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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.

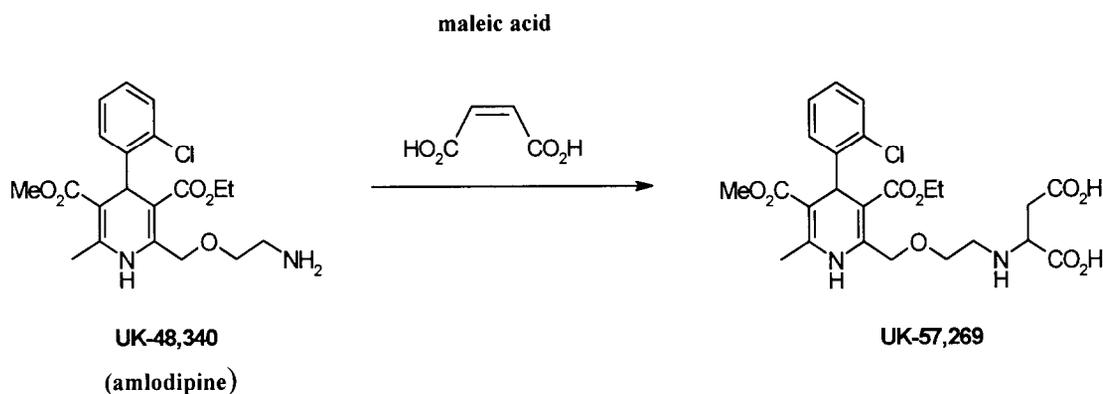
B. Factual Background

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 FFDCA'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 FDCA 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.^{25/} 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

^{25/} 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

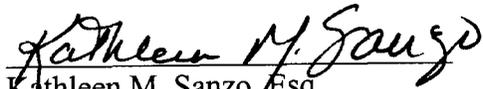
The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

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

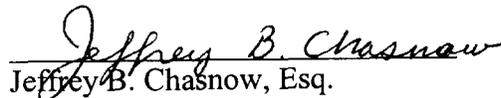
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Morgan Lewis
C O U N S E L O R S A T L A W

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Attachments