21 U.S.C. § 355(j), for a generic version of Cozaar®[1] 25mg, 50mg, and 100mg tablets other than Teva's ANDA No. 07-6958 prior to the conclusion of Teva's 180-day period of marketing exclusivity; and it is

FURTHER ORDERED that the FDA is ENJOINED from approving any ANDA for a generic version of Hyzaar® 50mg/12.5mg and 100mg/25mg tablets other than Teva's ANDA No. 07-7157 prior to the conclusion of Teva's 180-day period of marketing exclusivity.

[1] Merck and Co., Inc., holds two approved New Drug Applications, *see* 21 U.S.C. § 355(a) & (b), relating to losartan potassium/hydrochlorothiazide tablets, which it commercially markets under the brand name Cozaar® and Hyzaar®.

*See* Order [Dkt. #28]. Defendants now move to clarify, alter, or amend the March 16 Order asserting that the "further ordered" paragraphs rule out the possibility that Teva's exclusivity could be found to be forfeited under one of the other five forfeiture events provided for in the governing statute, 21 U.S.C. § 355(j)(5)(D)(i)(II) - (VI). They ask that the Order be amended to delete the "further ordered" paragraphs.

Teva objects, asserting that Defendants plan to declare that Teva forfeited its right to 180-day marketing exclusivity for generic losartan potassium products under the sixth forfeiture event, *see* 21 U.S.C. § 355(j)(5)(D)(i)(VI), because the patent that is the subject of the paragraph IV certification has expired due to the brand manufacturer's failure to pay maintenance fees.[2] Teva complains that Defendants raised this issue for the first time before the Circuit in opposing Teva's request for an emergency mandate.[3] Without commenting on this new issue, the Circuit granted the emergency mandate. Teva argues (1) that the granting of the mandate reveals the Circuit's rejection of the subparagraph VI forfeiture claim and (2) that the Circuit's holding that the failure to market provision does not permit a brand manufacturer to unilaterally vitiate a generic's exclusivity by delisting a patent under forfeiture event (I) applies with equal force to the claim Defendants make with regard to forfeiture event (VI). *See Teva Pharmaceuticals USA, Inc. v. Sebelius*, Nos. 09-5281 & 09-5308, 2010 WL 695446, * 14-15 (D.C. Cir. Mar. 2, 2010).

Defendants' motion to amend the March 16 Order is well-founded. The precise issue of a possible subparagraph VI forfeiture was not raised in the Complaint, and it was not addressed

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[2] The FDA opened the issue of a subparagraph VI forfeiture for comments under public docket number FCA-2010-N-0134 and plans to make a decision on March 26, 2010.

[3] The Circuit issued the mandate in this case on March 12, 2010.

by the Circuit in its March 2 Opinion or its March 12 mandate.[4]

Accordingly, Defendants' motion to amend [Dkt. # 29] is **GRANTED**; and it is

**FURTHER ORDERED** that this Court's March 16 Order [Dkt. # 28] is amended to provide as follows: it is hereby **ORDERED AND DECLARED** that Teva has not forfeited its right to 180-day marketing exclusivity for generic losartan potassium products under 21 U.S.C. § 355(j)(5)(D)(i)(I).

Accordingly, this case is closed. This is a final appealable order. *See* Fed. R. App. P. 4(a).

**SO ORDERED.**

Date: March 26, 2010

/s/
ROSEMARY M. COLLYER
United States District Judge

[4] If Defendants declare that Teva forfeited its exclusivity via one of the other five forfeiture events provided for in the statute, 21 U.S.C. § 355(j)(5)(D)(i)(II) - (VI), Teva may litigate the issue in a new lawsuit, filed as a case related to this one.

# EXHIBIT G

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

SENT VIA TELEFAX

Docket No. FDA-2010-N-0134

Dear ANDA Applicants:

This letter addresses whether the March 4, 2009 expiration of U.S. Patent No. 5,608,075 ('075 patent) affects the first applicant's eligibility for 180-day exclusivity for generic versions of Merck's Cozaar and Hyzaar drug products, and supplements the March 11, 2010 letter to ANDA applicants that was posted at www.regulations.gov in Docket No. FDA-2010-N-0134. As explained below, in light of the Court of Appeals' decision in Teva Pharms., USA, Inc. v. Sebelius, No. 09-5281 (D.C. Cir. Mar. 2, 2010) ("Teva slip op."), we have concluded that the expiration of the '075 patent does not result in a forfeiture of the first applicant's eligibility for exclusivity for ANDAs referencing Cozaar and Hyzaar.

**Background**

FDA has pending before it ANDAs referencing Cozaar (losartan potassium) Tablets and Hyzaar (losartan potassium and hydrochlorothiazide) Tablets. Among the patents submitted to FDA for Cozaar and Hyzaar, and thus relevant to the approval date for these ANDAs, is the '075 patent. FDA's Orange Book shows that the '075 patent was submitted by Merck, and that Merck later requested delisting of the patent. Merck has also recently informed FDA that the expiration date for the '075 patent should be revised from March 4, 2014, to March 4, 2009.[1] The Orange Book currently displays the March 4, 2009 expiration date for the '075 patent.

The timing of approval of ANDAs referencing Cozaar and Hyzaar will be affected by, among other things, any 180-day exclusivity under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act) available to a first applicant to challenge the '075 patent.[2] Under the Act, as amended by the MMA, a 180-day exclusivity period will not delay approval of any ANDA referencing Cozaar or Hyzaar if the exclusivity has been forfeited by the first applicant. See section 505(j)(5)(D)(i). The delisting of the '075 patent by Merck and the March 4, 2009 patent expiration date implicate two distinct 180-day exclusivity forfeiture provisions in the Act, sections 505(j)(5)(D)(i)(I) and (VI), respectively.

[1] Apotex notified FDA on March 9, 2010, that records of the U.S. Patent and Trademark Office (PTO) showed that the '075 patent had expired no later than March 30, 2009, due to non-payment of fees. Pursuant to the procedure described in 21 C.F.R. § 314.53(f), FDA sought information from Merck regarding the correct expiration date for the '075 patent. By letters of March 12, 2010, Merck stated that the correct expiration date for the '075 patent is March 4, 2009.

[2] The 180-day exclusivity for ANDAs referencing Cozaar and Hyzaar is governed by section 505(j)(5)(B)(iv) and related provisions, as modified by the Access to Affordable Pharmaceuticals provisions of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003) (the MMA).

**Delisting of the '075 Patent**

The U.S. Court of Appeals for the D.C. Circuit recently considered the effect of the delisting of the '075 patent on a first applicant's claim to 180-day exclusivity arising from a paragraph IV certification to that patent. Teva slip op. The court reviewed the delisting provision, section 505(j)(5)(D)(i)(I)(bb)(CC). The Agency had applied this provision in previous adjudications such that delisting of the patent for any reason by the NDA holder could result in forfeiture. Teva had asserted that FDA's interpretation of the delisting provision, although applied by FDA only in adjudications involving other drugs and different parties, was both subject to immediate review by the court and not supported by the statute.[3] The court, in a 2-1 decision, agreed with Teva on both grounds, and ruled that Merck's delisting of the '075 patent could not be the basis for forfeiture of exclusivity by the first applicant for generic Cozaar and Hyzaar. Slip op. at 29.

The D.C. Circuit, in response to a request from Teva, issued the mandate on an expedited basis on March 12, 2010, and remanded the case to the district court.[4] On March 26, 2010, the district court amended an order it had issued on March 16, 2010, to clarify that Teva has not forfeited its 180-day exclusivity under the Failure to Market provision, section 505(j)(5)(D)(i)(I). The district court stated that forfeiture due to patent expiration under section 505(j)(5)(D)(i)(VI) was not raised in Teva's Complaint and was not addressed by the D.C. Circuit in either its March 2, 2010 Opinion or in the March 12, 2010 issuance of the mandate. The district court ordered FDA to file a notice of its decision on the '075 patent expiration issue by 5 p.m. on March 26, 2010.

**Expiration of the '075 Patent**

When Teva first raised the question of 180-day exclusivity for ANDAs referencing Cozaar and Hyzaar before the district court in June 2009, FDA's records showed a March 4, 2014 expiration date for the '075 patent, and no outside party had brought any other expiration date for the patent to the Agency's attention. It was only after the March 2, 2010 Teva decision that FDA was notified by Apotex that the Patent and Trademark Office records showed that the '075 patent had expired for failure to pay fees. Now that Merck has confirmed to FDA that the '075 patent expired on March 4, 2009, FDA is addressing whether the patent expiration is a separate basis, apart from the delisting, for forfeiture of exclusivity.[5] To obtain comment from interested parties on the effect of the revised patent expiration date, FDA sent a letter to ANDA applicants on March 11, 2010, and opened a public docket for submission of comments (FDA-2010-N-0134).

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[3] On July 31, 2009, the U.S. District Court for the District of Columbia found that it had jurisdiction to review the matter, but granted judgment in favor of the government on the merits. Teva Pharms. USA, Inc. v. Sebelius, 638 F. Supp. 2d 42 (D.D.C. 2009).

[4] The Solicitor General is considering seeking rehearing of the Court of Appeals' decision. If rehearing is sought by the government and granted, the mandate would be recalled.

[5] In Teva, the government argued that the court should not address the dispute concerning 180-day exclusivity being pressed by plaintiff Teva until FDA had decided that issue. One basis for the government's position was the potential that factual and/or legal issues specific to the circumstances associated with the Teva claim would require an FDA analysis that would, at a minimum, be useful to the court in its decision-making. The court rejected that position. FDA believes that the new and complicated issues raised by the expiration of the patent at issue in this case provide a good example of why courts should await an agency decision in a particular matter rather than anticipate an agency's decision based on previous rulings in similar matters.

FDA has considered these submissions, as well as the relevant statutory provisions, regulations, and case law, in developing the views described in this response.[6]

Neither the district court nor the D.C. Circuit addressed the effect of the expiration of the '075 patent on the first applicant's eligibility for 180-day exclusivity, nor could they have done so because, as noted, when the courts ruled, neither they nor FDA was aware of the fact that the '075 patent had expired. Therefore, FDA is addressing the matter here. First, the Agency analyzes the issue as if it were writing on a clean slate, and interpreting and applying the statute without reference to the recent Teva decision. Second, the Agency describes the effect of the Court of Appeals' reasoning in the Teva delisting decision on the outcome in this particular patent expiration matter.

Merck, the NDA holder, has notified FDA that the sole patent giving rise to a claim of 180-day exclusivity for ANDAs referencing Cozaar and Hyzaar, the '075 patent, has expired. The patent information provided to FDA by the NDA holder controls for patent certification purposes. Teva Pharms., USA, Inc. v. Leavitt, 548 F.3d 103, 106 (D.C. Cir. 2008) ("FDA operates in a purely ministerial role, relying on NDA holders to provide the Agency with accurate patent information."). Therefore, in assessing the first applicant's claim to exclusivity, FDA will rely on Merck's statement that the '075 patent has expired.

The effect of a patent expiration on exclusivity is specifically addressed in the 180-day exclusivity provisions applicable to the ANDAs referencing Cozaar and Hyzaar. Section 505(j)(5)(B)(iv) of the Act, as amended by the MMA, states:

> Subject to subparagraph (D), if the application contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

"Subparagraph (D)" describes how a first applicant will forfeit its 180-day exclusivity period upon the occurrence of different types of a "forfeiture event" with respect to that applicant. Section 505(j)(5)(D). Among the defined events resulting in forfeiture is "Expiration of All Patents," which occurs when "[a]ll of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired." Section 505(j)(5)(D)(i)(VI). If this forfeiture event applies to a first applicant, the applicant forfeits exclusivity immediately upon the expiration of all patents as to which it qualified as a first

[6] Due to the limited amount of time remaining before April 6, 2010, when one or more ANDAs referencing Cozaar and Hyzaar are expected to be eligible for final approval, FDA initiated its request for comment on the effect of a March 4, 2009 expiration date for the '075 patent before it had received the confirmation from Merck of the correct expiration date. Further, because of the exceptional circumstances of this case, FDA is making a decision on 180-day exclusivity before April 6, 2010. Because of the possibility that relevant facts will change, it is FDA's usual practice to wait until at least one ANDA is otherwise eligible for final approval before the Agency makes decisions regarding 180-day exclusivity. Among other considerations underlying FDA's decision to address the patent expiration at this time is the Teva court's decision on 180-day exclusivity based on events involving the same patent at issue in the current matter.

applicant.[7] If there is only one patent that serves as a basis for 180-day exclusivity, when that patent expires, there will be no exclusivity for the drug product, and the Agency may approve any otherwise approvable ANDA.

Under FDA's longstanding interpretation, once a patent expires, eligibility for 180-day exclusivity based on that patent is extinguished. This is true under both the pre-MMA 180-day exclusivity provisions and the MMA exclusivity provisions applicable to the ANDAs referencing Cozaar and Hyzaar. The pre-MMA exclusivity provisions did not explicitly address whether 180-day exclusivity could survive the expiration of the patent. In addressing that statutory gap, FDA stated that once a patent expires, the correct certification to the patent is a "paragraph II" certification pursuant to section 505(j)(2)(A)(vii)(II)("that such patent has expired"). Once the application no longer contains a paragraph IV certification to the patent, the applicant no longer has a basis to obtain exclusivity as to that patent. This was held to be a reasonable interpretation of the pre-MMA exclusivity provision. Dr. Reddy's Labs., Inc. v. Thompson, 302 F. Supp. 2d 340, 356-57 (D.N.J. 2003). Moreover, even when the D.C. Circuit found in Ranbaxy Labs. Ltd. v. Leavitt, 469 F.3d 120 (D.C. Cir. 2006), that the pre-MMA exclusivity provisions would not permit an NDA holder's delisting of a patent to defeat a first applicant's claim on exclusivity, the court noted that "as Ranbaxy and Teva acknowledged at oral argument, the text and the structure of the [pre-MMA] statute suggest a distinction between expiration and delisting such that the first generic applicant may no longer retain exclusivity when the patent has expired." Id. at 126 n.3 (citing, inter alia, Dr. Reddy's Labs.). The forfeiture provision at section 505(j)(5)(D)(i)(VI), enacted in the MMA, thus embodies the familiar principle that 180-day exclusivity does not survive patent expiration.[8]

The issue presented by the expiration of the '075 patent is not whether, as a general rule, exclusivity will be forfeited pursuant to section 505(j)(5)(D)(i)(VI) upon the expiration of a patent, but whether a patent expiration for failure to pay fees is an exception to this rule.[9] The

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[7] The forfeiture events described in sections 505(j)(5)(D)(i)(II)-(V) are similarly immediate in effect if they are found to apply to a first applicant. It is interesting to note the contrast between these "immediate" forfeiture events, which provide no opportunity for the first applicant to use its exclusivity period once the forfeiture event has occurred, and the "Failure to Market" forfeiture event described in 505(j)(5)(D)(i)(I), which provides that upon the occurrence of certain events, rather than face immediate forfeiture, the first applicant will have the opportunity to begin commercial marketing of the drug product and thus start the running of its 180-day exclusivity period. For each of the events set out in 505(j)(5)(D)(i)(I)(bb), the first applicant has 75 days from the date of the specified event to begin marketing and receive the benefits of exclusivity. These provisions describe events that could occur with respect to "the first applicant *or any other applicant*" (emphasis added), as well as the patent delisting provision interpreted by the court in Teva. Presumably, Congress structured this exclusivity forfeiture provision so that, even if it is an applicant other than a first applicant that triggers a forfeiture by, for example, obtaining a final decision of non-infringement, the first applicant will nevertheless have a limited opportunity to benefit from being the first to challenge the patent. It is reasonable for FDA to conclude that, once at least one applicant has obtained a final court decision or settlement stating that the patent at issue is invalid or not infringed - or the patent has been delisted by the NDA holder because it does not meet the patent listing requirements - Congress sought to balance the benefits derived from the exclusivity incentive against the delay in the availability of generic drugs resulting from that exclusivity, and thus established a limit on the length of time during which the exclusivity would be available. In the case of patent expiration, Congress concluded that not even a limited 180-day exclusivity barrier to approval was warranted once the patent expired.

[8] The MMA did not revise the descriptions of patent certifications set forth at section 505(j)(2)(A)(vii).

[9] Teva, for example, appears to acknowledge that forfeiture will occur upon "natural patent expiry." March 18, 2010 Comment from Teva at 3.

Agency's view is that, if it were writing on a clean slate, it would interpret the statute so that patent expiration for any reason is a patent expiration forfeiture event. FDA believes that interpretation is most consistent with the plain meaning of the words of the statute and with a workable and appropriate approach to administration of the statute.

The text of the patent expiration forfeiture event provision does not provide a basis to distinguish between "natural patent expiry" and expiration for some other reason.[10] Section 505(j)(5)(D)(i)(VI) refers broadly to forfeiture when "all of the patents ... have expired." There is no language qualifying the type of expiration the Agency is to consider relevant for forfeiture.[11] Thus, there is no apparent statutory basis for the Agency to conclude that only some patent expirations result in forfeiture.

Some of the comments noted a number of reasons why FDA should create an exception to patent expiration forfeiture when the patent expires because the patent owner has failed to pay applicable fees. Among these are concerns about the lack of certainty regarding the expiration when the patent expires due to non-payment of fees. The March 18, 2010 comments from Teva and from Olsson, Frank & Weeda (OFW) identify situations in which a patent that has expired can be "revived" through payment by the patent owner of fees. Teva comment at 2-3; OFW comment at 3-4, 9-10.

Although it may well be the case that a patent that has expired for failure to pay fees could, in certain circumstances, be revived, this possibility alone is an inadequate basis to maintain that a later expiration date must control. As an initial matter, FDA will not change the applicable patent expiration date unless the NDA holder tells the Agency to do so. If the NDA holder (who is also likely to be the patent owner or licensee) notifies FDA that the patent has expired due to failure to pay fees, it can be presumed to have resolved at least to a reasonable certainty the finality of the patent expiration. Further, the concerns about uncertainty of expiration would presumably extend to all situations in which a patent has expired due to failure to pay fees, including those in which, although 180-day exclusivity is not an issue, reliance on a later expiration date could delay generic drug approvals. For example, if an NDA holder notified FDA that a patent on a drug as to which no ANDA had yet been submitted had expired due to failure to pay fees, but FDA refused to accept the NDA holder's representation because of uncertainty that the patent would remain "expired," future ANDA applicants would be required to submit patent certifications for a patent that may have its natural patent expiration years in the future. If the NDA holder is sufficiently certain its patent has expired that it notifies FDA of that fact, FDA believes that generic drug applicants are entitled to rely on that patent expiration date in seeking approval for their drug products.

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[10] Teva's comment does not define "natural patent expiry." For example, that term presumably could encompass both the expiration of the original 17 or 20 year term of a patent and the expiration of the term of certain patent claims that have been extended under 35 U.S.C. § 156. FDA's requirements do not limit the type of patent expiration information that may be submitted to FDA. 21 C.F.R. § 314.53.

[11] Based on the lengthy list of patents that expired on March 4, 2009, that was submitted as Attachment B to the March 9, 2010 Apotex letter raising the '075 patent expiration issue, expiration for failure to pay fees is not uncommon. Nonetheless, FDA is not aware of any other case in which it has been notified by an NDA holder that a patent that had been submitted to FDA and listed in the Orange Book has expired due to non-payment of fees.

Finally, in assessing what expiration date should control for purposes of 180-day exclusivity, it is appropriate for FDA to continue to rely on the NDA holder's representations to FDA. Teva v. Leavitt, 548 F.3d at 106. In this case, for example, although Apotex brought the question of the correct expiration date for the '075 patent to FDA's attention, the Agency did not consider the patent expiration date to be March 4, 2009 (and publish that date in the Orange Book) until Merck notified FDA that March 4, 2009 was the correct date. Had Merck maintained that the patent expiration date remained March 4, 2014, FDA would have retained the March 4, 2014 date in its records and relied on that date for patent certification, exclusivity, and application approval purposes. As stated in FDA's regulations,

> Unless the application holder withdraws or amends its patent information in response to FDA's request, the agency will not change the patent information in the list [the Orange Book]. If the new drug application holder does not change the patent information submitted to FDA, ... an abbreviated new drug application under section 505(j) of the act submitted for a drug that is claimed by a patent for which information has been submitted must, despite any disagreement as to the correctness of the patent information, contain an appropriate certification for each listed patent.

21 C.F.R. § 314.53(f). Even though information on patent expirations due to failure to pay fees is available from the PTO, it would not be an appropriate use of FDA resources for FDA to forgo its ministerial role in these matters and make its own assessments of patent expiration. In light of the commenters' concerns about the uncertain nature of these patent expirations, it would seem particularly important that the Agency continue to defer to the NDA holder's judgment regarding the expiration of its patent.

The expiration of a patent is a specific basis for forfeiture of exclusivity under the MMA, and it also necessitates a change in the ANDA applicants' patent certifications. The MMA patent certification provisions, like the pre-MMA provisions, state that the appropriate certification to an expired patent is a "paragraph II" (that such patent has expired). Section 505(j)(2)(A)(vii)(II). Upon expiration of a patent, a paragraph IV certification to the patent automatically becomes invalid. Ranbaxy Labs Ltd. v. FDA 96 Fed. Appx. 1 (D.C. Cir. 2004) (unpublished). Thus, a paragraph IV certification to the expired '075 patent is invalid, and the appropriate certification to the patent is "paragraph II." The 180-day exclusivity provision at section 505(j)(5)(B)(iv) directs that FDA determine whether an ANDA "contains a [paragraph IV] certification ... and is for a drug for which a first applicant has submitted an application containing such a certification." When a first applicant's ANDA does not contain a valid paragraph IV certification or a non-first applicant's ANDA no longer contains a paragraph IV certification, the 180-day exclusivity provision at section 505(j)(5)(B)(iv), by its own terms, does not apply.[12] Thus, permitting the first applicant to retain exclusivity as to an expired patent requires FDA to take an action that is not sanctioned by the words of the statute.

[12] The MMA also defines a "first applicant" eligible for exclusivity as an applicant that, among other things "submits a substantially complete application that contains *and lawfully maintains* [a paragraph IV certification]." Section 505(j)(5)(B)(iv)(II)(bb) (emphasis added). An applicant cannot lawfully maintain a paragraph IV certification to a patent that has expired.

For the reasons described above, FDA concludes that if it were assessing this issue without reference to the Teva decision, it would find that, under the plain language of the statute, because the '075 patent will have expired by the time any ANDA referencing Cozaar or Hyzaar is ready for approval, any first applicant previously eligible for 180-day exclusivity as to the '075 patent forfeits that exclusivity. Moreover, even if the statutory language is considered ambiguous, FDA concludes loss of exclusivity under these circumstances is most consistent with the statute's text and goals, and provides the most reasonable way of administering the statute.

**Effect of Teva Decision on Patent Expiration Forfeiture**

FDA does not believe it can assess the effect of expiration of the '075 patent due to nonpayment of fees on exclusivity for generic Cozaar and Hyzaar without consideration of the D.C. Circuit's Teva decision and the reasoning in that decision regarding the delisting of the '075 patent.

In Teva, the D.C. Circuit concluded that Teva is entitled to exclusivity, in spite of the fact that the NDA holder has requested delisting of the patent, based on the "structure" of the statute, regardless of the words of the statute.[13] Moreover, the court concluded that this analysis was appropriately considered under "Chevron step one," i.e., that there was no statutory ambiguity that FDA is free to resolve based on its understanding of the statute and the industry it regulates. Slip op. at 29. After rejecting Teva's "linguistic" argument, slip op. at 24, the court adopted a "structural argument" based on the pre-MMA Ranbaxy case. Slip op. at 24. It found that the structure of the MMA exclusivity provisions, as with the pre-MMA exclusivity provision considered in Ranbaxy, does not permit an NDA holder to "unilaterally" deprive the generic applicant of its exclusivity on the basis of delisting.[14] Slip op. at 5, 29. This reasoning thus appears to preclude a forfeiture of exclusivity on the basis of a patent expiration where the expiration is in the control of the NDA holder. Because the '075 patent expired due to Merck's

[13] The D.C. Circuit specifically stated:

> We see nothing in the 2003 amendments to the Food, Drug, and Cosmetic Act that changes the structure of the statute such that brand companies should be newly able to delist challenged patents, thereby triggering a forfeiture event that deprives generic companies of the period of marketing exclusivity they otherwise deserve. For that reason, the interpretation of the statute that the FDA has adopted in two recent adjudications, and that it regards itself as bound by law to apply to Teva's ANDAs for losartan products, fails at Chevron step one.

Slip op. at 29.

[14] The Teva court's decision suggests that it believed the statute would permit innovator companies to delist patents at will to deprive the first applicant of exclusivity, i.e., that "Brand manufacturers are . . . free to delist challenged patents whenever they please ...." Slip op. at 24, 25. Patent listing is not optional. In fact, NDA holders are required by statute to provide patent information to FDA if, but only if, the patent claims the drug product or an approved use of the product, and if "a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." Section 505(b)(1). Thus, the patent holder may not simply withdraw or change patent information previously submitted to FDA because of some desire to interfere with the 180-day exclusivity of a potential generic competitor. It is, of course, true that FDA does not have the patent expertise to enforce the statutory requirement that appropriate patents be listed or delisted. Because the continued listing of an inappropriate patent, with the resulting blocking of competition, can place the NDA holder in jeopardy of antitrust damages, considerations of antitrust liability may well be factors in innovator decisions to withdraw patent information previously submitted. In fact, settlement of disputes between innovator companies and the Federal Trade Commission can result in patent delistings. See, e.g., Report, In the Matter of Bristol-Myers Squibb Co., Docket No. C-4076 (Federal Trade Comm'n, June 20, 2003) (describing delisting of patents for Serzone, Buspar, and Taxol). The Teva decision could affect the availability and effectiveness of delisting as a remedy.

failure to pay applicable fees, that expiration, consistent with the Court of Appeals' reasoning in Teva, is not a grounds for forfeiture of the first applicant's exclusivity. Although FDA believes this result is inconsistent with the plain language of the statute, as discussed above, it believes it is appropriate to apply the Court of Appeals' reasoning to the present facts. In the event the D.C. Circuit reconsiders and revises the decision in Teva, FDA reserves the right to revisit these conclusions regarding 180-day exclusivity for ANDAs referencing Cozaar and Hyzaar.

FDA thus finds that, consistent with the reasoning of the Court of Appeals, despite having been delisted by the patent owner and having expired, the '075 patent nevertheless must be considered to remain a basis for 180-day exclusivity. FDA will not approve any other ANDA referencing Cozaar or Hyzaar until the first applicant has received approval of its ANDA, begun commercial marketing, and the 180-day exclusivity period has expired.[15] The Agency makes this finding even though it is not the result that FDA, as the agency that administers the statute, believes is appropriate given the relevant statutory language or the policies underlying the statute.

**Conclusion**

For the reasons described above, the Agency has concluded that, in light of the D.C. Circuit's decision in Teva, the March 4, 2009 expiration of the '075 patent for failure to pay applicable fees does not result in forfeiture of the first applicant's 180-day exclusivity for ANDAs referencing Cozaar and Hyzaar. If you have any questions regarding this decision, please contact Dave Read, Regulatory Counsel, Office of Generic Drugs at (240) 276-9310.

Sincerely,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

[15] We note that even though the Teva litigation has proceeded on the assumption that a first applicant will receive approval and begin marketing promptly after all applicable patent and exclusivity barriers expire, the rule derived from this case would presumably apply even if the first applicant did not promptly obtain approval and begin to market, e.g., because of changes in the application that required additional review, unsatisfactory inspections, or unavailability of materials. In such cases, FDA could be barred from approving otherwise approvable subsequent ANDAs until either the first applicant eventually triggered its exclusivity with commercial marketing and the 180-day period expired, or the delisted patent expired "naturally," with the result that competition from lower priced generic drugs would be delayed.

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GARY J BUEHLER
03/26/2010