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C O U N S E L O R S A T L A W

October 11, 2002

VIA HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

Re: **CITIZEN PETITION**

Dear Madam or Sir:

Pfizer Inc ("Pfizer") submits this petition under 21 C.F.R. § 10.30 to request that the Food and Drug Administration ("FDA" or "the Agency") revoke the acceptance for filing and receipt, and/or deny approval, of New Drug Application ("NDA") 21-435 for amlodipine maleate tablets, filed by Dr. Reddy's Laboratories, Inc./ Dr. Reddy's Laboratories, Ltd. ("Reddy") under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act ("FFDCA"). Alternatively, Pfizer requests that FDA take other actions as specified in this petition.

I. Actions Requested

- A. Pfizer requests that FDA immediately revoke its acceptance for filing and receipt of NDA 21-435, and/or deny approval of NDA 21-435:
1. if NDA 21-435 relies on any non-public, proprietary data in Pfizer's New Drug Application (19-787) for Norvasc[®] (amlodipine besylate) or any supplements thereto, or on FDA findings based on such data (collectively "NDA for Norvasc[®]"); on the ground that FDA does not have authority to rely on the NDA for Norvasc[®] to approve NDA 21-435; and/or
 2. if NDA 21-435 does not contain original data establishing the safety of Reddy's proposed amlodipine maleate product; on the ground that even if FDA could rely on the NDA for Norvasc[®] to review NDA 21-435, the NDA for Norvasc[®] does not establish the safety of Reddy's proposed product because Reddy's product has meaningfully different impurity and stability characteristics compared to the amlodipine maleate drug Pfizer studied.

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- B. If FDA approves Reddy's proposed product in reliance on the NDA for Norvasc[®], FDA should identify to Pfizer any elements of the NDA for Norvasc[®] upon which FDA relied so that Pfizer can determine whether FDA improperly relied on non-public proprietary data.
- C. If FDA approves Reddy's proposed product, it should not assign an "A" therapeutic equivalence rating to the product.

II. Statement of Grounds

A. Summary

1. FDA cannot properly approve NDA 21-435 based on non-public proprietary data in the NDA for Norvasc[®].^{1/} As is explained at length in the citizen petition submitted jointly by Pfizer and the Pharmacia Corporation in July 2001, which is incorporated herein by reference, FDA's reliance on or use of innovator proprietary data to evaluate a section 505(b)(2) application such as NDA 21-435 is prohibited under the FDCA, the Administrative Procedure Act ("APA"), and the Takings Clause of the Fifth Amendment to the Constitution.^{2/}
2. FDA cannot properly approve NDA 21-435 if NDA 21-435 does not contain original data establishing the safety of Reddy's proposed amlodipine maleate product. The proprietary data in the NDA for Norvasc[®] cannot establish the safety of Reddy's proposed product.^{3/} These data were generated from studies of a uniquely-manufactured amlodipine maleate product (in capsule form) that Pfizer never commercialized. Because the specific characteristics of Pfizer's amlodipine maleate product, including most importantly the levels of a separate degradant compound

^{1/} As noted above, in this petition the term "NDA for Norvasc[®]" refers collectively to the non-public, proprietary data in NDA 19-787 and all supplements thereto, as well as any FDA findings based on such data.

^{2/} Citizen Petition filed on behalf of Pfizer Inc and Pharmacia Corporation, No. 01P-0323 (filed July 27, 2001). Pfizer incorporates by reference the positions set forth in the Pfizer/Pharmacia petition and in the following documents that have been filed to the docket of the petition: Pfizer's/Pharmacia's Response to Comments Submitted by the Generic Pharmaceutical Association (GPhA) and Amendment to Citizen Petition (Apr. 4, 2002); Comments of Abbott Laboratories (July 10, 2002); Comments of Bristol-Myers Squibb Company (July 15, 2002).

^{3/} In this petition, the term "product" refers to the finished dosage form Reddy seeks to market. See 21 C.F.R. § 314.3(b) (2002).

known as UK-57,269, are unknown to Reddy, it is impossible for Reddy to show that its product's characteristics are sufficiently comparable to the characteristics of Pfizer's maleate product such that an inference of comparable safety can be drawn based on Pfizer's data. Thus, if NDA 21-435 seeks to rely on Pfizer's safety data and does not contain original data establishing the biological safety of Reddy's amlodipine maleate product, FDA should immediately revoke its acceptance for filing and receipt of NDA 21-435, and/or should not approve NDA 21-435.

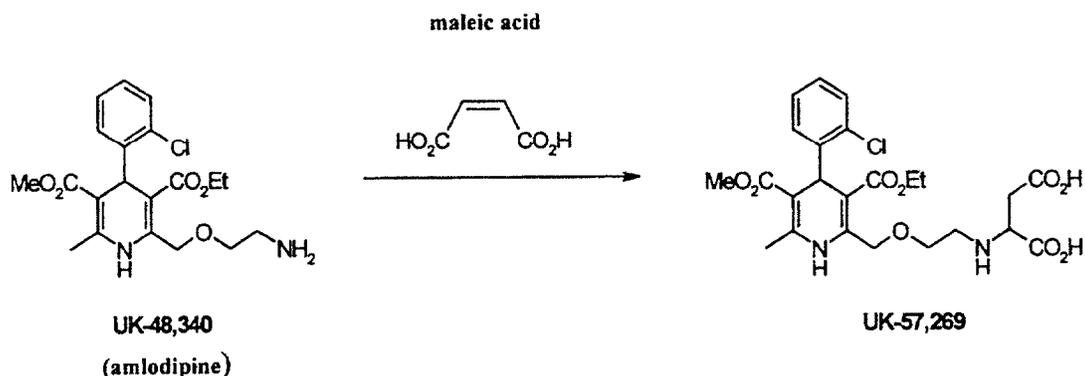
B. Factual Background

1. Pfizer's NDA for Norvasc[®]

Norvasc[®] (amlodipine besylate) is a long-acting dihydropyridine calcium antagonist that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Norvasc[®] acts as a peripheral arterial vasodilator, thereby decreasing peripheral vascular resistance and blood pressure. The resulting decrease in total peripheral resistance eases the heart's work by increasing its oxygen supply while decreasing its oxygen demand.

Although Norvasc[®] in its approved form contains the besylate salt of amlodipine, Pfizer conducted the majority of the preclinical and clinical studies for Norvasc[®] with a uniquely-manufactured maleate salt of amlodipine. When Pfizer filed the NDA for Norvasc[®] on December 22, 1987, it submitted these studies on the maleate salt, as well as additional studies demonstrating the safety and efficacy of the besylate salt.

Pfizer switched to the besylate salt after encountering stability and tableting problems with the maleate salt. These problems were subsequently determined to be attributable to a biologically-active degradation product, a separate compound known as UK-57,269, that arises during synthesis and production of the maleate salt. As Pfizer found, UK-57,269 is formed when the primary amine group of amlodipine reacts (by Michael addition) with the double carbon bond of the maleic acid counter-ion to form N-(2-[4-(2-chlorophenyl)-3-(ethoxycarbonyl)-5-(methoxycarbonyl)-6-methyl-1,4-dihydropyridyl] methoxy} ethyl) aspartic acid. This reaction can occur during the maleate salt formation step of synthesis, as well as during the manufacture and storage of capsule and tablet formulations of amlodipine maleate, as shown in the diagram below.



Pfizer managed the purity and stability issues related to UK-57,269 by instituting specific manufacturing, analytical, and study controls. These included developing specific manufacturing procedures to minimize the formation of UK-57,269 in batches of amlodipine maleate drug substance, and establishing a short shelf life for batches of amlodipine maleate capsules used in clinical studies. Employing these controls, Pfizer was able to ensure that the drug batches used in the preclinical studies that were subsequently submitted to the NDA for Norvasc[®] contained UK-57,269 at a level below 0.1%. By contrast, in experimental batches of potential commercial formulations in which these controls were not utilized, UK-57,269 appeared in levels up to 2%. Pfizer subsequently discovered that UK-57,269 is biologically active in several significant ways, and that in uncontrolled concentrations it may pose a risk to patient safety.

Pfizer's experience established that the level of UK-57,269 within a given batch of amlodipine maleate is critically dependent upon manufacturing processes and conditions. As Pfizer observed, formation of UK-57,269 can occur during maleate salt formation, recrystallization, drying, and storage. The processes and methods Pfizer developed and used to control the levels of UK-57,269 are trade secrets that Pfizer has not published, and that FDA could not properly release to a third party.

As noted, primarily because of the need to control UK-57,269, and because of certain tablet processing issues, Pfizer halted development of amlodipine maleate and undertook extensive studies to discover a superior alternative salt. This led to the discovery and development of amlodipine besylate (benzene sulphonate). The besylate salt was found to possess a unique combination of advantageous physicochemical properties, including adequate aqueous solubility, optimal chemical stability, non-hygroscopicity and optimal processability for tablet formulations. Of the other salts examined, none was found to possess the combination of properties offered by amlodipine besylate. Moreover, UK-57,269 is not formed in the manufacture of the besylate salt of amlodipine.

Pfizer submitted its NDA for Norvasc[®] on December 22, 1987. The application included reports of preclinical and clinical studies that Pfizer had conducted using its uniquely-manufactured maleate salt of amlodipine, including data from long-term

toxicity and impurity studies. To assure optimal safety, efficacy and quality of its amlodipine product, Pfizer also submitted (in the original NDA and later supplements) the following studies regarding amlodipine besylate:

- A bioequivalence study that showed amlodipine besylate to be bioequivalent to both an aqueous solution and to the capsule formulation of amlodipine maleate that Pfizer used in clinical development.
- Additional studies establishing the safety of amlodipine besylate, including acute and one month rat oral, Segments I and II rat oral and genetic toxicology studies.
- A clinical study establishing the safety and efficacy of amlodipine besylate in young and elderly patients with hypertension.
- An extensive clinical program that established the safety of amlodipine besylate in patients with congestive heart failure.

FDA approved the NDA for Norvasc[®] on July 31, 1992. Norvasc[®] is indicated as a once-daily treatment for hypertension, chronic stable angina, and confirmed or suspected vasospastic angina. Norvasc[®] may be used as a monotherapy or in combination with other antihypertensive or antianginal agents, and is available in doses containing 2.5, 5, and 10 mg of amlodipine. Physician reliance on Norvasc[®] and other second-generation calcium antagonists is significant, because they are potent vasodilators with high vascular selectivity.^{4/}

Norvasc[®], with 2001 U.S. revenues of \$ 1.6 billion, is Pfizer's second best-selling drug, the world's fourth best-selling drug, and the world's largest-selling hypertension medication.^{5/}

2. *Reddy's Section 505(b)(2) Application for Amlodipine Maleate*

Reddy filed NDA 21-435 in late 2001, seeking approval to market amlodipine, in maleate salt form, in 2.5 mg, 5 mg, and 10 mg tablets, for the treatment of hypertension, chronic stable angina, and vasospastic angina. These are the same indications that FDA has approved for Norvasc[®]. Reddy has informed Pfizer, and has disclosed publicly, that NDA 21-435 is a section 505(b)(2) application. Thus, Pfizer believes that Reddy is

^{4/} Bernard J. Gersh, Eugene Braunwald & Robert O. Bonow, *Chronic Coronary Artery Disease, in HEART DISEASE: A TEXTBOOK OF CARDIOVASCULAR MEDICINE* 1272 (Eugene Braunwald & Douglas P. Zipes eds., 6th ed. 2001). Amlodipine is the drug of choice in patients with chronic stable angina and sick sinus syndrome, sinus bradycardia, atrioventricular block, chronic obstructive pulmonary disease with bronchospasm or asthma, and Raynaud's syndrome. *Id.*

^{5/} Pfizer, *Pfizer 2001 Annual Report* (2002), available at <http://www.pfizer.com/pfizerinc/investing/pfizer2001.pdf> (see Attachment 1).

seeking to support NDA 21-435 by relying on non-public proprietary data that Pfizer submitted in its NDA for Norvasc[®], including data from long-term toxicity and impurity studies that Pfizer conducted on the uniquely-manufactured amlodipine maleate product that was a critical part of the development of Norvasc[®].

C. Argument

1. As A Matter of Law, FDA Cannot Rely On Pfizer's Proprietary Data to Accept for Approval or Approve NDA 21-435

In a 1999 Draft Guidance, FDA invited applications such as Reddy's that propose new salt forms of previously approved drugs. The Draft Guidance asserts that using section 505(b)(2), an applicant can "rely on the Agency's findings of safety and effectiveness for an approved drug to the extent such reliance would be permitted under the generic drug approval provisions of section 505(j)."^{6/} Section 505(b)(2) applications can be used in this way, the Draft Guidance maintains, when an applicant seeks "approval of a change to an approved drug that would not be permitted under section 505(j), because approval will require the review of clinical data."^{7/} As an example of such a change, the Draft Guidance specifically identifies "[a]n application for a change in an active ingredient such as a different salt . . ."^{8/}

As argued in the Pfizer/Pharmacia petition, FDA's position—that under section 505(b)(2) the Agency can freely rely on an innovator company's proprietary data to approve alternative versions of innovator products, including different salt forms—is inconsistent with, and repudiated by, the language, structure, and history of the FDCA's drug approval provisions. In particular:

1. Section 505(j), exclusively, authorizes FDA to rely on innovator data in order to expedite approval of a generic drug that is "identical" in critical respects to the innovator product, and thus can be automatically substituted for the innovator product in clinical practice.^{9/} As FDA has acknowledged, and as Pfizer's experience testing the maleate and besylate salts of amlodipine demonstrates, the process and logic of section 505(j) cannot be applied to a proposed generic drug that contains a different salt of the active drug compound, because "[d]ifferent salts . . . have different chemical structures

^{6/} FDA, *Guidance for Industry: Applications Covered by Section 505(b)(2): Draft Guidance 3* (1999) ("Draft Guidance").

^{7/} *Id.*

^{8/} *Id.* at 5.

^{9/} *See id.* at 1 (noting that to qualify for approval under section 505(j), a proposed product must be "identical in active ingredient, dosage form, strength, route of administration, labeling, quality, performance characteristics, and intended use, among other things, to a previously approved product").

and, quite often, different adverse event profiles.”^{10/} Thus, FDA’s assertion in the Draft Guidance that, using section 505(b)(2), an applicant seeking approval for an alternative salt can “rely on the Agency’s findings of safety and effectiveness for an approved drug *to the extent such reliance would be permitted under the generic drug approval provisions of section 505(j)*” (emphasis added) flies in the face of the clear limitations that govern applications under section 505(j).

2. FDA’s suggestion that section 505(b)(2) can be used as a sort of “super ANDA” for products that differ from reference drugs in ways not permitted under the ANDA procedures, conflicts with and undermines specific statutory limitations on the ANDA procedures. As previously noted, a proposed generic drug must be identical to the reference product after which it is patterned. Under section 505(j), only certain differences are permitted, and those generally must be aired publicly in a “suitability petition” to ensure that thorough consideration is given to the significance of the differences.^{11/} FDA’s Draft Guidance contends that section 505(b)(2) may be used for product variations that go far beyond those permitted by the statutory suitability petition procedure, and eliminates entirely the public petition process set forth in section 505(j). Were FDA to apply this approach to approve NDA 21-435, therefore, that action would be contrary to law and thus invalid.

3. FDA’s approach also conflicts with, and would render meaningless, section 505(l). Section 505(l) provides for public disclosure of the safety and effectiveness data in an NDA when “the first application under subsection (j) which refers to such [NDA] drug” is or could be approved. This is consistent with the operation of section 505(j), which authorizes reliance on data in an innovator company’s NDA once patent rights and other exclusivities have expired. Significantly, section 505(l) does not authorize a similar public disclosure upon approval of a section 505(b)(2) application. As Pfizer and others have argued, this is because section 505(b)(2) does not authorize reliance on proprietary data in another company’s NDA, and thus does not trigger the “release” of those data. By misinterpreting section 505(b)(2) as allowing reliance on proprietary NDA data, FDA undermines the policies reflected in section 505(l), and may improperly allow the “release” of NDA data prior to the time specified by Congress in section 505(l).

4. In contrast to section 505(j), which expressly authorizes FDA to review ANDAs in reliance on data submitted confidentially as part of an innovator drug

^{10/} Letter from Dennis Baker, FDA Assoc. Comm’r, to Donald O. Beers, *et al.*, in Docket Nos. 00P-1550 and 01P-0428 at 28 (filed Feb. 15, 2002). Because it contains a different salt of amlodipine and has a different safety profile, Reddy’s proposed product is not “identical” to Norvasc[®] for purposes of approval under section 505(j). From the standpoint of drug efficacy, however, each drug contains the therapeutically active amlodipine ion.

^{11/} See 21 U.S.C. § 355(j)(2)(C) (2001).

company's NDA, section 505(b)(2) allows reliance only on reports of "investigations" that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use . . ." Thus, section 505(b)(2) allows an applicant who has no right to "reference or use" NDA data submitted in confidence to FDA, to rely instead on "investigations" reported publicly.^{12/} This interpretation is consonant with the legislative history of section 505(b)(2), which makes plain that section 505(b)(2) was intended to codify FDA's "paper NDA" policy, under which FDA allowed reliance on publicly-available studies but steadfastly refused to allow reliance on proprietary data in an NDA.

Properly understood, therefore, section 505(b)(2) authorizes the use of publicly-available reports of investigations to satisfy the "full investigations" requirement for applications submitted under section 505(b). Section 505(b)(2) does not, however, authorize reliance on non-public proprietary data in an NDA; that authorization is provided exclusively in section 505(j). Thus, FDA has no authority to rely on or otherwise use the proprietary data in Pfizer's NDA for Norvasc[®] to approve NDA 21-435.

5. If FDA were to rely on the NDA for Norvasc[®] to approve NDA 21-435, it would effect an unconstitutional taking of Pfizer's proprietary data in violation of the Fifth Amendment of the United States Constitution. The courts, Congress, and FDA have historically recognized the inherent property rights in safety and effectiveness data that are submitted as part of an NDA: the courts have denied discovery requests for information in drug marketing applications on the ground that this information constitutes trade secrets^{13/} and have acknowledged that safety data is valuable commercial property^{14/}; Congress has acknowledged the inherent property rights in such information in several statutes, including the Trade Secrets Act^{15/}; and FDA has recognized the inherent and protected rights in such information and has established regulations to protect trade secret and confidential information in drug marketing applications.^{16/} The

^{12/} In the *Draft Guidance*, FDA contends that an applicant can use section 505(b)(2) "to rely, for approval of an NDA, on data not developed by the applicant," including confidential NDA data. *Draft Guidance* at 1. This misinterprets the plain language of section 505(b)(2). Section 505(b)(2) allows an applicant who has no "right of reference or use" regarding NDA data (or FDA findings based on those data) to rely on published "investigations." Section 505(b)(2) thus does not create a right of reference for such an applicant—as FDA appears to believe—but to the contrary expressly acknowledges that the applicant has no right to use the NDA data.

^{13/} See, e.g., *Serono Laboratories v. Shalala*, 35 F. Supp. 2d 1 (D.D.C. 1999).

^{14/} See, e.g., *Anderson v. Dep't of Health and Human Servs.*, 907 F.2d 936 (10th Cir. 1990).

^{15/} 18 U.S.C. § 1905 (2001); FFDCA, 21 U.S.C. § 331(j) (2001).

^{16/} 21 C.F.R. § 314.50(g) (2002); 21 C.F.R. § 314.430 (2002); 21 C.F.R. § 20.21 (2002); 21 C.F.R. § 20.61 (2002); 39 Fed. Reg. 44602, 44634 (Dec. 24, 1974) (FDA stating that

Supreme Court has also established the applicability of Fifth Amendment analysis to intellectual property, such as safety and effectiveness data.^{17/} Consequently, Pfizer has a property interest protected by the Fifth Amendment's Taking Clause in its proprietary safety and effectiveness data in the NDA for Norvasc®.

FDA reliance on Pfizer's proprietary data to evaluate or otherwise review NDA 21-435 for filing or approval raises serious constitutional concerns under the analysis that has evolved in recent takings jurisprudence. The studies and data that FDA would reference in its review of NDA 21-435—including genetic toxicology, chronic oral toxicity, and long-term rodent carcinogenicity studies, drug substance and drug product manufacturing processes, and the results from stability and impurity testing—are the confidential, commercially-valuable property of Pfizer. Pfizer has a reasonable investment-backed expectation that FDA will not rely on or use this proprietary information to review or approve section 505(b)(2) applications, such as NDA 21-435.^{18/}

Pfizer filed its IND for Norvasc® in 1983, and submitted its full NDA data package on December 22, 1987. Thus, when Pfizer developed and submitted the data, FDA had not yet published its erroneous interpretation of section 505(b)(2),^{19/} and Pfizer properly and reasonably understood from the statutory drug approval scheme that its data would be protected from generic use until the expiration of relevant patents and exclusivities (that is, until 2007).

As noted earlier, Norvasc® is an extremely important product for Pfizer. It is well understood that major pharmaceutical companies such as Pfizer are significantly

there is "tremendous economic value" in drug safety and effectiveness data, and that routine release of this information could adversely affect the "incentive for private pharmaceutical research").

^{17/} See *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986 (1984).

^{18/} In analyses of whether a regulatory taking is unconstitutional, particularly relevant is the reasonableness of the investment-backed expectations of the regulated entities. Where the government has communicated to regulated entities that it will keep submitted data confidential and exclusive, these regulated entities have a reasonable investment-backed expectation that their trade secret data will not be used by the government to the benefit of others. *Monsanto*, 467 U.S. at 1011.

^{19/} As discussed in the Pfizer/Pharmacia Citizen Petition, nothing in the FFDCRA or its legislative history suggests that Congress intended for section 505(b)(2) to abrogate the protection afforded trade secret information, including safety and effectiveness data submitted as part of an NDA. Although FDA's regulation on section 505(b)(2) applications, 21 C.F.R. § 314.54 (2002), makes an oblique reference to reliance on NDA data, the regulation was not enacted until 1992, well after Pfizer had submitted its NDA data. Most significantly, it was not until the 1999 *Draft Guidance* that FDA for the first time asserted that an applicant could, under section 505(b)(2), rely on NDA data to gain approval of an alternative salt.

dependent on the revenue streams from therapeutically significant products, such as Norvasc[®], to adequately fund ongoing research and development efforts and to remain financially sound. Thus, any reliance or use by FDA of Pfizer's proprietary data to approve NDA 21-435 would effect an unconstitutional taking of Pfizer's property.

* * * *

For these several reasons, and as explained more fully in Docket No. 01P-0323, Pfizer submits that FDA cannot lawfully rely on or use the NDA for Norvasc[®] to approve NDA 21-435.

Pfizer expects that, pursuant to the erroneous policy in the Draft Guidance, Reddy seeks approval for NDA 21-435 based on data in Pfizer's NDA for Norvasc[®] and has not submitted original data. If that is the case, and NDA 21-435 omits required elements of an NDA (such as long-term toxicology and safety studies of Reddy's maleate-salt formulation of amlodipine), then consistent with the requirements of 21 C.F.R. § 314.101, Reddy's application is incomplete and FDA must revoke its acceptance for filing.

By the terms of 21 C.F.R. § 314.101, the notice-and-comment history for this regulation, and related Agency guidance, FDA is required to conduct a review of section 505(b) applications to determine whether they are adequate for filing. FDA's regulation at 21 C.F.R. § 314.101 states that the Agency should refuse to file an application if it is "incomplete because it does not on its face contain information required under section 505(b)."^{20/} The history of this regulation makes clear that, to determine whether applications should be received and accepted for filing, they should be "reviewed for completeness" to confirm "that [they] comply with statutory and regulatory requirements and are sufficiently complete for substantive review to begin."^{21/} More specifically, the Agency explained that "FDA [may] refuse to file or approve, or to withdraw approval of, an application that omits required reports or an explanation of the omission."^{22/} FDA's

^{20/} 21 C.F.R. § 314.101(d)(3) (2002). See also 21 C.F.R. § 314.101(a)(2) (2002); FDA, *New Drug Evaluation Guidance Document: Refusal to File* (1993).

^{21/} Abbreviated New Drug Application Regulations; Proposed Rule, 54 Fed. Reg. 28872, 28889 (July 10, 1989); Abbreviated New Drug Application Regulations; Final Rule, 57 Fed. Reg. 17950, 17965 (Apr. 28, 1992). See also *New Drug Applications; Refusal To File; Meeting of Review Committee*, 58 Fed. Reg. 28983, 28983 (May 18, 1993) (explaining that "the practice of submitting an incomplete or inadequate application and then providing additional information during an extended review period is inherently inefficient and wasteful of agency resources. It also is unfair to those applicants who fulfill their scientific and legal obligations by submitting complete applications whose review may be delayed while incomplete applications, submitted earlier, undergo review and repair").

^{22/} *New Drug and Antibiotic Regulations; Final Rule*, 50 Fed. Reg. 7452, 7490 (Feb. 22, 1985).

guidance on “refusal to file” (“RTF”) decisions further clarifies that, while a RTF “is not an appropriate vehicle for dealing with complex and close judgments on such matters as balancing risks and benefits, magnitude of drug effect, acceptability of a plausible surrogate marker, or nuances of study design,” FDA will apply 21 C.F.R. § 314.101 “to refuse to file applications that on their face are not reviewable and at least potentially approvable as submitted.”^{23/}

Under these principles, FDA should revoke its acceptance for filing of NDA 21-435 if, rather than containing original safety data, the application relies on the NDA for Norvasc[®] to establish the safety of Reddy’s proposed product.

2. *Reliance on Pfizer’s Proprietary Data Would Be Scientifically Inappropriate*

Even if FDA could rely on Pfizer’s data, FDA cannot properly approve NDA 21-435 in the absence of original data establishing the safety of Reddy’s proposed amlodipine maleate formulation, because Reddy’s formulation is distinct from the amlodipine maleate formulation Pfizer studied as part of its NDA.

- a. **The Unique Stability and Impurity Profile of Pfizer’s Amlodipine Maleate Product Cannot Be Cross-Referenced by Reddy Because Pfizer’s Product Profile is Not Publicly Available**

As discussed in Section II(B) of this Petition, and in further detail below, Pfizer’s amlodipine maleate formulation had unique stability and impurity characteristics that have not been publicly disclosed. Because these characteristics are unknown to Reddy, Reddy’s product will necessarily be distinct from Pfizer’s amlodipine maleate product, and could pose potentially different risks to patients. Moreover, because Pfizer’s amlodipine maleate product does not exist, the differences between Pfizer’s and Reddy’s amlodipine maleate formulations cannot be addressed through a direct comparison of the two formulations.

- b. **FDA Cannot Approve Reddy’s Product Unless Reddy Completes Independent Toxicity and Impurity Testing**

The level of UK-57,269 in Reddy’s product could have clinical effects in patients, and thus should be independently investigated. Indeed, FDA scientists who reviewed the NDA for Norvasc[®] recognized the potential for toxicities resulting from the instability of the maleate salt.^{24/}

Ligand-binding and enzymatic assays Pfizer conducted on pure (> 99%) UK-

^{23/} FDA, *New Drug Evaluation Guidance Document: Refusal to File* at 1, 3 (1993).

^{24/} Ameeta Parekh, FDA, *Review & Evaluation of Pharmacology & Toxicology Data, Summary Basis of Approval of Norvasc NDA 19-787*.

57,269 revealed that UK-57,269 has a diverse range of bioactivities at a concentration of 100 nM, including: (1) stimulation of calcitonin gene related peptide, cannabinoid receptors, and nitric oxide synthase; (2) dose related inhibition of neuropeptide Y1 receptor and PDE_{IV} enzymes; and (3) depression of contraction of isolated heart tissue. A summary of these results is provided below in Table 1.

Table 1 Ligand binding and enzyme assays results for UK-57,269
CGRP = calcitonin gene related peptide; NOS = nitric oxide synthase;
PDE IV = phosphodiesterase type 4 isozyme

Receptor/Enzyme	% inhibition 100Nm	% inhibition of 10uM
CGRP	-33%	-19%
Cannabinoid	-42%	-41%
NOS	-11%	-35%
Neuropeptide Y1	16%	48%
PDE IV	22%	45%

As noted earlier, Pfizer controlled the levels of UK-57,269 in the amlodipine maleate product that Pfizer used in pre-clinical and clinical testing. Because Reddy cannot duplicate Pfizer's controls over UK-57,269, Pfizer's genetic toxicology and long-term carcinogenicity studies will not correlate with and are not relevant to Reddy's preclinical or clinical amlodipine maleate studies. In addition, UK-57,269 cannot be formed in Norvasc[®] (amlodipine besylate), which has been shown to be safe and effective during approximately twelve years of worldwide usage. Thus, in order to ensure patient safety, Reddy must independently identify, quantify, and qualify (*i.e.* establish the biological safety of) the impurities and degradation products associated with its amlodipine maleate product through an appropriate and comprehensive range of toxicological and other testing.

Because levels of UK-57,269 up to 2% were observed during stability studies of Pfizer's maleate formulation, Reddy's qualification of UK-57,269 should include appropriate *in vitro* genetic toxicology studies, as well as two long-term oral carcinogenicity studies in rodents.^{25f} Consistent with these requirements, Agency guidance states that "[f]or different salts, acids, or bases of the same therapeutic moiety, where prior carcinogenicity studies are available, evidence should be provided that there

^{25f} See FDA, ICH Q3A, *Guidance for Industry: Impurities in New Drug Substances* (1996). With respect to qualifying and quantifying impurities, FDA guidance states that impurity/degradation product levels above the stated thresholds of 0.1% should be adequately qualified by data establishing the biological safety of the individual impurity at the level specified.

are not significant changes in pharmacokinetics, pharmacodynamics, or toxicity.”^{26/} As noted, Reddy cannot, absent conducting independent testing, establish that there are not significant changes in toxicity for its amlodipine maleate. This deficiency, in conjunction with the chronic (≥6 months) use of amlodipine by a large and vulnerable patient population, demands the aforementioned studies.

Moreover, even if Reddy were able to manufacture a stable amlodipine maleate product with low levels of UK-57,269, the product would necessarily be significantly different from Pfizer’s amlodipine maleate because Reddy’s manufacturing process would not be identical to Pfizer’s. Consequently, in all circumstances, it would be scientifically unwarranted for FDA to rely on Pfizer’s amlodipine maleate studies/data to support the approval of Reddy’s product.^{27/}

Consistent with the foregoing, in order for Reddy to demonstrate that its drug is safe, it must independently establish the purity and stability of its amlodipine maleate product,^{28/} quantify and qualify any impurities (including *in vitro* toxicity and long-term oral carcinogenicity studies in rodents), and establish appropriate manufacturing specifications for its product. If Reddy has not done this, NDA 21-435 does not contain the information required by section 505(b), and FDA should revoke its acceptance for filing of the application.

3. *Reddy’s Product Cannot Receive an “A” Rating*

As explained in the Pfizer/Pharmacia petition and in supporting comments by Abbott, FDA may not assign “A” therapeutic equivalence evaluation codes to drug products approved under section 505(b)(2). “A” ratings are appropriate only for “drug products that FDA considers to be therapeutically equivalent to other *pharmaceutically*

^{26/} See FDA, ICH S1A, *Guidance for Industry: The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals* (1996).

^{27/} It would be impossible for Reddy to show equivalence to Pfizer’s maleate formulation through bioequivalence testing because Pfizer’s maleate drug is not available for testing. Reddy might attempt to make an indirect bioequivalence comparison by testing its maleate formulation against Norvasc[®] (amlodipine besylate), which Pfizer showed was bioequivalent to its maleate formulation. This approach would be invalid, however, because Reddy cannot establish that the besylate salt is a reliable “bridging” product between Reddy’s and Pfizer’s maleate products. Although the two amlodipine maleate formulations each individually may be bioequivalent to Pfizer’s besylate product, they may not be bioequivalent to each other. For example, while Pfizer’s maleate was bioequivalent to the besylate within the lower range of FDA’s mandated 80-125% bioequivalence confidence interval, Reddy’s maleate may only be bioequivalent to the besylate within the higher range of the confidence interval.

^{28/} See ICH, FDA, *Guidance for Industry: Q1A Stability Testing of New Drug Substances and Products* (2001).

equivalent products.”^{29/} Under FDA’s therapeutic equivalence coding system, Reddy’s amlodipine maleate product is not “pharmaceutically equivalent” to Norvasc[®] (amlodipine besylate) or to any other reference listed drug, but is a “pharmaceutical alternative” – a drug product that contains the same therapeutic moiety of a reference listed drug, but a different salt, ester, or complex of that moiety. Thus, if FDA were to approve NDA 21-435, it should not assign Reddy’s amlodipine maleate product an “A” rating.

D. Conclusion

FDA may not rely on the NDA for Norvasc[®] to approve NDA 21-435, because such reliance is authorized only for ANDAs that meet the conditions and limitations of section 505(j). Moreover, because Reddy’s proposed product is distinct from the maleate-salt formulation Pfizer studied, FDA cannot properly approve NDA 21-435, or accept it for filing, if it does not contain original long-term safety studies conducted using Reddy’s formulation.

III. Environmental Impact

The actions requested in this Petition are not within any of the categories for which an environmental assessment is required pursuant to 21 C.F.R. § 25.22. Additionally, the actions requested in this petition are exempt from requirement of an environmental assessment pursuant to 21 C.F.R. § 25.24(a)(11).

IV. Economic Impact

Information on the economic impact of this proposal can be provided if requested.

V. Certification

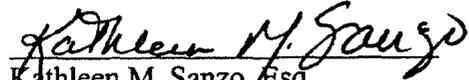
The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

^{29/} FDA, *Introduction to Approved Drug Products with Therapeutic Equivalency Evaluations* (2002) (emphasis added).

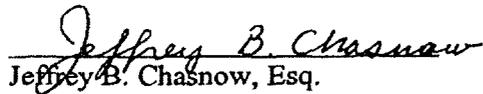
Dockets Management Branch
October 11, 2002
Page 15

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Respectfully Submitted,



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Attachments

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April 9, 2003

VIA HAND DELIVERY & FEDERAL EXPRESS

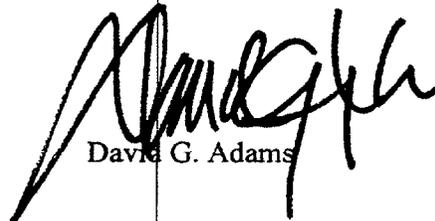
Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Docket Number 02P-0447 (Citizen Petition) - Submission of Comments
by Dr. Reddy's Laboratories, Inc.

Dear Sir or Madam:

Please accept the attached comments (in four copies) submitted on behalf of Dr. Reddy's Laboratories, Inc., in response to the Citizen Petition filed by Pfizer, Inc., on October 11, 2002.

Sincerely,

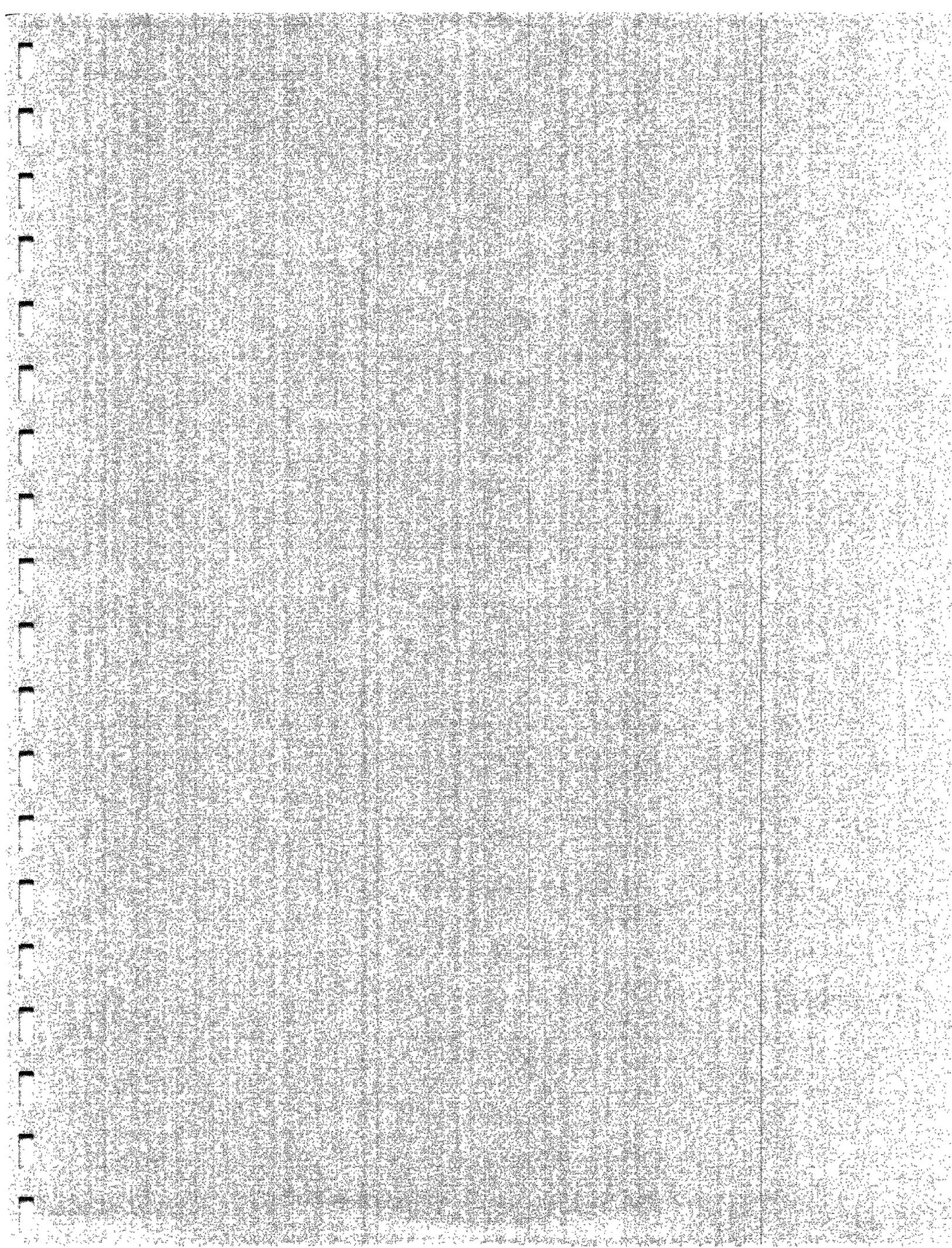


David G. Adams

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02P-0447

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April 28, 2003

BY HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1051, HFA-305
5630 Fishers Lane
Rockville, MD 20857

Re: Docket Number 02P-0447

Dear Madam or Sir:

The undersigned, on behalf of Pfizer Inc. ("Pfizer"), submit this reply to the comments of Dr. Reddy's Laboratories, Inc. (Reddy) on Pfizer's October 11, 2002 citizen petition ("Pfizer Petition") (Docket No. 02P-0447). That petition requests that the Food and Drug Administration ("FDA" or "Agency") revoke its acceptance for filing and receipt, and/or deny approval, of new drug application (NDA) 21-435, Reddy's section 505(b)(2) application for amlodipine maleate tablets.

Reddy's comments demonstrate a basic misunderstanding of the Pfizer Petition, FDA's "paper" NDA policy, and - most critically - the permissible scope of an application under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA). Pfizer thus takes this opportunity to clarify and reaffirm its position and the legal principles involved.

02P-0447

RC 1

Contrary to Reddy's assertion, Pfizer does not seek to "fully nullify FDA's entire system for approving modified versions of [abbreviated new drug applications (ANDAs)] under the NDA provisions of the statute" or to "overturn the Agency's seventeen-year-old interpretation of the 1984 Amendments." Reddy Comments at 1. As discussed in detail below, Pfizer seeks only to ensure that FDA does not use Pfizer's proprietary data in a manner that is inconsistent with the FDCA or the Constitution. Pfizer's arguments would not prevent FDA, in limited circumstances, from accepting applications for a modified version of the pioneer product if the applicant could have obtained an ANDA on the original product. Nor would Pfizer's arguments constrain FDA from approving supplements to previously approved ANDAs that are accompanied by either original or published data.¹

This reply explains further why FDA cannot, as a legal matter, rely on Pfizer's NDA for Norvasc®, or the Agency's findings based upon that NDA, to approve Reddy's application for an amlodipine maleate product. This reply also re-emphasizes that such reliance is improper as a scientific matter, noting that Reddy offers no refutation of Pfizer's arguments challenging the scientific validity of Reddy's reliance on data relating to the amlodipine maleate product Pfizer used in its preclinical and clinical studies.

¹ Thus, the doomsday scenario, postulated by Reddy and GPHA in comments on the Pfizer Petition and Pfizer and Pharmacia Corporation's earlier petition (Docket N. 01P-0323), that scores of previously approved drugs will have to have their approvals revoked is not just speculative but demonstrably false. See, discussion, *infra*, at pp. 20-21.

Discussion

- I. **As a matter of law, FDA may not rely on Pfizer's proprietary data to accept for approval or to approve Reddy's 505(b)(2) NDA.**
 - A. **The plain language of section 505(b)(2) does not provide an applicant a right to rely upon NDA data.**

Reddy's comments argue that section 505(b)(2) authorizes applicants to rely, without authorization, on third-party proprietary NDA data to obtain FDA approval of modified drugs that are ineligible for the ANDA procedures of section 505(j). Reddy Comments at 6. The plain language of the section does not support this argument, and in fact refutes it. Far from conferring any rights on an applicant, section 505(b)(2), by its terms, merely defines the content of an application submitted under that provision. Section 505(b)(2) allows an applicant to submit reports of investigations "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" 21 U.S.C. § 355(b)(2). This language does not purport to give a 505(b)(2) applicant any "right of reference" to pioneer data or to FDA's "prior findings" based on those data. It simply allows a 505(b)(2) applicant to *submit* reports of studies for which it has no right of reference or use. *See Eli Lilly & Co. v. Medtronic*, 496 U.S. 661, 676 (1990) (indicating that (b)(2) application relies on "published literature").

Rather than granting a right of reference to or use of NDA data, section 505(b)(2) expressly acknowledges the absence of such a right. Section 505(b)(2) explicitly applies only where an applicant has "no right of reference or use" to the data underlying the study reports that it submits to satisfy the full reports requirements of 505(b)(1)(A). To read this language, as Reddy would propose, as giving an applicant a right of reference or use to NDA data, or findings

based on those data, would render section 505(b)(2) illogical; such a reading would effectively repudiate the very criteria that are needed to be eligible to use section 505(b)(2).

Indeed, FDA's section 505(b)(2) regulations require an applicant seeking to rely on information contained in another applicant's NDA to submit "a written statement that authorizes the reference and that is signed by the person who submitted the information" to FDA originally. 21 C.F.R. § 314.50(g)(1); *see* 21 C.F.R. 314.54(a)(1)(i) (requiring 505(b)(2) applicant to submit information required by 21 C.F.R. § 314.50(g)). Such a written authorization requirement would be unnecessary if section 505(b)(2) authorized reliance on NDA data.

B. Section 505(b)(2) merely reflects Congress's intent to preserve FDA's paper NDA policy.

The history of section 505(b)(2)'s enactment as part of the 1984 Hatch-Waxman Amendments also militates against Reddy's proposed construction of 505(b)(2). The primary Congressional reports supporting the Hatch-Waxman Amendments consistently refer to NDAs covered by section 505(b)(2) as "paper NDAs." Courts also have described section 505(b)(2) applications as "paper NDAs." For example, the Supreme Court has confirmed that section 505(b)(2) authorizes "so called paper new drug application[s] . . . that rel[y] on published literature to satisfy the requirement of animal and human studies demonstrating safety and effectiveness" under section 505(b)(2). *Eli Lilly & Co.*, 496 U.S. at 676; *see also Burroughs Wellcome Co. v. Bowen*, 630 F. Supp. 787, 789 (E.D.N.C. 1986) ("A 'paper' NDA is one in which the required safety and effectiveness data are not the result of the original testing by the NDA applicant, but rather are obtained from literature reports of testing done by others.").

Congress's use of the term "paper NDA" in the legislative history to define 505(b)(2) applications is significant, because that term described a regulatory procedure that existed at the time the Hatch-Waxman Amendments were enacted. When Congress selects words identical to those used by an agency, there is a strong presumption that Congress intended those words to have the same effect in the statute as they did under the regulatory regime. *Toilet Goods Ass'n v. Finch*, 419 F.2d 21, 26 (2d Cir. 1969) (indicating government bears burden of establishing that when "Congress employed words similar to those previously in the FDA's regulations, it meant them to have a different effect"). "Paper NDA" was a term of art with a well-defined meaning in FDA parlance. Specifically, it referred to a policy that permitted reliance upon published literature but did not allow an applicant (or FDA) to rely on proprietary data contained in a competitor's NDA without the express approval of the NDA holder. 45 Fed. Reg. 82052 (Dec. 12, 1980).

Reddy argues, that despite FDA's contemporaneous assertions otherwise, the Agency's paper NDA policy in fact did allow FDA to use a prior NDA approval to support a paper NDA. Reddy Comments at 20 n.60.² This is clearly incorrect. As articulated in the "Finkel Memorandum," the paper NDA policy allowed applicants to rely on published reports to satisfy the "full reports" requirements of section 505. 46 Fed. Reg. 27396 (May 19, 1981) (publishing

² Reddy presupposes this to be the case in responding to Pfizer's takings argument. However, as demonstrated in Pfizer's earlier submission on this docket and the citizen petition filed on behalf of itself and Pharmacia Corporation (Docket No. 01P-0323), prior to the Hatch-Waxman Amendments, FDA had a longstanding policy of treating pioneer data as non-releasable, proprietary, trade secret information. Pfizer refers the Agency to those petitions and incorporates by reference the takings arguments set forth therein.

“Finkel Memorandum”); 45 Fed. Reg. at 82054, 82056. Without the permission of the NDA holder, however, a paper NDA applicant could not “reference the data in the pioneer manufacturer’s NDA.” *Id.* at 82059. Nor could FDA refer to data and reports in the pioneer NDA to support approval of a paper NDA. *Id.* at 82056. Rather, approval of a paper NDA was contingent upon the availability of adequate reports in the scientific literature. *Id.* at 82052. If available reports were not adequate to resolve issues about safety and effectiveness, the paper NDA sponsor would have to conduct further testing. *Id.* at 82056. It could not look to the NDA, or FDA’s approval of the NDA, to fill gaps in the literature. *Id.*

As it did for other pre-Hatch-Waxman regulatory devices, Congress carried FDA’s paper NDA procedure forward by codifying it in the Hatch-Waxman Amendments.³ The description Congress chose for that procedure in no way suggests any intent to remove the trade secret protection afforded to pioneer safety and effectiveness data. That is because Congress did not attempt to remove such protection. Rather, the description Congress selected evinces its desire to allow sponsors to continue to rely on published reports of studies conducted by others, even if they have no right of reference or access to the raw data underlying those reports -- that is, it reflects Congress’s intent to preserve FDA’s paper NDA policy. Congress thus defined “paper NDAs,” i.e., 505(b)(2) applications, as those submitting reports of investigations “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” 21 U.S.C. § 355(b)(2);

³ See, e.g., *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995) (noting that the Hatch-Waxman Amendments codified existing FDA policies on bioequivalence).

see H. Rep. 98-857, pt. 1., 32 (1984). Congress selected this particular language to differentiate, as FDA had previously done, between full NDAs which contain data from studies conducted by the sponsor or from studies for which a right of reliance or use to the underlying data has been secured, and paper NDAs for which no such right has been obtained. *See* 45 Fed. Reg. at 82052. As FDA explained in 1980, nearly all NDAs contain reports of investigations not prepared by or for the applicant. However, a full NDA relies upon and “contains reports of investigations for which raw data . . . are included or are available.” 45 Fed. Reg. at 82052. A paper NDA, in contrast, relies on reports for which the applicant does not have a right of reference or use to the underlying raw data. The language of 505(b)(2) reflects no more than this distinction.

As noted, an essential *legal* premise of FDA’s paper NDA policy was that an applicant could not rely on another company’s proprietary NDA data without authorization. *See* 45 Fed. Reg. at 85052; *see e.g., Upjohn Mfg. Co. v. Schweiker*, 681 F.2d 480 (6th Cir. 1982); *American Critical Care v. Schweiker*, No. 81-C-252, 1981 U.S. Dist. LEXIS 12363 (N.D. Ill. May 13, 1981). Under well-settled principles of statutory construction, that premise must be presumed to have been adopted when Congress codified the paper NDA policy in section 505(b)(2).

“[B]efore a court will hold Congress to have made a basic change in regulatory procedures, legislators must either use plain language or give other manifestation of intent.” *Toilet Goods Ass’n*, 419 F.2d at 27. As already discussed, the plain language of section 505(b)(2) does not express congressional intent to change the standard of what data are afforded trade secret protection under the Act, but to the contrary confirms that NDA data cannot be used without the owner’s authorization.

As already discussed, the legislative history of section 505(b)(2) also provides no indication of any congressional intent to amend the paper NDA policy to allow reliance on data contained in a previously approved NDA. In sharp contrast, the legislative history of section 271(e)(1), the so-called *Bolar* Amendment, explicitly demonstrates Congress's intent to reverse the holding of *Roche Products, Inc. v. Bolar Pharmaceutical Co.*, 733 F.2d 858, 861 (Fed. Cir. 1984). *Cf.* H. Rep. No. 98-857, pt. 2, at 27 ("The provisions of § 202 of the bill have the net effect of reversing the holding of the court in *Roche Products, Inc. v. Bolar Pharmaceutical Co.*").

C. Congress imposed patent and exclusivity restrictions upon 505(b)(2) applicants to codify FDA's paper NDA policy and to prevent the use of that policy to circumvent the patent and exclusivity provisions placed on ANDAs.

Failing to find an express statement in the statutory text or the legislative history supporting its argument that 505(b)(2) radically altered the "paper NDA" process to allow reliance on proprietary third-party NDA data, Reddy argues that this change in law is implied by the patent and exclusivity provisions that relate to section 505(b)(2). Reddy Comments at 9-10. Specifically, Reddy argues that the fact that the patent and exclusivity provisions for 505(b)(2) applications operate in parallel to those for ANDAs under 505(j) demonstrates that sections 505(b)(2) and 505(j) are themselves essentially identical approval mechanisms. This is not the case.

The applicability of patent and exclusivity provisions to section 505(b)(2) applications merely reflects the fact that Congress intended section 505(b)(2) - the "paper NDA" - to continue to be available as an alternative route for drug approvals *based on published data*. The operation of these provisions says nothing about an applicant's ability to rely on proprietary NDA data, and

certainly cannot be construed to have radically changed the existing law prohibiting such reliance. Rather, these provisions were necessary to avoid 505(b)(2) becoming a vehicle to evade the patent certification requirements and exclusivity rules that applied to ANDAs. If Congress did not place patent and exclusivity restrictions upon the paper NDA policy, the potential would have existed, as it did under the pre-Hatch-Waxman paper NDA policy, for a “generic manufacturer to obtain approval of a copy of an important new drug very soon after the approval of the pioneer product.” Alan Kaplan & Robert Becker, *An Examination of the ANDA/Patent Restoration Law*, *Pharmaceutical Executive* 60 (Dec. 1984). Generic applicants might then have attempted to use the paper NDA, i.e., 505(b)(2), process to circumvent the ANDA patent certification requirements. Thus, contrary to Reddy’s assertions otherwise, the parallel limitations to section 505(j) in section 505(b)(2) serve a very real purpose -- to close this loophole while leaving open the admittedly narrow paper NDA pathway to generic approval.⁴ Moreover, these protections served to encourage innovators to publish their clinical studies after approval. The lack of patent and exclusivity safeguards would have discouraged pioneers from

⁴ Indeed, the very product that first triggered litigation concerning the Paper NDA policy is instructive. When generic ibuprofen was approved via the Paper NDA route in 1981, ibuprofen was still subject to patent protection. See *Upjohn Mfg. Co. v. Schweiker*, 520 F. Supp. 58 (W.D. Mich. 1981), *aff’d*, 681 F.2d 480 (6th Cir. 1982). Had this still been the case at the time of Hatch-Waxman, ANDA applications for ibuprofen would have been subject both to restrictions on exclusivity and patent certification under 505(j). Thus, in the absence of parallel provisions in section 505(b)(2), applicants could simply have avoided those restrictions by submitting a paper NDA. Indeed, at the time of Hatch-Waxman, Upjohn and Boots had two years of exclusivity, see FDA, *Approved Prescription Drug Products with Therapeutic Equivalence Evaluations*, IV-65 (5th ed., cum. supp. 12, Aug. 84- Aug. 85), under 505(j)(5)(D)(v). Thus, ANDAs were prohibited for two years. Without parallel restrictions placed on 505(b)(2), see 505(c)(3)(D)(v), would-be generics could have easily circumvented that exclusivity period by submitting the same type of paper NDA, (i.e., one that did not rely on the approved product), under section 505(b)(2) that led to the original ibuprofen paper NDA approval.

publishing their clinical studies prior to the expiration of applicable patents for fear that a generic would obtain approval of a paper NDA during the patent term and therefore may have hindered the very generic competition the Hatch-Waxman Amendments were intended to foster.

Congress thus made the conditions for pursuing a paper NDA equivalent to the conditions for submission of an ANDA by amending

section 505(b)... to require an applicant filing a Paper NDA's [sic.] for a listed drug under section 505(j)(6) to make the same certifications regarding patents as mandated in the filing of ANDA's under new subsection (j). In addition, the FDA must make approvals for such Paper NDA's effective under the same conditions that apply to ANDA's submitted under subsection (j).

H. Rep. 98-857, pt. 1, at 32; *id.* pt. 2, at 18. The parallel structure of sections 505(b)(2) and 505(j) reflects this clear congressional intent. Compare 21 U.S.C. § 355(b)(2)(A) (patent certification procedures for (b)(2) applications), *with id.* § 355(j)(2)(A)(vii) (patent certification procedures for ANDAs), *and id.* § 355(c)(3) (timing approval of (b)(2) applications), *with id.* § 355(j)(5)(B) (timing of ANDA approval).

Thus, far from indicating that Congress intended section 505(b)(2) to encompass the same right to rely on pioneer data as section 505(j), *see* Reddy Comments at 9-10, the parallel provisions indicate only that the paper NDA, pursuant to section 505(b)(2), remained a viable route for approving qualified generic products but not a back door to circumvent the protections that Congress provided as part of the entire compromise contained in the 1984 amendments. *Cf.* H. Rep. No. 98-857, pt. 2, at 27 (overturning *Roche Products, Inc. v. Bolar Pharm. Co.*, 733 F.2d 858, 861 (Fed. Cir. 1984)). Far from expanding the paper NDA policy, the patent and exclusivity provisions that Congress added attached new limitations on its use.

D. FDA's 1999 Draft Guidance was a vast departure from the Agency's prior interpretations of section 505(b)(2).

Reddy comments that Pfizer was fully aware in filing the Norvasc® NDA that FDA had adopted an interpretation of 505(b)(2) that permitted reliance on proprietary data to approve modified version of the pioneer drug. Reddy Comments at 18-19. Nothing could be further from the truth. In the so-called "Parkman letter" in 1987, and in the Hatch-Waxman regulations FDA enacted in 1992, FDA proposed to use section 505(b)(2) as a means of implementing section 505(j) to facilitate the approval of a modified product where an applicant could have obtained an ANDA for the true generic. However, neither "Parkman" nor the Hatch-Waxman regulations were ever understood to permit a 505(b)(2) applicant to rely on a pioneer's NDA data. Indeed, both explicitly limited reliance to the extent allowed under section 505(j), thus recognizing that section 505(b)(2) provides no independent right to reference pioneer data. Until the 1999 Draft Guidance, FDA never suggested that a generic drug that *could not* be approved through the ANDA process could gain approval under 505(b)(2), or that 505(b)(2) provided any right to reference or rely upon pioneer data.

To elaborate, in an April 10, 1987 letter to all NDA and ANDA holders and applicants, Dr. Paul Parkman, the Acting Director of the Center for Drugs and Biologics, addressed the procedure by which ANDA applicants could make modifications to approved drugs if the modification would require submission of clinical data. Dr. Parkman's letter begins by discussing the situation in which an applicant wants to gain approval for a new indication. According to the letter, an applicant with an approved ANDA for the approved indication could submit a supplemental application with clinical reports to support the new indication. As the

letter acknowledges, however, an applicant might hope to gain approval of a modification of an approved product but have no desire to market the drug as approved. In this situation, Dr. Parkman said, FDA would “allow a generic applicant to submit a 505(b) ‘supplement’ (a form of NDA) for a change in an already approved drug that requires the submission of clinical data, without first obtaining approval of an ANDA for a duplicate of the listed drug.” *Id.* As with supplements to approved ANDAs, these applications would rely on the approval of the listed drug and the clinical data submitted in support of the change. Such reliance would be allowed “only to the extent that such reliance would be allowed under section 505(j): to establish the safety and effectiveness of the underlying drug.” *Id.*

FDA discussed this approach in the preamble to its proposed Hatch-Waxman regulations. There, the Agency explained that an applicant could submit a 505(b)(2) application “for a change in an already approved drug that requires the submission and review of investigations, without first obtaining approval of an ANDA for a duplicate of the listed drug.” 54 Fed. Reg. 28872, 28892 (July 10, 1989). Among the examples provided were new active ingredients in a combination product. *Id.* FDA provided no indication that it intended for, or the statute permitted, 505(b)(2) to be used to obtain approval of a change in active ingredient in a single-ingredient product. *Id.* at 28919 (proposed 21 C.F.R. § 324.54). Moreover, as in the Parkman letter, the Agency explicitly limited the extent to which reliance would be allowed to that which would be permitted “under section 505(j) of the act: to establish the safety and effectiveness of the underlying drug.” *Id.* at 28892.

Thus, FDA again recognized that while it was prepared to use section 505(b)(2) to implement section 505(j), the former section, by itself, provided no independent right to rely on

NDA data. Further, implicit in both the preamble to the proposed regulations and the Parkman letter was the premise that the 505(b)(2) applicant *could have obtained approval of an ANDA* for the product as marketed and that the applicant could thus rely on that “constructive approval” along with any necessary additional data to support the product change.

In sum, the Parkman letter created, and the Agency’s Hatch-Waxman regulations adopted, an administrative shortcut to permit an applicant seeking approval of a modified generic to rely upon an approval that *could* have been granted under section 505(j). In its 1999 Draft Guidance, FDA for the first time deviated from this settled understanding when it proposed to allow section 505(b)(2) applicants seeking approval of modified generics to rely on proprietary data in an NDA. That this interpretation was a significant change in policy is confirmed by the firestorm of comments and other responses regarding the proposed use of innovator proprietary data for purposes of approving 505(b)(2) applications that immediately followed. In contrast, FDA received only two comments in response to its proposed 505(b)(2) regulations, neither of which addressed the use of proprietary unpublished data. This is for the simple reason that interested parties did not understand the Agency to be proposing, nor was the Agency proposing, such reliance. As noted at the outset of this reply, what Pfizer is requesting is a continuation of FDA’s policies under the 1984 Amendments. Thus, Reddy is incorrect that FDA’s policies before the 1999 Draft Guidance put Pfizer on notice that its proprietary data might be used to support a competitor’s application.

E. Section 505(b)(2) must be read so as to give full meaning to section 505(l)(5).

Absent “extraordinary circumstances,” section 505(l)(5) of the FDCA provides for the release of safety and effectiveness data “upon the effective date of the approval of the first application under subsection (j) . . . which refers to such drug or upon the date upon which the approval of an application under subsection (j) . . . which refers to such drug could be made effective if such an application had been submitted.” 21 U.S.C. § 355(l)(5). To read section 505(b)(2) as authorizing an applicant to reference, or FDA to rely upon, the proprietary safety and effectiveness data contained in a pioneer NDA before that data are releasable under this provision would render section 505(l) ineffectual. The only interpretation that allows both sections 505(b)(2) and 505(l)(5) to remain fully operational is one that prohibits 505(b)(2) applicants from relying on or referencing proprietary safety or effectiveness data in an NDA until those data become publicly available under Section 505(l)(5).

Section 505(l) explicitly recognizes the proprietary character of innovator safety and effectiveness data. As the legislative history explains, in enacting section 505(l), except where it noted its intention otherwise, Congress did not intend to abrogate the recognition and protection of rights in trade secrets, including NDA safety and effectiveness data. H. Rep. 98-857, pt. 1, at 36. Recognizing that, ordinarily, there is diminished value in pioneer safety and effectiveness data after approval of an ANDA, however, Congress authorized FDA, absent extraordinary circumstances, to release such data once that occurred.⁵ See 21 U.S.C. § 355(l)(5). Notably,

⁵ However, safety and effectiveness data are not *per se* releasable upon ANDA approval as the data retains competitive value as commercial information that could be used to support applications in foreign jurisdictions. Such data may also constitute confidential trade secrets not (continued...)

Congress made no such provision for the release of pioneer data upon approval of a section 505(b)(2) application. This is because, unlike section 505(j), 505(b)(2) does not permit reliance on proprietary data in another's NDA and thus does not trigger the release of those data. Absent the triggering of this release by the approval of an ANDA, a 505(b)(2) applicant cannot rely upon or reference innovator data.

Release of data under 505(l)(5) cannot be triggered during the term of any patent protection. The legislative history makes clear that ANDA approval prior to a successful patent challenge does not justify disclosure of pioneer data. According to the House Report, Congress did "not intend that safety and effectiveness data and information be released under this section if an ANDA challenging the validity of a patent is approved before there has been a court decision holding the patent invalid and if the NDA holder brings an action to restrain the disclosure." H. Rep. 98-857, pt. 1, at 36.

F. Reliance by FDA on its own prior "findings" as to amlodipine would clearly amount to reliance on the underlying Pfizer Norvasc® data.

Just as FDA may not rely upon the data contained in Pfizer's Norvasc® NDA in considering Reddy's application, it may not rely on its own prior findings as to the safety and effectiveness of the drug when considering Reddy's application. No credible distinction can be drawn between the Agency's prior findings as to the safety and effectiveness of amlodipine and

releasable by FDA. *Cf. Public Citizen Health Research Group v. FDA*, 997 F. Supp. 56 (D.D.C. 1998) (finding "extraordinary circumstances" are not coextensive with competitive commercial harm but require more severe burden to overcome to prevent release), *aff'd in part, rev'd in part on other grounds*, 185 F.3d 898 (D.C. Cir. 1999).

the data contained in the Norvasc® NDA on which those findings were based.⁶ In a case such as this, where virtually all of the Agency's "knowledge" of the relevant drug is based upon NDA data, the two simply cannot be distinguished. Such a situation differs markedly from the one presented where the Agency has knowledge of the properties of the drug from independent sources. *Cf.* Letter from Ronald G. Chesemore to Ms. Gleason and Mr. Cuca of Aug. 26, 1998 (FDA Docket N. 98P-0167/PSA1) (given "atypical" nature of drug product at issue (i.e., present naturally in body in amounts far in excess of recommended drug dose and previously deemed safe as food additive), concluding that safety of the drug product was matter of "basic knowledge and experience" not requiring reliance on specific data).

That there is no distinction between FDA's reliance on its prior findings of safety and efficacy and its reliance on NDA safety and efficacy data is demonstrated by the case law discussing the Hatch-Waxman Amendments and the concept of the ANDA. Unlike a pioneer applicant who must establish the safety and efficacy of the active ingredient, the ANDA provisions of 505(j) allow a would-be generic to obtain approval upon establishing that its proposed product has, *inter alia*, the same active ingredient, labeling, and dosage form as, and is bioequivalent to, the pioneer product. 21 U.S.C. § 355(j)(2)(A). This process can be conceptualized as either allowing ANDA applicants who have made the requisite showing of "sameness" to rely on pioneer data or as permitting FDA to rely on its prior findings of safety

⁶ This situation is analogous to trade secret cases involving "inevitable disclosure" -- where an employee's general knowledge cannot be differentiated from his former employer's trade secrets so that it becomes impossible for the employee to do his or her new job without using the former employer's secrets. *See PepsiCo, Inc. v. Redmond*, 54 F.3d 1262 (7th Cir. 1995).

and effectiveness. Regardless of how this statutorily-permissible piggy-backing is characterized, however, it is substantively the same thing. In fact, courts variously refer to the ANDA process as allowing reliance on pioneer data or reliance upon prior Agency findings.

For example, the D.C. Circuit has interchangeably characterized an ANDA as “*relying on the NDA* filed by the original manufacturer,” *American Bioscience, Inc. v. Thompson*, 243 F.3d 579, 580 (D.C. Cir. 2001) (emphasis added), *on remand to*, 141 F. Supp. 2d 88, 91 (D.D.C.), *vacated by*, 269 F.3d 1077 (D.C. Cir. 2001); *see Bristol Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1495 (D.C. Cir. 1996) (“The principal advantage of securing approval [by an ANDA] is that the applicant may *rely* upon research paid for by the manufacturer of the listed drug.”) (emphasis added), and as an application “which *relies on the FDA’s previous determination that the drug is safe and effective . . .*” *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1063 (D.C. Cir. 1998) (emphasis added); *see Andrx Pharm., Inc. v. Biovail Corp.*, 256 F.3d 799, 801 (D.C. Cir. 2001) (ANDA “*relies on the FDA’s previous determination that the drug is safe and effective.*”) (emphasis added), *cert. denied*, 533 U.S. 931 (2002). As illustrated by the court’s alternating use of these terms, the D.C. Circuit has recognized reliance upon NDA data to be equivalent to reliance upon the Agency’s previous findings of safety and effectiveness based upon that data. The court is simply using different terminology to describe what is plainly the same thing.

Many courts have described the ANDA process as permitting a “generic producer of the fully tested drug to *rely on the safety and efficacy data of a prior applicant . . .*” *Merck & Co., Inc. v. Kessler*, 80 F.3d 1543, 1546 (Fed. Cir. 1996) (emphasis added) (citations omitted); *see e.g., Mylan Pharm., Inc. v. Thompson*, 268 F.3d 1323 (Fed. Cir. 2001), *cert. denied*, 123 S.

Ct. 340 (2002); *Granutec, Inc. v. Shalala*, No. 97-1873, 1998 U.S. App. LEXIS 6685, *4-5 (4th Cir. Apr. 3, 1998); *American Bioscience, Inc. v. Thompson*, 141 F. Supp. 2d 88, 91 (D.D.C.), *vacated by*, 269 F.3d 1077 (D.C. Cir. 2001); *in re Terazosin Hydrochloride Antitrust Litigation*, 164 F. Supp. 2d 1340, 1343-44 (S.D. Fla. 2000); *American Bioscience, Inc. v. Shalala*, 142 F. Supp. 2d 1, 4 (D.D.C. 2000), *vacated by*, *American Bioscience, Inc. v. Thompson*, 243 F.3d 579 (D.C. Cir.), *on remand to*, 141 F. Supp. 2d 88, 91 (D.D.C.), *vacated by*, 269 F.3d 1077 (D.C. Cir. 2001); *Teva Pharm. USA, Inc. v. FDA*, C.A. No. 99-67 (CCK), 1999 U.S. Dist. LEXIS 14575, *4 (D.D.C. Aug. 19, 1999); *Zenith Labs, Inc. v. Abbott Labs*, C.A. No. 96-1661, 1997 U.S. Dist. Lexis 23954, (D.N.J. Oct. 3, 1997); *Pfizer Inc. v. FDA*, 753 F. Supp. 171, 172 (D. Md. 1990); *Glaxo Inc. v. Heckler*, 623 F. Supp. 69, 72 (E.D.N.C. 1985). An ANDA thus “rel[ies] principally on the safety and effectiveness data developed and submitted by pioneer drug companies.” *Abbott Labs. v. Geneva Pharm., Inc.*, No. 96-C-331, 1998 U.S. Dist. LEXIS 13864, *6 (N.D. Ill. Sept. 1, 1998); *see Upjohn Co. v. Kessler*, 938 F. Supp. 439, 441 (W.D. Mich. 1996) (same). This is the case even if that reliance is termed reliance “on the FDA’s previous determination that the pioneer is safe and effective.” *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191, 194 (D.D.C. 2002). Because FDA’s “previous determination” as to safety and efficacy rests upon the data underlying those conclusions, reliance on the former is necessarily reliance on the pioneer data.

There is thus no basis for FDA to differentiate between reliance on its prior findings of safety and effectiveness of a drug and reliance on pioneer data establishing the same. An ANDA relying “on the approved application of another drug with the same active ingredient to establish safety and efficacy,” 21 U.S.C. § 321 (aa), may fairly be described as relying upon the Agency’s

prior finding of safety and effectiveness. A 505(b)(2) application, which relies on investigations “not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use,” however, cannot be so characterized. Nor can it be approved based on such prior findings. Legislative enactments since the Hatch-Waxman Act confirm this fact.

First, in passing the Generic Drug Enforcement Act of 1992 (“GDEA”), Pub. L. No. 102-282, 106 Stat. 149 (1992), Congress sought to restore the integrity of the approval process for “abbreviated drug application[s],” defined as “an application submitted under section 505(j) for the approval of a drug that *relies on the approved application* of another drug with the same active ingredient to establish safety and efficacy.” 21 U.S.C. § 321(aa) (emphasis added). In the context of the GDEA, Congress did not address 505(b)(2) applications because they were not prone to the same sort of abuses that Congress sought to rectify with respect to ANDAs that rely on an innovator’s proprietary data and relatively limited scientific inquiries. By omitting any discussion of section 505(b)(2) applications in relation to the GDEA, Congress effectively ratified its historical position that FDA cannot approve such applications in reliance on an innovator’s proprietary data or the Agency’s prior findings of safety and effectiveness.

The legislative history of the FDA Modernization Act of 1997 (“FDAMA”), Pub. L. No. 105-115, 111 Stat. 2296, 2348 (1997), further shows this congressional understanding. Section 118 of FDAMA, required FDA to issue guidance to describe when abbreviated study reports could be submitted in lieu of full reports. Congress enacted this provision to address the problems with individual NDA reviewers having significant discretion to impose more or less detailed submission requirements on NDA sponsors. In passing this provision, Congress did not differentiate between the impact it would have on 505(b)(1) applications and 505(b)(2)

applications. Nor does the statutory language or legislative history provide any suggestion that Congress sought to permit less than full reports of investigations to support a 505(b)(2) application or to permit FDA to rely on proprietary innovator data, or Agency findings based upon such data, to approve a 505(b)(2) application.

G. Reddy's list of "threatened" approvals is replete with both speculation and demonstrably false assertions.

Although Reddy suggests that acceptance of Pfizer's arguments would destabilize "many important products and many important labeling amendments that have been approved under section 505(b)(2)," Reddy Comments at 2, this scare tactic is unsupported and misleading. Pfizer's petition contends only that Reddy may not support its 505(b)(2) application for amlodipine maleate using non-public information in Pfizer's NDA for Norvasc®, including specifically long-term toxicity and impurity studies Pfizer conducted on an amlodipine maleate product that it never marketed. In light of the unique circumstances surrounding the Pfizer Petition, FDA's acceptance of Pfizer's position would impact the approval of few, if any, currently-effective 505(b)(2) applications.

For example, several products on the list of 505(b)(2) approvals that Reddy contends are in jeopardy are true paper NDAs that do not rely on another company's proprietary data, but rely only on the applicant's own data as well as public information. These include Mucinex, Thalomid, Avandamet, Glucovance, Zerit XR, Tavist Allergy/Sinus/Headache, and Versed. These are clearly unaffected by any relief sought by Pfizer.

Other products such as Avinza, (morphine sulfate extended release); Avita (tretinoin); Canasa (mesalamine) Suppositories; Children's Advil Cold; (clindamycin phosphate) Topical

Gel; Diltiazem; Ibuprofen; Olux (clobetasol propionate) Foam; Pamidronate disodium Injection; Repronex (menotropins for injection); Roxycodone (oxycodone hydrochloride); Sulfamethoxazole/trimethaprim USP and phena-zopyridine tablets; and Tri-Nasal (triamcinolone acetonide) Nasal Spray are all variations, either in dosage form, or labeling (but not active ingredient), of approved drugs previously subject to an ANDA and therefore involve either “Parkman” type NDAs or ANDA supplements. FDA has the necessary information to determine whether any of these products would be affected by the granting of the Pfizer Petition.

The only product on the Reddy list that would appear to be affected by the granting of the Pfizer Petition is Asimia (paroxetine mesylate) Tablets, which is a different salt of an approved product and is currently only tentatively approved and the subject of an ongoing patent infringement suit. *SmithKline Beecham Corp. v. Synthron Pharm. Ltd.*, 210 F.R.D. 163 (M.D.N.C. 2002).

Thus far from the avalanche of potential revocations that Reddy suggests will occur if FDA grants the Pfizer Petition, few if any existing products will be affected, but confidential and trade secret data essential to development of new and needed pharmaceuticals will be appropriately preserved.⁷

⁷ Even if individual 505(b)(2) approvals were based on proprietary data, they might not be affected by acceptance of Pfizer’s arguments. First, the owner of the data may not object for business reasons. Second, FDA could decide to grant the relief Pfizer requests for this petition and for other 505(b)(2) applications prospectively. There is precedent for such an approach. For example, after a district court decision finding that FDA’s interpretation of “court” as used in the 180-day exclusivity context was inconsistent with the statute’s plain meaning, *Mylan Pharm., Inc. v. Shalala*, 81 F. Supp. 2d 30, (D.D.C. 2000), FDA issued a guidance document stating it would “implement the new interpretation of the term ‘court’ prospectively. . . .” Guidance for (continued...)

II. Even if it were legally permissible for FDA to rely upon Pfizer's data, to do so would be scientifically unjustified.

As a matter of law, neither FDA nor Reddy may rely on the proprietary data contained in Pfizer's Norvasc® NDA. Moreover, even if it could rely on Pfizer's data, as set forth in the Pfizer Petition, FDA cannot properly approve NDA 21-435 without original data establishing the safety of Reddy's proposed amlodipine maleate formulation because Reddy's formulation differs from the amlodipine maleate formulation Pfizer studied as part of its NDA.

Rather than respond to this argument or offer any explanation of the data it has submitted to establish the safety and effectiveness of its product, Reddy attempts to dismiss this point by simply stating that "FDA's approval of the Norvasc NDA is relevant to Reddy's amlodipine maleate product." Pfizer has no doubt that the approval of its Norvasc® NDA is "relevant" to Reddy's amlodipine product. Reddy's Comments at 21. Reddy's attempt to free ride upon Pfizer's time-consuming and costly proprietary data to obtain approval of its product confirms this point. The relevance of the Norvasc® approval, however, is not the issue. The scientific appropriateness of Reddy relying on data contained in the Norvasc® NDA -- whether Pfizer's NDA data provides any basis for finding Reddy's indisputably different product to be safe and effective -- is.

As set forth in greater detail in Pfizer's initial citizen petition, Pfizer conducted the majority of its preclinical and clinical studies on a uniquely-manufactured maleate salt of amlodipine but, after encountering stability and tableting problems with the maleate salt,

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switched to besylate salt found in Norvasc®. These problems were attributable to a biologically-active degradation product, a separate compound known as UK-57,269, that arises during synthesis and production of the maleate salt. Pfizer thus instituted specific manufacturing, analytical, and study controls to manage purity and stability issues related to UK-57,269. These controls are trade secrets that Pfizer has not published and that FDA could not properly release to a third party. Because the stability and impurity profile of Pfizer's amlodipine maleate product is unknown to Reddy, Reddy's product will necessarily be distinct from Pfizer's product. Accordingly, it could pose potentially different and perhaps serious risk to patients.

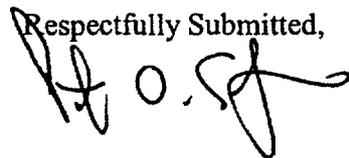
Reddy does not respond to this or any other facet of Pfizer's scientific argument. In fact, Reddy clearly concedes that its product cannot receive a therapeutic equivalence rating. Nevertheless, Reddy asks FDA to rely on Pfizer's Norvasc® data and to make assumptions about its amlodipine maleate product without coming forward with any information to justify that reliance or those assumptions. Reddy fails to explain how its submissions in support of its application address the degradation issue. Nor does Reddy provide any basis to believe that it was able to replicate Pfizer's manufacturing, analytical, and study controls or that it has independently identified, quantified, and qualified the impurities and degradation products associated with its amlodipine maleate product through an appropriately comprehensive range of toxicological and other testing.

It is Reddy's burden to establish the safety and efficacy of its product, not Pfizer's or FDA's. Assuming *arguendo*, however, that Reddy could rely on Pfizer's data to make that showing, as a precondition, Reddy would have the additional burden of demonstrating that such

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reliance would be scientifically justified. Reddy has failed to come forth with any information suggesting that it has satisfied that prerequisite.

Pfizer appreciates this opportunity to respond to Reddy's comments.

Respectfully Submitted,


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