2220 '03 APR 28 P2:07

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); Roxicodone (oxycodone hydrochloride); Sulfa-methoxazole/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. Synthon 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,

---

Industry: Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act 4 (March 2000).

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.

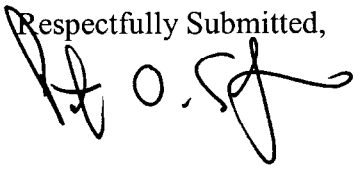
It is Reddy's burden to establish the safety and efficacy of its product, not Pfizer's or FDA's. Assuming *arguendo,* however, that Reddy could rely on Pfizer's data to make that showing, as a precondition, Reddy would have the additional burden of demonstrating that such

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,



Peter O. Safir
Counsel for Pfizer Inc.
Covington & Burling
1201 Pennsylvania Ave, NW
Washington, DC 20004

Jeffrey B. Chasnow
Senior Corporate Counsel
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

COVINGTON & BURLING

1201 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004-2401
TEL 202 662.6000
FAX 202 662.6291
WWW.COV.COM

WASHINGTON
NEW YORK
SAN FRANCISCO
LONDON
BRUSSELS

PETER O SAFIR
TEL 202.662 5162
FAX 202.778.5162
PSAFIR @ COV COM

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:

Enclosed please find an original and three copies of the reply of Pfizer Inc. to the comments of Dr. Reddy's Laboratories, Inc. on Pfizer's October 11, 2002 citizen petition, FDA Docket No. 02P-0447.

Sincerely,

Peter O. Safir

Enclosures