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Dockets Management Branch
Food and Drug Administration
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

Re: Docket Numbers 01P-0323 and 02P-0447: Supplemental Comments by the Generic Pharmaceutical Association in Response to Petitions Filed by Pfizer Inc, and Pharmacia Corporation

The Generic Pharmaceutical Association ("GPhA") submits the following comments in response to the July 27, 2001 Citizen Petition filed by Pfizer Inc. and Pharmacia Corporation (Docket No. 01P-0323), the October 11, 2002 Petition of Pfizer Inc. (Docket No. 02P-0447), and Pfizer's additional comments filed April 4, 2002, April 28, 2003, and June 26, 2003 (hereafter collectively referred to as "the Petitions"). These comments supplement the comments filed by the GPhA on December 10, 2001 in Docket No. 01P-0323 and address the authority of the Food and Drug Administration ("FDA") to approve new drug applications ("NDAs") under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act ("FFDCA" or "the Act"). 21 U.S.C. § 355(b)(2). We will, however, not address the specific question of FDA's authority to review applications for biologic drugs under that section or the April 23, 2003 Petition of the Biotechnology Industry Organization ("BIO") on that subject. GPhA will submit a separate response to the BIO petition, and BIO's supplemental comments from August 8, 2003, at a later time.

I. SUMMARY

The Petitions to which these comments are addressed seek to overturn FDA's nearly two-decade-old policy regarding section 505(b)(2) applications. The section 505(b)(2) application process was established in the Drug Price Competition and Patent Term Restoration Act of 1984 ("the 1984 Act") and built upon earlier FDA efforts to expedite the approval and marketing of new drugs that were similar or identical to already-approved drugs. The basic question raised in the Petitions is whether under section 505(b)(2), a new drug applicant may rely on the FDA's finding of safety and efficacy for an already-approved brand drug, just as it may rely on such a finding under the Abbreviated New Drug Application ("ANDA") procedures set forth in section 505(j) of the FFDCA. As we demonstrate below, the answer to this question is "yes."

2001P-0323

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The plain language and structure of section 505(b)(2) and the relevant portions of the Act's legislative history, none of which Petitioners address in any of their submissions, fully support this reading of section 505(b)(2). Moreover, for almost two decades, FDA has consistently interpreted section 505(b)(2) to permit an applicant under that section to rely on the Agency's findings of safety and efficacy for a related, already-approved brand drug. Since the Agency's interpretation of section 505(b)(2) has been consistent from the time that statutory provision was enacted, that interpretation would be entitled to substantial deference if it were challenged in the courts. And in any event, Petitioners have advanced no legitimate reason for FDA to reverse its position.

Further, none of the arguments proffered by Petitioners as to why FDA's current reading of the statute is incorrect withstand scrutiny. Petitioners' claim that FDA's current interpretation of section 505(b)(2) effects an unconstitutional taking of property is worthy of particular mention. Essentially, Petitioners argue that permitting a section 505(b)(2) applicant to rely on an FDA approval of the reference drug product amounts to a taking of the NDA holder's data that underlay the original FDA approval, in violation of the brand company's Fifth Amendment rights.

In a case squarely on point, *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986 (1984), the U.S. Supreme Court held that the use by the Environmental Protection Agency of data from one pesticide producer in evaluating an application from another producer did not effect a taking of property. In *Monsanto*, the Court held the pesticide producer claiming a taking should have anticipated that its data would be used by a federal agency in evaluating other companies' applications. Here, by virtue of the language of section 505(b)(2) and FDA's longstanding interpretation of that language, which has been codified in a regulation since 1992, Petitioners and other brand companies also should have anticipated that FDA's approval of their products will be used by applicants under section 505(b)(2).

In fact, the principle that FDA's findings upon which to base an approval of the brand product may be used by subsequent applicants is a core concept of the 1984 Act, which provides that once an NDA holder's statutory exclusivities have expired and the applicable patent certification provisions are met, the FDA findings for approval of that product is available for use by ANDA and 505(b)(2) applicants. Thus, Petitioners' takings argument is not only untenable in light of the controlling Supreme Court precedents, it is also fundamentally inconsistent with the structure and purpose of the 1984 Act. The weakness of Petitioners' takings argument is evidenced by the fact that Petitioners do not even advance the argument in their more recent (April 28, 2003 and June 26, 2003) submissions.

Petitioners agree that FDA's existing regulations permit section 505(b)(2) applicants to rely on a prior Agency finding of safety and effectiveness. July 27, 2001 Petition, p.2. And FDA's regulations, and the Federal Register discussions explaining them, clearly suggest no limitation on the timing of section 505(b)(2) NDAs that contain a reference to an approved NDA. As we discuss in detail below, FDA must follow its regulations until it has complied with the Administrative Procedures Act's notice and comment requirements for amending a regulation. Unless and until it complies with these requirements, FDA must continue to follow its current reading and consistent administration of section 505(b)(2) (as described in the Agency's 1999

Draft Guidance), and to approve applications under that section that rely on prior Agency findings of safety and efficacy for related, approved drugs, regardless of whether an ANDA could have been approved for a duplicate of the reference drug product.

While the APA constrains FDA's action with regard to section 505(b)(2), *any* change in FDA's current interpretation of section 505(b)(2), even if it were done in conformance with the Administrative Procedures Act and even if it were permissible under the 1984 Act, would be contrary to sound public policy. Not only would FDA's adoption of Petitioners' reading of section 505(b)(2) call into question the legitimacy of past section 505(b)(2) approvals and therefore threaten the availability of many products that are being used by consumers today, it would also preclude future approvals and, in so doing, significantly undermine the availability of important, safe and effective affordable pharmaceuticals.

The 1984 Act was designed in large part (1) to expedite the approval and marketing of more affordable drug products; (2) to encourage innovation in the pharmaceutical arena; and (3) to eliminate the need to subject patients and animals to unnecessary duplicative studies to prove the safety and efficacy of drugs that FDA has already determined to be safe and effective. The section 505(b)(2) process is a vital part of Congress' plan to meet *all* of these objectives. Section 505(b)(2) provides pharmaceutical companies with the incentive to research and develop improvements and modifications to existing drug products without being required to conduct potentially unethical, costly, and duplicative preclinical and clinical studies. Section 505(b)(2) is a vehicle that companies – brand and generic alike – have used, and are using, to bring consumers access to new products that, in many cases, the market-leading NDA holder is fiscally uninterested, or unable to undertake. "[N]ew drugs in a class, or new formulations of existing drugs, are frequently priced lower than older ones and often provide new cost-effective uses or more efficient treatment for patients." PhRMA Press Release, June 11, 2002 (discussing NIHCM Report).

America continues to struggle with high prescription drug costs, and Americans seek affordable therapeutic and medical interventions. Affordable new products made possible by section 505(b)(2) can make our lives better and more productive. If Petitioners' reading of section 505(b)(2) were adopted by the Agency, innovation in this critical area would be suppressed and, even where such innovation did occur, introduction of innovative new products under section 505(b)(2) would be substantially delayed. If Petitioners' reading of the statute is rejected, however, these new pharmaceuticals can be viable, cost-effective alternatives to already existing products and can provide tremendous health and economic benefits to our health care system.

Section II of these comments sets forth the background and context of section 505(b)(2). Section III demonstrates how Petitioner's argument is inconsistent with the text, structure, and legislative history of section 505(b)(2). Section IV reviews FDA's own position on this issue, explains why the change in the Agency's interpretation advocated by Petitioners would be arbitrary and capricious, and why the Administrative Procedure Act and established case law require FDA to adhere to its existing regulation until the regulation has been amended by appropriate notice and comment procedures. Section V explains why Petitioner's takings argument should be rejected and also refutes various other arguments made by Petitioners in

support of their position. And Section VI focuses on the public policy ramifications of adopting Petitioners' reading of section 505(b)(2).

II. BACKGROUND

Section 505(b)(2) and the 1984 Act in general were extensions of earlier efforts to facilitate FDA approvals of certain drug products without requiring unnecessary and duplicative safety and efficacy studies. The history of section 505(b)(2) demonstrates that even before enactment of the 1984 Act, FDA had in certain instances relied on the findings from pioneer data to determine the safety of new versions of innovator drugs, and that section 505(b)(2) was one of the ways in which Congress codified *and expanded* that practice in the 1984 Act.

Under section 505(b)(1)(A) of the FFDCA, a company seeking approval of a new drug application must submit "full reports of investigations" of that drug to demonstrate safety and effectiveness. 21 U.S.C. § 355(b)(1)(A). Prior to 1984, FDA had already determined that manufacturers of drugs that were similar or identical to certain previously-approved drugs ("reference drugs") could satisfy the requirements of section 505(b)(1) without undertaking the burden and expense of safety and efficacy studies that had been required of the reference drug.

FDA's pre-1984 implementation of this policy differed depending on the date of approval for the reference drug. In the case of drugs that were identical or similar to reference drugs approved *prior to 1962*, FDA, by regulation, permitted manufacturers to file abbreviated new drug applications ("ANDAs"). FDA approved such ANDAs based in part on the Agency's own findings during the so-called DESI process that the innovator drug was *effective*. *See* 54 Fed. Reg. 28872, 28873 (July 10, 1989) (proposed rule implementing the 1984 Act; noting that the Agency's pre-1984 approval of ANDAs "was based on the theory that the evidence of effectiveness necessary for approval of a new drug application had been provided . . . during the DESI process.") However, in determining that an ANDA drug was *safe*, the Agency relied on innovator data that had been submitted as part of the reference drug NDA. *Id.* (noting that "[t]he evidence of safety [for pre-1984 ANDA approvals] had been determined on the basis of information included in *the pioneer new drug application* and by subsequent marketing experience with the drug") (emphasis added). *See also* 57 Fed. Reg. 17950 (April 28, 1992) (final rule) (same). In other words, even before the 1984 Act, FDA approved ANDAs based in part on findings from the information in the pioneer application.

For drugs that were similar or identical to reference drugs approved by FDA *after 1962*, FDA adopted a "paper NDA" policy which permitted it to approve versions of post-1962 approved drugs on the basis of published scientific papers demonstrating safety and efficacy. *See* 46 Fed. Reg. 27396 (May 19, 1981) (July 31, 1978 Memorandum of Marion J. Finkel, M.D., Associate Director for New Drug Evaluation, describing and formalizing the "paper NDA" policy) (hereafter "Finkel Memorandum"). The flaw in the paper NDA system was that published studies were not available for most drugs approved after 1962, thereby precluding the marketing of duplicate or similar versions of post-1962 reference drugs in the absence of new safety and efficacy studies. *See* H. Rep. Rpt. 98-857, Part 1 at 16 (June 21, 1984) (noting that such studies were unavailable for 85 percent of post-1962 drugs).

By the early 1980's, FDA was considering extending the ANDA program to post-1962 drugs in order to eliminate duplicative and expensive clinical studies and in order to expedite competition in the pharmaceutical area. *Id; see also* 46 Fed. Reg. at 27396 (noting FDA's consideration of expanding ANDA program). Had FDA taken such action, ANDAs based on both pre-1962 and post-1962 drugs would have been approved by the Agency in reliance on pioneer safety data from the original NDA. However, concerned that FDA would not act with sufficient speed, Congress itself began considering amendments to the FFDCA that would require the agency to expeditiously adopt an ANDA policy applicable to all drugs.

The result of these congressional efforts was the Drug Price Competition and Patent Term Restoration Act of 1984. The twin goals of this legislation were (1) to create greater competition in the prescription drug market by expediting FDA approvals of affordable generic drugs, and (2) to encourage drug innovation by extending patent terms for brand-name reference drugs, by providing market exclusivity to newly approved drugs and/or new uses of drugs, and by imposing limitations on the marketing of generic drugs during patent litigation between brand and generic companies. 57 Fed. Reg. at 17951 ("Congress intended [the 1984 Act] to provide a careful balance between promoting competition among brand-name and duplicate or 'generic' drugs and encouraging research and innovation.").

To accomplish the first of these goals, the 1984 Act amended section 505 of the FFDCA to establish abridged statutory procedures for duplicate and related versions of drugs already approved by FDA. Under these procedures, FDA received explicit statutory authority to approve generic drugs on the basis of less than the full information required for the brand name product. The 1984 Act provides two mechanisms under which an applicant may obtain abridged approval for a drug product. Each of these mechanisms provided for the potential of a different level of FDA review, depending on the need for more clinical or other scientific data to prove safety and effectiveness of the proposed product.

Where the proposed drug is pharmaceutically equivalent and the labeling is identical or similar and no additional clinical or preclinical data are necessary to show safety and effectiveness, the applicant may file an ANDA under *section 505(j)* of the Act that provides basic information showing that the proposed and reference NDA-approved drugs are bioequivalent.[1] For an innovative product that is similar to, but distinct from, the reference drug and that cannot be approved under an ANDA because, *inter alia,* it requires limited clinical or other scientific studies on some new aspect of the product (for example, a new indication, dosage form, route of administration, or a modified active ingredient) in order to establish safety and/or effectiveness or because the product is not bioequivalent to the reference drug, the 1984 Act established the *section 505(b)(2)* regulatory route. Section 505(b)(2) of the FFDCA, in short, facilitates approval of innovative products that required literature or *some, but not full,* new clinical or preclinical studies by permitting reliance on past safety and efficacy determinations by

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[1] Under section 505(j), certain slight modifications between the reference drug and the ANDA drug are allowed. Where such modifications exist, however, FDA must confirm through a public petition process (the "suitability petition process") that the application can be approved based on bioavailability without the need for additional clinical data.

FDA for reference drugs and/or published literature, while at the same time providing FDA with the flexibility to require additional studies or literature to address the safety and/or efficacy effects of modifications to the reference drug.

Under section 505(b)(2), a manufacturer seeking to market a drug may rely on "investigations . . . not conducted by or for the applicant and for which the applicant has not obtained a right of reference" to demonstrate the safety and efficacy of the new drug. 21 U.S.C. § 355(b)(2). However, additional clinical or other scientific studies may be required of section 505(b)(2) applicants to show that any deviations from the approved brand product do not make the new product unsafe or ineffective. *See* 54 Fed. Reg. at 28891 ("505(b)(2) applications will generally be submitted for never before approved changes in already approved drug products, where the change cannot be reviewed under section 505(j). . . . Therefore, a 505(b)(2) application will be appropriately submitted for a drug product where the safety and effectiveness of the change must be, at least in part, established by clinical investigations.") Hence, FDA clearly contemplated reliance on previous findings of safety and efficacy, since the only studies necessary are those needed to support the product "change".

While the process established under section 505(j) was similar to FDA's previous ANDA policy regarding generic versions of drugs approved by FDA before 1962,[2] it is clear that Congress did *not* intend the process established under section 505(b)(2) to merely copy the "paper NDA" policy FDA had applied to generic versions of drugs approved after 1962 (and had considered replacing with its pre-1984 ANDA policy). The "paper NDA" policy permitted generic drug companies to rely only on *published reports* to show safety and efficacy. The sources permitted under section 505(b)(2), by contrast, are not so limited. Rather, section 505(b)(2) permits applicants under that section to rely, without limitation, on "investigations . . . not conducted by or for the applicant and for which the applicant has not obtained a right of reference." 21 U.S.C. §355(b)(2). As discussed below, the structure and legislative history of the 1984 Act confirms the intended breadth of the section 505(b)(2) process, as does FDA's own longstanding and consistent interpretation of this statutory provision.

Thus, the structure of the 1984 Act makes clear that sections 505(j) and 505(b)(2) are both designed to achieve the same objective: to permit manufacturers to market identical or modified versions of already-approved drugs on an abridged basis, after the expiration of all statutory exclusivities and in compliance with all patent certification procedures, and to avoid the need for manufacturers to undertake duplicative, expensive, and unnecessary clinical or other scientific tests before doing so. The two sections cover different types of products: in the case of section 505(j), products that are labeled the "same" as the reference drug (21 U.S.C. § 355(j)(2)(A)) and that require no additional clinical data before approval, in which case applicants may rely fully on FDA's approval of a past NDA; and in the case of section 505(b)(2),

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[2] It should be noted, however, that Congress did not codify an exact copy of the then-existing FDA ANDA policy. Under FDA's pre-1984 ANDA policy, bioequivalence was normally not required and generic drug labeling was not required to duplicate brand-drug labeling to the same degree required under the 1984 Act. In sum, Congress created a new paradigm with the 1984 Act that differed from both FDA's pre-1984 ANDA *and* Paper NDA policies.

different or enhanced versions of approved products that may require literature or some additional clinical or other scientific investigation, due to modifications from the reference drug, but that are also similar enough to the reference drug that they may also rely on FDA findings for the approval of a past NDA to support safety and efficacy. Despite these differences, the goals of the two sections are the same: "to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug." *Guidance for Industry: Applications Covered by Section 505(b)(2)* (October 1999) (hereinafter, "*1999 Draft Guidance*") at 3.

That sections 505(b)(2) and 505(j) are parallel is further reflected by the fact that both section 505(j) applicants *and* section 505(b)(2) applicants are subject to the patent and exclusivity provisions of the 1984 Act.[3] For example, like a section 505(j) applicant, a section 505(b)(2) applicant must certify to all patents listed by a brand company in the Orange Book and is subject to the 30-month stay governing patent disputes between brand companies and ANDA applicants. 54 Fed. Reg. at 28891 ("[T]he patent certification and exclusivity provisions apply equally to applications described under section 505(b)(2) or 505(j) . . . .") In short, the 1984 Act provided both section 505(j) and section 505(b)(2) applicants with similar rights – the ability to rely, in whole or in part, on FDA's findings to establish safety and efficacy after the expiration of brand company patent protections and statutory exclusivities. Furthermore, the patent certification provisions applicable to section 505(b)(2) NDAs, like those applicable to section 505(j) ANDAs, allow for the timely resolution of patent disputes that could otherwise block the public's access to affordable, enhanced drug products. Specifically, the paragraph IV patent challenge process applies to both ANDAs and section 505(b)(2) NDAs and thus allows section 505(b)(2) applicants to bring appropriate challenges to patents that the applicant believes are not infringed or invalid. As FDA has repeatedly acknowledged, these disputes are between the NDA holder and the section 505(b)(2) applicant and, with the exception of the "30-month stay" provision," do not implicate FDA's review and approval of the section 505(b)(2) NDA. Congress envisioned, and even encouraged, these patent challenges and made no distinction as to whether the challenge came in the form of an ANDA or a section 505(b)(2) NDA. Had Congress intended to limit section 505(b)(2) to permit patent challenges only after a successful challenge by an ANDA applicant, it certainly could have done so.

III. THE TEXT, STRUCTURE, AND LEGISLATIVE HISTORY REQUIRE THAT FDA REJECT PETITIONERS' RESTRICTIVE READING OF SECTION 505(B)(2).

Petitioners now seek to impose a significant, new limitation on the use of section 505(b)(2) applications that is clearly not applicable to section 505(j) applications. They claim that while a section 505(j) applicant may rely on FDA's past safety and efficacy determinations for brand company reference drugs, the language of section 505(b)(2) precludes such reliance, even after all applicable patents and statutory exclusivities have expired. Petitioners' principal

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[3] Appendix B to the April 4, 2003 Comments of Dr. Reddy's Laboratories in Docket No. 02P-0447 (hereinafter "April Dr. Reddy Comments") sets forth a comparison of the patent certification provisions applicable to 505(b)(2) and 505(j) applicants.

support for this argument is their claim that Congress intended section 505(b)(2) to merely replicate the "paper NDA" policy followed by FDA before enactment of the 1984 Act with respect to generic versions of drugs approved after 1962. As we demonstrate below, petitioners' position is inconsistent with the text, structure, and legislative history of the 1984 Act.

1. *Text*. The plain language of section 505(b)(2) demonstrates that that provision does not limit the data on which a section 505(b)(2) applicant may rely in the manner suggested by Petitioners, and that Congress intended section 505(b)(2) to be significantly broader than the pre-1984 "paper NDA" policy.

Section 505(b)(2) authorizes FDA and applicants under that section to rely upon "investigations . . . not conducted by or for the applicant and for which the applicant has not obtained a right of reference." 21 U.S.C. § 355(b)(2). This language contains no limitations on the type or source of such investigations – there is therefore no basis whatsoever for the restrictive reading of the section advanced by Petitioners. Brand company investigations on which FDA relied to approve the original brand drug NDA are not conducted by the section 505(b)(2) applicant; nor does the applicant obtain a right of reference or use of such investigations. These are therefore precisely the kinds of investigations that may be relied upon by section 505(b)(2) applicants according to the plain language of the statute.

In light of the text of section 505(b)(2), it is understandable that the Petitioners concede that "Congress used language in section 505(b)(2) that is arguably broader than necessary to codify the paper NDA policy." July 27, 2001 Pfizer Petition at 14. What is less understandable is Petitioners' argument that this language, given its breadth, should be limited in a manner that the language simply does not suggest. Courts and agencies alike must adhere to clear and unambiguous statutory language. *See Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837, 842-843 (1984) ("If the intent of Congress is clear, that is the end of the matter, for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress."). And a party seeking to narrow the clear, broad language of a statute bears the heavy burden of showing that Congress intended the statutory language to operate restrictively. *National Public Radio, Inc. v. FCC*, 254 F.3d 226, 230 (D.C. Cir. 2001) ("Because statutory language represents the clearest indication of Congressional intent . . . we must presume that Congress meant precisely what it said. Extremely strong, this presumption is rebuttable only in the 'rare cases [in which] the literal application of a statute will produce a result demonstrably at odds with the intentions of its drafters.'") (citation omitted). The language of section 505(b)(2) is unambiguous – it contains no limitation that would preclude reliance by a section 505(b)(2) applicant on investigations conducted by a brand company in conjunction with its original NDA, nor does it limit when a section 505(b)(2) NDA may be filed beyond the clearly articulated market exclusivity and patent certification provisions. Petitioners' efforts to import this restriction into the statute has no textual basis whatsoever and must be rejected.

2. *Structure*. The structure of section 505(b)(2) confirms the meaning of the text. As discussed above, section 505(b)(2) applicants are subject to the same patent and market exclusivity provisions as section 505(j) applicants. In fact, section 505(b)(2) specifically states, and is designed to ensure, that a section 505(b)(2) applicant who has relied on "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" must meet the same patent certification and litigation requirements as ANDA applicants under section 505(j). 21 U.S.C. § 355(b)(2)(A), (B). The application of identical limitations on ANDAs and section 505(b)(2) NDAs makes sense when one recognizes that the ANDA applicant and the section 505(b)(2) applicant receive the same benefit when referencing FDA findings of an approved NDA. The ability to rely on prior FDA findings of safety and/or efficacy derives from independent statutory authorities (section 505(b)(2) versus section 505(j)), but the limitations on each application are the same in order to provide adequate protection and incentives to the original NDA holder. Petitioners appear to seek the benefits of the linkage between sections 505(b)(2) and 505(j) without accepting the burdens. But the structure of section 505(b)(2) creates a parallelism between applicants under that section and section 505(j) applicants that Petitioners should not be permitted to ignore and that is consistent with the broad scope of the statutory language.

The structure of section 505(b)(2) also undermines Pfizer's more recent contention, discussed in greater detail below, that section 505(b)(2) is reserved for products which were, or could have been, the subject of an ANDA under section 505(j). Congress' use of parallel, but not identical, provisions in section 505(b)(2) and section 505(j) shows that Congress obviously did not intend for section 505(b)(2) to be used for exact duplicates of approved drugs – the ANDA process fulfils that role. The patent challenges initiated under section 505(b)(2) will, almost by definition, involve different patent infringement issues than those that would occur in a challenge of the same patent by an ANDA applicant. There is no suggestion in the statute that these differing patent infringement issues have any bearing on the type of information that a section 505(b)(2) applicant may incorporate by reference. On the contrary, the requirement of a paragraph IV provision for section 505(b)(2) NDAs leads to the inescapable conclusion that Congress intended section 505(b)(2) applicants to bring patent challenges different than those permissible under section 505(j). Thus, Pfizer's argument that a section 505(b)(2) applicant's ability to challenge a listed patent is limited to only those circumstances where an ANDA applicant could also mount such a challenge is illogical and inconsistent with the paragraph IV certification requirement for section 505(b)(2) applications.

3. *Legislative History.* A reading of section 505(b)(2) that does not include the limitation urged by Petitioners is also fully supported by the legislative history of the 1984 Act. Petitioners argue that section 505(b)(2) was designed to replicate FDA's limited pre-1984 "paper NDA" policy. July 27, 2001 Petition, at 10-14; Pfizer April 28, 2003 Comments at 4. In fact, quite the opposite is true. The legislative history of the 1984 Act makes clear that Congress expressly rejected as too limited the Agency's pre-1984 policy and intended the section 505(b)(2) process to be more expansive than, and to avoid the shortcomings of, that policy.

Contrary to Petitioners' contentions, the repeated references to the term "paper NDA" throughout the legislative history of section 505(b)(2) do not "provide[] significant evidence that Congress intended to codify the Agency's prior paper NDA policy in section 505(b)(2)." July 27, 2001 Pfizer Petition at 11. In fact, these references show the exact opposite -- that Congress intended to replace the paper NDA approach with approaches more in line with its goals of getting generic drugs to market more quickly (much as Congress replaced FDA's pre-1984

ANDA regulation for versions of pre-1962 drugs). That Congress viewed the paper NDA policy as an obstacle to its efforts is clear from the House Commerce Committee Report on the 1984 Act, which is one of the principal sources of the Act's legislative history:[4]

> Some have suggested that "Paper NDAs" be used to approve generic equivalents of pioneer drugs approved after 1962. Under the Paper NDA procedure, the generic manufacturer may submit scientific reports, instead of clinical trials, to support findings of safety and efficacy. *This procedure is inadequate, however,* because FDA estimates that satisfactory reports are not available for 85 percent of all post-1962 drugs.

H. Rep. Rpt. 98-857, Part 1 (June 21, 1984) at 16 (emphasis added). The House Judiciary Committee Report also focused on the flaws of the paper NDA policy. H. Rep. Rept. 98-857, Part 2 (August 1, 1984) at 4.

Congress addressed the flaws in the paper NDA policy by requiring FDA to extend the ANDA policy to post-1962 drugs in section 505(j) *and* by adopting section 505(b)(2). Thus, instead of codifying the pre-1984 paper NDA policy, Congress chose to *redefine and expand* the policy in order to further the clear pro-competitive goals of the 1984 Act. Indeed, the House Commerce and Judiciary Committee Reports each set forth a *new* definition of "paper NDA" that mirrored the section 505(b)(2) process that was eventually enacted into law in the 1984 Act. Under this definition:

> Paper NDA's are defined as any application submitted under section 505(b) of the FFDCA 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 from whom the studies were conducted.

H. Rep. Rpt. 98-857, Part 1 at 32 (Commerce Committee Report); H. Rep. Rpt. 98-858, Part 2 at 19 (Judiciary Committee Report). The fact that Congress (1) criticized the paper NDA policy and (2) chose to expressly redefine "paper NDA" rebuts the presumption, relied upon by Petitioners, that language used by an Agency has the same meaning when used by Congress. April 28, 2003 Reply by Pfizer Inc. at 5. It is significant that in their 70 pages of discussion in support of their petitions, Petitioners never mention this legislative history.

In short, the fact that the legislative history of the 1984 Act refers to "paper NDAs" does not help Petitioners because it is evident that Congress expressly broadened the term's definition to permit reliance on data that could not be relied on under the old, "inadequate" pre-1984 policy. FDA itself has recognized that Congress intended section 505(b)(2) to reach beyond the old paper NDA policy: "[a]lthough similar to FDA's 'paper NDA' policy, section 505(b)(2) of

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[4] The House Commerce and House Judiciary Reports are the critical sources of legislative history for the 1984 Act. There is neither a Senate Report nor a Conference Report for this legislation.

the Act has broader applicability. . . . Thus, section 505(b)(2) of the Act covers not only literature-supported NDA's for duplicates of approved drugs, but any NDAs for drug products that rely for approval on studies not conducted by or for the applicant or for which the applicant does not have a right of reference." 54 Fed. Reg. at 28875. *See also id.* at 28890 ("Despite certain similarities between section 505(b)(2) of the [1984 Act] and the 'paper NDA policy,' the new statutory provision is broader than the paper NDA policy.")

Petitioners' reading of section 505(b)(2) would impose barriers to the marketing of innovative changes to approved products above and beyond those recognized or established in the 1984 Act. Section 505(b)(2), like section 505(j), provides for the approval of drug products after patent protections, statutory exclusivities, and other pro-brand name limitations on generic competition have expired. The basic statutory approach of the 1984 Act is that after those protections are provided and all exclusivities have expired, ANDA and 505(b)(2) applicants may rely on the FDA findings of approval of the pioneer product to the extent that those findings are relevant to their application. To read section 505(b)(2) as additionally limiting approvals under that section to products that satisfy the old paper NDA requirements (and to less than 15% of the eligible drugs approved after 1962) would be to expand anti-competitive brand company protections in a manner that Congress did not envision.[5]

IV. THE RELIEF SOUGHT IN THE PETITION WOULD BE INCONSISTENT WITH FDA'S LONGSTANDING INTERPRETATION OF SECTION 505(b)(2), WHICH IS CODIFIED IN THE AGENCY'S 1992 REGULATION. CHANGING THAT POSITION WOULD BE ARBITRARY AND CAPRICIOUS AND IN ANY EVENT WOULD REQUIRE COMPLIANCE WITH THE ADMINISTRATIVE PROCEDURE ACT'S NOTICE AND COMMENT PROCEDURES.

A. Pfizer's Argument Is Inconsistent With FDA's Longstanding Interpretation of Section 505(b)(2).

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[5] Petitioners also suggest that prior to 1984 FDA had been held not to have authority to rely on a prior NDA approval in approving a generic drug. This is incorrect. In fact, as discussed above, in implementing its pre-1984 ANDA policy applicable to pre-1962 drugs, the Agency relied on its approval of the pioneer drug for its safety (though not its efficacy) determination. See 54 Fed. Reg. at 28873. Also, prior to enactment of the 1984 Act, FDA had considered extending the Paper NDA policy to post-1962 drugs. *See* Finkel Memorandum, 46 Fed. Reg. at 27396 ("the problem [of post-1962 generic drugs not being able to obtain approval] will disappear if the Agency adopts a policy of bringing post-1962 drugs into the current DESI-ANDA system"); H. Rep. Rpt. 98-857, Part 1 (June 21, 1984) at 16 ("While the FDA has been considering since 1978 an extension of the pre-1962 ANDA policy to post-1962 drugs, it has not extended the regulation"). The Petitioners' claim (July 27, 2001 Petition at 12) that two district courts have observed that FDA did not allow generic companies to rely on the studies submitted by the brand company is beside the point. Since FDA never adopted a post-1962 ANDA policy the issue of the Agency's authority to implement such a policy was neither decided by FDA nor tested in the courts.

FDA has for nearly two decades adhered to the position that 505(b)(2) applicants, like 505(j) applicants, may rely on FDA's finding of safety and efficacy of a brand company reference drug, and that the 505(b)(2) process is in fact more expansive than the pre-1984 "paper NDA" policy. The Agency first announced this position in 1987, in an April 10 letter written to the industry by Dr. Paul Parkman. *See Misc. Guide 04/10/87 Drug Price Competition and Patent Term Restoration Act Letter – April 10, 1987* (hereafter "Parkman Letter"). FDA's 1989 proposed regulations to implement the 1984 Act took the same position, and neither Pfizer nor any other brand company objected on this point.[6] The final FDA rule on the 1984 Act reaffirms FDA's position on this issue. *See* 57 Fed. Reg. 17950 (April 28, 1992); 21 C.F.R. § 314.54. And during the period between enactment of the 1984 Act and the Pfizer's July 27, 2001 petition, FDA approved dozens of drugs under its interpretation of section 505(b)(2). *See* Dr. Reddy Comments at 2-6. Finally, in a 1999 Draft Guidance, FDA once again reaffirmed its consistent position on the meaning of section 505(b)(2).

1. *The Parkman Letter.* FDA first formally announced its position on this issue in 1987, in the so-called "Parkman Letter." In that letter, Dr. Parkman explained the policy that the Agency had adopted in implementing the 1984 Act where generic companies sought to "make modifications in approved drugs if the modifications require the submission of clinical data." Parkman Letter at 1. Section 505(j) of the Act specifies the types of data required for an ANDA in clauses (i) – (viii) of section 505(j)(2)(A) and then states that "[t]he Secretary may not require that an abbreviated application contain information in addition to that required" by those provisions. 21 U.S.C. § 505(j)(2)(A). Thus, where, "[f]or example, an applicant . . . wish[ed] to obtain approval of a new indication for a listed drug that is only approved for other indications" (Parkman Letter at 1), section 505(j) was not available. The Parkman Letter explained that "FDA would process [an application seeking approval of a new indication and supported by clinical data] under section 505(b)."

The Parkman Letter explains that such an ANDA applicant could submit a section 505(b)(2) application and "rely[] on approval of the listed drug . . . to the extent that such reliance would be allowed under section 505(j)". Thus, Dr. Parkman stated that "an application that relies in part on the approval of a listed drug and in part on new clinical data will, for this purpose, be considered an application described in section 505(b)(2) . . . ." Parkman Letter at 2. Dr. Parkman concluded that to prevent such reliance in cases where a generic company simply sought to modify an existing product would be inconsistent with Congress's intent in the 1984 Act "because it would serve as a disincentive to innovation and would require needless duplication of research." *Id.* at 1-2.

In its April 28, 2003 and June 26, 2003 filings, Pfizer, departing from its consistently-expressed view that section 505(b)(2) was intended to codify the paper NDA policy, argues for the first time that section 505(b)(2) is broader than the paper NDA policy, but is nonetheless limited to situations where the applicant filed, or could have filed, an ANDA under section

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[6] In fact, FDA received only two comments overall on its 505(b)(2) regulation (which became 21 C.F.R. § 314.54), neither of which related to the point raised by the Petitions. *See* 57 Fed. Reg. at 17954-55.

505(j). April 28, 2003 Comments at 2, 11-13; June 26, 2003 Comments at 3. There is, however, absolutely no statutory or regulatory support for the proposition that the right to proceed under section 505(b)(2) is dependent on the right to proceed under section 505(j). FDA has never articulated such a theory and there is no evidence whatsoever that Congress viewed section 505(b)(2) in this way when it enacted the 1984 Act.

Nor does the Parkman Letter itself support Petitioners' newly-spun theory. The Parkman Letter's references to allowing section 505(b)(2) applicants to rely on prior FDA approvals "to the extent that such reliance would be allowed under section 505(j)" (Parkman Letter at 2), does not mean that section 505(b)(2) is limited by section 505(j). Rather, it means that that a section 505(b)(2) applicant derives the same benefit from a reference to an approved drug as a section 505(j) applicant – namely, the avoidance of having to independently prove the safety and effectiveness of the reference drug. Likewise, Petitioners' assertion that FDA and the pharmaceutical industry understood that the Parkman Letter was limited to only situations where an ANDA "could have been approved," is not supported by history. For example, Petitioners cannot explain why such an important limitation on section 505(b)(2) NDAs is so conspicuously absent from the regulation FDA promulgated five years later, or why the entire industry failed to correct FDA's supposed oversight during the comment period.[7]

In short, it is apparent that Petitioners have concluded that the extreme position they took in their past submissions is untenable and they are attempting to offer FDA a compromise position that will serve their interests. However, neither the Parkman Letter nor any other congressional or FDA pronouncement supports this new interpretation of section 505(b)(2), and FDA should reject it.

2. *FDA's Proposed and Final Rules on the 1984 Act.* The preamble to FDA's proposed rules for implementation of the 1984 Act, which were published in 1989, was even more explicit than the Parkman Letter. Relying on the language of section 505(b)(2), the preamble declared that "[d]espite certain similarities between section 505(b)(2) of the act" and the "paper NDA policy," the new statutory provision is "broader than" the paper NDA policy. 54 Fed. Reg. at 28890. As it had in the Parkman Letter, the FDA stated that section 505(b)(2) could be used where new clinical investigations were required to support approval. In such cases, section 505(b)(2) applications could be "supported by a combination of . . . new clinical investigations and the agency's finding that a previously approved drug is safe and effective." *Id.* at 28891. In other words, the preamble explicitly stated that a section 505(b)(2) applicant, like an ANDA applicant, could rely on FDA's approval of a pioneer drug if that approval was relevant to the application. To afford protection of the pioneer's patent and other property rights, Congress made all the patent and exclusivity protections contained in section 505(j) applicable to

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[7] As the July 3, 2003 Comments of Dr. Reddy's Laboratories, Inc. point out, Pfizer itself has even acknowledged (in its June 26 Comments on page 3) that the Parkman Letter permits reliance on innovator data where the new product seeks changes to the approved product that *could not* be proposed under an NDA, such as a new indication. In general, GPhA agrees with and adopts by reference here the response of Dr. Reddy to Pfizer's interpretation of the Parkman Letter that appears in Dr. Reddy's July 3 Comments.

section 505(b)(2) applications (FFDCA section 505(c)(3)), so that the proposed modified drug product may obtain approval only after applicable patents and exclusivities have expired or been litigated under the terms of the Act.

Thus, according to FDA, section 505(b)(2) "appl[ies] to any application that relies on investigations which the applicant has not conducted, sponsored, or obtained a right of reference to, regardless of the similarity or dissimilarity of the drug product to an already approved drug product." 54 Fed. Reg. at 28890. In contrast to Pfizer's argument that the section 505(b)(2) process is reserved for applications that could be approved under section 505(j) by filing an initial application and an amendment (April 28 Comments at 11-13), the proposed rule explicitly stated that 505(b)(2) may be used for "drug products that could *not* be approved under section 505(j) of the act." 54 Fed. Reg. at 28891 (emphasis added). As noted above, neither Petitioners nor any other interested party objected to FDA's interpretation of section 505(b)(2) and the Agency's proposed rule was codified in 21 C.F.R. § 314.54.

Section 314.54 of the Agency's regulations reiterates the conclusions of the Parkman Letter and the 1989 Preamble. It also states that "[t]he act does not permit approval of an abbreviated new drug application for a new indication, nor does it permit approval of other changes in a listed drug if investigations, other than bioavailability or bioequivalence studies, are essential to the approval of the change." 21 U.S.C. § 314.54. Therefore, under the regulation, any person seeking a modification, such as "a new indication or a new dosage," where such investigations "are essential to the approval of the changes may . . . submit a 505(b)(2) application." *Id.* Since the application "*need contain only that information needed to support the modification(s) of the listed drug*," *id.* (emphasis added), it may rely on the FDA's finding of safety and efficacy of the pioneer in the same way as a section 505(j) application.

Petitioners do not deny that 21 C.F.R. § 354.14 clearly adopts the Agency's earlier determination that section 505(b)(2) applicants may rely on FDA's findings of safety and effectiveness in the same way as can section 505(j) applicants. Indeed, they contend that FDA regulations interpret section 505(b)(2) in a manner Petitioners deem to be contrary to law. *See, e.g.*, July 27, 2001 Petition at 1 (requesting that FDA "amend its . . . regulations at 21 C.F.R. § 314.54 to reflect that [FDA] cannot rely on or otherwise use any non-public proprietary information in an innovator's [NDA] or other non-public filings to approve [505(b)(2)] applications . . . .") As we have discussed, however, Petitioners' statutory argument is belied by the text, structure, and history of the 1984 Act.

3. *The 1999 Draft Guidance.* In 1999, FDA issued a draft guidance for the purpose of "identifying the types of applications that are covered by section 505(b)(2) [and to provide] further information amplification regarding FDA's regulations at 21 CFR § 314.54. *1999 Draft Guidance* at 1. Contrary to Pfizer's claim that the Guidance "was a vast departure from the Agency's prior interpretations of section 505(b)(2)," April 28, 2003 Comments at 11, the Guidance was actually a restatement of past policy and a comprehensive listing of the types of applications that could be submitted under section 505(b)(2). Thus, in the Draft Guidance, the FDA explained that under section 505(b)(2), the "approval of the application relies on the Agency's previous finding of safety and/or effectiveness of a drug[, and that t]his mechanism, *which is embodied in a regulation at 21 CFR 314.54*, essentially makes the Agency's

conclusions that would support the approval of a 505(j) application available to an applicant who develops a modification of a drug." *1999 Draft Guidance* at 2 (emphasis added). FDA emphasized yet again that "[t]his approach is intended to encourage innovation in drug development without requiring duplicative studies to demonstrate what is already known about a drug while protecting the patent and exclusivity rights for the approved drug." *Id.* at 3.

B. FDA May Amend Its Regulation Only After Complying With the Administrative Procedures Act.

We have discussed above that FDA's interpretation of section 505(b)(2) is mandated by the text of the 1984 Act. Thus, under step 1 of the now-familiar *Chevron* analysis, FDA *must* adhere to that interpretation, and any decision not to do so cannot withstand judicial review. *Chevron*, 467 U.S. at 842-43. Even if the text of the statute were ambiguous, however, FDA's interpretation of 505(b)(2) is, at a minimum, a permissible construction of the statute given the text, structure, legislative history, and policy goals of the 1984 Act and therefore is sustainable under the second *Chevron* prong. *Id.* at 843 The fact that FDA's interpretation of section 505(b)(2) was contemporaneous with the statute's enactment and has remained consistent ever since entitles it to particular deference. *E.g., Equal Employment Opportunity Comm'n v. Associated Drygoods Corp.*, 449 U.S. 590, 600 n.17 (1981) (affording "special deference" to agency's contemporaneous construction of its governing statute "when it has remained consistent over a long period of time"); *Helton v. NLRB*, 656 F.2d 883, 891 (D.C. Cir. 1981) ("An administrative agency's consistent, longstanding interpretation of the statute under which it operates is entitled to considerable weight.")

If FDA should choose to depart from its longstanding interpretation of section 505(b)(2), it bears a heavy burden to explain in detail the reasons for this departure. "An agency changing its course must supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored, and if any agency glosses over or swerves from prior precedents without discussion it may cross the line from the tolerably terse to the intolerably mute." *Greater Boston Tel. Corp. v. FCC*, 444 F.2d 841, 852 (D.C. Cir. 1970). *See also Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Aut. Ins. Co.*, 463 U.S. 29, 57 (1983) (citing *Greater Boston*).

Moreover, any decision by the Agency to depart from its past precedents with respect to section 505(b)(2) must be accompanied not only by a reasoned explanation for its decision, but *also* by public notice and an invitation for public comment, in accordance with the procedures prescribed by the Administrative Procedures Act. 5 U.S.C. § 553(c). As discussed above, Petitioners are clear that what they are seeking is an amendment of FDA's regulations regarding section 505(b)(2), which they claim to be inconsistent with the 1984 Act. *See, e.g.,* July 27, 2001 Petition at 1 (requesting that FDA "amend its . . . regulations at 21 C.F.R. § 314.54 to reflect that [FDA] cannot rely on or otherwise use any non-public proprietary information in an innovator's [NDA] or other non-public filings to approve [505(b)(2)] applications . . . ."). Any such amendment cannot be undertaken without notice and comment procedures. *See Utility Waste Activities Group v. EPA*, 236 F.3d 749 (D.C. Cir. 2001) (holding that even technical changes to agency regulations require notice and comment).

Until such notice and comment procedures are observed, FDA is not at liberty to deviate from its current reading of section 505(b)(2). FDA, like all federal agencies, is bound by the plain language of its own regulations. *See Service v. Dulles*, 354 U.S. 363 (1957). FDA therefore cannot arbitrarily set aside 21 C.F.R. § 314.54 while the Agency considers Petitioners' arguments. FDA *must* continue to apply its regulations and to approve section 505(b)(2) applications that rely on FDA's previous findings of safety and effectiveness and that otherwise qualify for approval.

V. NONE OF PETITIONERS' OTHER ARGUMENTS IN OPPOSITION TO FDA'S INTERPRETATION OF SECTION 505(b)(2) WARRANTS A CHANGE IN AGENCY POSITION.

As we have discussed in detail, the text, structure, legislative history, and underlying policies of the 1984 Act mandate FDA's current interpretation of section 505(b)(2). In addition to claiming, erroneously, that the legislative history of the 1984 Act supports their position, Petitioners have proffered several other arguments as to why FDA's current interpretation is impermissible. None of them has any basis.

A. FDA's Interpretation of Section 505(b)(2) Does Not Effect an Unconstitutional Taking.

Petitioners have repeatedly contended that the FDA, by relying on prior findings of safety and effectiveness in approving section 505(b)(2) applications, effects an unconstitutional taking of the original applicant's proprietary data. That argument is squarely foreclosed by governing Supreme Court case law.

The landmark decision in this area is *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986 (1984). In *Monsanto*, a pesticide producer brought a takings claim analogous to Pfizer's here, alleging that a taking arose as a result of certain statutory provisions that allowed the EPA to take data submitted by the producer in connection with its already-approved application for registration and to consider that data in connection with an application by another producer for a related pesticide. *See id.* at 992. The Supreme Court first held that the producer could have a property interest in its underlying data, to the extent that the data were protected under state law as a trade secret. *See id.* at 1003-04. The Court then proceeded to consider whether a taking of that property had occurred. *See id.* at 1004-14. The Court reasoned that several factors were relevant in determining the existence of a taking, including the character of the governmental action, its economic impact, and, most importantly, its interference with reasonable investment-backed expectations. *See id.* at 1005.

The Court concluded that no taking of that property had been effected during two specified periods. *See id.* at 1004-10. As to the period after 1978, the Court concluded that the producer lacked a reasonable, investment-backed expectation that the EPA would keep the data confidential beyond the limits prescribed in the statute itself. *See id.* at 1006. The Court reasoned that, during this period, the statute allowed the EPA to use the data without the producer's permission after 10 years; to use the data without compensation after 15 years; and to disclose much of the data to the general public at any time. *See id.* at 1006-07. Similarly, as to

the period before 1972, the Court noted that while no provision of law gave the EPA the express authority to disclose the producer's data, no provision promised that the EPA would *not* disclose the data, either. *See id.* at 1008. Indeed, the Court observed that, during that period, the practice of using data submitted by one company during consideration of the application of another was "widespread and well known." *Id.* at 1009. (The Court did conclude that a taking may have occurred during the period from 1972 to 1978, when federal law expressly prohibited the EPA from disclosing publicly, or considering in connection with the application of another producer, data that the producer and EPA determined to constitute trade secrets. *See id.* at 1010-14.)

Monsanto disposes of Pfizer's takings claim. From the time that the 1984 Act became law, drug manufacturers could not possibly have had a reasonable, investment-backed expectation that the FDA would decline to consider proprietary data in approving section 505(b)(2) applications. The statute expressly contemplates that the FDA and section 505(b)(2) applicants will rely on "investigations . . . not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use." 21 U.S.C. § 355(b)(2). The statute therefore could not be clearer in indicating that information relating to those investigations can be used both by the FDA and by section 505(b)(2) applicants. *Compare Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 140-41 (3d Cir. 1987) (upholding takings challenge, in context of generic animal drug applications, in light of regulation barring FDA from using data submitted by another manufacturer unless manufacturer authorized use in written statement). As discussed above, this reading of the text of section 505(b)(2) is consistent with the underlying purpose of the section – namely, to allow drug manufacturers to obtain expedited approval for new indications for, or other changes to, already-approved drugs. Brand companies simply could not have misunderstood the effect of that section.

The April 1987 Parkman Letter, subsequent FDA Federal Register notices, and the 1992 regulation further emphasized that FDA intended to interpret the statute in a manner consistent with the statutory text and to permit section 505(b)(2) applicants and FDA to rely on investigations conducted by the original NDA applicant. Like the statute itself, the implementing regulations make clear that a section 505(b)(2) applicant need only submit "information needed to support the modification(s) of the listed drug" and need not submit redundant data that support the safety and effectiveness of the drug as originally approved. 21 C.F.R. § 314.54. In fact, the Petitioners were on notice *before* 1984 that FDA was considering the ANDA policy to post-1962 drugs (see fn. 5, *supra*), further undercutting any argument that FDA's interpretation of section 505(b)(2) interfered with their reasonable investment-backed expectations.

Pfizer refers to the Trade Secrets Act (18 U.S.C. § 1905), a provision of the FFDCA (21 U.S.C. § 331(j)), and various FOIA regulations (*e.g.*, 21 C.F.R. § 20.21) that impose certain limitations on the *release* of trade-secret information. As a threshold matter, it is clear that federal law does not prevent the FDA from *ever* releasing proprietary data to the public: to the contrary, the FFDCA expressly states that safety and effectiveness data *shall* ordinarily be released on the earliest date that an ANDA approval could be made effective, among other times. *See* 21 U.S.C. § 355(*l*). Even assuming that these provisions barred FDA outright from *releasing* proprietary data, however, such provisions "cannot be construed as any sort of assurance against internal agency *use* of submitted data during consideration of the application of a subsequent

applicant for registration." *Monsanto*, 467 U.S. at 1009 (emphasis added). The FDA does *not* disclose proprietary data to section 505(b)(2) applicants; instead, it releases only a summary basis of approval for new drug applications, which merely describes the underlying safety and effectiveness studies in general terms. Because the FDA's use of *its* conclusions about safety and effectiveness, based on proprietary data, in approving section 505(b)(2) applications is evidently contemplated by statute, no taking has occurred here, and Pfizer's argument fails.

Finally, Pfizer could perhaps argue that, by requiring an applicant to agree to allow the FDA to use its proprietary data in reviewing subsequent applications as a condition of getting approval in the first place, the FDA places an unconstitutional condition on Pfizer's right to obtain the valuable governmental benefit of FDA approval. But that argument, too, is foreclosed by *Monsanto*. There, the Supreme Court reasoned that a similar condition on the right to market and use pesticides constituted a "burden[] we all must bear in exchange for the advantage of living and doing business in a civilized community." 467 U.S. at 1007 (internal quotation omitted). The Court added that "[t]his is particularly true in an area, such as pesticide sale and use, that has long been the source of public concern and the subject of government regulation." *Id.* So too is it reasonable to expect drug manufacturers to make data about safety and effectiveness available to others as a condition of being allowed to market and sell their drugs to the general public. Like Pfizer's takings argument, any argument that the section 505(b)(2) approval system somehow violates the unconstitutional-conditions doctrine is unavailing.

B. FDA's Interpretation of Section 505(b)(2) Does Not Conflict with Section 505(l) of the FFDCA.

Section 505(l) of the FFDCA provides that safety and effectiveness data from an NDA may be made publicly available under certain circumstances – for example, when an ANDA is or could be submitted for approval. 21 U.S.C. § 355(l)(5). Because this provision identifies the approval of an ANDA as one of the triggers for release of this data, but does not identify approval of a section 505(b)(2) application as a trigger, Petitioners contend that FDA's interpretation of section 505(b)(2) would render section 505(l) "meaningless" (October 11, 2002 Petition at 7) because it would permit release of information, in conjunction with a section 505(b)(2) application, in cases not authorized under section 505(l).

This argument is fundamentally flawed because it fails to recognize the difference between releasing data to the public and allowing FDA reference of data. Section 505(l) does not address the use of information in the section 505(b)(2) context, because the use of safety and efficacy data in a 505(b)(2) application does not rise to the level of a "public release" of information governed by section 505(l). As discussed above, FDA does not provide reference drug safety and efficacy data to 505(b)(2) applicants. Rather, as also discussed above, FDA only releases a summary basis of approval of the NDA to a 505(b)(2) applicant, *not* the data itself. Obviously, Congress intended FDA to reference data in an NDA when reviewing the first ANDA to be submitted for a given drug product because one of the triggers for the public release of data is the *approval*, not *submission*, of an ANDA. Likewise, Congress also intended FDA to reference data in NDAs when reviewing section 505(b)(2) NDAs before a public release of data is authorized under 505(l). The use of information in the 505(b)(2) process therefore does not

rise to the level addressed in section 505(l), and the failure of section 505(l) to address section 505(b)(2) creates no tension whatsoever between the two sections.

C. FDA's Position on Section 505(b)(2) Does Not Undermine the Suitability Petition Process.

Petitioners argue that FDA's interpretation of section 505(b)(2) "eliminates entirely the public petition process set forth in section 505(j)." October 11, 2002 Petition at 7. Petitioners are claiming that if FDA's interpretation of section 505(b)(2) is correct, there would be no need for suitability petitions, since products that contain modifications to the reference drug could go the section 505(b)(2) route instead of the section 505(j) suitability petition route.

As discussed in the April Dr. Reddy Comments, this analysis ignores the fundamental fact that FDA's interpretation of section 505(b)(2) has in fact *not* rendered the suitability petition process meaningless. FDA receives and reviews scores of suitability petitions per year from generic drug applicants whose products differ slightly from the reference drug in the limited ways permitted under section 505(j). For products that have previously received a section 505(j) approval, the suitability petition process is a far more desirable route than the section 505(b)(2) process, which permits FDA to make a full inquiry into safety and efficacy and to require whatever data it deems necessary, including clinical data, as a condition of approval. For drugs that are not eligible for section 505(j) treatment because clinical or preclinical data is necessary for approval, and for companies that intend to market a variation of another company's section 505(j) drug but are ineligible for the suitability petition process because they do not have a section 505(j) approval, section 505(b)(2) is available. Thus, both the suitability petition process found in section 505(j) and the section 505(b)(2) process serve important and complementary functions within the 1984 Act's generic approval regime, and FDA's reading of the latter has been shown to do no damage to the former.

In making their suitability petition argument, Petitioners ignore the possibility that there are, in fact, circumstances in which a company may choose not to create a bioequivalent version of an approved drug product but will develop an improved or modified version of a reference drug, for which some clinical studies are necessary. In such cases, a suitability petition is usually not appropriate.

D. Later Statutes Do Not Undermine FDA's Interpretation of Section 505(b)(2).

Petitioners argue that later-enacted statutes, principally the Generic Drug Enforcement Act (GDEA) and the Food and Drug Administration Modernization Act (FDAMA), "confirm" Petitioners' reading of section 505(b)(2). July 27, 2001 Petition at 14. Petitioners are wrong.

1. GDEA -- Petitioners argue that the GDEA was designed to address abuses in section 505(j) applications and that the failure of Congress to address abuses in section 505(b)(2) applications reflected its recognition that the latter could not incorporate non-public proprietary data and therefore was not subject to the same abuse as section 505(j) applications. This argument fails for two reasons.

First, GDEA *does* in fact address section 505(b)(2) applications because it provides for debarment of individuals "convicted of a felony under Federal law for conduct . . . relating to the development or approval . . . *of any drug product*, or . . . otherwise relating to the regulation of *any drug product*." 21 U.S.C. § 335a(a)(2) (emphasis added). Thus, it is not true that Congress ignored section 505(b)(2) applications because it deemed them less subject to abuse than section 505(j) applications.

Second, and more important, Petitioners' analysis cannot obscure the facts that (1) the text, structure, legislative history, and underlying policies of section 505(b)(2) clearly do not support the limitation Petitioners seek to add to that section, (2) FDA's interpretation of section 505(b)(2) at the time the GDEA was passed clearly did not support such a limitation, and (3) nothing in the GDEA purports to introduce, "ratify", or even mention that limitation. Black letter principles of statutory construction hold that Congress will be deemed to repeal existing statutes only if it does so explicitly. *Pfizer v. FDA*, 753 F. Supp. 171, 178 (D. Md. 1990) ("Congress is assumed to know the judicial or administrative gloss given to particular statutory language, and therefore is assumed to have adopted the existing interpretation unless it affirmatively indicates otherwise.") In this case, therefore, Congress must be deemed to have known about FDA's interpretation of section 505(b)(2) when it enacted the GDEA and, in the absence of expressly stated action by Congress to overturn that interpretation, it must stand.

2. FDAMA – Petitioners fare no better under FDAMA. Section 118 of that statute, on which Petitioners rely, required FDA to develop guidances relating to NDAs and Biologics License Applications ("BLAs"). Petitioners admit that this section did not change any substantive provisions of section 505(b)(2). Given FDA's interpretation of section 505(b)(2) at the time of FDAMA's passage, and Congress' presumed awareness of that interpretation (*Pfizer v. FDA, supra*), FDAMA's silence on section 505(b)(2) is simply not enough to support an argument that that statute embraced a limited reading of that section.

E. Petitioners Are Wrong to Argue that Drugs Approved Under Section 505(b)(2) May Not Receive an "A" Rating.

Petitioners also argue that FDA is not authorized to assign "A" therapeutic equivalence codes to products approved under section 505(b)(2). GPhA addressed this issue in its December 10, 2001 Comments. As noted therein, the criteria by which FDA may assign therapeutic equivalence ratings does not depend on the regulatory pathway chosen, it depends on scientific evaluation. As discussed above, while only section 505(j) applications *require* bioequivalence data, section 505(b)(2) applications may contain such data, and the fact that the Orange Book refers to the bioequivalence definition in the ANDA portion of the 1984 Act does not support Pfizer's argument that applicants under other statutory sections cannot demonstrate bioequivalence or receive an "A" rating. Indeed, as GPhA has noted, the Orange Book itself notes that section 505(j) merely describes "one set of conditions under which a test and reference listed drug shall be considered bioequivalent," and FDA has in the past given "A" therapeutic equivalence ratings to section 505(b)(2) drugs. [Further, the Orange Book is intended to provide recommendations regarding interchangeability of products. This recommendation is not based on the type of submission, but rather the agency's scientific determination of therapeutic equivalence.] Petitioners offer no basis for a change in FDA's position.

VI. ADOPTION OF PETITIONERS' INTERPRETATION OF SECTION 505(b)(2)WOULD HAVE SERIOUS AND ADVERSE POLICY IMPLICATIONS.

Certain of the comments filed with FDA in response to the Petitions have pointed out that a determination by the Agency that section 505(b)(2) does not permit reliance on innovator data would result in the withdrawal from the market of many valuable drugs that have already been approved under section 505(b)(2). Petitioners have dismissed that argument by insisting that (1) it has not requested withdrawal of any product approved under section 505(b)(2); (2) it has no basis for knowing which products approved under section 505(b)(2) relied on innovator data; and (3) affirmative findings of lack of safety and effectiveness would have to precede withdrawal of a section 505(b)(2)-approved product, and such findings would, in turn, have to be preceded by a hearing on the proposed withdrawal. *See, e.g.,* Pfizer April 4, 2002 Comments at 5-6.

Petitioners' efforts to minimize the impact of their requests fail. It appears that FDA has issued section 505(b)(2) approvals over the past decade and a half that are based on information that Petitioners are saying could not be relied upon under the 1984 Act. *See* April Dr. Reddy Comments at 2-6; December 10, 2001 GPhA Comments.[8] And even if there is some dispute on this matter in a given case, the process for resolving this dispute will unquestionably cause enormous uncertainty for not only the particular manufacturer engaged in the dispute, but also for any other company with a 505(b)(2) product on the market. This uncertainty is detrimental to competition and is precisely what the 1984 Act sought to combat. Indeed, for Petitioners to challenge FDA's 505(b)(2) policy after it has been in effect for almost 20 years and then to claim that its challenge will not significantly disrupt the expectations of generic manufacturers with 505(b)(2) drugs on the market is both audacious and flatly untrue.

There is no mistaking the fact that Petitioners' arguments, if accepted by FDA, would in fact have enormous adverse effects, both retroactive and prospective. Petitioners seek to place significant limitations on the ability of drug companies, both generic and brand, to obtain approval of important products, even after relevant patents and other exclusivities have expired. The products that are covered under section 505(b)(2) represent one of the fastest growing segments of the drug market and provide public access to affordable enhanced versions of existing drugs. These products provide consumers with substantial cost benefits and with innovative new treatments. If Petitioners' reading of section 505(b)(2) were adopted by the Agency, the incremental innovation that the current system encourages would all but cease except in those cases where the original NDA holder has the economic incentive and the ability to seek approval of the changes. Even under Petitioners' more limited theory presented in the Pfizer April 28, 2003 comments, innovation would be stifled by the section 505(b)(2) applicant's inability to obtain FDA approval for enhancements of an approved drug that clearly do not

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[8] Petitioners suggest otherwise (*see* Pfizer April 28, 2003 Comments at 20-21), but in so doing fail to account for almost half of the products listed in the Dr. Reddy Comments. Additionally, the April 28, 2003 Comments specifically acknowledge that at least 13 drug products *could* be affected by a grant of its petition, and at least one drug product (other than amlodipine maleate) *would* be affected. *See id.*

infringe on the NDA holder's patents. It would be poor public policy to impose a barrier to innovation that does not infringe on other innovators' patents.

If permitted to rely only on published literature, manufacturers of innovative modifications would be delayed for decades while waiting for a sufficient body of articles to be published. In fact, there may never be sufficient published literature because Petitioners' interpretation would create an incentive for NDA holders to block the approval of competing section 505(b)(2) NDAs by denying their investigators the right to publish the results of clinical studies. Thus, Petitioners' reading of section 505(b)(2) would not only stifle innovation of useful enhancements to existing drugs, it would also place a "freeze" on the publication of scientific findings.

Lastly, and perhaps most important, Petitioners' interpretation would directly result in the conducting of unnecessary, duplicative, and potentially unethical studies. If the section 505(b)(2) route is foreclosed, the only viable alternative (short of not seeking approval) will be to conduct all of the studies required under section 505(b)(1). As a result, manufacturers will be forced to enroll human and animal subjects in studies in order to prove what FDA and the public already know. More troubling, adopting Pfizer's argument may require that studies include a placebo control. As a result, human subjects could be denied effective treatments for serious conditions for no justifiable reason.

In short, Petitioners' reading of section 505(b)(2) would impact manufacturers, consumers, and health care providers alike, would directly undermine every one of the basic goals of the 1984 Act, and would in general adversely affect the public health. Petitioners should not be permitted to hide from, or to dismiss, the consequences of their position.

VII. CONCLUSION

FDA, more than any company, trade association or individual, has been in the best position over the past 19 years to carefully review applications under section 505(b)(2). Drug products that are the subjects of these applications are and will continue to be valuable to consumers. Giving any credence at all to the Petitions would seriously undermine the express language of the 1984 Act, further distort the balance of the Act, and undermine the Act's drug approval procedures at a time during which serious consideration is being given to whether the Act's balance has *already* been tilted too far in favor of original NDA holders.

For these and all the other reasons set forth in these comments, GPhA requests that FDA deny both the July 27, 2001 and the October 11, 2002 Petitions in their entirety.

Respectfully submitted,

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