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June 4, 2003

**VIA HAND DELIVERY**

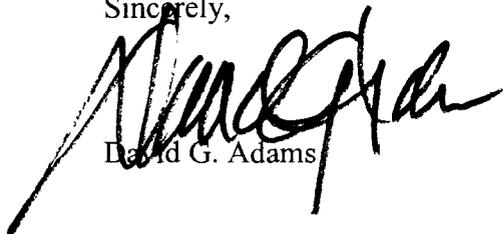
Dockets Management Branch  
Food and Drug Administration  
5630 Fishers Lane, Room 1061 (HFA-305)  
Rockville, MD 20852

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

Dear Sir or Madam:

Please accept the attached supplemental 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

02P-0447

SUP 1

June 4, 2003

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

Dear Sir or Madam:

These supplemental comments are submitted on behalf of Dr. Reddy's Laboratories, Inc., (Reddy) with regard to the Citizen Petition filed by Pfizer, Inc., (Pfizer) on October 11, 2002 (Pfizer Petition). These supplemental comments respond to comments filed by Pfizer on April 28, 2003 (Pfizer Comments).

**INTRODUCTION**

FDA's policy permitting the filing of Reddy's NDA for amlodipine maleate under section 505(b)(2) of the Food, Drug, and Cosmetic Act (FDCA) rests on six basic propositions:

1. The FDCA is designed to permit and to encourage modifications to approved drugs.
2. The holder of an approved NDA or ANDA does not have to reestablish the safety and effectiveness of the approved product when it seeks approval for a modification of the product.
3. Where an ANDA holder seeks approval for a modification that cannot be approved under section 505(j), the modification must be submitted under section 505(b)(2).
4. Where an ANDA holder submits a 505(b)(2) NDA for a modification, the 505(b)(2) NDA relies on the approval of the original reference listed drug (RLD) to the same extent that the original ANDA relied on the RLD.
5. Where an applicant who does not have an approved ANDA seeks approval for a modified version of an RLD, the applicant does not need to obtain an ANDA

approval prior to submitting a 505(b)(2) NDA for the modification. The applicant can shortcut the process by submitting an original NDA for the modified version that relies on the RLD to the same extent that an ANDA for an unmodified version could have relied on the RLD.

6. Reddy seeks approval of a modified version of Norvasc that relies on the Norvasc NDA to the same extent that a Reddy ANDA for an unmodified version of Norvasc could have relied on the NDA.

Pfizer now appears to agree with every proposition but the last. Pfizer argues in its most recent comments that, because Reddy's modification involves the salt form of the active ingredient, Reddy's application does not rely on the Norvasc NDA in the same manner that a Reddy ANDA would rely on the Norvasc NDA. This means, according to Pfizer, that Reddy must reestablish the safety and effectiveness of the original Norvasc formulation even though a Reddy ANDA could be approved for that formulation. Pfizer fails utterly to explain how section 505(b)(2) requires this peculiar outcome.

## DISCUSSION

### **A. Pfizer Acknowledges that Applications Submitted under Section 505(b)(2) May Rely on Other Approved NDAs to the Extent Reliance Would Be Allowed under Section 505(j).**

In its April 28 comments, Pfizer substantially retreats from the position taken in its petition that section 505(b)(2) is limited in scope to applications that could have been submitted as "paper NDAs" under FDA's 1981 policy.<sup>1</sup> Pfizer's original position, as the company acknowledges, would not allow for the approval of what Pfizer refers to as "Parkman" type NDAs and ANDA supplements, which have been approved on numerous occasions over the past fifteen years.<sup>2</sup> Pfizer now states that its revised position "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."<sup>3</sup>

Pfizer even goes so far as to assert that Reddy made "false assertions" that Pfizer's position challenged FDA's prior approval of numerous NDAs under section 505(b)(2).<sup>4</sup> Pfizer now contends that "[t]he only product on the Reddy list [of possibly threatened 505(b)(2) NDAs] 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

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<sup>1</sup> 46 Fed. Reg. 27396 (1981).

<sup>2</sup> See Pfizer Comments at 20-21, *citing* Letter to all NDA and ANDA holders and applicants from Paul D. Parkman, M.D., dated April 10, 1987 (Parkman Letter).

<sup>3</sup> Pfizer Comments at 2.

<sup>4</sup> *Id.* at 20. Pfizer does not identify the assertions by Reddy that it alleges to be "false." There is no false assertion in Reddy's comments. Pfizer's claim is reckless and obviously wrong.

product.”<sup>5</sup> Pfizer now says that other products on Reddy’s list, involving “Parkman” type NDAs and ANDA supplements, do not appear to be affected by its position.<sup>6</sup>

Pfizer describes a “Parkman” type NDA as one that relies on the approval of another NDA “only to the extent that such reliance would be allowed under section 505(j): to establish the safety and effectiveness of the underlying drug.”<sup>7</sup> The “Parkman” concept, according to Pfizer, would “permit an applicant seeking approval of a modified generic to rely upon the approval that *could* have been granted under section 505(j).”<sup>8</sup> The central premise was that “the 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.”<sup>9</sup>

While Pfizer concedes that “Parkman” type modifications can be filed under section 505(b)(2), Pfizer asserts that Reddy’s particular modification of the salt form of an active ingredient cannot be filed under that section.<sup>10</sup> There is no basis in law, policy, or common sense for Pfizer’s proposed distinction.

**B. Reddy’s NDA Relies on the Norvasc NDA to the Extent that Reliance Would Be Allowed under Section 505(j).**

In its 505(b)(2) NDA, Reddy relies on the Norvasc NDA to the extent that it could have relied on that NDA in an ANDA submitted for the Norvasc formulation.<sup>11</sup> Reddy relies on the Norvasc NDA to “establish the safety and effectiveness of the underlying

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<sup>5</sup> *Id.* at 21. Contrary to Pfizer’s assertion, FDA has approved other modifications to salt forms of active ingredients under section 505(b)(2). *See* Part D.4, *infra*.

<sup>6</sup> *Id.*

<sup>7</sup> *Id.* at 12, *quoting* Parkman Letter.

<sup>8</sup> Pfizer Comments at 13.

<sup>9</sup> *Id.*

<sup>10</sup> Referring to the preamble to FDA’s regulation implementing the policy of the Parkman Letter, Pfizer states: “FDA provided no indication that it intended for, or the statute permitted, 505(b)(2) to be used to obtain approval of a change an active ingredient in a single-ingredient product.” Pfizer Comments at 12, *citing* 54 Fed. Reg. 28,872, 28,892 (1989). *See also* Pfizer Comments at 21, distinguishing “Parkman” type NDAs for variations in dosage form or labeling from changes to the active ingredient.

<sup>11</sup> On May 7, 2003, the law firm of Frommer Lawrence & Haug, LLP, (Frommer) filed comments in this docket arguing that FDA cannot approve Reddy’s NDA because, according to Frommer, Reddy’s NDA would rely on data from the Norvasc NDA involving amlodipine maleate that FDA did not rely on to approve the Norvasc NDA. Frommer misunderstands Reddy’s submission. Reddy’s NDA relies on the Norvasc NDA to the extent that an ANDA would rely on the Norvasc NDA. Reddy’s NDA relies on FDA’s determination that Norvasc is safe and effective and thus on the data supporting that determination. Frommer also misunderstands FDA’s approval of the Norvasc NDA. The SBA for the Norvasc NDA shows that Norvasc was approved based on studies performed both on amlodipine besylate and amlodipine maleate.

drug.”<sup>12</sup> The underlying drug is the Norvasc formulation.<sup>13</sup> Reddy relies on the demonstrated safety and effectiveness of the Norvasc formulation, containing amlodipine besylate, to the extent that Reddy could have relied on the Norvasc NDA for approval of an ANDA containing the same amlodipine besylate active ingredient. This means that Reddy relies on the Norvasc safety and efficacy data to support the safety and efficacy of Reddy’s formulation to the extent that Reddy’s formulation is the same.

Reddy then supplements its “constructive approval” of the Norvasc-type formulation with the “additional data to support the product change.”<sup>14</sup> The product change involves modifying the salt form of the active ingredient from amlodipine besylate to amlodipine maleate. Reddy’s NDA provides the additional data required by FDA to support the safety and effectiveness of this change.

Pfizer appears confused by this application of section 505(b)(2) and by FDA’s 1999 policy statement.<sup>15</sup> Pfizer agrees that the policy reflected in FDA’s regulation, allowing reliance without right of reference on safety and efficacy data under “Parkman” type NDAs, is consistent with the 1984 Amendments. Pfizer states that “what Pfizer is requesting is a continuation of FDA’s policies under the 1984 Amendments” prior to the 1999 policy statement.<sup>16</sup> Pfizer appears to believe that FDA’s 1999 policy statement abandoned the Parkman Letter approach and reinterpreted section 505(b)(2) to provide an “independent right to rely on NDA data.”<sup>17</sup> Such is not the case.

It is true, of course, that Congress expressly recognized in section 505(b)(2) that certain NDAs may be approved based on safety and/or efficacy data to which the applicant has no claim of ownership and no right of reference. The reliance allowed under section 505(b)(2) for modified ANDAs, however, is not based solely on that section. This reliance, described in the Parkman Letter as reliance “to the extent that such reliance would be allowed under section 505(j),” is a function of authority derived from 505(j) in conjunction with 505(b)(2).

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<sup>12</sup> See Pfizer Comments at 12, *quoting* Parkman Letter.

<sup>13</sup> Pfizer’s new position is somewhat unclear. Pfizer may view the “underlying drug” referred to in the Parkman Letter as the active ingredient rather than the finished product (formulation). This does not appear to be the intent of the letter, given the many references in the letter to the “drug” as the approved product. Regardless, even if the Parkman Letter were deemed to refer to the active ingredient as the “drug,” the analysis would be the same. Reddy would rely on the safety and effectiveness of amlodipine besylate to the extent Reddy’s amlodipine maleate ingredient is the same (they have the same amlodipine active moiety), and would present evidence to FDA that the change in the salt form from a besylate to a maleate is safe and effective.

<sup>14</sup> See Pfizer Comments at 13.

<sup>15</sup> *Guidance for Industry: Applications Covered by Section 505(b)(2): Draft Guidance (1999)*.

<sup>16</sup> Pfizer Comments at 13.

<sup>17</sup> *Id.* at 12-13.

Pfizer's failure to acknowledge this point is puzzling. Pfizer goes to great lengths in its comments to establish that approved ANDAs rely on the safety and effectiveness data in other approved applications.<sup>18</sup> Given the Pfizer's acknowledgment that (1) ANDA applicants rely on safety and effectiveness data in other applications and (2) under the Parkman Letter 505(b)(2) applicants can rely on data from approved applications to the extent that such reliance would be allowed under section 505(j), it is difficult to comprehend Pfizer's assertion that, in the 1999 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."<sup>19</sup> In fact, FDA approved a modification to an approved salt form under section 505(b)(2) years before it issued the 1999 Guidance.<sup>20</sup>

**C. ANDA's Are Approved Based on Statutory Authorization to Rely on the Safety and Efficacy Data in other Approved Applications.**

Prior to the 1984 Amendments FDA had no express statutory authority to approve a generic drug based safety and efficacy data in another application without a right of reference. In the absence of such express authority, FDA developed a mechanism for approving ANDAs based on agency administrative determinations (DESI findings) related to the agency's review of drugs approved prior to 1962. By expanding these administrative determinations to include all identical, similar, and related products, FDA applied determinations of safety and efficacy to applications submitted for closely related drugs. These drugs were approved as DESI ANDAs based on bioequivalence. In the 1984 Amendments, Congress obviated this mechanism by providing express statutory authority for ANDA applicants to rely on the safety and efficacy of other approved drugs. Under section 505(j), the ANDA applicant need only refer to another listed drug and demonstrate bioequivalence.

Pfizer emphasizes in its comments that, when FDA approves an ANDA based on the safety and effectiveness of another drug, the agency relies on safety and efficacy data contained in another application.<sup>21</sup> Pfizer points out that, "[b]ecause 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."<sup>22</sup> Pfizer notes that "[n]o credible distinction can be drawn between the Agency's prior findings as go the

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<sup>18</sup> *Id* at 15-18.

<sup>19</sup> *Id.* at 13.

<sup>20</sup> Primisol® (trimethoprim hydrochloride) was approved based on an NDA for Trimplex® (trimethoprim).

<sup>21</sup> *See id.* at 15-18. Pfizer cites numerous cases for the proposition that "courts variously refer to the ANDA process as allowing reliance on pioneer data or reliance upon prior Agency findings." *Id.* at 17.

<sup>22</sup> *Id.* at 18.

safety and effectiveness of amlodipine and the data contained in the Norvasc NDA on which those findings were based.”<sup>23</sup>

Pfizer thus recognizes an important point. The statutory right to an ANDA approval under section 505(j) constitutes a statutory right to rely, without right of reference, on the safety and efficacy data in a another applicant’s approved application. This is precisely the type of reliance that Congress described in section 505(b)(2). Reddy’s reliance on Norvasc studies under section 505(b)(2) is, in fact, the same reliance that would be permitted in the approval of an ANDA referring to Norvasc under section 505(j). This was the point of the Parkman Letter and is the continuing basis for the agency’s interpretation of 505(b)(2).

Because ANDAs are approved based on the safety and efficacy data supporting the reference listed drug (RLD), they embody a statutory right to rely those data that is the same in effect as a right of reference to the data. In the place of a right of reference from the owner of the data, the applicant is permitted to refer to the listed drug and, by operation of statute, rely on the underlying safety and efficacy data by relying on the drug’s approval. The statute makes clear that, following approval, ANDAs continue to embody this statutory reliance on the safety and efficacy supporting the RLD. Section 505(j)(7) expressly permits ANDA applicants to refer to approved ANDAs as well as NDAs, and FDA occasionally designates drugs approved in ANDAs as RLDs. An ANDA can be approved based on the approval of another ANDA because the previously approved ANDA embodies a statutory reliance on the safety and efficacy data from a pioneer NDA.

**D. Holders of Approved ANDAs Do Not Lose Their Right to Rely on the Underlying Safety and Efficacy Data when They Modify Their Products.**

**1. Pfizer Agrees that Modified ANDAs Can Be Approved Under Section 505(b)(2).**

An important principle underpinning the drug approval process is the applicant’s ability to make changes and improvements in its approved products. Holders of approved NDAs and ANDAs can modify their approved products without having to reestablish the safety and effectiveness of the approved product. The modifications are approved based on data demonstrating the safety and effectiveness of the modification.<sup>24</sup> It is clear that Congress intended that companies be allowed to modify their products without undue regulatory burdens.<sup>25</sup>

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<sup>23</sup> *Id.* at 15-16.

<sup>24</sup> *See, e.g.*, 21 C.F.R. 314.71.

<sup>25</sup> *See, e.g.*, Section 403 of the FDA Modernization Act of 1997, Pub. L. No. 105-115, § 403, 111 Stat. 2296, 2367 (1997).

Thus the agency made clear in the Parkman Letter that there was no statutory limitation on an ANDA applicant's ability to modify a product approved in an ANDA. Where the modification could be approved under section 505(j) it would be approved under that section. Where the modification could not be approved under section 505(j), the modification would have to be reviewed under the NDA provisions of the act. The "NDA supplement" to the ANDA would incorporate the ANDA by reference and would contain such additional data as would be necessary to establish the safety and effectiveness of the change. Because these modified ANDAs were based on original ANDAs that were approved based on safety and efficacy data in other applications, they were appropriately submitted under section 505(b)(2) as NDAs that relied without a right of reference on studies in other applications. These are what Pfizer refers to as "Parkman" type ANDA supplements.<sup>26</sup>

Pfizer now acknowledges that ANDA applicants can modify their approved products through these "Parkman" type *ANDA supplements* in which they rely on their original ANDA approval and supplement it with clinical data supporting the modification. Pfizer also acknowledges that ANDA applicants can follow an "administrative shortcut" by relying on a "constructive ANDA" that the applicant could have filed, but did not file.<sup>27</sup> These are what Pfizer refers to as "Parkman" type *NDAs*.

Pfizer's sole disagreement with the agency at this point is Pfizer's contention that certain ANDA modifications cannot be allowed under the "Parkman" approach. While Pfizer would allow generic applicants to rely on their approved ANDAs (or on "constructive" ANDAs) to make certain types of modifications, such as new dosage forms, new indications, and changes in active ingredients in combination products, Pfizer would not allow a modification of the salt form of the active ingredient in a single-ingredient product.<sup>28</sup> Pfizer claims that Congress intended to take away an ANDA holder's ability to rely on its own approved ANDA where the active ingredient molecule is modified with regard to its salt form, as opposed to being replaced with an entirely new molecule (in a combination product). Pfizer thus argues that, to change a salt form, the ANDA holder must reinvent the wheel and reestablish the safety and effectiveness of the its original ANDA formulation – not because it is required by science, but because Congress intended to protect NDA holders from generic competitors marketing new salt forms of their products.

## **2. Neither the Wording nor Legislative History of Section 505(b)(2) Suggests any Limitation on How ANDAs Can Be Modified.**

There is nothing in the wording of the statute or legislative history to support the restriction on new salts now being proposed by Pfizer. Section 505(b)(2) refers to

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<sup>26</sup> See, e.g., Pfizer Comments at 21.

<sup>27</sup> This Pfizer refers to as the "administrative shortcut" based on a "constructive approval." Pfizer Comments at 13.

<sup>28</sup> Pfizer Comments at 21.

applications in which the applicant relies without a right of reference on studies that were not conducted by or for the applicant. There is no suggestion in the wording of section 505(b)(2) that the applicant's ability to rely on others' studies is limited to studies submitted in support of the same salt form of the active ingredient, or is limited in any other way. Nor is there any such suggestion in the legislative history. In fact, Pfizer still argues that Congress was thinking only of FDA's 1981 paper NDA policy when it drafted section 505(b)(2).<sup>29</sup>

Although Pfizer states that its arguments "would not prevent FDA, in some circumstances, from accepting applications [under section 505(b)(2)] for a modified version of the pioneer product if the applicant could have obtained an ANDA on the original product,"<sup>30</sup> Pfizer reverts to the argument made in its petition that Congress intended section 505(b)(2) to be limited to "paper NDAs" under FDA's 1981 policy. Pfizer concedes that the wording of section 505(b)(2) does not limit the applicant's reliance on others' studies to *published* studies. Pfizer argues that Congress failed to provide this express limitation because Congress was simply trying to describe the *primary* distinction between paper NDAs and full NDAs, i.e., reliance on others' studies without permission.<sup>31</sup> This, however, does not explain why Congress expressly limited 505(b)(2) to applications relying on studies without a right of reference but did not expressly limit that section to applications relying on *published* studies.

This is an obvious and profoundly important limitation that Congress should have included in section 505(b)(2) had Congress intended such a limitation. Prior to Congress' passage of the 1984 Amendments, FDA had a stated policy allowing ANDA holders to modify their products based on new clinical data without losing their right to rely on FDA's DESI determination of safety and efficacy.<sup>32</sup> Such a modified ANDA would have been indistinguishable from what Pfizer describes as a "Parkman" type ANDA supplement. Pfizer thus proposes that FDA read an unstated limitation into section 505(b)(2) that would remove what FDA regarded as a statutory right prior to the enactment of that section. Such a proposal is contrary to Congress' clear intent to extend FDA's DESI policies to drugs approved after 1962 and to bring more generic drugs onto the market.<sup>33</sup>

Although Pfizer marches back through the legislative history presented in its petition, the fact remains that the legislative history suggests that Congress redefined the

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<sup>29</sup> *Id.* at 4-8.

<sup>30</sup> *Id.* at 2.

<sup>31</sup> *Id.* at 7.

<sup>32</sup> See P. Bryan and G. Knapp, "Problems in Implementing Paper NDA's and Post-1962 ANDA's: FDA Perspectives," at 20 (1982) (attached as Tab 3 to Reddy's Submission of Comments dated April 9, 2003).

<sup>33</sup> See H.R. Rep. No. 857 (Part I), 98 Cong. 2d Sess., at 14-17 (1984); H.R. Rep. No. 857 (Part 2), 98 Cong. 2d Sess., at 5 (1984).

phrase “paper NDA” to include any NDA that relies without permission on another company’s studies. Indeed, Pfizer has referred to Reddy’s 505(b)(2) NDA for amlodipine maleate as a “paper NDA” on numerous occasions in court filings.<sup>34</sup> Pfizer’s reference to *Eli Lilly & Co. v. Medtronic*,<sup>35</sup> where the Court stated that section 505(b)(2) authorizes applications “that rely on published literature,” hardly compels a different conclusion. The statement was dicta describing the types of applications subject to patent certification provisions.<sup>36</sup> FDA was not a party to the case and the scope of section 505(b)(2) was not at issue.

**3. Section 505(b)(2) Is Not Limited to Modifications that Are ANDA-Suitable.**

Although Pfizer’s exact position is somewhat unclear, Pfizer appears to argue that a modification to the active ingredient in an approved ANDA cannot be approved under section 505(b)(2) because the modification would result in a drug that no longer meets the sameness criteria of section 505(j).<sup>37</sup> Such a proposition would limit the scope of section 505(b)(2) to the types of changes permitted in ANDA suitability petitions.

This argument, however, would make no sense because Pfizer has acknowledged that “Parkman” type NDAs can be submitted for new indications, which would not be suitable for ANDAs.

Furthermore, there is no basis in the wording of the statute or in the legislative history for limiting section 505(b)(2) to modifications falling under the sameness criteria of section 505(j). The sameness criteria of section 505(j) were not designed to protect NDA holders from having their data used by FDA to approve certain types of competing products. They were rather based on a practical scientific consideration – the limited

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<sup>34</sup> In the appeal of its patent litigation challenging Reddy’s amlodipine maleate, Pfizer stated:

Dr. Reddy’s NDA is what is known as a “paper NDA.” . . . “Paper NDA’s are defined as any application submitted under section 505(b) of the FDCA in which the investigations relied upon by the applicant to show safety and effectiveness were not conducted by or for the applicant and the applicant has not obtained a right of reference or use from the person who conducted the studies or for whom the studies were conducted.” . . . Dr. Reddy’s paper NDA relied on the studies and data that Pfizer conducted on amlodipine as part of its development of Norvasc®. . . .

Brief for Plaintiff-Appellant Pfizer, Inc., at 28, *Pfizer, Inc. v. Dr. Reddy’s Laboratories*, LTD (Fed. Cir. 2003) (Nos. 03-1227, -1228) (citations omitted) (Tab A). Pfizer has referred to Reddy’s NDA as a “paper NDA” throughout the litigation. See, e.g., *id.* at 22, 34; Memorandum of Plaintiff Pfizer Inc. in Support of the Court’s Entry of Its Proposed Order, at 4, 7, 8, 2002 WL 31833744 (D.N.J. 2003) (No. 02-CV-2829) (Tab B); Reply Memorandum of Plaintiff Pfizer Inc. in Support of the Court’s Entry of Its Proposed Order, at 4, 7 (D.N.J. 2003) (Tab C).

<sup>35</sup> 496 U.S. 661, 676 (1990).

<sup>36</sup> *Id.*

<sup>37</sup> Pfizer comments at 12.

approval criteria of section 505(j).<sup>38</sup> The statute directs that drugs meeting the sameness criteria of section 505(j) (ANDA suitable drugs) must be approved based on a demonstration of bioequivalence, and expressly precludes the agency from requiring additional clinical or preclinical data.<sup>39</sup> The ANDA sameness criteria clearly were not designed to protect NDA holders from certain variations on competing products.

Indeed, the statutory sameness criteria were based on FDA's pre-1984 ANDA suitability criteria, which were themselves based solely on whether ANDA review criteria were adequate for approval. The agency's 1983 ANDA regulation provided that, "[i]f preclinical or clinical evidence is needed to support the safety, or if clinical evidence is needed to support the effectiveness, of the proposed product, then an abbreviated new drug application is not suitable for the similar or related drug product."<sup>40</sup>

Thus, the question under section 505(b)(2) is not whether the ANDA holder's *proposed modification* could be approved under section 505(j) but rather whether the approved *unmodified version* of the product was properly approved under section 505(j). In the case of an applicant submitting an original application under section 505(b)(2), the question is not whether the *proposed modification* to the RLD could be approved under section 505(j) but rather whether an *unmodified version* of the RLD could have been approved under section 505(j).

#### **4. FDA Has Approved Modifications to Salt Forms of Active Ingredients Under Section 505(b)(2).**

Although Pfizer suggests that Reddy's NDA raises a new issue that would not affect other NDAs approved under section 505(b)(2), such is not the case. FDA has approved at least two 505(b)(2) NDAs for products in which the salt form of the active ingredient was modified. Primisol® (trimethoprim hydrochloride) was approved based on an NDA for trimethoprim, and Betimol® (timolol) was approved based on an NDA for timolol maleate.

#### **5. Subsequent Enactments Do Not Support Pfizer's Proposed Limitation.**

Pfizer attempts to rely on the Generic Drug Enforcement Act of 1992 (GDEA) to support the proposition that section 505(b)(2) is limited to paper NDAs under FDA's 1981 policy. Pfizer notes that GDEA imposed restrictions on ANDAs based on abuses in

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<sup>38</sup> Section 505(j)(2)(C) provides for the approval of an ANDA suitability petition unless the product cannot be approved without investigations "to show the safety and effectiveness of the drug" or of any modification related to the statutory sameness criteria (505(j)(2)(C)(i)) or, in the case of the substitution of one ingredient in a combination product, without "information required to be submitted in an abbreviated application (505(j)(2)(C)(ii))."

<sup>39</sup> FDCA § 505(j)(2)(A) provides that "[t]he Secretary may not require that an abbreviated application contain information in addition to that required by [section 505(j)(2)(A)(i)] through (viii)."

<sup>40</sup> 21 C.F.R. 314.2(c) (1983), promulgated at 48 Fed. Reg. 2755 (1983).

the ANDA approval process, but did not impose similar restrictions on section 505(b)(2) NDAs.<sup>41</sup> Pfizer argues that Congress must have assumed that section 505(b)(2) permitted only paper NDAs supported by published studies because, according to Pfizer, 505(b)(2) NDAs that rely on an RLD rather than on published studies would be subject to the same abuse as ANDAs.<sup>42</sup> Pfizer's assumption reflects a misunderstanding of the abuses addressed by GDEA and the nature of FDA's review of a literature-supported NDA. The abuses addressed in GDEA involved fraudulent bioequivalence studies.<sup>43</sup> Literature-supported NDAs, like ANDAs and "Parkman" type NDAs, are approved based on bioequivalence studies.<sup>44</sup> Congress limited the GDEA to the ANDA approval process because all of the recorded abuses were limited to the ANDA approval process.<sup>45</sup>

Pfizer also attempts to find support for its "paper NDA" interpretation in the FDA Modernization Act of 1997 (FDAMA). Pfizer points to the requirement in section 118 of FDAMA that FDA issue guidance to describe when abbreviated study results can be submitted in lieu of full reports.<sup>46</sup> Pfizer notes that this provision does not distinguish between applications submitted under section 505(b)(2) and other NDAs.<sup>47</sup> This, according to Pfizer, suggests that Congress did not intend section 505(b)(2) to permit less than full reports or to permit reliance on data in another NDA. In fact, the provision suggests just the opposite. Full reports may be required under 505(b)(2) with regard to data supporting the modification of the original ANDA. FDA's guidance should apply to full reports submitted under either section 505(b)(1) or section 505(b)(2). Moreover, Pfizer's argument is inconsistent with its acknowledgment that FDA may forego the requirement of submission of full reports where it relies on data from another NDA to approve a "Parkman" type NDA.

## **6. Pfizer Demonstrates that Section 505(l) Is Not Relevant.**

Pfizer attempts to renew its argument that the disclosure provisions of section 505(l) are inconsistent with FDA's reliance on safety and efficacy data from other applications under section 505(b)(2). Given, however, Pfizer's acknowledgment that

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<sup>41</sup> Pfizer Comments at 19.

<sup>42</sup> *Id.*

<sup>43</sup> H.R. Rep. 102-272, 102 Cong., 1<sup>st</sup> Sess. at 11 (1991).

<sup>44</sup> 46 Fed. Reg. at 27,397.

<sup>45</sup> The first section of GDEA states Congress' findings of evidence of corruption in FDA's process of approving drugs under "abbreviated applications" and the need to establish procedures to restore the integrity of the "abbreviated drug application approval process." Pub. L. No. 102-282, 106 Stat. 149, § 1(c)(1), (2) (1992). GDEA defined "abbreviated drug application" as "an application submitted under section 505(j) or 507 . . ." *Id.* § 6, codified at 21 U.S.C. 321(bb). *See also* H.R. Rep. 102-272, 102 Cong., 1<sup>st</sup> Sess. at 11 (1991).

<sup>46</sup> Pfizer Comments at 19.

<sup>47</sup> *Id.* at 19-20.

FDA *can* rely on data from other applications in “Parkman” type NDAs, Pfizer’s argument makes no sense. Pfizer now contends that reliance on data from other applications cannot be allowed under 505(b)(2) where the products in the two applications contain different salt forms of the active ingredient. Pfizer’s new proposed limitation on 505(b)(2) has nothing to do with disclosure of safety and efficacy data under section 505(1). Under section 505(1), FDA can disclose the data when an ANDA could be approved had one been submitted. If, as Pfizer acknowledges, FDA can rely on the data under section 505(b)(2) prior to that time for the approval of a modified version of the ANDA product, section 505(1) would be no more injured by reliance on the data to approve a modified active ingredient than by reliance on the data to approve a modified dosage form or modified indication for use.

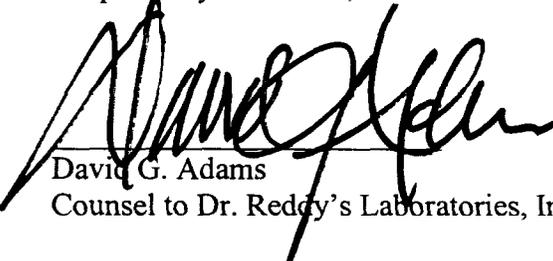
**E. Reddy’s Product Is Safe, Effective, and Bioequivalent to Norvasc.**

Pfizer continues to argue that it would be scientifically inappropriate for FDA to rely on Norvasc data to approve Reddy’s NDA for amlodipine maleate. Pfizer’s arguments are without merit and will, to the extent appropriate, be addressed in FDA’s review of Reddy’s NDA. Reddy believes that its NDA should be approved because Reddy has demonstrated in its NDA that its product is safe, effective, and therapeutically equivalent to Norvasc.

**CONCLUSION**

Pfizer’s proposal to limit section 505(b)(2) to modifications that do not involve the salt form of the active ingredient has no basis in law or in logic. There is nothing to support Pfizer’s notion that Congress intended to allow modifications involving new dosage forms, new indications for use, and entirely new active ingredients under section 505(b)(2) but intended to protect NDA holders from competitors seeking to modify the salt form of the active ingredient.

Respectfully submitted,



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