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BY HAND DELIVERY

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

Re: Docket No. 98P-0610: Comment to WellPoint citizen petition

These supplemental comments are submitted on behalf of Pfizer, Inc., on citizen petition 98P-0610/CP1, filed by Blue Cross of California (the "WellPoint Petition"). The WellPoint Petition requests that the Food and Drug Administration (FDA) convert from prescription to nonprescription status three drugs - fexofenadine hydrochloride (Allegra®), loratadine (Claratin®), and cetirizine hydrochloride (Zyrtec®) - each marketed by a different single manufacturer under an approved new drug application (NDA). Pfizer is the manufacturer of Zyrtec®.

Several comments previously submitted to this docket have argued that FDA lacks the authority to force a prescription drug to switch to OTC status. Most notably, on April 23, 2003, Wiley Rein & Fielding LLP, on behalf of the American Association of Physicians and Surgeons and the Competitive Enterprise Institute, filed comments arguing that FDA lacks the authority, under any procedure, to force a manufacturer to market its approved drug OTC. These comments questioning FDA's ultimate authority to force a switch deserve FDA's thoughtful consideration.

Although we believe that the comments submitted by Wiley Rein and others raise a serious threshold question, Pfizer's previous comments submitted to this docket on May 11,

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2001, addressed only the question of what procedures must FDA use if, assuming that it might have the authority, the Agency attempts to force a switch. Pfizer argued that the only potentially available provision would be section 505(e) of the FDCA, which requires that the Agency afford Pfizer a formal evidentiary hearing.[1] We remain convinced that this is the correct reading of the law.

The WellPoint Petition nonetheless argues that FDA may force an OTC switch by regulation, pursuant to section 503(b)(3) of the FDCA.[2] On the assumption that FDA may attempt to proceed through an informal rulemaking procedure pursuant to section 503(b)(3), these comments focus on requirements of that process to which FDA must adhere. Specifically, if FDA were to proceed by rulemaking, it would have the burden of providing evidence demonstrating that the Rx requirements currently in place for Zyrtec "are [no longer] necessary for the protection of the public health."[3] In meeting this burden, FDA could not rely on confidential data and information contained in Pfizer's NDA for Zyrtec, nor could it rely on prior Agency "findings" regarding Zyrtec's safety or effectiveness.

I. FDA Bears the Initial Burden of Proof in a Rulemaking Context

If FDA were to proceed through a rulemaking, it would bear the burden of establishing that the Rx restrictions are no longer necessary to protect the public health. Although the burden of proof requirements contained in section 556(d) of the Administrative Procedure Act (APA) do not apply to informal rulemaking proceedings,[4] a body of case law has developed, recognized by

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[1] 21 U.S.C. § 355(e).

[2] The WellPoint Petition does not provide any proposed OTC labeling for FDA review. As a result, the WellPoint Petition does not allow FDA to evaluate whether Zyrtec is "safe and effective for use in self-medication as directed in proposed labeling." 21 C.F.R. § 310.200. As a result, the WellPoint Petition is defective on its face.

[3] 21 U.S.C. § 353(b)(3).

[4] See American Trucking Ass'ns, Inc. v. United States, 344 U.S. 298, 319-320 (1953).

administrative law scholars, which places an initial burden of coming forward with a factual predicate for proposed rules on Federal agencies. For instance, even in informal rulemaking, the burden of proof typically rests with the party that seeks to change the status quo.

This allocation of the initial burden is a recognized general principle of administrative law,[5] and it has been specifically applied on more than one occasion in the food and drug context. In United States v. Nova Scotia Food Products Corp., FDA sought to impose industry-wide requirements for the control of C. botulinum bacteria Type E in smoked fish. In striking down the agency's rule on procedural grounds, the court emphasized that FDA bore the "burden of proof of adducing a reasoned presentation supporting the reliability of its methodology."[6] More recently, in Contact Lens Mfrs. Ass'n v. FDA, the D.C. Circuit expressed approval for assigning the burden of proof to FDA where it is the party, as it would be in a forced OTC switch, "seeking to change the status quo."[7]

The judicial expansion of the concept of adequate notice in informal rulemaking procedures has imposed a *de facto* burden of proof on agencies. In Portland Cement Ass'n v. Ruckelshaus, discussed in greater detail below, the D.C. Circuit held that agencies must make the factual and scientific basis underlying a proposed rule available for public comment.[8] As has been recognized by administrative law scholars, this places an initial burden on the agency of coming forth with a factual predicate that can survive the arbitrary and capricious standard.[9] The

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[5] See, e.g., James V. DeLong, Informal Rulemaking and the Integration of Law and Policy, 65 Va. L. Rev. 257, 297-98 (1979) (discussing initial burden facing a Federal agency in an informal rulemaking procedure).

[6] United States v. Nova Scotia Food Prods. Corp., 568 F.2d 240, 251 (2nd Cir. 1977).

[7] Contact Lens Mfrs. Ass'n v. FDA, 766 F.2d 592, 599 (D.C. Cir. 1985)

[8] Portland Cement Ass'n v. Ruckelshaus, 486 F.2d 375, 393 (D.C. Cir. 1973).

[9] See DeLong, supra, note 5 ("[t]he recent cases have changed [the burden of proof] model in an unarticulated and perhaps inadvertent way by requiring fuller explanations from the agency throughout the proceeding, by emphasizing the agency's duty to make clear to the court 'the (continued...)

D.C. Circuit articulated this concept in Nat'l Lime Ass'n v. EPA, noting that "[t]he locus of administrative burdens of going forward or of persuasion may shift in the course of a rulemaking proceeding, but we think an initial burden of promulgating and explaining a non-arbitrary, non-capricious rule rests with the Agency . . . ."[10]

II. FDA Must Base Any Proposed or Final Rule Only on Information and Data in the Administrative Record

According to FDA's own regulations, informal rules must be based solely on the administrative record.[11] The contents of that record, in turn, must be made available to the public for endorsement, criticism, or rebuttal.[12] Thus, FDA must identify the information and data on which it relies, and make that material available for public comment. Furthermore, section 10.40(b) requires that any notice of proposed rulemaking must summarize the facts underlying the proposal and include "references to all information on which the Commissioner relies."[13]

Confirming FDA's own regulations, the courts have held that the APA imposes an independent burden on federal agencies to disclose to the public all information relied upon in rulemaking procedures. In Portland Cement, for example, the court struck down an EPA regulation because the agency had not properly identified the scientific basis for its proposal and made it available for public comment.[14] In its Notice of Proposed Rulemaking for a stationary source standard for cement plants, EPA stated that its proposal was based only on "stationary

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choices open . . . and those made,' and by requiring that decisions have a basis in the rulemaking record." (internal citation omitted).

[10] 627 F.2d 416, 433 (D.C. Cir. 1980) (citing DeLong, supra note 5).

[11] See 21 C.F.R. §§ 10.40(b) & (c).

[12] See 21 C.F.R. §§ 10.20(j) & 10.40(g).

[13] 21 C.F.R. § 10.40(b).

[14] Portland Cement Ass'n v. Ruckelshaus, 486 F.2d 375 (D.C. Cir. 1973).

source testing conducted by [EPA] and/or its contractors." EPA failed to make the details/methodology of its source testing available to the public until after it had adopted its final rule. Thus, neither industry nor other interested parties ever had an opportunity to make meaningful comment on the data on which EPA's rule was based.

Portland Cement filed suit in Federal Court arguing that the rule was arbitrary and capricious. The court agreed, and reversed and remanded the rule, stating "[w]e find a critical defect in the decisionmaking process in arriving at the standard under review in the initial inability of petitioners to obtain - in timely fashion - [its] test results and procedures . . . which formed a partial basis for the emission control level adopted."[15] Thus the court essentially held that it is arbitrary and capricious for an agency to fail to identify the information and data on which it relies in forming its proposed rule. The court explained, "[i]t is not consonant with the purpose of a rulemaking proceeding to promulgate rules on the basis of inadequate data, or on data that [in] critical degree, is known only to the agency."[16]

Administrative law scholars have applauded this expansion of the concept of adequate notice as an improvement in informal rulemaking procedure. Professor Pierce, for example, writes

> The purpose of the notice required by § 553(b) [of the APA] is to permit potentially affected members of the public to file meaningful comments under § 553(c) criticizing (or supporting) the agency's proposal. That purpose is clear from consideration of the sequence of procedures mandated by § 553 and from the legislative history of § 553(b). Yet, it is impossible to file meaningful comments critical of a proposed action that is premised on particular data unless that data is available in time for comments. Analysis of the data may reveal major problems in measurement, sampling, methodology, or statistical validity.

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[15] Id. at 392.

[16] Id. at 393.

> Consideration of such criticism might well cause an agency to modify its proposal. Because no such criticism is possible without access to the data, access to the data that putatively supports a proposed rule is critical to the right to comment on the rule and, hence, is part of the notice required by § 553(b).[17]

The Nova Scotia court took a similar approach in striking down FDA's smoked fish regulation. After FDA brought an enforcement action against Nova Scotia Food Products Corp., the company defended, in part, on the ground that the rule was invalid because FDA "improperly relied upon undisclosed evidence in promulgating the regulation and because it [was] not supported by the administrative record."[18] In submitting the administrative record to the court for review, the Agency admitted that it had relied on substantial amounts of scientific data (in the form of published journals, articles, studies, etc.) that it had not identified in its Notice of Proposed Rulemaking. The Second Circuit struck down FDA's regulation as arbitrary and capricious, stating:

> it is 'arbitrary and capricious' for an agency not to take into account all relevant factors in making its determination. . . . If the failure to notify interested persons of the scientific research upon which the agency was relying actually prevented the presentation of relevant comment, the agency may be held not to have considered all 'the relevant factors.'[19]

In discussing this line of cases, administrative law scholars have stressed the obligation of agencies to identify unpublished studies on which they rely. Where all interested parties do not have ready access to important data relied upon by an agency, the potential for a failure of the system is at its greatest. In such cases, interested parties are denied the opportunity to review the

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[17] Richard J. Pierce, Jr., Administrative Law Treatise, § 7.3 (4th ed. 2002).

[18] Nova Scotia, 568 F.2d at 243.

[19] Id. (citing Portland Cement, 486 F.2d 375, 393 (D.C. Cir. 1973)).

data and the methodologies supporting it, and offer critical comments. Such comments could cause the agency to alter its proposal.[20]

III. To Justify a Forced OTC Switch, FDA Would Have to Establish the Drug's Safety for OTC Use, Which Would Require Reference to Data in Pfizer's NDA

According to Section 503(b)(1) of the FDCA, and FDA's own regulations, in order for FDA to force a switch of Zyrtec to OTC status, the Agency would have to find that the Rx requirements:

> are not necessary for the protection of the public health by reason of the drug's toxicity or other potentially harmful effect, or method of its use, or the collateral measures necessary to its use, and . . . that the drug is safe and effective for use in self-medication as directed in proposed labeling.[21]

FDA would have the initial burden of assembling evidence to establish each of these factors. In order to do so, FDA would almost certainly have to rely on data in Pfizer's NDA for Zyrtec. Pfizer first began serious research into cetirizine in 1978 and began its formal clinical research program in 1982. The program included 117 clinical studies as well as countless other animal and *in vitro* studies. The result is a compilation of safety data in Pfizer's NDA that likely exceeds all of the publicly available data combined.[22] FDA has presumably reviewed all this safety data, which now constitutes a fundamental part of FDA's basic knowledge of Zyrtec's safety profile. It simply would not be possible for FDA now to ignore that data in making a determination regarding Zyrtec's safety for OTC use.

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[20] See Pierce, supra note 17.

[21] 21 U.S.C. § 353(b)(1); 21 C.F.R. § 310.200.

[22] Few, if any, of the studies and other data in Pfizer's NDA have been published. They, therefore, remain confidential.

In order to make the statutorily mandated finding of safety for OTC use, FDA would have to analyze cetirizine's safety from a variety of standpoints including, for example, acute and chronic toxicity, food interactions, potential for abuse, potential for and effect of tolerance development, and label comprehension.[23] FDA has specifically noted that when considering an OTC switch, it must also consider whether the drug has a large margin of safety, whether its frequency of dosing affects its safe use, whether its safety profile has been defined at high dosage levels, and whether there is a full understanding of its pharmacodynamics.[24]

It is simply inconceivable that FDA could responsibly address all of these (and other) issues without frequent reference to any of the confidential data in Pfizer's NDA. Indeed, FDA's own stated policies indicate that it must rely on the pioneer's NDA in evaluating a switch. In an April 2001 Memorandum from FDA's OTC Antihistamine Review Team to members of the Pulmonary and OTC Advisory Committee, FDA noted that when it considers an OTC switch, "[s]afety assessments typically rely on information presented in the NDA," among other things.[25] Even if FDA pretended to "ignore" the safety data in Pfizer's NDA, it could not legitimately do so. The vast body of safety data contained in Pfizer's NDA provides the core of FDA's understanding of cetirizine's safety. It simply could not, by analogy, shut off that part of its brain when evaluating cetirizine's safety for OTC use.

In keeping with the Portland Cement line of cases discussed above, in order for FDA to rely on the data in Pfizer's NDA, it would have to disclose the data in time for public comment. Yet as Pfizer has previously argued, it could not lawfully disclose this data, for to do so would constitute a violation of the Trade Secrets Act, as well as the FDCA itself.

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[23] See Peter Barton Hutt, A Legal Framework for Future Decisions on Transferring Drugs from Prescription to Nonprescription Status, 37 Food Drug Cosmetic L. J. 427, 433-39 (1982).

[24] Memorandum to Nonprescription Drugs Advisory Committee and Pulmonary Allergy Drugs Advisory Committee Members, Consultants, and Guests, from OTC Antihistamine Review Team (April 5, 2001) (identifying the "Peck Principles" for OTC switches).

[25] Id.

IV. Disclosure of Confidential Data in Pfizer's NDA Would Violate the FDCA, the Trade Secrets Act, and FDA's Own Long-Standing Policy

Pfizer's previous comments submitted on May 11, 2001 explained in great detail that disclosure of confidential data in Pfizer's NDA would violate section 301(j) of the FDCA, the Trade Secrets Act, and FDA's own longstanding policy. As discussed in that prior comment, section 301(j) of the FDCA prohibits the disclosure of trade secrets and confidential commercial information obtained by the Agency through the IND and NDA processes. The provision prohibits FDA or its employees from revealing "any method or process which as a trade secret is entitled to protection."[26] FDA has long interpreted the definition of "trade secrets," in both section 301(j) of the FDCA and the Trade Secrets Act to extend to confidential data and information in an NDA.[27] The courts have confirmed FDA's interpretation of these two statutory provisions.[28]

Disclosure of data in Pfizer's NDA would also violate the Trade Secrets Act, which prohibits federal employees from disclosing, among other things, "trade secrets."[29] The Act provides for criminal sanctions against any "employee of the United States Government who discloses, in any manner not authorized by law, any trade-secret information that is revealed to him during the course of his official duties."[30] The courts have construed the Trade Secrets Act

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[26] 21 U.S.C. § 331(j).

[27] See, e.g., "Interagency Coordination in Drug Research and Regulation," Hearings Before the Subcomm. on Reorganization and Int'l Orgs., Senate Comm. on Government Ops., 88th Cong. 1891 (1963).

[28] See, e.g., Pharm. Mfrs. Ass'n v. Weinberger, 401 F.Supp. 444, 445 (D.D.C. 1975) (explaining that FDA receives information "of a very sensitive nature" from manufacturers, and that FDA agrees manufacturers "do maintain a property interest in certain sensitive information" particularly because if that information were disclosed, "a substantial loss could be incurred by the drug company. . . . The importance of maintaining the confidentiality of such information . . . is reflected in two statutes which prohibit disclosure of certain information by the FDA").

[29] 18 U.S.C. § 1905.

[30] Ruckelshaus v. Monsanto Co., 467 U.S. 986, 1008 (1984).

to be "at least co-extensive with" the scope of Exemption 4 of the FOI Act.[31] Exemption 4, in turn, encompasses confidential information required to be submitted to the government if its disclosure would cause substantial competitive harm to the submitter (*e.g.*, an NDA).[32]

As was also discussed in greater detail in Pfizer's May 11, 2001 comments, it has long been FDA's own policy that it may not ordinarily rely on unpublished information in a sponsor's NDA. FDA has specifically defended this policy on more than one occasion.[33] Thus, were FDA to attempt to force an OTC switch of Zyrtec, the FDCA, the Trade Secrets Act, and FDA's own longstanding policy would preclude it from relying on the data in Pfizer's NDA.[34]

V. FDA Could Not Base its Decision on Supposed Prior "Findings" in Lieu of "Evidence"

FDA also may not rely on its own prior "findings" regarding Zyrtec's safety profile to fulfill its burden of that proving Zyrtec is safe and effective for OTC use. First, the only prior "finding" that FDA has made is that Zyrtec is safe and effective *for prescription use only*. This finding cuts against the finding FDA would need to make to force a switch. Second, the

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[31] See CNA Fin. Corp. v. Donovan, 830 F.2d 1132, 1151 (D.C. Cir. 1987).

[32] See Nat'l Parks v. Morton, 495 F.2d, 765, 770 (D.C. Cir. 1974). See also, Public Citizen Health Research Group v. FDA, 185 F.3d 898 (D.C. Cir. 1999) (holding that four abandoned INDs fell within Exemption 4 of the FOI Act); Citizens Comm'n on Human Rights v. FDA, 45 F.3d 1325 (9th Cir. 1995) (holding that safety and effectiveness information in the NDA for Prozac, a prescription antidepressant drug, was exempt from disclosure).

[33] See, e.g., Memorandum to Division Directors from Marion J. Finkel, Associate Director for New Drug Evaluation (July 31, 1978), 46 Fed. Reg. 27,396, at 27,397 (May 19, 1981) (stating that for a paper NDA, medical reviewers must rely on their "own knowledge *from the published literature* of the clinical safety of the drug at issue." See also 37 Fed. Reg. 9,128, 9,130 - 31 (May 5, 1972); 39 Fed. Reg. 44,602, 44,612 - 14, 44,634 - 38 (December 24, 1974) (regulations implementing the FOI Act and formalizing FDA's well-established policy of protecting confidential data in NDAs).

[34] For a more detailed analysis of section 301(j) of the FDCA, the Trade Secrets Act, and FDA's longstanding policy, see Comments Submitted on Behalf of Pfizer, Inc., 98P-0610/C20 (May 11, 2001).

Agency's findings on cetirizine stem exclusively from FDA's evaluation of the data contained in Pfizer's NDA at the time of its submission. Virtually all of FDA's most sophisticated knowledge of cetirizine's safety profile is based upon FDA's review of Pfizer's NDA. Thus, there is no principled distinction between FDA's prior findings as to cetirizine's safety and the data contained in the Zyrtec NDA on which those findings were based.

The case law governing the Hatch-Waxman Amendments to the FDCA support the foregoing analysis. The ANDA provisions of section 505(j) permit approval of an ANDA based on a showing that the proposed generic product has, among other things, the same active ingredient, labeling, and dosage form as the pioneer, and is bioequivalent to the pioneer.[35] Thus, no new showing of safety and effectiveness is required. The courts have interchangeably characterized this process as "reliance" on the pioneer's data or permitting FDA to rely in its prior "findings" of safety and effectiveness.[36] Thus, the courts have recognized that relying on the data in a pioneer's NDA and relying on FDA's prior findings of safety and/or effectiveness simply cannot be distinguished.

Because there is no difference between relying on data in an NDA, and relying on prior findings based on a review of that NDA, FDA cannot meet its burden in this case through a prior finding regarding cetirizine's safety. To do so would be equivalent to relying on confidential

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[35] 21 U.S.C. § 355(j).

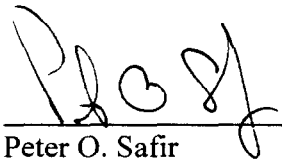
[36] See, e.g., Andrx Pharm., Inc. v. Biovail Corp., 256 F.3d 799, 801 (D.C. Cir. 2001) (stating that an ANDA "relies on the FDA's previous determination that the drug is safe and effective."); American Bioscience, Inc. v. Thompson, 243 F.3d 579, 580 (D.C. Cir. 2001) (characterizing the process as "relying on the NDA filed by the original manufacturer."); Mova Pharm. Corp. v. Shalala, 140 F.3d 1060, 1063 (D.C. Cir. 1998) (characterizing the process as one "which relies on the FDA's previous determination that the drug is safe and effective."); Bristol Myers Squibb Co. v. Shalala, 91 F.3d 1493, 1495 (D.C. Cir. 1996) (ANDA applicant may "rely upon research paid for by the manufacturer of the listed drug.").

trade secret data in Pfizer's NDA.[37] FDA may not do this without disclosing that data. FDA may not disclose this data, however, because such a disclosure would violate section 301(j) of the FDCA as well as the Trade Secrets Act.

VI. Conclusion

If FDA wishes to force an OTC switch of Zyrtec, it bears the burden of proof of establishing that the prescription-only restriction is no longer necessary. In meeting this burden, FDA may not rely on confidential data and information contained in Pfizer's NDA, nor may it rely on previous agency "findings" regarding cetirizine's safety profile. Rather, it must introduce sufficient evidence from outside sources to meet its burden.

Respectfully Submitted,



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[37] Of course, as discussed above, such prior findings are of no use anyway, because they establish only that Zyrtec is safe for *prescription* use.