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

RE: Docket No. 98P-0610: Comments on Petition to Convert Three Prescription Antihistamines from Rx to OTC Status

Dear Sir or Madam:

I have been requested by Pfizer Inc to submit my views on the procedures the Food and Drug Administration (FDA) must follow when it proposes to eliminate the prescription marketing status of an approved new drug. Currently, I am a partner in the law firm of Hyman, Phelps & McNamara, P.C., where I advise clients on legal and regulatory issues involving the FDA. I was Chief Counsel of the FDA from 1981 to 1989. I was Associate Chief Counsel for Regulations and Hearings from 1978 to 1979 and a staff attorney from 1973 to 1978.

The FDA is considering a petition from Blue Cross of California (now known as Wellpoint Health Networks) to issue a regulation requiring three antihistamines to be

98P-0610

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marketed as over-the-counter (OTC) drugs.[1] The three antihistamines are fexofenadine hydrochloride (Allegra), loratadine (Claritin), and cetirizine hydrochloride (Zyrtec). Each is the subject of an approved new drug application (NDA). Each is marketed as a prescription drug. In each case, prescription marketing status is a condition for the safe and effective use of the drug under the approved NDA. It is my view that the FDA cannot grant the petition.

Summary

The Blue Cross petition relies on a provision of the Food, Drug, and Cosmetic Act (FDCA) enacted in 1951 to authorize the FDA to remove drugs subject to the NDA provisions from the FDCA's Rx dispensing requirements. That provision became obsolete after the NDA section of the FDCA was amended in 1962. Today, the marketing status of an approved drug is governed by its NDA. If the FDA believes the three antihistamine products identified in the Blue Cross petition are not appropriately limited to prescription dispensing, the agency must propose to modify each of the approved NDAs to remove that condition of use. Such action must be taken in accordance with the statutory procedures governing NDAs. Those procedures require that each NDA applicant be provided with an opportunity for an evidentiary hearing to dispute the factual basis for proposing to alter the terms of the approved NDA to provide for OTC marketing.

This conclusion is explained further below.

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[1] The Blue Cross petition was the subject of a joint advisory committee meeting on May 11, 2001. See 66 Fed. Reg. 17431 (March 30, 2001). The Blue Cross petition also raises an issue that was discussed as part of last year's public hearing on the FDA's approach to regulating OTC drug products (Docket No. OON-1256, 65 Fed. Reg. 24704 (April 27, 2000). Two of the questions the agency asked were "[u]nder what circumstances should FDA actively propose OTC marketing for a drug in the absence of support from the drug sponsor?", and "[s]hould FDA be more active in initiating switches of prescription products to OTC use?" Id. at 24706.

The Provision the Petition Relies on
Does Not Authorize the Action Requested

The Blue Cross petition asks the FDA to issue a regulation under section 503(b)(3) of the FDCA[2] to remove fexofenadine, loratadine, and cetirizine from the prescription marketing requirements of the FDCA. However, this provision of the FDCA, enacted as part of the Durham-Humphrey Amendment in 1951,[3] is obsolete. In any case, section 503(b)(3) was not intended to authorize the FDA to impose OTC status over the opposition of the NDA holder.

Historical context of section 503(b)(3). The Durham-Humphrey Amendment was intended, among other things, to eliminate inconsistencies in the use of the Rx legend. Examples were brought to Congress's attention in which the same drug was marketed by different manufacturers with or without the Rx legend, depending on the manufacturer's technical judgment and business strategy. To bring about greater uniformity, the 1951 law created three Rx categories – habit-forming drugs under section 502(d)[4]; drugs unsafe for use without professional supervision; and drugs limited to Rx status by an effective application[5] under section 505 – and a requirement that a given drug had to be either Rx or OTC.

The Durham-Humphrey Amendment explicitly authorized the FDA "by regulation" to remove drugs "subject to . . . section 505 from the requirements" of prescription dispensing when the requirements "were not necessary for the protection of public health." This provision must be viewed in historical context. In 1951, a large proportion of important drugs then in use originated in the pre-1938 era, and were therefore subject to the standard of the Rx category for drugs not safe for use except under supervision. Section 505 drugs were within the FDA's pre-market review authority. It was pointed out several times in the hearings that, as a precautionary matter, given the lack of experience with these novel drugs in general clinical use, the FDA

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2 The petition does not cite this section of the FDCA, but paraphrases its text.

3 The history of the Durham-Humphrey Amendment is summarized in Dunn, "The New Prescription Drug Law," 6 FDC L.J. 951 (1951).

4 Section 502(d) and the related Rx drug category have been removed from the FDCA.

5 The wording of this category was changed in 1962 to conform with the premarketing approval requirement enacted that year.

routinely imposed Rx status as a condition of NDA approval on drugs that entered the market through section 505.[6]

The FDA's practice was given effect in section 503(b)(1)(C). By specifically including drugs "limited by an effective application under section 505 to use under the professional supervision of a practitioner licensed by law," this provision obviated the need to separately evaluate section 505 drugs under the criteria of section 503(b)(1)(B). Section 503(b)(3), in turn, provided a mechanism for removing the Rx restriction that section 503(b)(1)(C) imposed. The mechanism was not, however, intended to provide a separate grant of authority to the FDA to change the marketing status of an NDA drug without regard to the NDA applicant's rights under section 505. Rather, it was an administrative adjunct to facilitate removal of the Rx requirement with the concurrence of NDA applicants at a time when the NDA procedures did not provide a suitable vehicle for doing so.

Today, "an approved NDA" is an ongoing process. In 1951, "an effective NDA" resulted from a one-time event, consisting of the FDA's conclusion that, based on the applicant's premarket notification, the drug was "safe." Under the 1951 version of the NDA process, an NDA became effective in 60 days unless the FDA affirmatively postponed the time for an additional 120 days or refused to permit it to become effective. Once the NDA became effective, the FDA and the NDA applicant did not, as they do now, engage in systematic follow-up communications. For example, there were no NDA reporting requirements in 1951. Moreover, as is well known, "me-too" versions of NDA drugs were commonly introduced outside the section 505 process. As to those products section 505 was unavailable as a basis for continuing FDA oversight and management. The officially accepted widespread presence of me-too NDA drugs in the pre-1962 era underlines the fact that section 505 was not seen by the FDA, or the regulated industry, as a framework for addressing the conditions of use of NDA drugs on an ongoing basis.

The reason for including NDA drugs in section 503(b)(3) emerges clearly from this background. A section 503(b)(3) regulation was a necessary mechanism for the FDA to authorize companies marketing NDA or post-1938 me-too prescription drugs to

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[6] See, e.g., Hearings on H.R. 3298 Before the Committee on Interstate and Foreign Commerce, House of Representatives, 82d Cong., 1st Sess. 164-65 (1951) (L.D. Harrop, General Counsel, Amer. Drug Mfrs. Assoc.); Hearings on S. 1186 and H.R. 3298 Before the Subcommittee on Health of the Committee on Labor and Public Welfare, United States Senate, 82d Cong., 1st Sess. 16 (1951) (Statement of George P. Larrick, Deputy Comm'r of Food and Drugs, FDA, Federal Security Agency).

remove the Rx legend based on a history of safe use after introduction at a time when section 505 did not provide a workable method for doing so. This interpretation is reflected in the legislative history of section 503(b)(3). The House report states:

> This paragraph permits the Administrator by regulations to remove habit-forming and new drugs from the prescription requirement of paragraph (1) when that requirement is not necessary for the protection of the public health. These drugs are the ones covered by subparagraphs (A) and (C) of paragraph (1). This relaxation is necessary to permit the sale without prescription of drugs containing small amounts of habit-forming drugs as components, and to permit the sale of new drugs without prescription when that safeguard is unnecessary.

H.R. Rep. No. 700, 82d Cong., 1st Sess. 16 (1951).

Use of section 503(b)(3) today. With respect to whether the FDA can – today – use section 503(b)(3) to require an NDA applicant to convert an NDA prescription drug to an OTC drug, the legislative history of the provision, and its evident purpose as part of the structure of the amended prescription drug section of the FDCA, are inconsistent with such an assertion of authority.

First, even with respect to the pre-1962 period, it is not plausible to interpret section 503(b)(3) as having authorized the FDA to order an Rx drug to be marketed OTC over the opposition of the NDA applicant. Congress's objective was plainly to provide a specific procedure by which manufacturers of NDA drugs could be relieved of the burden of unnecessary Rx conditions of use imposed out of precaution when NDAs were initially approved. There is nothing in the statute or its history to suggest that the agency was being given authority to forcibly modify "effective" NDAs in ways the NDA applicants believed were inappropriate without regard to the procedural requirements for suspending the effectiveness of NDAs.[7]

Second, section 503(b)(3) was enacted at a time when section 505 was a completely different regulatory control mechanism than it became in 1962. In 1951,

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[7] The last use of section 503(b)(3) to switch an NDA drug was in 1971. See 36 Fed. Reg. 824 (Jan. 19, 1971) (tolnaftate). A review of regulations issued under that authority identified no instance in which section 503(b)(3) was the basis for unilateral action by the FDA to eliminate Rx status over the objection of an NDA applicant.

manufacturers whose drugs were cleared through section 505 with Rx labeling, or that were me-too versions of such drugs, but believed that OTC marketing was justified would have had little recourse, after enactment of section 503(b)(1)(C), other than to obtain a ruling from the agency that the section 503(b)(1) requirements were inapplicable. Section 503(b)(3) provided a statutory basis for the FDA to issue such a ruling, as well as a form – "by regulation" – that would communicate the change in status to all concerned at a time when me-toos were common and pharmacists were concerned about confusion due to inconsistent use of the Rx legend.

As explained below, section 505 underwent major revision in 1962. Section 503(b)(3) became redundant and fell into disuse. Today, it is a vestigial remnant of a superseded drug regulatory system. Whatever independent authority section 503(b)(3) may originally have provided with respect to section 505 drugs was nullified by the later-enacted 1962 drug effectiveness amendments.

The 1962 Amendments

The nature of the section 505 NDA review mechanism changed fundamentally as a result of the Drug Amendments of 1962.[8] Under the Amendments, an NDA had to be approved, rather than going into effect automatically. Evidence of effectiveness had to be provided. The FDA could require post-approval reporting. The grounds for refusing to approve, and withdrawing approval of, an NDA were expanded.

These changes meant that NDAs contained much more data to begin with, and, once approved, were used by the FDA to monitor the results of the drug's marketing through required NDA reports. This monitoring was not limited to determining whether a drug was "unsafe," but extended to whether it could still be said that the drug was "shown to be safe" or was still supported by evidence of effectiveness.

In the post-1962 period, the FDA also paid increasing attention to product-specific characteristics of drugs proposed in NDAs, such as drug chemistry, manufacturing, and bioavailability. Given this focus, and given the necessity of applying the effectiveness standard to all drugs in the marketplace as of 1962, the FDA could no longer acquiesce in the marketing of drugs without NDAs. Although the evolution of the NDA system was made more gradual by interim measures (pre-1962 ANDAs, the DESI review, the use of enforcement discretion), the end result – the system we have today – is a drug product

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[8] The Amendments are described in the 1973 Supreme Court cases. See, e.g., Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973).

licensing system in which every non-trivial attribute of a manufacturer's drug is specified in the NDA and subject to positive control by the agency through mandatory supplements requiring prior approval or strict adherence to standards set forth in the NDA itself or in regulations or guidance documents.

When section 505 was enacted in 1938, it was said that "[t]his is not a license provision, but is intended merely to prevent the premature marketing of new drugs not properly tested for safety." H.R. Rep. 2139, 75th Cong., 3d Sess. 9 (1938). That statement is no longer accurate. As of 1962, and certainly as it has evolved with respect to prescription drugs and "new" OTC drugs, section 505 is a license provision for authorizing the initial and continuing marketing of a particular drug of a particular manufacture in accordance with detailed specifications set forth in the NDA. Moreover the NDA itself is no longer simply an application; it is a continually updated compendium of the terms and conditions on which the manufacturer is permitted to market its drug product.

Rx Status Is an Approved Condition of Use
Subject to the NDA Procedures of Section 505

One of the terms and conditions specified in an NDA is Rx vs. OTC marketing status. In the modern era of FDA drug regulation, whether a drug is to be prescribed by physicians, or instead may be sold directly to patients for self-administration, affects not only how the drug is reviewed by the agency, but also the content of the labeling. The professional labeling of an Rx drug is a source of detailed use information to physicians. Virtually all new drug entities reviewed under section 505 are initially limited to Rx dispensing. That limitation is basic to the medical and risk-benefit judgments that go into determining the safety and effectiveness of a drug under its directions for use, as well as to the other conditions of drug use that are spelled out in the labeling. The Rx vs. OTC status of an NDA drug is, in other words, a centrally important condition of use that is closely tied to all the factually-specific attributes of the drug's safety and effectiveness that affect whether the NDA initially is, and after approval remains, eligible for approved status under section 505.

Under the FDCA, both the FDA and the NDA applicant are entitled to speak to the issue of which conditions are necessary for the safe and effective use of a section 505 drug. Prescription vs. OTC marketing status is one such condition of use. The regulatory framework for resolving disagreements between the agency and the NDA applicant is specified in the statute. As enacted in 1938, the statute provided that, "after due notice" and "an opportunity for hearing" to the applicant, the FDA could refuse to permit the NDA to become effective, or suspend its effectiveness, on safety grounds. These

procedures were revised in 1962 to conform with the affirmative approval structure that replaced the premarket notification system of the 1938 Act, and to include the conditions of approval added by the 1962 amendments. Notice and opportunity for a hearing now must precede an FDA decision to refuse to approve, or to withdraw approval of, an NDA (except in cases where an imminent hazard to public health is believed to exist). A hearing under section 505 is an adjudicatory proceeding in which the NDA applicant is the named respondent. The proceeding relates to facts that are specific to the drug covered by the NDA, and usually includes consideration of the NDA applicant's proprietary data relating to the matters in dispute.

The FDA's regulations specify in detail how the notice and hearing procedures of section 505 relate to the actions the FDA takes as part of the NDA review process. In the event of disagreement between the FDA and the applicant – that is, when an NDA is other than unqualifiedly "approved" – the regulations explain the steps that will occur should the disagreement not be resolved. See 21 C.F.R. §§ 314.101(a)(3) (filing over protest), 314.110 (approvable letter), 314.120 (not approvable letter), 314.125 (refusal to approve an NDA), 314.127 (refusal to approval an ANDA), 314.150 (withdrawal of approval), 314.200 (notice of opportunity for hearing). All of these procedures for the resolution of disagreements between the agency and the NDA applicant ultimately include the adjudicatory hearing procedure of sections 505(d) and (e) of the FDCA.

To be sure, these procedures are seldom actuated. Communications between agency drug reviewers and applicants for marketing approval occur on a continuous basis within the context of the NDA review, and in post-approval reporting and monitoring. Differences of opinion are resolved informally, or are left unresolved but uncontested by the applicant, in all but the rare case. Nevertheless, when the FDA takes a position that differs from the applicant's position as reflected in the NDA, and if the difference is not eliminated by agreement, the FDA's position is officially conveyed in a form that explicitly offers the applicant the right to use the statutory adjudication procedures if it wishes to continue asserting its own position.

The FDA's regulations guarantee the availability of these procedures to resolve disagreements over any and all attributes of a proposed drug. Under 21 C.F.R. §§ 314.125 and 314.150, there is no aspect of the physical composition of a drug, the circumstances of its manufacture, or the conditions of use specified in its labeling that would not be required to be considered in a hearing should there be an issue between the agency and the applicant. There is no legal basis for creating an exception for the particular – and basic – condition of use consisting of Rx marketing status.

The adjudicatory procedures of section 505 cannot be side-stepped by a regulation. It is, of course, lawful for an agency to issue across-the-board rules, and then apply them

in specific cases by means of mandated adjudicatory procedures, as the FDA itself has done. See, e.g., Upjohn Co. v. FDA, 811 F.2d 1583 (1987) (criteria for exemption from certain NADA requirements); PMA v. Richardson, 318 F. Supp. 301 (D. Del. 1970) ("substantial evidence" regulations for purposes of NDA approval and withdrawal). But an agency "cannot, merely by invoking its rulemaking authority, avoid the adjudicatory procedures required for granting or modifying individual licenses." Committee for Effective Cellular Rules v. FCC, 53 F.3d 1309, 1318 (D.C. Cir. 1995) (upholding across-the-board FCC rule affecting individual licenses without statutory adjudication, but distinguishing Aeronautical Radio, Inc. v. FCC, 928 F.2d 428 (1991), in which the court struck down a case-specific FCC "rule" that circumvented individualized adjudicatory proceedings).

The fact that section 503(b)(3) specifically authorizes the issuance of a regulation to remove an NDA drug from Rx status does not alter that conclusion. Ever since Abbott Labs. v. Gardner, 387 U.S. 136 (1967), the agency has taken the position that regulations under section 701(a) of the FDCA are substantive, binding rules as to the matters addressed. Yet a section 701(a) rule cannot override the adjudicatory procedures set forth in the FDCA when the FDA proposes particularized action. A rule issued under section 503(b)(3) has no greater legal weight than a post-Abbott Labs rule issued under section 701(a), and therefore the origin of such a rule in a specific statutory provision would not provide any additional legal basis for disregarding the procedures of section 505(d) and (e).

The NDAs for fexofenadine, loratadine, and cetirizine are company-specific and product-specific. The conditions of use specified in the NDAs for these products include prescription marketing. For the FDA to change that condition of use to require OTC marketing would constitute the modification of these individual NDAs. The purported basis for any such change would be safety information relating to each of the three drugs. This scenario is not one in which adjudicatory procedures can be dispensed with. Even if sections 505(d) and (e) did not exist, a modern NDA has the characteristics of a "license" under the Administrative Procedure Act, 5 U.S.C. § 551(8). See Air North America v. Dept. of Transp., 937 F.2d 1427, 1436-37 (9th Cir. 1991). Except where an agency issues a general rule, as noted above, license modifications without adjudicatory procedures are a violation of the APA, 5 U.S.C. § 558(c). See American Airlines, Inc. v. CAB, 359 F.2d 624, 631 (D.C. Cir. 1966).

Historically, the FDA has been meticulous in observing the adjudicatory requirements of section 505 for drugs subject to NDAs. For example, in the OTC Drug Review, the agency typically issues a notice of opportunity for hearing under section 505(e) and 21 C.F.R. § 314.200 when it proposes to withdraw the approval of an NDA for a drug that has been found to be generally recognized as safe and effective for OTC

use, see, e.g., NOOH for NDA 16-883, Antiminth (pyrantel pamoate), 52 Fed. Reg. 45868 (Dec. 2, 1987), and for a drug that has been found not to be safe and effective, see, e.g., NPRM for Topical Hormone OTC Drugs, 54 Fed. Reg. 40618, 40620 (Oct. 2, 1989). In 1990, the agency determined that the in vivo bioequivalence data requirement for conjugated estrogens should no longer be waived. Although 32 ANDAs for that drug were affected in the same way by this decision, the FDA did not issue a rule, but provided each applicant an NOOH on proposed individual withdrawals of approval. 55 Fed. Reg. 5074 (Feb. 13, 1990).

In light of the FDA's past practices, it would be anomalous, as well as legally unsupportable, for the agency to proceed without regard to the section 505 adjudication procedures to change the Rx condition of use in the NDAs for the three drugs covered by the Blue Cross petition. Whether fexofenadine, loratadine, and cetirizine should be Rx or OTC is a factually-based medical and public health issue that must be resolved on the merits. I have no view on that subject. As to the procedure the agency must employ if it concludes that Rx status is no longer justified, however, there is, in my view, no credible argument that resolution of the merits can occur outside the procedural framework of section 505.

Respectfully submitted,

Thomas Scarlett

TS/sas