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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 (GPhA) and Amendment to Citizen Petition

Dear Madam or Sir:

This letter (i) responds to the submission of the Generic Pharmaceutical Association (“GPhA”) on December 10, 2001 (“GPhA 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27, 2001), Docket No. 01P/0323CP1 (requesting the Food and Drug Administration to amend its October 1999 505(b)(2) Draft Guidance and regulations at 21 C.F.R. § 314.54, to reflect that the Agency may not rely on or otherwise use an innovator’s non-public proprietary data or information to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).

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As discussed more fully below, the GPhA 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 GPhA 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 GPhA'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 GPhA'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 GPhA Comments address certain aspects of the Petition arguments supporting this position, and the Petitioners see no reason to reiterate their positions here. Importantly, however, GPhA 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

^{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, *GPhA* 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, *GPhA* contends that section 505(b)(2) was intended instead to broaden that policy in order to remedy perceived inadequacies in the policy. *GPhA* supports this argument by quoting certain language from a House Report. *GPhA* 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 *GPhA* 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 GPhA 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 GPhA’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 GPhA Comments Demonstrates that FDA Can Assign “A” Therapeutic Equivalence Ratings to Drug Products Approved Under Section 505(b)(2)

GPhA 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, GPhA 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)

GPhA 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, GPhA'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 GPhA 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 FDCA 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_hA*'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_hA* Comments.

V. Conclusion With Respect to *GP_hA* Comments

GP_hA thus has provided no basis to deny the Petition. Given the *GP_hA* Comments' flawed and inaccurate assertions, the Agency should reject *GP_hA*'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

^{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 phrase “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

^{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).

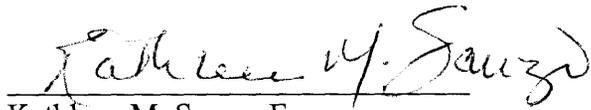
^{16/} The only committee report to address this issue, the report of the House Committee on Energy and Commerce, addressed the meaning of section 104 of the House bill H.R. 3605 (that added section 505(l) in terms identical to the final bill) as follows: “These conditions under which such safety and 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).

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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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Counsel for Pfizer Inc and Pharmacia Corporation

cc: Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA

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