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## CITIZEN PETITION

Pfizer Inc ("Pfizer") submits this petition under sections 505, 505A, and 506A of the Federal Food, Drug, and Cosmetic Act ("FDCA") to request that FDA apply Pfizer's pediatric exclusivity rights for amlodipine to NDA 20-364, the Novartis Pharmaceuticals Corporation ("Novartis") new drug application ("NDA") for Lotrel® (amlodipine besylate; benazepril hydrochloride). As set forth in this petition, Pfizer believes that FDA is required, as a matter of law, to rescind approval of Novartis's Lotrel® NDA, and withhold approval of any supplements to the Lotrel® NDA, in order to effectuate the pediatric exclusivity that FDA granted to Pfizer for amlodipine under section 505A of the FDCA.

### A. Actions Requested

Pfizer requests that FDA take the following actions to enforce its pediatric exclusivity for amlodipine:

1. Deem the Lotrel® NDA a section 505(b)(2) application subject to Pfizer's pediatric exclusivity for amlodipine;

2. Rescind final approval of the Lotrel® NDA and reclassify approval as tentative; and

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3. Withhold final approval of any supplemental NDA ("sNDA") submitted by Novartis to its Lotrel® NDA because any such sNDA is a section 505(b)(2) NDA subject to Pfizer's pediatric exclusivity for amlodipine.[1]

## B. Statement of Grounds

### I. Background

#### 1. Pfizer's Pediatric Exclusivity for Amlodipine

Pfizer holds NDA 19-787, the reference listed drug for amlodipine besylate, which Pfizer markets under the trade name Norvasc®. Pfizer owns, and submitted for listing in FDA's "Orange Book," two patents claiming amlodipine: United States Patent 4,572,909 ("'909 patent") and United State Patent 4,879,303 ("'303 patent").

In November 2001, FDA granted Pfizer pediatric exclusivity for amlodipine pursuant to section 505A of the FDCA. As reflected in the Orange Book, the pediatric exclusivity associated with the '909 patent expired on January 31, 2007, and the pediatric exclusivity for the '303 patent expires on September 25, 2007. Pfizer has successfully enforced the pediatric exclusivity associated with the '303 patent by prevailing in patent litigation against every ANDA applicant that has challenged the patent. Thus, no generic amlodipine besylate product will be marketed prior to expiration of the pediatric exclusivity for amlodipine (i.e., prior to September 25, 2007).

#### 2. Pfizer's License Agreement With Novartis Regarding Lotrel®

In 1989, Pfizer executed a License Agreement with Ciba-Geigy Corp., a predecessor to Novartis, authorizing Ciba-Geigy to seek approval of, and market, a combination product containing amlodipine and benazepril. The License Agreement granted Ciba-Geigy a license under Pfizer's '909 and '303 patents, and also a right of reference to Pfizer's IND and NDA for amlodipine. Pursuant to the License Agreement, in June 1993 Pfizer filed with FDA a right of reference to Pfizer's approved NDA 19-787.[2] This right of reference enabled Novartis to submit a section 505(b)(1) application for Lotrel®. *See* 21 C.F.R. §314.50(g); *see also* FDA, *Applications Covered by Section 505(b)(2) (Draft Guidance)*, at 3 (1999) ("*505(b)(2) Draft Guidance*") ("If the applicant had a right of reference to all of the information necessary for approval, even if the applicant had not conducted the studies, the application would be considered a 505(b)(1)

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[1] Concomitantly with this petition, Pfizer is submitting a Petition for Stay of Action requesting that FDA withhold approval of any supplements to the Lotrel® NDA until the expiration of the amlodipine pediatric exclusivity period.

[2] At Novartis's request, and under the terms of the License Agreement, Pfizer submitted a revised right of reference in July 2006. The purpose of the July 2006 submission was to clarify that Novartis was authorized to "refer to Pfizer's Investigational New Drug Application IND #'s 40,703 and 48,971 for amlodipine and to refer to Pfizer's NDA No. 19-787 for all matters that relate to the manufacture, use, and sale of amlodipine in support of NDA 20-364."

application."). In reliance on this right of reference, FDA approved Novartis's Lotrel® NDA in March 1995.

### 3. Termination of Novartis's Right of Reference

Under the License Agreement, Novartis's right of reference to Pfizer's amlodipine IND and NDA "shall expire automatically upon the termination or expiration of this Agreement." Although Pfizer believes that the Agreement remains in effect through September 25, 2007 (when the pediatric exclusivity for amlodipine expires), Novartis recently informed Pfizer that it is repudiating the agreement and will not pay royalties under the agreement after March 25, 2007. Novartis insists, however, that it can continue to sell Lotrel® during the amlodipine pediatric exclusivity period.

On March 21, 2007, in response to Novartis's repudiation of the License Agreement, Pfizer notified FDA that Pfizer is revoking Novartis's right of reference to Pfizer's amlodipine IND and NDA, effective midnight, March 25, 2007. (Attachment A). As explained in the notice of revocation, Pfizer believes that:

> As the result of this revocation, as of midnight March 25, 2007, Novartis's approved NDA No. 20-364 will no longer have a valid right of reference to Pfizer's NDA No. 19-787. Thus, it is Pfizer's view that as of that date and time, Novartis cannot continue to market Lotrel® under NDA No. 20-364 unless Novartis first obtains a valid right of reference to data supporting NDA No. 20-364, or another legal basis (if available) for approval of its Lotrel® product.

The legal reasons supporting this position are set forth below. Pfizer believes that FDA, as a matter of law, is required to rescind approval of Novartis's Lotrel® NDA, and withhold approval of any supplements to the Lotrel® NDA, in order to effectuate Pfizer's pediatric exclusivity for amlodipine.

## II. Argument

### 1. Without a "Right of Reference," the Lotrel® NDA is a 505(b)(2) Application

As of midnight March 25, 2007, Novartis's Lotrel® NDA no longer has a right of reference to Pfizer's Norvasc® NDA. (Attachment A). In the absence of a right of reference, Novartis's application is necessarily a 505(b)(2) application.

> A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

*505(b)(2) Draft Guidance* at 2 (quoting 21 USC §355(b)(2)).

This is confirmed by FDA's treatment of Novartis's NDA 21-990 for Exforge® (amlodipine and valsartan). The NDA for Exforge® relies on Norvasc® as the reference listed drug, but with no authorized right of reference. FDA explicitly is treating the Exforge® NDA as an application under section 505(b)(2). As set forth in a tentative approval letter FDA issued for Exforge® in December 2006, FDA regards the Exforge® NDA as an application "submitted pursuant to section 505(b)(2) . . .". (Attachment B.)

There is no basis to differentiate between the Lotrel® and Exforge® NDAs. Neither has a right of reference or use to the Norvasc® NDA. Both are thus section 505(b)(2) applications.

Novartis has argued to Pfizer that revocation of the right of reference does not change the regulatory status of the Lotrel® NDA, and thus that Novartis can continue to sell Lotrel® without a right of reference to the Norvasc® NDA. Both the FDCA and FDA's regulations make clear, however, that a 505(b)(1) application must contain either "full reports of investigations" supporting approval or a right of reference to such data. 21 USC § 355(b)(1). Because, as of March 25, 2007, the Lotrel® NDA has neither, its approval can no longer be considered valid under the terms of section 505(b)(1). *See A.L. Labs., Inc. v. Philips Roxane, Inc.*, 803 F.2d 383 (8th Cir. 1986) ("FDA had agreed that if the right of reference were invalidated it would void any drug approvals . . . obtained through use of the . . . data."). Novartis is clearly incorrect, therefore, that its original 505(b)(1) NDA remains valid notwithstanding withdrawal of the right of reference to the data supporting the NDA's approval.

### 2. Because the Lotrel® NDA Is A 505(b)(2) Application, It Is Subject to Pfizer's Pediatric Exclusivity for Amlodipine

All 505(b)(2) applications are subject to patent and exclusivity rights applicable to the listed drug, including pediatric exclusivity. *505(b)(2) Draft Guidance* at 7 (citing 21 CFR § 314.50(i), 314.107, 314.108 and 21 USC § 355a). Here, Pfizer's pediatric exclusivity precludes final approval of any section 505(b)(2) application referencing Norvasc® until after the expiration of the pediatric exclusivity period for amlodipine — until after September 25, 2007. This is equally true whether the section 505(b)(2) application relies on published literature, Pfizer's Norvasc® data, or FDA's "findings" of safety and effectiveness for Norvasc®.[3]

FDA's treatment of Exforge® confirms that the Lotrel® NDA is subject to Pfizer's pediatric exclusivity for amlodipine. FDA explicitly held that Exforge® cannot be approved until the end of the amlodipine pediatric exclusivity period:

> The listed reference drug product (Norvasc®), upon which you base your application, is subject to a period of patent protection and exclusivity

[3] Pfizer has filed previous petitions challenging FDA's interpretation and application of section 505(b)(2). Nothing in this petition should be construed as modifying Pfizer's position on section 505(b)(2).

protection, and therefore, final approval of your application under section 505(c)(3) of the Act (21 USC 355(c)(3)) may not be made effective until this period has expired, i.e., September 25, 2007.

(Attachment B). Because the Lotrel® NDA, like the Exforge® NDA, is a 505(b)(2) application, the Lotrel® NDA is similarly subject to the amlodipine pediatric exclusivity.

### 3. FDA Must Convert Final Approval of the Lotrel® NDA to Tentative Approval In Order to Effectuate Pfizer's Pediatric Exclusivity

Because the Lotrel® NDA is an application under section 505(b)(2) subject to pediatric exclusivity, FDA must rescind final, effective approval of the NDA and convert the NDA's approval status to "tentative approval." This occurs by operation of law, consistent with how FDA has effectuated pediatric exclusivity against ANDA applications holding final approval.

Exactly like an ANDA, a 505(b)(2) application must contain a patent certification. 21 USC §355(b)(2)(A). FDA has clearly held that, at the time a patent expires, an ANDA or 505(b)(2) application should be deemed to contain a paragraph II certification—and thus be subject to pediatric exclusivity—as a matter of law. *See Mylan Labs. v. Thompson,* 389 F.3d 1272, 1282-83 (DC Cir. 2004) (upholding FDA's conclusion that upon patent expiry, patent certification changes to a paragraph II certification and pediatric exclusivity attaches). In those circumstances, it is necessary and appropriate for FDA to rescind approval of the application in order to give effect to pediatric exclusivity. Thus, because the Lotrel® NDA contains a paragraph II certification and is subject to pediatric exclusivity, FDA should rescind its final approval and maintain its approval as "tentative" until after September 25, 2007. 21 USC § 355a(c)(2)(A)(i).

FDA need not invoke the procedures of section 505(e) in order to effectuate this change in status from final approval to approval with a delayed effective date. As FDA itself has explained, that provision merely sets forth the specific circumstances under which FDA must withdraw approval after notice and hearing, not the exclusive circumstances in which FDA may do so. *Mylan Labs.*, 389 F.3d at 1281. The provision "does not prohibit the FDA from withdrawing approval under other circumstances – or more precisely does not prohibit the FDA from changing a final into a tentative approval under circumstances different from those named in section 355(e)." *Id.*

### 4. FDA Must Defer the Effective Date of Any sNDA for Lotrel® until Pfizer's Pediatric Exclusivity Has Expired

Until now, Pfizer has been supplying amlodipine to Novartis for use in manufacturing Lotrel®. As a consequence of Novartis's repudiation of the License Agreement, however, Pfizer is no longer supplying amlodipine to Novartis. Thus, Pfizer

expects that Novartis may seek FDA approval for a manufacturing supplement in order to substitute an alternative amlodipine source.[4]

Pfizer submits that FDA is prohibited by the pediatric exclusivity provisions of the FDCA from approving any sNDA for Lotrel® until after the pediatric exclusivity for amlodipine has expired. "[A] supplement to an application is a new drug application." *505(b)(2) Draft Guidance* at 1. Thus, any manufacturing supplement to the Lotrel® NDA must be considered as an NDA. Moreover, any such NDA must be treated as an NDA under section 505(b)(2), because the Lotrel® NDA no longer contains a right of reference to the data supporting its approval. For the reasons explained above, such a 505(b)(2) NDA cannot be approved until after the expiration of the pediatric exclusivity period for amlodipine.

### III. Conclusion

FDA has acknowledged that "[t]he pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date. S. Rep. 107-79 at 5 (2001) (citing FDA's January 2001 Status Report to Congress). FDA has thus been careful to preserve the incentive and to ensure that grants of pediatric exclusivity are certain. The agency has repeatedly rejected attempts by generic applicants to manipulate the system so as to deprive pioneers who have invested the extensive time and resources required for pediatric studies of their exclusivity.[5]

Similarly, FDA should not in this case permit Novartis to circumvent Pfizer's pediatric exclusivity. As set forth above, FDA should rescind approval of Novartis's Lotrel® NDA, and withhold approval of any supplements to the Lotrel® NDA, in order to effectuate the pediatric exclusivity that FDA granted to Pfizer for amlodipine under section 505A of the FDCA.

## C. Environmental Impact

The petition is subject to a categorical exclusion from the requirement of an environmental impact assessment. *See* 21 C.F.R. §25.31(a).

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[4] Because Novartis would be seeking approval of a new manufacturing process as well as a new manufacturing site, a prior approval supplement is necessary. 21 CFR 314.70(b); FDA, *Changes to an Approved NDA or ANDA* 3, 9-14 (2004). If Novartis submits a "Changes Being Effected" supplement, FDA should notify Novartis that a prior approval supplement is required.

[5] *See e.g., Mylan Labs. v. Thompson,* 389 F.3d 1272 (DC Cir. 2004) (upholding FDA's rejection of Mylan's claim that it was not subject to pediatric exclusivity for fentanyl); *Ranbaxy Labs. Ltd. V. FDA,* Civ. No. 04-5079, 2004 U.S. App. LEXIS 8311 (DC Cir. 2004) (upholding FDA's rejection of Ranbaxy's claim that it was not subject to pediatric exclusivity for fluconazole); *Barr Labs., Inc. v. Thompson,* 238 F. Supp. 2d 236 (DDC 2002) (upholding FDA's rejection of Barr's claim that it was not subject to pediatric exclusivity for tamoxifen).

## D. Economic Impact

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

## E. Certification

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

Respectfully submitted,

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