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VIA HAND DELIVERY

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

Re: **CITIZEN PETITION**

Dear Madam or Sir:

The undersigned submits this petition under 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs ("the Commissioner): (1) amend its October 1999 505(b)(2) Draft Guidance Document[1/] and its regulations at 21 C.F.R. § 314.54 to reflect that the Food and Drug Administration ("FDA") cannot rely on or otherwise use any non-public proprietary information in an innovator's New Drug Application ("NDA") or other non-public filings to approve applications submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FFDCA" or "the Act"); (2) not rely on or otherwise use non-public proprietary information in an innovator's NDA or other non-public filings to approve section 505(b)(2) applications; and (3) not assign "A" therapeutic equivalence evaluation codes to drug products approved pursuant to section 505(b)(2) of the Act, and modify FDA's equivalency rating practices accordingly.

I. Action Requested

Pfizer Inc and Pharmacia Corporation request that the Commissioner take the actions noted above.

II. Executive Summary

FDA has, through a draft guidance and public statements, communicated that it will approve section 505(b)(2) applications in reliance on non-public proprietary information in an innovator's NDA, and that it will assign "A" therapeutic equivalence evaluation codes to drugs approved under section 505(b)(2). For the reasons set forth in this petition, the FDA legally can do neither because:

1/ FDA, Guidance for Industry: Applications Covered by Section 505(b)(2), Draft (1999).

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- FDA's unauthorized reliance on or use of an innovator's proprietary data to approve a section 505(b)(2) application is not supported by any reasonable construction of Section 505 of the FFDCA, its legislative history, later enactments to the Act, and other statutory protections for the proper and legal use of proprietary data;

- Reliance on FDA's prior findings of safety and effectiveness in an innovator's NDA to approve a section 505(b)(2) application constitutes an unconstitutional taking of valuable proprietary data in violation of the Fifth Amendment; and

- FDA's assignment of "A" therapeutic equivalence evaluation codes to drugs approved under section 505(b)(2) is not supported by any reasonable construction of the FFDCA, its legislative history, and FDA's regulations.

FDA must, therefore, take the above requested actions to comply with the FFDCA and other applicable laws.

III. Statement of Grounds

A. FDA Must Amend 21 C.F.R. § 314.54 and the 505(b)(2) Draft Guidance Document Because the FFDCA Does Not Permit FDA to Approve Section 505(b)(2) Applications in Reliance on an Innovator's Proprietary Data Without Innovator Authorization

In FDA's 505(b)(2) Draft Guidance Document[2/] ("Draft Guidance Document"), the Agency stated that it will accept and approve section 505(b)(2) applications for new drug products that rely on "the Agency's finding of safety and effectiveness for an approved drug, without regard to a right to rely on such data."[3/] Through such reliance, the Agency intends to and will improperly appropriate an innovator's non-public proprietary and commercially valuable safety and effectiveness data ("proprietary data") to approve another company's drug product.[4/] FDA

2/ Id.

3/ See id. at 2.

4/ See id. at 2 (noting that the Agency will accept: "a 505 (b)(2) application for a change in a drug when approval of the application relies on the Agency's previous finding of safety and/or effectiveness for a drug. This mechanism, which is embodied in a regulation at 21 C.F.R. 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

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suggests that this policy is permitted and embodied by the Agency's regulations at 21 C.F.R. § 314.54.

Section 505(b)(2) of the FFDCA provides for the submission to FDA of applications submitted under section 505(b)(1) "for which the investigations . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person or for whom the investigations were conducted." The statute, on its face, does not authorize FDA or an applicant to rely on or use an innovator's proprietary data to approve a section 505(b)(2) application, and such an interpretation is not supported by any reasonable construction of Section 505 of the FFDCA, its legislative history, and other protections for the proper and legal use of proprietary data.[5/] In particular, this interpretation ignores the language and structural differences between sections 505(b) and 505(j) of the FFDCA—only the latter authorizes FDA to approve a generic drug based on an innovator's non-public proprietary safety and effectiveness data.

FDA's interpretation of its authority under Section 505(b)(2) as described in the Draft Guidance Document and regulations is therefore beyond its statutory authority under the FFDCA and is invalid. FDA thus must amend its 505(b)(2) Draft Guidance Document and its regulations at 21 C.F.R. § 314.54 to reflect that the Agency cannot approve 505(b)(2) applications in reliance on or use of an innovator's proprietary data in its NDA.

1. Under a Proper Construction of Sections 505(j) and 505(b)(2), FDA Can Not Rely On An Innovator's Proprietary Data to Approve 505(b)(2) Applications

The language and structural differences between sections 505(j) and 505(b)(2) of the FFDCA illustrate the diverse purposes and requirements of the drug approval mechanisms authorized by these provisions.[6/] Section 505(j) requires applicants to demonstrate among other things that the

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4/(...continued)
a drug.").

5/ See, e.g., 18 U.S.C. § 1905, 21 U.S.C. § 331(j). See also, Hoffmann-La Roche, Inc. v. Harris, 484 F. Supp. 58, 60 (D.D.C. 1979) (discussing FDA's paper NDA policy, the court stated that "the 'raw data' made available by the pioneer applicant is protected and not available as such either to the duplicate applicant or FDA" to approve a generic drug).

6/ See Martini v. Federal National Mortgage Ass'n, 178 F.3d 1336, 1345-46 (D.C. Cir. 1999) ("Under Chevron's first step . . . we have a duty to conduct an independent examination of the statute in question, looking not only to the particular statutory

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conditions of use for the unapproved new drug have been previously approved and that active ingredient(s) of an "[unapproved] new drug are the same as those of [a] listed drug" (i.e., a previously approved drug product) and, thus, authorizes the Agency to approve a generic drug based on the FDA's prior findings of safety and effectiveness for the ingredients in the innovator product.[7] The language of the Act, however, does not state or even suggest that approvals based on prior findings of safety and effectiveness of an innovator's product are permitted under section 505(b)(2). Unlike section 505(j), section 505(b)(2) says nothing about reference to prior listed drugs or determinations of sameness based on a comparison with a previously approved new drug.

If Congress had intended for the Agency to approve applications under section 505(b)(2) that rely on an innovator's proprietary data to establish safety and efficacy, it would have included the same express language in section 505(b)(2) that is included in section 505(j).[8] Moreover, section 505(l)(5) of the Act specifically states that safety and effectiveness data in a 505(b) application can be released upon request to the public once that data has been referenced as the basis for approval of a 505(j) application, thus acknowledging that reference to the 505(b)

6/(...continued)
language at issue but also to the language and design of the statute as a whole.") (internal citations omitted); Pilot Life Insurance Co. v. Dedeaux, 481 U.S. 41, 51 (1987) ("In expounding a statute, we must not be guided by a single sentence or member of a sentence, but look to the provisions of the whole law . . .").

7/ See 21 U.S.C. § 355(j)(2)(A)(i) and (ii)(I), (II).

8/ See Christine Todd Whitman v. American Trucking Associations, Inc., 121 S. Ct. 903, 2001 U.S. LEXIS 1952, *16-17 (2001) ("We have refused to find implicit in ambiguous sections of the CAA an authorization to consider costs that has elsewhere . . . been expressly granted."); Leisnoi, Inc. v. Stratman, 154 F.3d 1062, 1066 (9th Cir. 1998) (where the legislature has carefully employed a term in one place and excluded it in another, is should not be implied where excluded). BFP v. Resolution Trust Corporation, 511 U.S. 531, 537 (1994) ("It is generally presumed that Congress acts intentionally and purposefully when it includes particular language in one section of a statute but omits it in another.") (quoting Chicago v. Environmental Defense Fund, 511 U.S. 328 (1994)); Id. at 570 (Souter J., dissenting) (in the ordinary case, absent any "indication that doing so would frustrate Congress' clear intention or yield patent absurdity, our obligation is to apply the statute as Congress wrote it.").

proprietary data is expected for a 505(j) approval.[9/] In fact, this provision, which encompasses both section 505(b)(l) and 505(b)(2) applications, suggests that Congress expected section 505(b)(2) applications might also contain proprietary data that may be used to support the approval of section 505(j) applications.

The express language of the statute also makes clear that where Congress intended to permit reliance on FDA's prior findings of safety and effectiveness, and the underlying proprietary data as the basis for approval of section 505(j) applications, Congress intended to require such drugs to be the same or to allow such drugs to differ only in specifically identified and limited ways from listed drugs. Thus, drugs approved pursuant to section 505(j) may only differ from listed drugs in route of administration, dosage form, strength, or in one active ingredient for combination drugs, without having to replicate full reports of safety and effectiveness.[10/]

Nothing in sections 505(b)(2) or 505(j) suggests that Congress intended to allow FDA to approve other more extensive changes to copies of prior approved drugs by relying on an innovator's proprietary data and conducting limited clinical investigations.[11/] Rather, the statute supports the conclusion that Congress intended to allow reliance on prior findings of safety and effectiveness in only limited circumstances, involving well understood and largely quantifiable deviations to the listed drug. To the extent that the product deviations are more significant, they are required to be the subject of a suitability petition, that is generally published in the Federal Register, and

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9/ See 21 U.S.C. § 355(i)(5).

10/ See 21 U.S.C. § 355(j)(2)(C); see also H.R. Rep. 9-857, Part 1, 98th Congress, 2d Sess. 36, reprinted in 1984 U.S. Code. Cong. Admin. News 2656 (stating that a section 505(j) applicant may petition for approval of a drug product that varies from the listed drug in route of administration, dosage form, strength, or where one of the active ingredients differs from those in a listed drug that is also a combination drug, and that "these are the only changes that are permitted"); 54 Fed. Reg. 28872, 28874, (July 10, 1989) (recognizing that "the [abbreviated application], therefore, provides for agency review of the same quality of product information required in a full new drug application but omits the reports of investigations establishing safety and effectiveness of the drug which are already established.") .

11/ See United States v. Cardenas, 864 F.2d 1528, 1534 (10th Cir. 1989) ("In spite of the esoteric sound of the expressio unius maxim, it is generally accurate to assume that when people say one thing they do not mean something else.") (quoting 2A N. Singer, Sutherland Statutory Construction § 47.01 (Sands 4th ed. 1984)).

subject to public comment.[12/] Despite these express procedural safeguards on the review of product deviations, FDA's section 505(b)(2) regulations and Draft Guidance Document provide for approval of drugs with significant chemical and other modifications based on reference to listed products without the benefit of full reports and without the requisite public notice and comment. The Agency's regulations and Draft Guidance Document therefore not only exceed the authority granted under the Act but, if read literally, render the section 505(j) suitability petition procedure and protections meaningless.

The judicial presumption, however, is that Congress has a definite purpose in every enactment and formulates subsidiary provisions in harmony with that purpose.[13/] FDA's proposed implementation of section 505(b)(2) contradicts this judicial precedent and disrupts that harmony and balance. Therefore, to the extent the Agency relies on 21 C.F.R. § 314.54 and the Draft Guidance Document to approve section 505(b)(2) applications for drug products that include more significant changes to listed drugs in reliance on an innovator's findings of safety and effectiveness, the regulation and Draft Guidance Document violate the FFDCA and are illegal.

In addition to language differences, the carefully delineated structure of sections 505(j) and 505(b)(2) also illustrate their distinct purposes and intended differences. Section 505(b)(2) is a subsection of section 505(b), which sets forth the approval requirements for full new drug applications ("NDAs"). Section 505(b)(2) applications are, therefore, a type of NDA. As discussed in Section III.A.2. of this petition, the conclusion that section 505(b)(2) applications are NDAs is supported by numerous Congressional statements equating section 505(b)(2) applications with "paper NDAs" (also, by definition, a type of NDA), and other statutory provisions such as 505(l). In contrast, section 505(j) sets forth the approval requirements for generic drugs approved specifically through an abbreviated generic drug application. Neither Congress nor FDA has stated or suggested that section 505(b)(2) applications are a type of generic drug application.

12/ 21 C.F.R. § 314.93.

13/ See Faircloth v. Lundy Packing Co., 91 F.3d 648 (4th Cir. 1996), cert. denied, 519 U.S. 1077 (1997) (interpreting statutes requires courts to both implement the policy of the legislature and to harmonize all provisions of the statute).

Separate subsections of a statute, such as sections 505(j) and 505(b)(2) of the FFDCA, may operate distinctly.[14/] The fundamental placement and structure of these two provisions in the FFDCA underscore their distinctly different purposes. For example:

- Section 505(b)(2) requires full reports to demonstrate safety and efficacy while section 505(j) only requires a showing of "sameness" to the listed drug and bioequivalence.

- FDA cannot require section 505(j) applications to include independent clinical trial data to support their approval,[15/] whereas no such prohibition applies to section 505(b)(2) applications. This distinction is consistent with Congress' deliberate approval structure because there is no need for more safety and efficacy data for a true copy of a previously approved drug, but a genuine need for such data exists for drugs that are not copies and that cannot rely on or use prior findings and proprietary data.

- Section 505(j)(2)(C) of the FFDCA requires applicants seeking approval of generic drugs that are different from reference listed products, in route of administration, dosage form, strength, or in one active ingredient for combination drugs, to file a suitability petition subject to public comment.[16/] This requirement arises from Congress' assumption that generic drugs can only be deemed safe and effective if they are the same as the innovator products, and even minor variations must be subject to significant agency and public scrutiny.[17/] There is no similar requirement of public review for the product variations

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14/ See Public Citizen Health Research Group v. FDA, 185 F.3d 898 (D.C. Cir. 1999) (noting that distinct FOIA treatment for INDs and NDAs is supported by the fact that they are addressed in "separate subsections"); In re Skaggs, 196 B.R. 865, 867 (Bankr. W.D. Okla. 1996) (where subsections of a statute deal with distinct topics, they should not be interpreted based on language from other independent provisions except when such language is expressly referred to).

15/ See 21 U.S.C. § 355(j)(2)(A) ("The Secretary may not require that an [abbreviated] application contain information in addition to [the statutory requirements].").

16/ See 21 U.S.C. § 355(j)(2)(C) (requiring an applicant to petition the Agency for approval of a drug product that is different from the listed drug).

17/ The importance of this need for review is underscored by the fact that several previously-approved abbreviated applications have, in practice, been found or asserted to be bio*in*equivalent with listed drugs. See SangStat Medical Corp.; Withdrawal of Approval of an Abbreviated New Drug Application Cyclosporine, 65 Fed. Reg. 75717 (Dec. 4,

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involved in section 505(b)(2) applications because their approval is intended to be supported by full reports of safety and effectiveness of that product, not by reliance on prior findings and innovator's proprietary data.

- Section 505(j)(6) of the Act requires that drugs approved via generic drug applications be withdrawn if the NDAs to which they refer have been withdrawn or suspended for safety or effectiveness reasons. The purpose of this provision is to remove from the market generic drugs approved in reliance on the prior findings of safety and effectiveness which are no longer valid. The FFDCA contains no companion provisions for section 505(b)(2) applications for a simple reason—FDA cannot approve these applications in reliance on prior findings of safety and effectiveness, so the withdrawal of a related NDA is not necessarily detrimental to a 505(b)(2) approval.

- Section 505(j) provides 180 days of market exclusivity from further generic competition for certain generic drugs under certain circumstances.[18/] Section 505(b) contains no equivalent provision with respect to any section 505(b)(2) applications. Rather, as for all section 505(b) applications, section 505(b)(2) applications may be granted: (1) three years of marketing exclusivity if one or more of the clinical investigations, other than bioavailability/bioequivalence studies, were essential to approval of the application and were conducted or sponsored by the applicant[19/]; (2) five years of exclusivity for a new chemical entity[20/]; (3) orphan drug exclusivity[21/]; and (4) pediatric exclusivity.[22/]

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2000) (announcing the withdrawal of SangStat's Abbreviated application); Elisabeth Pina, Not as Good as the Brand, Med Ad News, Oct. 2000, at 48 (reporting SangStat recalled its generic cyclosporine product because it was determined to be bio*in*equivalent with Neoral) (Attachment A); Thomas M. Burton, FDA-Approved Generic Drug Has Disturbing Effects in Studies, Wall Street Journal, Oct. 24, 2000 (reporting Ivax Corporation's generic version of Clozaril has been shown to be present at lower levels in the bloodstream than the innovator product) (Attachment B).

18/ See 21 U.S.C. § 355(j)(5)(B)(iv).

19/ See 21 U.S.C. § 355(c)(3)(D)(iii); 21 C.F.R. §§ 314.50(j), 314.108(b)(4), (5).

20/ See 21 U.S.C. § 355(c)(3)(D)(ii); 21 C.F.R. §§ 314.50(j), 314.108(b)(2).

21/ See 21 U.S.C. §§ 360aa, 360bb, 360cc; 21 C.F.R. §§ 314.20-316.36.

22/ See 21 U.S.C. § 355a.

Congress sought to reward certain generics first to the market with 180 days of exclusivity from further generic competition because these products potentially provide to the public lower-cost, alternative copies of marketed drugs. In contrast, consistent with the requirement that section 505(b) applications include full reports of safety and effectiveness, Congress sought to reward section 505(b)(2) applicants with various forms of marketing exclusivity for clinical studies that support significant modifications to innovator products. The different incentives Congress provided for the filing of abbreviated applications compared to the filing of section 505(b)(2) applications reflect Congress' intention that these two approval mechanisms are distinct and separate.[23/]

- Section 505(l)(5) provides for the disclosure of the safety and effectiveness data in an NDA when "the first application under subsection (j) which refers to such [NDA] drug" is or could be approved. There is no similar provision in the Act authorizing release of NDA data upon approval of a section 505(b)(2) application. Again, this difference supports the view that innovator data can be relied upon in section 505(j) applications but not in section 505(b)(2) applications. NDA data properly may be released when an abbreviated NDA ("ANDA") is approved because at that point the data are subject to third-party use—by the ANDA applicant, in support of its application—and thus no longer commercially sensitive.[24/] That Congress did not authorize the release of NDA data upon the approval of a section 505(b)(2) application reflects Congress' understanding that a section 505(b)(2) application cannot reference or use NDA data.[25/]

23/ See Beach v. Ocwen Federal Bank, 523 U.S. 410, 418 (1998) ("Where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion.") (quoting Russello v. United States, 464 U.S. 16, 23 (1983)); Immigration and Naturalization Service v. Cardoza-Fonseca, 480 U.S. 421, 432 (1987) (where one section of a statute contains a particular standard, the existence of a different standard in a similar section indicates that Congress intended the two standards to differ).

24/ FDA has, however, acknowledged that the release of trade secret or confidential information is not authorized if the data retains value in obtaining approval in foreign countries or for other purposes. See Statement by FDA Chief Counsel, Drug Price Competition and Patent Term Restoration Act of 1984: Hearing on S. 2748 before Sen. Comm. On Labor and Human Resources, 98th Cong., 2d Sess. 262 June 28, 1984).

25/ See H.R. Rep. 9-857, Part 1, 98th Congress, 2d Sess. 73-74, reprinted in 1984 U.S. Code. Cong. Admin. News 2669 ("when an Abbreviated application may be filed with FDA, the

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All of the above differences that exist between the structure of the drug approval mechanisms set out in sections 505(b)(2) and 505(j) underscore Congress' intent that these are distinct approval mechanisms that are intended to operate differently.[26/] Consequently, consistent with the language of these provisions, FDA can only approve section 505(j) applications, not section 505(b)(2) applications, in reliance on prior findings of safety and efficacy based on an innovator's data.[27/]

2. *FDA's Paper NDA Policy Principles, Including the Prohibition Against Reliance on Innovator Proprietary Data, Were Included in Section 505(b)(2)*

The legislative history surrounding the enactment of sections 505(b)(2) and 505(j) of the Act also supports the view that these provisions represent distinct approval mechanisms, and that Congress did not intend FDA to rely on innovator proprietary data to approve section 505(b)(2) applications. Specifically, the legislative history demonstrates that Congress, through the Hatch-Waxman Amendments, added section 505(b)(2) to the FFDCA to codify FDA's "paper NDA" policy, as defined by the Finkel Memorandum,[28/] which does not permit FDA to rely upon innovator data.

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full data are [then] not needed [for approval of a drug]").

26/ To allow the convergence of the statutory requirements for these sections would undermine the statutory framework and Congress' express intent of how these distinct mechanisms are to function. United Food & Commercial Workers Local 751 v. Brown Group, 517 U.S. 544 (1996) (A natural reading of a statute's text, which will give effect to all of the statute's provisions, will always prevail over a mere suggestion to disregard or ignore duly enacted law as legislative oversight.).

27/ The above distinctions are not any less clear because of modest similarities in the language of the two provisions. In the case of sections 505(j) and 505(b), for example, both sections contain provisions that address when and how abbreviated applications and section 505(b)(2) applications should be filed with respect to ensuring no infringement of patent and/or market exclusivity, respectively. These similar provisions were incorporated into both provisions to ensure the filing of orderly patent lawsuits and to protect innovation, and have no bearing on an applicant's or FDA's right to rely on proprietary data to obtain product approvals.

28/ 46 Fed. Reg. 27396 (May 19, 1981) (publishing FDA internal memorandum by Dr. Marion Finkel ("Finkel Memorandum") dated July 31, 1978 which described the paper NDA process prior to enactment of the Hatch-Waxman Amendments).

Prior to the enactment of the Hatch-Waxman Amendments, under pressure from generic drug companies and the public, FDA developed the paper NDA policy to provide a mechanism by which it could approve generic versions of certain new drugs approved after 1962. Specifically, the policy permitted an applicant to submit published literature to support the safety and efficacy of a duplicate drug product that was first approved for marketing after 1962—the policy was limited to copies of drug products, or closely related forms, marketed after 1962 and offered for the same indications as the innovator drugs.

The Agency developed this policy without an explicit statutory mandate and, as described below, the legality of the policy was repeatedly questioned during its existence. The Agency and Congress, therefore, sought to settle the longstanding questions about the legality of the paper NDA policy, and to legitimize the policy by codifying it into section 505(b)(2) of the FFDCA, independent of the approval process created at the same time in section 505(j). The term "paper NDA" is liberally cited throughout the legislative history of section 505(b)(2), providing significant evidence that Congress intended to codify the Agency's prior paper NDA policy in section 505(b)(2).[29/]

The paper NDA policy was defined by the Finkel Memorandum, prior FDA interpretations, and the courts, to limit its use to literature-based NDAs that do not rely on the proprietary data in an innovator's NDA. The Finkel Memorandum recognizes that "no data in an NDA can be utilized to support another NDA without express permission of the original NDA holder."[30/] Likewise, FDA's December 1980 Federal Register notice states that FDA's 505(b)(2) policy, as defined by

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29/ Section 505(b)(2) was intended to permit an applicant to substitute literature to satisfy the "full reports" requirement of section 505(b)(1) of the Act. See H.R. 98-857, Part I, 98th Cong. 2d. Sess. 36 reprinted in 1984 U.S. Code Cong. Admin. News 2647, 2649 (stating that "under the Paper NDA procedure, the generic manufacturer may submit scientific reports, instead of clinical trials, to support findings of safety and efficacy"); Id. at 2703 (using term "Paper NDA"); Id. at 2665 (noting section 505(b)(2) addresses the filing of "Paper NDAs"). See also Burroughs Wellcome Company v. Owen, 630 F. Supp. 787 (E.D. N.C. 1986) (the 1984 Amendments created two new kinds of drug applications, abbreviated applications (section 505(j)) and "paper" NDAs (section 505(b)(2))—"A 'paper' NDA is one in which the required safety and effectiveness data are not the result of original testing by the NDA applicant, but rather are obtained from literature reports of testing done by others.") (emphasis added).

30/ 46 Fed. Reg. 27396 (May 19, 1981).

the Finkel Memorandum, "acknowledges that data [and reports] in a pioneer NDA cannot . . . be used to support an NDA for a generic version of the pioneer product."[31/]

Relatedly, the courts in American Critical Care v. Schweiker, Food, Drug, Cosm. L. Rep. (CCH) 1980-81 Transfer Binder ¶ 38, 110 (N. D. Ill. 1981), and Upjohn Manufacturing Company v. Schweiker, 520 F. Supp. 58, 63 (W.D. Mich. 1981), confirmed that existing law did not permit FDA to rely, without permission, on data in an NDA to approve another NDA. The American Critical Care court, which ordered FDA to publish the Finkel Memorandum in the Federal Register, prohibited the Agency from including in that published memorandum a paragraph that stated that FDA approval of any paper NDA that was submitted after the Agency had approved another paper NDA for the same drug could rely on FDA's Summary Basis of Approval of the first paper NDA.[32/] The court determined that existing law did not contemplate FDA's reliance on data in a paper NDA (a type of NDA) to support the approval of another NDA, without express permission of the NDA holder.[33/] Similarly, the Upjohn Manufacturing Company court, interpreting FDA's paper NDA policy soon after it issued, determined that FDA could not rely on trade secret information in a pioneer's NDA to approve a duplicate NDA.[34/] These court

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31/ 45 Fed. Reg. 82052, 82056 (Dec. 12, 1980) (emphasis added). The notice explains that although FDA refers to the pioneer NDA to determine whether the results reported in the published literature are consistent with what is known about the active drug compound (to determine if published reports deviate significantly from the data in an NDA in order to determine if a study is "adequate"), the information from the pioneer NDA cannot be used to provide critical information missing from the published literature. That is, the data in the pioneer NDA can be used to deny approval of a subsequent product, but not to support such approval. Id.

32/ American Critical Care v. Schweiker, Food, Drug, Cosm. L. Rep. (CCH) 1980-81 Transfer Binder ¶ 38, 110 (N. D. Ill. 1981).

33/ The stated subject of the Federal Register notice publishing the Finkel Memorandum is "NDA's for Duplicate Drug Products of Post-1962 Drugs." See 46 Fed. Reg. 27396 (May 19, 1981) (emphasis added). Paper NDA's were therefore a type of NDA, and nothing in the Finkel Memorandum suggests that the policy resulted in a new regulatory approval mechanism. Further, Attachment A of the Finkel Memorandum states, "A new drug manufacturer desiring to market a drug which is identical to one which is already marketed and the subject of an approved new drug application should submit a full new drug application for that product." Id. (emphasis added).

34/ See Upjohn Manufacturing Company v. Schweiker, 520 F. Supp. 58, 63 (W.D. Mich.

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decisions prohibiting the Agency from relying on NDA data to approve other NDAs delimited the paper NDA policy that Congress codified in section 505(b)(2).

Furthermore, the Finkel Memorandum, as well as FDA regulatory and court interpretations of this document, indicate that published reports were to constitute the documentation of safety and effectiveness for paper NDAs. Reference to and/or reliance on innovator proprietary data to document safety and effectiveness was therefore not contemplated as part of the paper NDA policy, and therefore is not permissible for section 505(b)(2) applications. The Finkel Memorandum states that "in the case of duplicate NDAs for already approved post-'62 drugs, the Agency will accept published reports as the main supporting documentation for safety and effectiveness."[35/] Contrasting NDAs and paper NDAs in its December 1980 Federal Register notice, FDA explained that while "[NDAs contain] reports of investigations for which raw data. . . are included or are available . . .[,] paper NDAs have been submitted when adequate reports exist in the scientific literature."[36/] Moreover, the American Critical Care court's order that FDA remove language from the published Finkel Memorandum permitting subsequent paper NDA applicants from relying on FDA's Summary Basis of Approval of the first paper NDA, demonstrates that every paper NDA must include published literature.

Consistent with its inclusion of the Finkel Memorandum principles in section 505(b)(2), Congress did not intend 505(b)(2) applicants to rely on the unauthorized use of an innovator's proprietary data to establish safety and effectiveness. FDA cannot sua sponte give a different meaning to a term and statute beyond that intended by Congress, particularly when any such change would have the enormous economic consequences presented here.[37/] Congressional enactment of section 505(b)(2) thus properly must be interpreted as including and perpetuating

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1981) (FDA could not lawfully rely on trade secret information in Upjohn's NDA to approve Boots NDA—the Agency expressly denied it did so and asserted that the Boots Summary Basis of Approval ("SBOA") justified its decision without reference to information outside of the Boots NDA).

35/ Id. (emphasis added).

36/ 45 Fed. Reg. 82052, 82052 (Dec. 12, 1980).

37/ See The Toilet Goods Association v. Finch, 419 F.2d 21, 27 (2d Cir. 1969) (stating that, for a court to conclude that Congress intended "to have made a basic change in regulatory procedures, legislators must either use plain language or give other clear manifestation of intent," and invalidating FDA's attempts to impose listing and certification requirements on a diluent.)

the FDA's paper NDA policy existing at the time of passage of the Hatch-Waxman Amendments. As was the case before the Hatch-Waxman Amendments, Congress remains the only entity with the authority to create new rights under the FFDCA. Accordingly, FDA's proposed approval of section 505(b)(2) applications in reliance on an innovator's proprietary data exceeds the Agency's statutory authority and, thus, is unlawful under the FFDCA and the Administrative Procedure Act.

Because Congress used language in section 505(b)(2) that is arguably broader than necessary to codify the paper NDA policy, FDA has asserted that section 505(b)(2) is more expansive than the paper NDA policy.[38/] The Agency's position, however, is unsupported not only by the aforementioned contrary legislative history, but also the language/structure and context of sections 505(b) and 505(j) of the FFDCA (see Sections III.A.1. and III.A.3. of this petition, respectively). Taken together, these legislative pronouncements and statutory provisions weigh conclusively against FDA's position, which the Agency exclusively supports on the basis of assertedly vague language of section 505(b)(2).

FDA's interpretation is also flawed in that it ignores the fact that had Congress truly intended 505(b)(2) applications to be approved in reliance on an innovator's prior findings of safety and effectiveness in the same manner as abbreviated applications, it would have incorporated similar language relating to sameness, NDA withdrawals, and related provisions into section 505(b)(2). The only reason why Congress incorporated the 505(b)(2) mechanism into section 505(b) is that it meant to create a new type of full NDA, that had not previously been authorized. And that is exactly what Congress did; it codified the paper NDA policy into section 505(b)(2).

3. *Later Enactments to the FFDCA Have Confirmed That Only Applications Under Section 505(j) May be Approved In Reliance on FDA's Prior Findings of Safety and Effectiveness and an Innovator's Proprietary Data*

Congressional enactments subsequent to Hatch-Waxman have confirmed that FDA can only use an innovator's findings of safety and effectiveness to approve section 505(j) applications. In assessing the meaning of a specific issue in a statute, the analysis should not be confined to examining the particular statutory provision in isolation—the meaning or ambiguity of statutory language may only become evident when placed in context.[39/] Of particular importance, the meaning of one statute may be affected by other Acts, particularly where Congress has

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38/ See 54 Fed. Reg. 28872, 28890 (July 10, 1989).

39/ See FDA v. Brown & Williamson Tobacco Corp., 120 S.Ct. 1291, 1304, 1297, 146 L. Ed. 2d 121, 134, 127 (2000) (agency authority cannot be exercised "in a manner that is inconsistent with the structure that Congress enacted into law").

subsequently addressed the issue at hand and/or related matters.[40] Since 1984, Congress has substantively addressed the approval requirements and procedures for generic drugs on two occasions—in passing the Generic Drug Enforcement Act of 1992 ("GDEA")[41], and to a more limited extent, in passing Section 118 of the FDA Modernization Act of 1997 ("FDAMA").[42] Both times, Congress confirmed that only section 505(j) applications can be approved on the basis of FDA's prior findings of safety and effectiveness and an innovator's proprietary data.

The GDEA was passed to restore and ensure the integrity of the approval process for "abbreviated drug applications," which the GDEA defined as "an application submitted under section 505(j) or 507 for the approval of a drug that relies on the approved application for another drug with the same active ingredient to establish safety and efficacy."[43] The GDEA did not address section 505(b)(2) applications because they are not subject to the same types of abuses (i.e., fraud and other criminal behavior in connection with bioequivalence data for generic drugs) that Congress sought to address with respect to abbreviated applications that rely on an innovator's non-public proprietary data and relatively limited scientific inquiries. Because of these limited testing requirements, it was much easier for abbreviated applicants to manufacture fraudulent data and engage in criminal activities that undermined the validity of the approval process. Congress did not consider these abuses to be relevant to section 505(b)(2) applications because Congress expected these applications to be supported by independent full reports and/or published literature.

The legislative history of the GDEA also evidences that at the time of passage Congress equated "generic drug applications" with "abbreviated drug applications."[44] While Congress understood

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40/ See Id. at 1306 (a broad statute when passed "may have a range of plausible meanings," but subsequent acts can narrow those meanings "where the scope of the earlier statute is broad but the subsequent statutes more specifically address the topic at hand.").

41/ See Generic Drug Enforcement Act of 1997, Pub.L. No., 102-282, 106 Stat. 149 (1992); H.R. 102-272, 102nd Cong. 2d. Sess. 103.

42/ See Food and Drug Administration Modernization Act of 1997, Pub.L. No., 105-115, 111 Stat 2296, 2348 (1997).

43/ See 106 Stat. at 161 (emphasis added).

44/ See H.R. 102-272, 102nd Cong. 2d. Sess. 103 ("The bill would give the FDA authority to not accept or review abbreviated drug applications for generic drugs . . ."; "the term 'generic drug application' [refers to] an abbreviated drug application"). The House

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that section 505(b)(2) could be used to approve modifications of pioneer products, it did not consider section 505(b)(2) applications to constitute "generic drug applications." By omitting any discussion of section 505(b)(2) applications and/or the paper NDA policy in relation to "generic drug applications" or "abbreviated drug applications" in deliberating and passing the GDEA, Congress effectively ratified its historical position that section 505(b)(2) applications are simply a type of full NDA, and that FDA, therefore, cannot approve these applications in reliance on an innovator's proprietary data and FDA's prior findings of safety and effectiveness.[45/]

Moreover, in approving Section 118 of FDAMA, which requires FDA to issue guidance to describe when abbreviated study reports in lieu of full reports may be submitted with NDAs, Congress did not differentiate the impact of this provision on section 505(b)(1) and 505(b)(2) applications. Congress passed Section 118 to address problems associated with individual NDA reviewers having substantial discretion to impose on NDA sponsors either more detailed or less detailed submissions.[46/] Nothing in the statutory language or the legislative history, however, suggests that Congress, in passing Section 118, sought to permit less than full reports of investigations to support an NDA (a 505(b)(1) or 505(b)(2) application), or to permit FDA to rely on proprietary innovator data to approve NDAs (including section 505(b)(2) applications).[47/]

44/(...continued)
Report refers to the GDEA affecting the "generic approval process," "generic drug applications," or "generic drugs" in twelve separate instances. See id.

45/ See FDA v. Brown & Williamson Tobacco Corp., 120 S.Ct. at 1313; Bob Jones Univ. v. United States, 461 U.S. 574, 600-601 ("it is hardly conceivable that Congress [in passing a statute]. . . was not abundantly aware of what was going on.").

46/ See H.R. 105-310, 105th Cong. 1st. Sess. In practice, some reviewers require that every report of a clinical or preclinical study be submitted with individual case reports or other detailed back-up data, while others impose these requirements only for pivotal studies and permit data from certain studies to be submitted in a more abbreviated or summary form.

47/ FDA's guidance mandated by Section 118 confirms that all NDA applicants must continue to meet the full reports requirement, and that full study reports need to be submitted for all clinical and human pharmacology investigations that contribute to the evaluation of effectiveness for the proposed indication, or that otherwise support information included in labeling. See FDA, Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications (1999), at 2-3. The guidance also explains that for clinical efficacy studies for which an abbreviated

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4. Reliance on FDA's Prior Findings of Safety and Effectiveness in an Innovator's NDA to Approve a 505(b)(2) Application Constitutes an Unconstitutional Taking

FDA cannot properly authorize an applicant to use and/or rely on an innovator's safety and effectiveness data to approve a section 505(b)(2) application. For FDA to do so would constitute an unconstitutional taking of valuable proprietary data in violation of the Fifth Amendment of the United States Constitution. Under the Fifth Amendment, the government may not appropriate another's property without just compensation. In its 505(b)(2) Draft Guidance Document (in reliance on 21 C.F.R. § 314.54), however, FDA has stated that it will rely, without authorization, on an innovator's proprietary property to approve section 505(b)(2) applications. The Draft Guidance Document thus directly contradicts, and therefore violates, this constitutional protection.

The inherent property right in safety and effectiveness data that is submitted as part of an NDA has been historically recognized by the courts, Congress, and the Agency. The courts have denied discovery requests for information in drug marketing applications on the grounds that this information constitutes trade secrets,[48/] and have acknowledged that safety data is valuable

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47/(...continued)
report is appropriate, abbreviated reports must contain a full report of information related to safety and enough information to allow the reviewers to fully assess whether the efficacy results, if any, cast doubt on the effectiveness of the product for the proposed indication. Id. at 8.

48/ See Serono Laboratories v. Shalala, 35 F. Supp. 2d 1 (D.D.C. 1999). The Serono court denied a discovery request for certain information in a generic drug manufacturer's application on the ground that the information was a trade secret, recognizing the commercial value of data submitted to support approval of drug products. In support of this denial, the Serono court commented that "In a field as competitive and technical as the pharmaceutical industry, success or failure will turn in large measure on innovation and the members of the industry justifiably hoard their trade secrets as jealously as a miser hoards his gold . . . concerned companies may have to disgorge their trade secrets so that the agency can fulfill its responsibilities. They would resist doing so with all their power if doing so permitted their competitors instantaneous access to what they had so carefully guarded from them. The obvious public interest in inducing the drug companies' utmost cooperation with the government's investigation of the new drug would suffer." Id. at 2. The Serono court also recognized that a protective order cannot relieve FDA from a statutory obligation, and the Agency must keep trade secrets confidential and cannot abrogate its statutory obligation. Id. at 3. See also, Zeneca Inc.
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commercial property.[49/] Congress also has acknowledged the inherent property rights in such information in several statutes, including the Trade Secrets Act, 18 U.S.C. § 1905 and the FFDCA at 21 U.S.C. § 331(j). Likewise, FDA has recognized the inherent and protected rights

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48/(...continued)
v. Shalala, Food, Drug, Cosm. L. Rep. (CCH) ¶ 38581 (D. Md., 1999) (denying in part a discovery motion seeking production from FDA of the administrative record underlying approval of an abbreviated application on the basis that some of the information was protected and, thus, not eligible for disclosure to a challenging party because it is a trade secret, and noting the party's interest in the trade secret); Id. at 38590 ("In a field as competitive and technical as the pharmaceutical industry, success or failure will turn in large measure on innovation and the members of the industry justifiably hoard their trade secrets as jealously as a miser holds his gold."); A.L. Labs Inc. v. Philips Roxane, Inc., 803 F.2d 378, 383-85 (8th Cir. 1986) (upholding punitive damages and injunction against manufacturer because manufacturer had relied on an innovator's data without authorization to obtain approval of an animal drug application, thus recognizing the property right in the data.).

49/ See Anderson v. Department of Health and Human Services, 907 F.2d 936 (10th Cir. 1990) (documents under the descriptive category of "manufacturing and processing information, including formulations, chemistry and quality assurance procedures" are within the definition of trade secrets; the majority of information in an IND, NDA, and IDE are likely trade secrets); Tri-Bio Laboratories, Inc. v. United States, 836 F.2d 135 (3d Cir. 1987), cert denied, 484 U.S. 818 (1988) (recognizing that approval of a generic animal drug based on an innovator's NADA is a taking of the innovator's trade secret rights in the innovator's data; Public Citizen Health Research Group, 704 F.2 1280, 1290 (D.C. Cir. 1983) (because documentation of the health and safety experience of drug/device products is instrumental in gaining marketing approval for such products, manufacturers have a commercial interest in such health and safety information); Public Citizen Health Research Group, 997 F. Supp. 56, 62 (D.D.C. 1998) (safety and effectiveness information about a manufacturer's drug may be of great assistance to competing drug manufacturers—the release of the types of data and information in NDA and IND files constitute "substantial commercial harm"); Upjohn Manufacturing Company v. Schweiker, 520 F. Supp. 58, 63 (W.D. Mich. 1981) (finding Upjohn had standing on the basis of its claim that trade secret data and information contained in its NDA would be publicly disclosed because of FDA's approval of a duplicate NDA).

in such information,[50/] and has established regulations to protect trade secret and confidential information in drug marketing applications.[51/]

50/ See e.g., 21 C.F.R. § 314.50(g) (FDA recognition of the inherent property right of clinical and other NDA data as trade secrets and, thus, recognizing it as protected from public dissemination/disclosure by requiring an application that contains "a reference to information submitted to the agency by a person other than the applicant . . . to contain a written statement that authorizes the reference and that is signed by the person who submitted the information"); see also 39 Fed. Reg. 44612 (Dec. 24, 1974) (drug manufacturers maintain a property interest in the sensitive information which is supplied to the Agency); 39 Fed. Reg. 44635 (Dec. 24, 1974) (refusing to approve generic copies of drugs first approved after 1962 without submission of new safety and effectiveness data for those generic copies prior to enactment of Hatch-Waxman Amendments on the grounds that such information was trade secret and protected from public dissemination), *accord* 42 Fed. Reg. 3094, 3106 (Jan. 14, 1977); 39 Fed. Reg. 44635 (Dec. 24, 1974) (recognizing the trade secret status of safety and effectiveness data in an NDA as a property right and the right to charge a competitor for reference to that data if the competitor wishes to obtain approval of a generic copy of the product); 45 Fed. Reg. 82,052 (Dec. 12, 1980) (quoting and defending Finkel Memorandum regarding paper NDA policy and stating that a "present interpretation of the law is that no data in an NDA can be utilized to support another NDA without express permission of the original NDA holder."); Id. at 82,056 (stating that "data in the pioneer NDA cannot now be used to support an NDA for a generic version of the pioneer product . . . [D]ata in the file for the pioneer NDA could be used to deny approval of the subsequent product, but not to support such approval."); 46 Fed. Reg. 27396 (May 10, 1981) ("the Finkel Memorandum") (stating that "no data in an NDA can be utilized to support another NDA without express permission of the original NDA holder" and thus, stating that for "duplicate NDAs for already approved post [19]62 drugs, the Agency will accept published reports as the main supporting documentation for safety and effectiveness"); Statement by FDA Chief Counsel, Drug Price Competition and Patent Term Restoration Act of 1984: Hearing on S. 2748 before Sen. Comm. On Labor and Human Resources, 98th Cong., 2d Sess. 262 June 28, 1984) (stating FDA's understanding that release of trade secret or confidential would not be authorized if the data retained value in obtaining approval in foreign countries or for other purposes).

51/ See 21 C.F.R. § 20.21 (trade secrets and commercial information are not available for public disclosure; 21 C.F.R. § 20.61 (a trade secret "may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end

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The standards for and analysis of unconstitutional takings have evolved considerably over the past quarter-century, with increasing protection afforded against governmental takings. The Supreme Court has stressed that Fifth Amendment takings analyses are "essentially ad hoc factual inquiries."[52/] The Court has identified three principal factors of significance in each factual context: the economic impact of the regulation, the character of the governmental action, and "particularly, the extent to which the regulation has interfered with distinct investment-backed expectations.[53/]" In its decisions over the years since Penn Central, the Supreme Court has made clear the applicability of Fifth Amendment analysis to intellectual property[54/] and, most recently, that a regulation that deprives the owner of a substantial part, but not essentially all of the economic use or value of the property, nonetheless constitutes a partial taking, and as such is unconstitutional and compensable.[55/] The circuit courts, following this expansive trend in the Supreme Court, have also found regulatory takings unconstitutional under the Fifth Amendment.[56/]

The FDA's Draft Guidance Document raises serious constitutional concerns under the analysis that has evolved in recent takings jurisprudence. First, it is clear that the data which would be referenced has been treated as confidential, commercially-valuable property of the innovator companies. Second, an extraordinary level of expenditures are made by innovator companies in

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product of either innovation or substantial effort"); 21 C.F.R. 20.61(b) (commercial information that is privileged or confidential is, "valuable data or information which is used in one's business and is of a type customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public by the person to whom it belongs"); 21 C.F.R. § 314.430(e)(3) (a protocol for a test or study, contained in an NDA, abbreviated application, supplemental NDA, IND, or drug master file, cannot be disclosed if it is a trade secret or confidential commercial information); 21 C.F.R. § 314.430(g)(1) ("Manufacturing methods or processes, including quality control procedures," are not available for public disclosure unless they have been previously disclosed to the public or relate to a product or ingredient that has been abandoned, and they do not represent a trade secret or confidential commercial information).

52/ Penn Central Transportation Co. v. New York City, 438 U.S. 104, 124 (1978).

53/ Id.

54/ Ruckelshaus v. Monsanto Co., 467 U.S. 986 (1984).

55/ Lucas v. South Carolina Coastal Council, 505 U.S. 1003 (1992).

56/ See, e.g., Florida Rock Industries, Inc. v. United States, 18 F. 3d 1560 (Fed. Cir. 1994).

order to obtain NDA approval. As such, the Draft Guidance Document would interfere with investment-backed expectations to a degree unprecedented and unsurpassed by any other area of government-required expenditures, with the possible exception of electric power generation and transmission facilities, whose significant investment-backed expectations vis-a-vis applicable regulatory requirements have been examined by the courts. Third, NDA sponsors are and were not aware that their proprietary data had been or would be disclosed or used internally by FDA to support the approval of section 505(b)(2) applications. Consequently, under prevailing judicial analysis of regulatory takings, in the factual context in which the Draft Guidance Document would operate, the FDA's proposed approach would be an unconstitutional taking in violation of the Fifth Amendment.

As the Agency is aware, the Draft Guidance Document would result in the FDA approving drug products that can substantially deviate from the innovator products, in reliance on proprietary innovator data. While there is a recognized legitimate government interest in facilitating the approval of near-identical copies of innovator drugs that no longer have patent or other forms of protection, the same cannot be said of copies that can substantially deviate from innovator products, which non-identical copies may themselves be subject to some type of market exclusivity.

Further, the scope of the financial obligation required of innovator companies by FDA to obtain NDA approval presents legitimate expectations of recovery of investments of virtually unsurpassed magnitude. Recent estimates of the costs of obtaining NDA approval for one drug are nearly one-half billion dollars. Moreover, even after initial NDA approval, innovator companies must continue to invest significant amounts to meet FDA regulations and, often, on research to support supplements for additional indications or to support other enhancements to their products (e.g., new dosage forms) that become part of their NDAs.[57/]

In analyses of whether a regulatory taking is unconstitutional, particularly relevant is the reasonableness of the investment-backed expectations of the regulated entities. Where the government has communicated to regulated entities that it will keep submitted data confidential and exclusive, these regulated entities have a reasonable investment-backed expectation that their trade secret data will not be used by the government to the advantage of others.[58/] "With respect to a trade secret, the right to exclude others is central to the very definition of the property

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57/ Again by contrast, the pesticide registration process expense considered in Monsanto involves submission of data costing substantially less than $20 million dollars.

58/ Monsanto, 467 U.S. at 1011.

interest."[59/] Once the data that constitutes the trade secret is disclosed to others or others are allowed to benefit from those data, the holder of the trade secret has lost its property interest.[60/]

There is simply no proper basis, under the relevant statutory provisions and legislative pronouncements concerning section 505(b)(2) or the broader regulatory scheme for approving drugs, that allows the Agency to conclude that NDA sponsors were "on notice" that their proprietary data would be disclosed or used internally by FDA to support the approval of section 505(b)(2) applications.[61/] Nothing in the FFDCA or its legislative history suggests that Congress intended to abrogate the protection afforded trade secret information, such as safety and effectiveness data submitted as part of an NDA. This is particularly so in relation to section 505(b)(2), which does not state or suggest that FDA will use data in innovator NDAs to support the approval of section 505(b)(2) applications. While 505(b)(2) states that applicants may rely upon investigations for which they have not "obtained a right of reference," it does not state or suggest that the investigations to be appropriated are disposable or that applicants could abrogate the existing protections FDA established to protect trade secret and confidential information in drug marketing applications.[62/] In contrast, section 505(j) plainly requires FDA to reference full NDAs to approve abbreviated applications. Abbreviated application sponsors must demonstrate, in part, that (i) the active ingredient of the generic copy is the "same as" that of the listed drug, and (ii) the generic copy is bioequivalent to the listed drug. These and other comparisons and determinations mandated by section 505(j) necessarily require reference to, and reliance, on information in the full NDAs of the listed drugs.

In fact, the situation with section 505(b) applications is precisely the opposite. The FFDCA, and FDA's regulations and other pronouncements concerning protecting trade secrets and confidential information in drug marketing applications, have and continue to create the clear

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59/ Id.; see also Kaiser Aetna, 444 U.S. at 176 (The right to exclude others is "one of the most essential sticks in the bundle of rights that are commonly characterized as property.").

60/ Id.

61/ Regardless of whether a property holder had notice of an earlier-enacted state restriction, the holder is not barred from claiming a taking based on the restriction. See Palazzolo v. Rhode Island, 2001 U.S. LEXIS 4910, *40 (2001) ("A blanket rule that purchasers with notice have no compensation right when a claim becomes ripe is too blunt an instrument to accord with the duty to compensate for what is taken.").

62/ See supra note 50.

expectation by NDA applicants of privacy and exclusivity for such information.[63] Of particular significance is the prohibition at 21 U.S.C. § 333(j) against "the using by any person to his own advantage, or revealing, other than to the Secretary or officers or employees of the Department ... any information acquired under authority of section ... 505 ... concerning any method or process which as a trade secret is entitled to protection."

In determining whether a regulated entity was "on notice" that data submitted to the government might be used for a given purpose, the courts have found particularly relevant to a determination of adequacy of notice the existence of closely-situated statutory provisions protecting such data,[64] and have held less authoritative forms of notice to be insufficient.[65] In the case of the FFDCA, the foregoing explicit protection of trade secrets is directly relevant to and references 21 U.S.C. 355, the statutory provision that sets forth the approval process and requirements for section 505(b)(2) applications; section 505(b)(2) itself does not affirmatively permit the use of trade secret data in pioneer NDAs to support the approval of such applications.

While section 505(l)(5) of the FFDCA permits the disclosure of safety and effectiveness data in a section 505(b) application "upon the effective date [or potential effective date] of the approval of the first application under subsection (j) which refers to such drug," this section cannot reasonably be interpreted to invalidate the trade secret status of an innovator's safety and effectiveness data. Congress stated that it did not intend for section 505(l) to abrogate the recognition and protection of rights in trade secret information, including safety and effectiveness data submitted as part of an NDA.[66] Further, a party seeking access to such data is

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63/ See Monsanto, 467 U.S. at 1010-1011.

64/ Id. at 1023; see also Tri-Bio Laboratories, Inc. v. U.S., 836 F.2d 135, 139 (3rd Cir. 1987). ("Because the FFDCA indicates no evidence of congressional intent contemplating payment for the "property interest in test data to support their new drug applications". There is "no realistic alternative to the policy" that this proprietary interest not be appropriated without just compensation.").

65/ See Nollan et ux v. California Coastal Commission, 483 U.S. 825, 833 (1987) (holding that a mere government announcement that an application for or granting of a permit will require the yielding of a property interest cannot be regarded as establishing a voluntary "exchange"); Levesque v. Sheehan, 821 F.Supp 779, 789 (D.Me. 1993) ("If an administrative agency acts contrary to the expectations engendered by statute, that is an indication that the agency may have taken the property." (emphasis added)).

66/ See H.R. Rep. 9-857, Part 1, 98th Congress, 2d Sess. 36, reprinted in 1984 U.S. Code.

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required to file a request under 21 C.F.R. § 20.40 which permits the NDA holder to assert its property rights under 21 C.F.R. § 20.45, or alternatively to seek relief in court. And, FDA's NDA regulations make apparent that the 505(l) disclosure requirement is subject to trade secret limitations.[67/]

Innovator drug companies thus reasonably expected that their proprietary data would remain confidential.[68/] Industry behavior, by innovator pharmaceutical companies, biotechnology companies, and the investment community, before and after FDA's promulgation of 21 C.F.R. § 314.54, establishes that this expectation remained unchanged. Innovator drug companies and biotechnology companies have continued to fund the increased investments required for significant clinical trials of potential drug candidates; the investment community has continued to provide external funds and make valuations of companies on the basis of such data being confidential. None of these industry participants thus has acted from an economic investment standpoint in any manner that recognizes FDA has abrogated the longstanding statutory and regulatory protections against the disclosure or use of trade secret information to the advantage of others.

The fundamental purpose of the protection afforded to the innovator drug company's proprietary data is to induce the company to make the extremely large investments required by FDA to support NDA approval.[69/] While there is clear statutory authority for FDA to rely on such data to support the approval of abbreviated applications, the same is not true for section 505(b)(2) applications. FDA implies in its Draft Guidance Document that the same policies are advanced

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effectiveness data and information be released under this section if an abbreviated application] 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."); Statement by FDA Chief Counsel, Drug Price Competition and Patent Term Restoration Act of 1984: Hearing on S. 2748 before Sen. Comm. On Labor and Human Resources, 98th Cong., 2d Sess. 262 June 28, 1984) (stating FDA's understanding that release would not be authorized if the data retained value in obtaining approval in foreign countries or for other purposes).

67/ See supra note 50.

68/ See Monsanto, 467 U.S. at 1014 n.17 ("the relevant consideration for our purposes is the nature of the expectations of the submitter at the time the data were submitted.").

69/ See generally J. Gregory Sidak & Daniel F. Spulber, Deregulatory Takings and the Regulatory Contract 102 (1998).

by its reliance on innovator data to approve abbreviated applications and section 505(b)(2) applications. They are not. These are distinct approval mechanisms with distinctly different purposes and requirements. Finally, in view of the magnitude of the financial investment that must be made by innovator companies, it is not credible that any clear notice has been provided that their data could be used to support approval of competitive products. Any such policy by the Agency would simply hinder investment in pioneer drug development and limit innovation.

Because neither the courts, Congress, nor the FFDCA permit FDA to rely on the proprietary findings of safety and effectiveness of an innovator's drug product without authorization to approve a section 505(b)(2) application, FDA may not implement the Draft Guidance Document or 21 C.F.R. § 314.54 to expropriate the commercial value of such safety and effectiveness data. FDA's proposed unauthorized reliance on innovators' proprietary safety and effectiveness data to approve section 505(b)(2) applications thus would clearly be unconstitutional in violation of the Fifth Amendment.

B. FDA Is Not Authorized to Assign "A" Therapeutic Equivalence Evaluation Codes to Drug Products Approved Pursuant to Section 505(b)(2), and Must Modify its Equivalency Rating Practices Accordingly

Pursuant to the principles of statutory construction described above, it is plain that Congress did not intend FDA to assign therapeutic equivalence ratings, and in particular "A" therapeutic equivalence codes, to section 505(b) applications.

FDA's prior Director of Pharmaceutical Science, Dr. Roger Williams, stated—while he was at FDA—that the Agency is "postulating a path for certain molecules that [get] an AB rating in the Orange Book, that does not come in under the [abbreviated application] route, it comes under the (b)(2) route," and that in order to obtain this rating a generic applicant would need to establish "that the molecules are pharmaceutically equivalent [but] not identical."[70/] Further, FDA has assigned AB therapeutic equivalence ratings to drugs approved under section 505(b)(2). Notwithstanding these statements and practices, however, any decision by FDA to assign an "A" therapeutic equivalence code (i.e., AB, AA, AN, AO, or AP ratings) to drugs approved under section 505(b)(2) is inconsistent with the statute and legislative history of the FFDCA and FDA's policy development and definition of therapeutic equivalence.

70/ See FDA Generic Recombinant Protein Process Will Use "Paper" NDAs, Health News Daily, March 30, 1999, at 1 (Attachment C); Generic Recombinant Protein "Paper" NDA Approval Process Outlined by FDA, F-D-C ("The Pink Sheet"), April 5, 1999, at 32 (Attachment D). Dr. Williams has since left the Agency to become the Chief Executive Officer of U.S. Pharmacopeia.

FDA determines drug products to be therapeutically equivalent if they meet the following criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity[71]; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable in vitro standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.[72] As set forth below, dating back to the implementation of this test and policy, and consistent with Congress' structure for drug approvals, only products approved pursuant to abbreviated applications can be considered therapeutically equivalent to listed drugs.

The proposed and final rules regarding therapeutic equivalence determinations explain that FDA developed this policy to address equivalence issues for generic drugs approved pursuant to abbreviated applications.[73] The rules do not state or otherwise suggest that products approved pursuant to paper NDAs—as previously identified under the Finkel Memorandum—or section 505(b)(2) applications can be determined to be therapeutically equivalent to listed drugs. Therefore, in view of FDA's original intent, and absent contrary legislative history or language, drugs approved under section 505(b)(2) cannot be deemed therapeutically equivalent to listed drugs.

Under the Hatch-Waxman Amendments, the bioequivalence requirement, which is fundamental to making therapeutic equivalence determinations, is exclusively required for section 505(j)

71/ See 21 C.F.R. § 320.1(c).

72/ See FDA, Approved Drug Products with Therapeutic Equivalence Evaluations: Preface (2000) ("Orange Book").

73/ See e.g., 44 Fed. Reg. at 2941, 2942, 2943 (explaining FDA's impetus and context for addressing bioequivalence issues was in response to ANDA submissions); 45 Fed. Reg. at 72589-90 (explaining FDA's impetus and context for addressing bioequivalence issues was in response to ANDA submissions); see also FDA, Guidance for Industry: Placing the Therapeutic Equivalence Code on Prescription Drug Labels and Labeling (1998) (explaining FDA's basis for developing its therapeutic equivalence policy was in relation to ANDAs).

applications, based on a presumption of sameness.[74/] The language and legislative history of section 505(b)(2) do not discuss or reference any relationship between or consequence of the bioequivalence requirement, or the therapeutic equivalence policy.

Congress addressed in detail how the patent certification requirements and market exclusivity protections apply to both section 505(j) and 505(b)(2) applications.[75/] Given this deliberate parallelism in construction of the Act, had Congress intended the bioequivalence requirement, and in turn the notion of therapeutic equivalence, also to apply to section 505(b)(2) applications, it would have addressed these requirements in the Act similarly or otherwise revealed its intent in the legislative history.

Consistent with the legislative history and the Hatch-Waxman Amendments to the FFDCA, FDA has codified in its regulations and in the preface to the Orange Book that the bioequivalence requirement, and therefore the therapeutic equivalence policy, pertains to abbreviated applications. For example, FDA's regulations state abbreviated applications must include evidence of bioequivalence, while NDAs, including section 505(b)(2) applications, need to include evidence of bioavailability.[76/] Likewise, the preface to the Orange Book states a test product and a reference listed drug shall be considered "bioequivalent" if the test product meets the requirements of "[s]ection 505(j)(7)(B) of the Act."[77/]

In discussing the statistical criteria for bioequivalence, the preface to the Orange Book explains that the Hatch-Waxman Amendments require manufacturers of generic drugs to submit data demonstrating that their drug product is bioequivalent to the pioneer (innovator) drug product.[78/] The Orange Book also states "[a] reference listed drug (21 C.F.R. 314.94(a)(3)) means the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of

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74/ See 21 U.S.C. §§ 355(j)(2)(A)(iv), (j)(8); FDA, Approved Drug Products with Therapeutic Equivalence Evaluations; Preface (2000).

75/ See 21 U.S.C. §§ 355(j)(2)(A)(vii), (j)(2)(A)(vii), (j)(2)(B), (j)(5)(D), (b)(2)(A), (b)(2)(B), (b)(3), (c)(3).

76/ See 21 C.F.R. §§ 320.21(a), (b).

77/ See FDA, Approved Drug Products with Therapeutic Equivalence Evaluations; Preface (2000).

78/ See id.

its ANDA."[79] Therefore, FDA has defined the concept of a reference listed drug, which is fundamental to bioequivalence determinations, and in turn therapeutic equivalence determinations, specifically in the context of the approval of abbreviated applications under section 505(j), that rely on prior findings of safety and efficacy.[80]

A policy or regulation to provide "A" equivalence ratings to products approved pursuant to section 505(b)(2), is unsupportable by the plain meaning of the Act, contrary to legislative history, and inconsistent with a policy that was developed pursuant to public notice and comment procedures. FDA cannot therefore depart from its longstanding policy that positive therapeutic equivalence determinations can only be made for drug products approved pursuant to abbreviated applications under 505(j) and not for 505(b)(2) applications and, therefore, cannot assign "A" equivalence ratings to drug products approved under section 505(b)(2).

Moreover, even if FDA had the statutory authority to do so, the Agency would have to follow appropriate rulemaking procedures to modify its existing therapeutic equivalence policy in the Orange Book.[81] The above test for therapeutic equivalence was proposed and implemented

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79/ See id. (emphasis added).

80/ FDA's actions with respect to the therapeutic equivalence rating of Repronex IM confirm this view, and exemplify the practical and legal significance of the Agency's assignment of therapeutic equivalence ratings. Ferring originally received marketing approval for Repronex IM (intramuscular) via an ANDA, referencing Serono's Pergonal. As part of its subsequent section 505(b)(2) application for Repronex—for both subcutaneous and intramuscular routes of administration—Ferring sought to reference in the Repronex IM labeling studies that it had conducted but that were not cited in the Pergonal labeling. FDA determined that if Repronex IM was to be approved based on the studies submitted in the section 505(b)(2) application—thereby permitting these studies to be referenced in product labeling—it could no longer have an "AB" rating vis-a-vis Pergonal because it would no longer be the "same as" Pergonal. As evidenced by these facts, only products approved via an ANDA can be assigned "A" therapeutic equivalence ratings because only these products have been determined to be the "same as" innovator products. See Group Leader Memorandum to the Repronex Original NDA, Shelley R. Slaughter, M.D., Ph.D. (Aug. 13, 1999).

81/ The courts have recognized the legal status of the Orange Book. See e.g., Zeneca Inc. v. Shalala, 1999 WL 728104, *11 (D.Md. 1999) (while the court was not required to address whether Orange Book ratings are reviewable, it stated in footnote 13 that "given the increased significance attributed to an Orange Book listing . . . it would appear that an

(continued...)

through the public notice and comment rulemaking process.[82/] FDA's rulemaking practice requires the Agency to re-propose the rule if it intends to make substantive changes to it. Accordingly, to eliminate confusion in the pharmaceutical industry and to prevent future illegal and improper actions by FDA, FDA must clarify in the preface to the Orange Book that "A" equivalence ratings cannot be assigned to drug products approved pursuant to section 505(b)(2).

Moreover, there are significant public health policy reasons why FDA should not assign "A" therapeutic equivalence codes to drugs approved under section 505(b)(2). Government and private-sector payors generally presume that drugs with "A" therapeutic equivalence ratings are the "same as" and therefore interchangeable with the innovator products to which they refer. The practical effect is that pharmacists are often permitted under state law to switch drugs with "A" therapeutic equivalence ratings for their innovator counterparts without physician oversight. Because drugs approved under section 505(b)(2) are not required to be the "same as" innovator drugs, they properly should not be considered interchangeable with innovator drugs. Potentially serious consequences could occur if, without physician oversight, pharmacists are able to switch innovator drug products with non-equivalent alternatives.

C. Conclusion

Based on the foregoing, FDA cannot approve section 505(b)(2) applications in reliance on an innovator's non-public proprietary information, or assign "A" therapeutic equivalence evaluation codes to drugs approved under section 505(b)(2). In turn, the Agency must: (1) amend its October 1999 505(b)(2) Draft Guidance Document and its regulations at 21 C.F.R. § 314.54 accordingly; (2) not rely on or otherwise use an innovator's non-public proprietary information to approve section 505(b)(2) applications; and (3) not assign "A" therapeutic equivalence evaluation codes to drugs approved under section 505(b)(2), and modify its equivalency rating practices accordingly.

IV. Environmental Impact

The actions requested in this Petition are not within any of the categories for which an environmental assessment is required pursuant to 21 C.F. R. § 25.22. Additionally, the actions

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81/(...continued)
Orange Book designation constitutes a final agency action.").

82/ See 44 Fed. Reg. 2932 (Jan. 12, 1979) (proposed rules for therapeutic equivalence evaluation policy); 45 Fed. Reg. 72582 (Oct. 31, 1980) (final rules for therapeutic equivalence evaluation policy).

requested in this petition are exempt from the requirement of an environmental assessment pursuant to 21 C.F.R. § 25.24(a)(11).

V. Economic Impact

Information on the economic impact of this proposal will be submitted if requested by the Commissioner.

VI. Certification

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

Respectfully submitted,

Kathleen M. Sanzo

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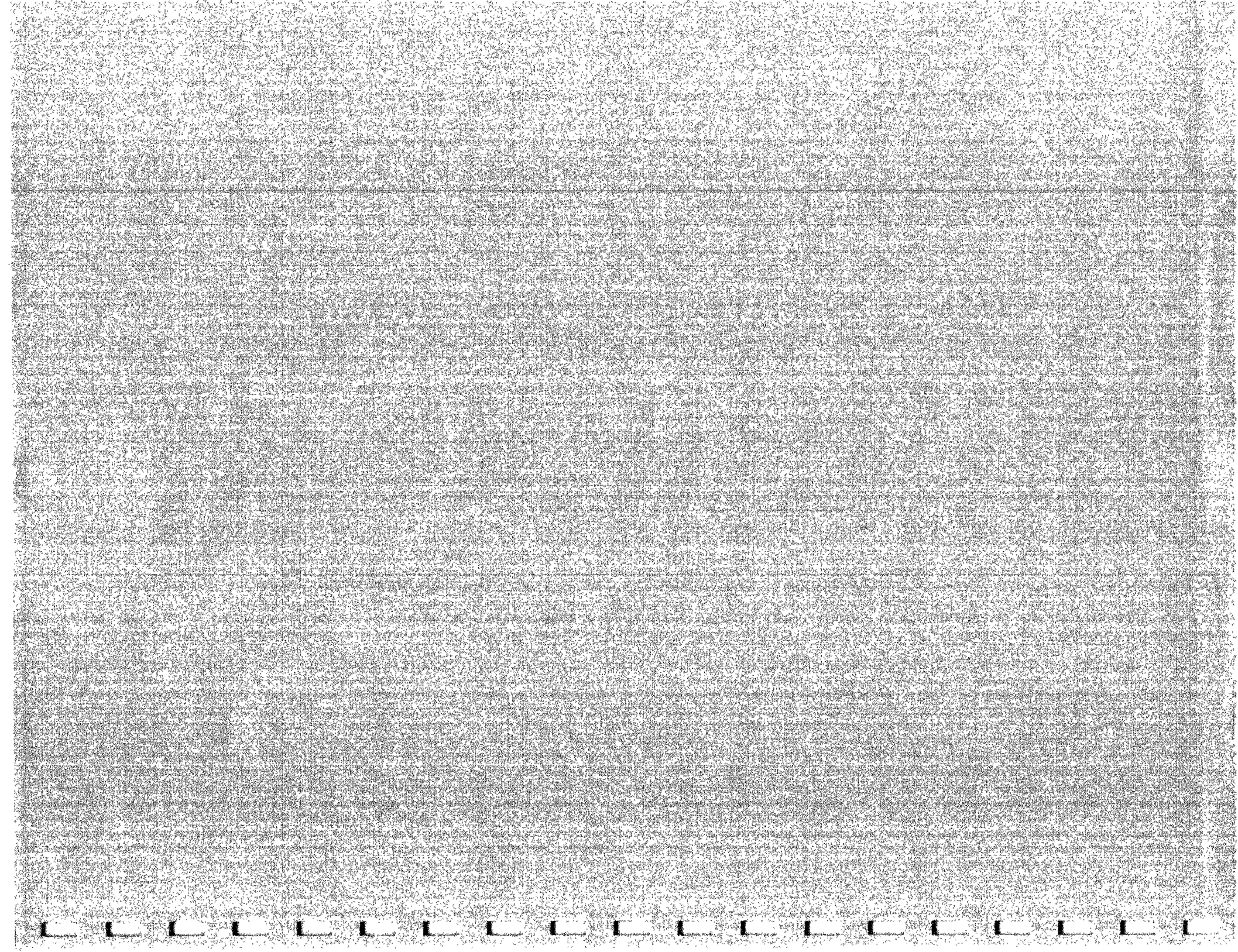
Attachments



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December 17, 2001 3054 '01 DEC 18 P4:48

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

Re: *FDA Docket No. 01P-0323; Comments of Amgen Inc.*

Dear Sir or Madam:

Amgen Inc. ("Amgen") submits the following comments under 21 CFR 10.30(d) in support of the citizen petition submitted jointly by Pharmacia Corp. and Pfizer Inc. on July 27, 2001 (the "Joint Petition").

INTRODUCTION

The Joint Petition requests the Commissioner of Food and Drugs to recognize immediately that the Food and Drug Administration ("FDA") cannot rely upon confidential information submitted in support of one sponsor's new drug application ("NDA") to approve another sponsor's NDA. Among other things, the Joint Petition requests that the Commissioner amend the draft document titled *Guidance for Industry: Applications Covered by Section 505(b)(2)* (Oct. 1999) (the "*Draft Guidance*") to reflect this core legal principle. In addition, the agency must refrain from approving NDAs submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the "FDCA") that rely on proprietary information submitted by another sponsor. Finally, the Joint Petition requests that the agency refrain from assigning "A" level therapeutic equivalence ratings to products approved under 505(b)(2) applications.

Amgen is the world's largest independent biotechnology company and stands as a world leader in molecular and cellular biology, target discovery, and therapeutic delivery. Amgen markets two of the most successful and renowned biotechnology products, EPOGEN® (epoetin alfa) and NEUPOGEN® (filgrastim), along with the recently approved products, Aranesp® (darbepoetin alfa) and Kineret® (anakinra). In addition, Amgen has a number of drug and biological products under development and several currently under FDA review.

01P-0323 C2

Amgen supports the arguments in the Joint Petition in all respects and believes strongly that the proposed interpretation of section 505(b)(2) is in excess of the agency's legal authority. In particular,

- FDA cannot incorporate by reference, nor permit an applicant to incorporate by reference, information in another sponsor's application without obtaining legal authorization from the first applicant to rely on the data, or without statutory authorization to do so (Joint Pet. at 3, 10-13).

- Outside of section 505(j) of the FDCA, the agency has no statutory authority to rely in whole or in part on a pioneer manufacturer's proprietary data (Joint Pet. at 13).

- Outside of section 505(j), the agency has no statutory authority to rely on "prior findings of safety and effectiveness" based in whole or in part on a pioneer manufacturer's data (Joint Pet. at 14).

- FDA's proposed use of section 505(b)(2) would represent an uncompensated taking of property (Joint Pet. at 17-25).

In addition to these points, Amgen's focus in submitting comments is on the proposed use of section 505(b)(2) for products that will be marketed as "pharmaceutical equivalents to" or "duplicates of" complex drug substances, including recombinant drug products. Specifically, the *Draft Guidance* states that section 505(b)(2) may be used for the review and approval of drug products with naturally derived or recombinant ingredients "where clinical investigations are necessary to show that the active ingredient is *the same as* an active ingredient in a listed drug." *Draft Guidance* at 5 (emphasis added). In various contexts, present and former FDA officials have suggested that such products, approved under section 505(b)(2), would also carry "A" level therapeutic equivalence ratings.[1/]

1/ *See* Tab 1, Presentation of Yuan-Yuan Chiu (Director, FDA Office of New Drug Chemistry) at the National Association of Pharmaceutical Manufacturers' Bulk Drug Program (Mar. 20, 2001) titled "Biotechnology-Derived Drug Substances for AB-Rated Drug Products – A CDER Perspective" (arguing that section 505(b)(2) is a feasible pathway for approval of multi-source biotech protein products that could be interchangeable with a listed drug); Tab 2, Remarks of Roger Williams, U.S. Pharmacopoeia, reported in *FDA Week* (Mar. 23, 2001) (stating that 505(b)(2) was meant to address interchangeability of recombinant proteins); Tab 3, "Generic Recombinant Protein 'Paper' NDA Approval Process Outlined by FDA," *F-D-C Reports* (April

For the reasons stated in the Joint Petition and discussed below, we believe this proposed use of section 505(b)(2) is ill considered and unlawful. The idea of a "short-form" or "hybrid" application for the marketing of "generic" or "duplicate" recombinant products not only threatens the proprietary rights of pioneer sponsors, it also poses a direct threat to patient health and safety. Consequently, Amgen is compelled to file these comments.

COMMENTS

Comment 1: FDA cannot use section 505(b)(2) as a pathway for products that will be marketed as "A-rated" duplicates.

As applied to naturally occurring and recombinant drug products,[2/] the *Draft Guidance* violates the basic structure of the FDCA. FDA's proposed interpretation would, for all intents and purposes, allow the agency to turn "failed generics" under section 505(j) into "passing generics" under section 505(b)(2).[3/] The law cannot be bent and twisted in this way.

Section 505(b) of the FDCA establishes the requirements for the submission of NDAs. Among other things, section 505(b)(1) provides that an NDA must contain "*full reports of investigations* which have been made to show whether or not such drug is safe for use and . . . effective in use" (emphasis added). Section 505(b)(2) incorporates all of the requirements of

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[Footnote continued]

5, 1999) at 32 ("'We are postulating a path for a recombinant molecule that gets an AB rating in the Orange Book, that does not come in the "(j)" route, it comes in the "(b)(2)" route,' [Roger] Williams [FDA Director of Pharmaceutical Science] said.").

2/ Most biological products are marketed under section 351 of the Public Health Service Act (the "PHS Act") and thus are not eligible for approval under section 505(b)(2) of the FDCA. Consequently, such products would not be subject to the *Draft Guidance*. However, for reasons that are largely historical, several categories of products with biological origins have been approved under section 505 of the FDCA and are regulated solely as new drugs (*e.g.*, insulin and human growth hormone).

3/ We note and agree with the conclusion that recombinant drug products cannot be approved under section 505(j) because such products require the submission and review of independent clinical data. *See Draft Guidance* at 4 and references cited in footnote 1, above. Any other approach would necessarily put patients at risk.

505(b)(1), with one adjustment: 505(b)(2) allows the applicant to submit investigations that were conducted by another person and for which the applicant lacks a "right of reference." All other data requirements described in 505(b)(1) remain the same.

At the center of the *Draft Guidance* is the agency's argument that a 505(b)(2) applicant may rely on "prior findings of safety and effectiveness" in place of submitting "full reports of investigations." *Draft Guidance* at 7-8. According to the *Guidance*, an applicant under section 505(b)(2) may rely on prior findings for a pioneer product *to the same extent* that an applicant under section 505(j) may rely on such findings. *Id.* at 2-3.4/

This interpretation, without more, would render sections 505(b)(2) and 505(j) redundant. To guard against this problem, FDA makes clear that a 505(b)(2) application must incorporate *a significant change to the pioneer product*. On at least five occasions, the *Draft Guidance* states that the proposed product *cannot be or purport to be a duplicate* of the approved product. *Id.* at 2, 3, 4, 6, 8 ("Section 505(b)(2) permits approval of applications *other than those for duplicate products* . . . ." *Id.* at 2.). FDA's related regulation, 21 CFR 314.54, also includes this important qualifier. Otherwise, an applicant who cannot meet the standards set forth in section 505(j) could simply "end run" the statute by proceeding under section 505(b)(2). *See also* 21 CFR 314.101(d)(9).

In this light, the proposed use of section 505(b)(2) to demonstrate the "sameness" of recombinant drug products, is in error. Under FDA's proposed approach, a 505(b)(2) applicant would be permitted to rely on prior findings of safety and effectiveness as if the sponsor were proceeding under section 505(j). In addition, the 505(b)(2) applicant would be permitted to submit clinical studies in support of the application, studies which the applicant could *not* submit under section 505(j). At the end of the process, the applicant would be able to market its product as a "duplicate to" or as "interchangeable with" an approved pioneer. The 505(b)(2) product would be

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4/ Section 505(j) is intended for two categories of products: (1) those that will be marketed as duplicates of pioneer products (*i.e.*, "generic drugs" or "pharmaceutical equivalents"); and (2) those that include certain minor differences for which no clinical data is needed to support the difference (*i.e.*, "suitability petition products" or "pharmaceutical alternatives"). That is, section 505(j) is intended for products that are "the same as" an already-approved product.

marketed as if it had been submitted and approved under 505(j) when, in fact, the product cannot satisfy the legal requirements of section 505(j).[5/]

As applied to recombinant drug products, the agency's interpretation effectively reads section 505(j) out of the FDCA, in favor of the agency's own vision of a much more flexible "generic process" under section 505(b)(2). The agency would, of course, be legislating rather than merely interpreting, were it to embark down this path. FDA cannot through "interpretation" or "policy" rewrite the carefully structured requirements under 505(j) for the marketing of generic drug products.

Amgen urges the agency in response to the Joint Petition to strike from the *Draft Guidance* the proposed use of 505(b)(2) to demonstrate the "sameness" of recombinant products, where such products could be marketed as duplicates of approved pioneer drugs. *See Draft Guidance* at 5.

Comment 2: The proposed use of section 505(b)(2) cannot be scientifically sustained at this time.

An essential element of the *Draft Guidance* is the concept of "bridging" from one application to another. According to the *Draft Guidance*:

> Complete studies of safety and effectiveness may not be necessary if appropriate bridging studies are found to provide an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s).

[5/]The *Draft Guidance* refers to the April 10, 1987 "Parkman Letter" and the "hybrid NDA" regulation, 21 CFR 314.54, to suggest that the agency is simply building on prior policies. These prior interpretations, however, are inapplicable to recombinant therapeutic proteins. The Parkman Letter and the regulation rely on the idea that the underlying product – *without the proposed change or modification* – could have been approved under section 505(j). *See* 54 FR 28872, 28892 (July 10, 1989). The Parkman Letter and the regulation were intended to streamline the application process, where the underlying product could have been approved under 505(j) and the change could have been approved through a 505(b) supplemental NDA. Rather than submit both applications, FDA resolved that the 505(j) step could be eliminated. The sponsor could go directly to 505(b) and submit only the additional data needed to support the change (along with bioequivalence data). Nevertheless, the premise is that the *product must have been eligible in the first instance to be approved under section 505(j).* Otherwise, neither the applicant nor FDA would be authorized to rely on prior findings of safety and effectiveness. Again, reliance on "prior findings" is authorized under, and only under, section 505(j). The reasoning behind the Parkman Letter simply does not apply to recombinant and other difficult-to-characterize products, where such products in the first instance could not have been approved under 505(j).

Draft Guidance at 8. The "bridging" concept, however, lacks meaning when applied to complex drug substances, including recombinant DNA products.

The regulation of biologically derived products is premised on the idea that the physical and pharmacodynamic properties of such products are dependent on source materials, assays, specifications, and on the specific manufacturing process. Each element contributes to the characteristics of the final product such that a second manufacturer with different materials or a different process is, despite best efforts, likely to yield a product with clinically meaningful differences. Simply comparing the rate and extent of absorption of such products may overlook crucial differences. Indeed, even seemingly minor or subtle differences in the quantity or quality of the variations in each product can have a significant impact on potency, pharmacodynamics, and immune response.[6]/

Even more, the ability to characterize these differences is limited, and the ability to predict whether these differences will lead to immunogenic responses, antibody production, or non-recognition by the host is perilous absent a full clinical program. Unlike small molecule drugs, end-product comparisons for biologics manufactured from different materials using different processes are simply inadequate. For all intents and purposes, the clinical data developed by the manufacturer of such a product is specific to that manufacturer's own cell line and production process.[7]/

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[6]/*Compare* approved labeling for Saizen® (somatropin (rDNA origin) for injection) (stating that half-life for subcutaneous administration is 1.75 hours); Humatrope® (somatropin (rDNA origin) for injection) (stating that half-life for subcutaneous administration is 3.8 hours); and Norditropin® (somatropin (rDNA origin) for injection) (stating that half-life may be as long as 10 hours and that "the absolute bioavailability for Norditropin® after the SC route of administration is currently not known.").

[7]/ This is consistent with FDA's April 1996 "Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products." The guidance outlines how a single sponsor may demonstrate "product comparability" before and after a manufacturing change, through analytical and functional testing rather than full clinical study. As described in the guidance, "comparability" involves the evaluation of incremental changes made to a carefully controlled manufacturing process, performed by the individuals who developed that process. The raw materials, master cell bank, equipment, process controls, key intermediates, assays, and validation studies are all within the control of the sponsor who undertakes a showing of comparability. This level of intra-manufacturer control is not present when a new and different sponsor undertakes to make the "same" biologically-based product using different cellular materials, equipment, and processes. The end result of an original attempt at making "the same" biological product is a new and unique biological product.

There may be no better illustration of this point than the recent disclosure of an unexpected cluster of approximately forty cases reported worldwide of patients suffering from antibody positive pure red blood cell aplasia after being treated with the recombinant product known as Eprex® (epoetin alfa recombinant), manufactured by a subsidiary of Johnson & Johnson.[8]/ In contrast, in the twelve years since the introduction EPOGEN®, Amgen's epoetin alfa recombinant product, there has been only one reported case of an antibody positive patient suffering from pure red blood cell aplasia after treatment with EPOGEN®. Even though the two products are marketed for the same uses and bear the same generic name, they are manufactured by different companies in different locations. To date, the cause of this phenomenon is unknown.

A full discussion of the science is well beyond the scope of the Joint Petition and these comments. More significant, however, is the fact that FDA included in the *Draft Guidance* an approach to the approval of "duplicate" recombinant products *without* a full analysis of the basic science.

The idea of using 505(b)(2) to approve "duplicate" recombinant drug products is ill considered and flawed. To "bridge" from one manufacturer's product to another manufacturer's version in this context represents a significant and untested departure for the agency *and the public*. The science has not been publicly vetted and, suffice to say, brief mention in a draft guidance is not an appropriate vehicle for addressing these issues.

Comment 3*: *The proposed use of 505(b)(2) would create an unlawful regulatory imbalance.

Most biological products are marketed under licenses issued pursuant to section 351 of the PHS Act by FDA's Center for Biologics Evaluation and Research ("CBER"). All such products, including therapeutic recombinant DNA products, are subject to CBER's full clinical data requirements. *See* 21 CFR 601.2. Moreover, CBER continues to emphasize that, unlike small molecule drugs, biological products present unique technical and medical issues. As the Director of CBER recently explained:

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[8]/ *See, e.g.,* Tab 4, Medicines Control Agency, "Important Safety Message: Eprex (epoetin alfa): Reports of Pure Red Cell Aplasia (PRCA)," 11/19/01.

> One cannot completely characterize the biological product and that in itself is an issue, and quite frankly with biological products you really don't have a homogeneous product, you have a defined range of biological components for which you find consistency in a particular clinical outcome. The challenges of analytical technology are still very great for characterizing biologics.

Remarks of K. Zoon, Ph.D., as noted in *FDA Week* (April 20, 2001), attached under Tab 5. CBER officials have consistently expressed concern about the introduction of adventitious agents into biological manufacturing processes and genetically engineered cell lines, the risks of propagating infectious agents, and the need for immunogenic studies on recombinant and modified protein products.[2/] *See also* Tab 6, FDA letter dated Nov. 8, 1999 ("[CBER] has no means of establishing that two biological products from different sponsors can be expected to have the same effectiveness and safety.").

Most biologically-derived protein products remain under the jurisdiction of CBER, where there is no regulatory path for the approval of "duplicates" and where officials remain cautious about the underlying science. It would be arbitrary and capricious, in this context, for CDER to move forward with its own approach, and to begin approving "A-rated" or "duplicate" therapeutic proteins based on clinical data derived from other sponsors' applications. *See generally Bracco Diagnostics, Inc. v. Shalala*, 963 F.Supp. 20, 27 (D.D.C. 1997) (it is unlawful for an agency to apply different legal standards to similarly situated products).

CONCLUSION

The issues involved in trying to establish therapeutic equivalence among biological products, including proteins manufactured using rDNA technology, are complex. The brief mention in a draft guidance of the use of section 505(b)(2) for the approval of recombinant products is a poor vehicle for vetting these fundamental scientific and medical issues.

[2/] *See, e.g.*, K. Stein, Ph.D, Director (CBER Division of Monoclonal Antibodies), "Immunogenicity of Recombinant Proteins" (Feb. 22, 2001) (available on the FDA/CBER website); K. Zoon, Ph.D., Director (CBER), "Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals (May 17, 1993) (available on the FDA/CBER website); *see also* 66 FR 4688, 4690 (Jan. 18, 2001) (discussing the ongoing work of the rDNA Advisory Committee under the National Institutes of Health's Office of Biotechnology Activities).

Amgen vigorously supports the legal analysis and conclusions reached in the Joint Petition and urges the agency, for the reasons described above, to grant the Petition. In doing so, the agency must revoke all proposals and policies that would allow for the use of section 505(b)(2) (or any other abbreviated or "hybrid" process) to approve recombinant drug products.

ENVIRONMENTAL IMPACT

The actions requested in these comments are not within any of the categories for which an environmental assessment is required pursuant to 21 CFR 25.22.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted if requested by the Commissioner.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, these comments include all information and views on which the comments rely and representative data and information known to the undersigned which are unfavorable to the comments.

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3963 '02 APR -5 A8:41

April 4, 2002

VIA OVERNIGHT MAIL

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

Re: Docket No. 01P-0323/CP1: Response to Comments Submitted by the Generic Pharmaceutical Association (GP*h*A) and Amendment to Citizen Petition

Dear Madam or Sir:

This letter (i) responds to the submission of the Generic Pharmaceutical Association ("GP*h*A") on December 10, 2001 ("GP*h*A Comments") in response to the Citizen Petition filed on behalf of Pfizer Inc ("Pfizer") and Pharmacia Corporation ("Pharmacia") ("the Petitioners") on July 27, 2001 ("the Petition"),[1/] and (ii) supplements the Petition with respect to the assertion that reliance on FDA's prior findings of safety and effectiveness in an innovator's New Drug Application ("NDA") to approve a section 505(b)(2) application constitutes an unconstitutional taking in violation of the Fifth Amendment of the United States Constitution.

1/ See Citizen Petition filed on behalf of Pfizer Inc and Pharmacia Corporation (July 27, 2001), Docket No. 01P/0323CP1 (requesting the Food and Drug Administration to amend its October 1999 505(b)(2) Draft Guidance and regulations at 21 C.F.R. § 314.54, to reflect that the Agency may not rely on or otherwise use an innovator's non-public proprietary data or information to approve section 505(b)(2) applications or assign "A" therapeutic equivalency ratings to drug products that are approved under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act).

01P-0323

LET 2

As discussed more fully below, the GP*h*A Comments fail to identify any new information to support the position that FDA has the statutory or constitutional authority to rely on, use, or otherwise appropriate any non-public proprietary information in an innovator's NDA to approve applications submitted under section 505(b)(2) of the Federal, Food, Drug, and Cosmetic Act ("FFDCA" or "the Act").[2/] Moreover, the GP*h*A Comments fail to demonstrate that FDA is authorized to assign "A" therapeutic equivalence evaluation codes to drug products approved under section 505(b)(2) of the Act. As set forth in the Petition, therefore, FDA cannot rely on non-public, proprietary innovator information to approve section 505(b)(2) applications, or assign "A" therapeutic equivalence evaluation codes to drugs approved under section 505(b)(2).

Finally, notwithstanding GP*h*A's predictions of significant commercial and public health consequences of granting Petitioner's Citizen Petition, the Petitioners note that they have not requested that FDA withdraw approval of any drug products previously approved under section 505(b)(2). Nor do Petitioners believe that, by granting the Petition, FDA is required to initiate withdrawal proceedings. Rather, Petitioners are merely requesting withdrawal of an illegal regulation and guidance document, and prospective compliance by FDA with the Act.

I. Contrary to the GP*h*A's Assertion, a Proper Construction of Sections 505(j) and 505(b)(2) Does Not Permit FDA to Rely on Proprietary Innovator Data to Approve Section 505(b)(2) Applications

As explained in the Petition, the FFDCA does not permit FDA to rely on proprietary innovator data to approve section 505(b)(2) applications. The GP*h*A Comments address certain aspects of the Petition arguments supporting this position, and the Petitioners see no reason to reiterate their positions here. Importantly, however, GP*h*A had no response to the Petition argument that section 505(l) of the Act indicates that Congress did not intend to authorize FDA to rely on or use proprietary, non-public innovator data to approve section 505(b)(2) applications.

As discussed in the Petition, section 505(l) authorizes the disclosure of safety and effectiveness data and information in new drug applications ("NDAs") submitted under subsection (b) of the FFDCA once the "first application under subsection (j) which refers to such [NDA] drug" is or could be approved,[3/] and assuming that the data and information do not contain confidential commercial information within exemption 4 to the Freedom of

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2/ This response does not specifically address all of the issues raised in the Comments. The Petitioners reassert and incorporate by reference the substantive positions that are set forth in the Petition in response to all other issues raised in the Comments.

3/ 21 U.S.C. § 355(l)(5).

Information Act ("FOIA").[4/] Section 505(l) reflects Congress' intent that NDA data otherwise not restricted by the FOIA can be disclosed when an ANDA is approved because, at that time, the data are subject to authorized third-party reliance and/or use. By contrast, no similar provision authorizes the release of any NDA data upon approval of a section 505(b)(2) application. This strongly indicates that Congress did not intend section 505(b)(2) applications to rely on or reference non-public proprietary information contained in another company's NDA.

Despite the weight and clarity of the foregoing argument, GP*h*A made no effort to respond in its comments. FDA, however, must address this and similar aspects of the FFDCA before taking action on the Petition.

II. Section 505(b)(2) Codified FDA's "Paper NDA" Policy

Responding to the argument in the Petition that section 505(b)(2) was intended to codify FDA's Paper NDA Policy, GP*h*A contends that section 505(b)(2) was intended instead to broaden that policy in order to remedy perceived inadequacies in the policy. GP*h*A supports this argument by quoting certain language from a House Report. GP*h*A has taken this language out of context, however, and thus misrepresented its true meaning. In context, the language clearly relates that Congress intended section 505(j)—not section 505(b)(2)—to address the potential inadequacies of using the Paper NDA Policy to approve identical generic drugs. Importantly, the passage that GP*h*A omits states:

> . . . A manufacturer of a generic drug must conduct tests that show that the generic drug is the same as the pioneer drug and that it will be properly manufactured and labeled. This information is submitted in an abbreviated new drug application ("ANDA"). The only difference between a NDA and an ANDA is that the generic manufacturer is not required to conduct human clinical trials. . . . The FDA allows this ANDA procedure only for pioneer drugs approved before 1963. There is no ANDA procedure for approving generic equivalents of pioneer drugs approved after 1962. While the FDA has been considering since 1978 an extension of the ANDA policy to post-1962 drugs, it has not extended the regulation. Because of the agency's failure to act, Title I of

4/ As explained in Section VI of this Petition, the "extraordinary circumstances" exception to section 505(l) does not allow the disclosure of confidential commercial information that is subject to exemption 4 of the FOIA. See 21 U.S.C. § 552(b)(4).

> H.R. 3605 is necessary to establish a post-1962 ANDA policy.[5/]

The foregoing passage and that quoted by GP*h*A were set forth in the House Report under a section titled "Background and Need for the Legislation . . . Title I — Abbreviated New Drug Application." Read in context, therefore, the legislative history indicates that Congress created the abbreviated new drug application mechanism in section 505(j), and not in section 505(b)(2), to address the lack of a formal ANDA policy for drug products approved after 1962.[6/] Contrary to GP*h*A's claims, the legislative history does not indicate that Congress created section 505(b)(2) to broaden or address inadequacies with the existing paper NDA policy.

III. Nothing in the GP*h*A Comments Demonstrates that FDA Can Assign "A" Therapeutic Equivalence Ratings to Drug Products Approved Under Section 505(b)(2)

GP*h*A contends that FDA has the authority to assign "A" therapeutic equivalence evaluation codes to drug products approved under section 505(b)(2) of the Act, based on historical practice. Specifically, GP*h*A asserts that "the criteria by which FDA may assign therapeutic equivalence ratings are scientific, and are not based on statutory semantics or the regulatory pathways by which a drug is approved."[7/] An administrative agency, however, may not develop substantive procedures sua sponte that have no basis in its organic statute or regulations, regardless of anyone's views of potential scientific bases for determinations.

The structure of the Act strongly supports the view that Congress only intended FDA to assign therapeutic equivalence ratings to drugs approved under section 505(j), not section 505(b). As set forth in the Petition, FDA determines drug products to be therapeutically equivalent if they meet several criteria. Of particular importance is the criterion that the proposed drug product be demonstrated bioequivalent to a previously-approved drug product. Under the FFDCA, and as supported by its legislative history, bioequivalence determinations are reserved exclusively for drugs approved under section 505(j). By contrast, neither the language nor the legislative history of section 505(b)(2) contains any reference to the relationship or effect of the bioequivalence requirement or the therapeutic equivalence policy on 505(b)(2) applications.

5/ H.R. Rep. 98-857, Part 1, 98th Congress, 2d Sess. 73-74, reprinted in 1984 U.S. Code. Cong. Admin. News 2647, 2649 (emphasis added).

6/ See Id.

7/ Comments of the Generic Pharmaceutical Association to FDA Docket No. 01P-0323/CP1, at 7 (Dec. 10, 2001).

Likewise, the regulatory history concerning therapeutic equivalence determinations reflects FDA's intention to develop the therapeutic equivalence rating policy to address only equivalence issues that are raised by generic drugs approved under abbreviated new drug applications.[8/] Nothing in the Act, legislative history, or regulatory history suggests that FDA has the authority to assign "A" therapeutic equivalence ratings to drug products approved under section 505(b)(2).

IV. FDA Will Not be Forced to Withdraw Approval of Drugs Previously Approved Under Section 505(b)(2)

GP*h*A maintains that granting the Petition will require FDA to withdraw approval of drugs that have assertedly previously been approved under section 505(b)(2). As a procedural matter, the Petitioners did not request such action in their Petition, so there is no such request requiring any Agency response whatsoever. Moreover, GP*h*A's contention assumes that every drug approved via section 505(b)(2) involved improper FDA reliance on proprietary innovator data. Because the drug application process is not transparent, the Petitioners are unable to determine definitively which drugs may be affected if the Petition were granted. Nonetheless, based on the list of drugs approved under section 505(b)(2) provided in the GP*h*A Comments, at least some, and perhaps many, of these drug products appear to rely properly on a combination of published literature and data properly referenced in 505(b)(1) applications, rather than on non-public proprietary NDA data and information. If the Petition were granted, therefore, FDA would not need to consider whether it should act to withdraw approval of those 505(b)(2) applications.

Moreover, even assuming that a number of other section 505(b)(2) applications were approved by FDA based on unlawful reliance on proprietary NDA data, granting the Petition will not require the automatic withdrawal of these drugs. Nothing in the FFDCA requires FDA to withdraw approved NDAs, absent a specific finding, among other things, that:

- clinical or other experience, tests, or scientific data show that the drug product is unsafe for use under the conditions of use upon the basis of which the application was approved;
- new clinical evidence shows that the drug is not shown to be safe for use under the approved conditions of use; or
- new information, assessed with information included in the application, shows that there is a lack of substantial evidence that the drug will have the effect it

8/ See e.g. 44 Fed. Reg. at 2941, 2943 (discussing the rationale and context for addressing bioequivalence issues to respond to ANDA submissions).

purports or is represented to have under the conditions of use prescribed or recommended in the labeling.[9/]

Absent such a finding, these withdrawal procedures are not self-executing. Contrary to GP*h*A's position, therefore, granting the petition would not result in the automatic withdrawal of all approved NDAs for which FDA improperly relied on proprietary NDA data.

Finally, even if FDA makes a specific finding that, without reference to the proprietary NDA data, there is a lack of substantial evidence that demonstrates the safety and effectiveness of a drug, FDA must afford applicants the opportunity for a hearing on the proposed withdrawal (unless it finds that the drug presents an imminent hazard to the public). In at least some of these cases, if the applicant can demonstrate that new evidence, other than an innovator's proprietary data, establishes the product's safety and effectiveness, FDA would not be required to withdraw approval of the product.

Thus, nothing in section 505(e) of the Act, its legislative history, or implementing regulations obligates FDA to engage in the withdrawal process for drug products that are approved under section 505(b)(2) if the Petition is granted. Consequently, none of the actions requested in the Petition will result in a "massive and expensive administrative nightmare for FDA" or adverse public health consequences as maintained in the GP*h*A Comments.

V. Conclusion With Respect to GP*h*A Comments

GP*h*A thus has provided no basis to deny the Petition. Given the GP*h*A Comments' flawed and inaccurate assertions, the Agency should reject GP*h*A's request to deny the Petition and: (1) amend the October 1999 505(b)(2) Draft Guidance and its regulations, 21 C.F.R. § 314.54, accordingly; (2) not rely on or otherwise use an innovator's proprietary data to approve section 505(b)(2) applications; and (3) not assign "A" therapeutic equivalence codes to drug approved under section 505(b)(2).

VI. Supplement to Argument That Reliance on FDA's Prior Findings of Safety and Effectiveness in an NDA to Approve a Section 505(b)(2) Application Constitutes an Unconstitutional Taking

The Petition maintains that FDA's use or reliance on an innovator's proprietary safety and effectiveness data to approve a section 505(b)(2) application constitutes an unconstitutional taking of valuable proprietary data in violation of the Fifth Amendment of the United States

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9/ 21 U.S.C. § 355(e).

Constitution. More specifically, the Petition asserts that where the government has communicated to regulated entities that it will keep submitted data confidential and exclusive, these regulated entities have a reasonable investment-backed expectation that their trade secret data will not be used by the government to the advantage of others.

The language and legislative history of section 505(l) of the Act provides further support for the position that FDA has repeatedly and continuously acknowledged the significant economic value of drug safety and effectiveness data, and for this reason, has treated proprietary data in NDAs confidential and exclusive. Section 505(l) states:

"Safety and effectiveness data and information which has been submitted in an application under subsection (b) for a drug and which has not previously been disclosed to the public shall be made available to the public, upon request, *unless extraordinary circumstances are shown* ... (5) upon the effective date of the approval of the first application under subsection (j) which refers to such drug ..."[10/]

FDA has consistently interpreted the limiting phrase "unless extraordinary circumstances are shown" to include a showing that the requested records contain confidential commercial information as defined within exemption 4 to the FOIA. That is, if a showing of confidential commercial information can be made under FOIA exemption 4 with respect to, for example, data or other records in an NDA, the data and other records contained therein cannot not be disclosed to the public.

The exemption from public release of information based on a showing of "extraordinary circumstances" was initially announced and interpreted by FDA in the context of establishing the Agency's FOIA disclosure requirements, expressly to prevent inappropriate release of confidential safety and effectiveness data in NDAs.[11/] In promulgating its regulations implementing FOIA, prior to the adoption of section 505(l) of the Act, FDA confirmed the competitively valuable content of NDAs. The Agency stated that there is "tremendous economic value" in drug safety and effectiveness data, and that routine release of this information could adversely affect the "incentive for private pharmaceutical research."[12/] FDA also made clear that it did not seek to narrow the statutory exemption from disclosure

10/ 21 U.S.C. § 355(l) (emphasis added).

11/ See 41 Fed. Reg. 9317 (March 4, 1976).

12/ See 39 Fed. Reg. 44602, 44634 (Dec. 24, 1974).

under FOIA through the use of the "extraordinary circumstances" test. FDA's FOIA regulations also provide that any record within a FOIA exemption will not be released even if it would otherwise be disclosable under the Agency's regulations.[13/] Moreover, FDA explained that "extraordinary circumstances" includes a showing that competitive harm would flow from release of the records, equating the Agency's non-disclosure standard with that for FOIA exemption 4.[14/]

At the time of the Hatch-Waxman legislation, including the passage of section 505(l), FDA dispelled any remaining doubt about its interpretation of the phase "extraordinary circumstances." In a September 12, 1984 letter from FDA Commissioner Frank Young to Senator Hatch, Commissioner Young stated that "the Agency interprets the term 'extraordinary circumstances' as including a situation in which the safety and effectiveness data have commercial value as confidential business information."[15/] The legislative history demonstrates that Congress intended to codify precisely FDA's understanding and policy of non-disclosure when it included the same term in section 505(l).[16/]

As support for the position that FDA's use or reliance on an innovator's proprietary safety and effectiveness data to approve a section 505(b)(2) application constitutes an unconstitutional taking, Petitioners therefore amend the Petition to reference and incorporate

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13/ See 21 C.F.R. §§ 4.60(a), 4.100(a) (1975); 21 C.F.R. §§ 20.60(a), 20.100(a) (1998); 39 Fed. Reg. at 44621 ("all of the exemptions from disclosure" under FOIA apply "to each of the specific categories" addressed in FDA's regulations).

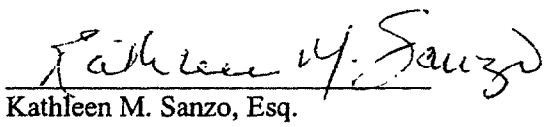
14/ FDA stated in the preamble to its FOIA regulations that "extraordinary circumstances" includes a showing that competitive harm would flow from release of the records. See 39 Fed. Reg. at 44633.

15/ 130 Cong. Rec. S10988 (daily ed. Sept. 12, 1984).

16/ The only committee report to address this issue, the report of the House Committee on Energy and Commerce, addressed the meaning of section 104 of the House bill H.R. 3605 (that added section 505(l) in terms identical to the final bill) as follows: "These conditions under which such safety and effectiveness data shall be released upon request, unless extraordinary circumstances are shown, are merely restatement of the current regulation. The committee intends that all terms in new section 505(l) be given the same meaning that they have in the regulation. It is not the intent of the Committee to alter the rights of the public under the Freedom of Information Act." H. Rep. No. 857, 98th Cong. 2nd Sess., part 1, at 35-36 (1984). See also, 130 Cong. Rec. S10912 (daily ed. August 10, 1984) (Senator Hatch stated that, "under the current practice, which will be the practice under the bill, extraordinary circumstances are present for example when the information is trade secret or confidential or commercial information"); 130 Cong. Rec. S10988-89 (daily ed. Sept. 12, 1984) (Senator Hatch confirmed that it was his intent to ratify FDA's present interpretation of the extraordinary circumstances regulation).

FDA's longstanding and continuous efforts to maintain proprietary data in NDAs confidential and exclusive, as reflected in the language and legislative history of section 505(l) and FDA's FOIA regulations.

Respectfully submitted,



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