

Aventis Pharmaceuticals



July 27, 2001

VIA OVERNIGHT MAIL

Ms. Sandy Titus
U.S. Food and Drug Administration
FDA/CDER/HFD-21
5600 Fishers Lane
Rockville, MD 20857

Dear Ms. Titus:

We write regarding the May 11, 2001 joint meeting of the Nonprescription Drugs Advisory Committee and the Pulmonary – Allergy Drugs Advisory Committee (“Committee”). According to the Agenda for that meeting, the Committee was convened to consider a Citizen’s Petition filed by Blue Cross of California (Docket No. 98P-0610) requesting that the U.S. Food and Drug Administration (the “Agency” or “FDA”) convert three prescription antihistamines, including fexofenadine hydrochloride (Allegra®), to over-the-counter (“OTC”) status. Although the potential switch of these drug products to OTC status raises numerous important issues, the FDA sought input from the Committee on only one of these issues. As a result of the narrow scope of the question presented to the Committee, the vote addressed neither the merits of the Citizen’s Petition nor the propriety of any future Agency action to attempt to force the sale of Allegra® over-the-counter. Indeed, several Committee members were clearly troubled by the narrow scope of the hearing and qualified their votes with additional comments on critical issues not presented to the Committee for a vote or recommended action.

Relatedly, the Committee’s limited conclusions have no bearing upon the legal issues under Section 505(e) of the Federal Food, Drug and Cosmetic Act (“FD&C Act”) if the Agency were to attempt to “force” Allegra® to be sold over-the-counter without Aventis’ consent. Finally, even if the May 11th Advisory Committee Hearing had encompassed all of the relevant issues, it could not take the place of the formal evidentiary hearing to which Aventis would be entitled under Section 505(e) of the FD&C Act, should the Agency attempt to force such a switch.

I. FDA Sought Input from the Committee on Only One Narrow Issue and Effectively Precluded Committee Consideration Of Other Key Issues Raised By The Citizen’s Petition

A. The Agency Foreclosed Consideration of Issues Relating to the Antihistamine Monograph

The Agency unduly limited the Committee deliberations by presenting the Committee with one very narrow issue — “does fexofenadine have a safety profile acceptable for OTC marketing, *i.e.*, can it be used safely without a learned intermediary?” See Transcript of Joint Meeting of Nonprescription Drugs Advisory Committee and Pulmonary - Allergy Drugs Advisory Committee (May 11, 2001) (hereinafter “TR”), at page 296, line 24 to page 287, line 5. Committee members were instructed to vote “yes” if any product containing fexofenadine at any marketed dose in any patient population with any conceivable labeling may be used safely without a prescription. TR, at page 287, line 6 to page 288, line

2. As set forth more fully below, additional pivotal assumptions concerning the impact and significance of the existing antihistamine monograph imposed by the Agency further limited the scope of the questions upon which the Panel ultimately voted. In the end, as the Agency itself acknowledged, the question presented to the Committee concerned only the safety of the molecule itself. TR, at page 304, line 20 to page 305, line 8.

Relying upon the antihistamine monograph initially developed in the 1970's, the FDA instructed the Committee to assume that allergic rhinitis is an appropriate OTC indication and that antihistamines are appropriate for over-the-counter marketing. This key limitation on the Committee's deliberations was explained by Dr. Martin, a Regulatory Review Chemist with the Division of OTC Drug Products, at the conclusion of his presentation: "The Agency has carefully evaluated the risk inherent in the OTC availability of antihistamines and has [already] concluded that with appropriate labeling these products can be considered reasonably safe and effective to use in an OTC environment." TR, at page 141, lines 9-14.

Similarly, Dr. Meyer, Director of the Division of Pulmonary and Allergy Drug Products, opened his presentation by advising the Committee that FDA "accepts allergic rhinitis to be an appropriate OTC indication" and "accepts antihistamines as appropriate for the (sic) OTC use." TR, at page 143, lines 2-5. As a result, Dr. Meyer explained that the Agency was "not seeking advice today . . . about allergic rhinitis as an OTC indication." TR, at page 143, lines 23-25. Dr. Meyer also advised the Panel that there is no distinction between the indications or therapeutic class of the first and second generation antihistamines. TR, at page 254, line 6 to page 255, line 3.

Echoing the Agency's comments, and based upon the charter given him by the Agency, the Committee Chairman also instructed the Committee to assume that allergic rhinitis is an appropriate OTC indication:

. . . [P]revious panels and the FDA have reviewed in detail the data that support or don't support whether allergic rhinitis and allergic related conditions are, in fact, self-diagnosable and treatable. We may disagree with those past judgments and *there may, in fact, be new data. The problem is we haven't seen it* and have no basis for re-addressing an issue that has been evaluated on a scientific basis extensively *in the past*.

TR, at page 238, line 19 to page 239, line 7 (emphasis supplied).

The Agency thus directed the Committee to accept as a given that, by virtue of a 20-year old monograph, allergic rhinitis is an appropriate OTC indication for which no physician intermediary is necessary for any type of patient. This instruction was, in fact, contrary to the testimony of all of the medical and academic disciplines that addressed the need for physician/patient interaction during the course of the hearing. *See, e.g.*, TR, at page 101, line 1 to page 103, line 25 (Dr. Schenkel); page 105, line 12 to page 109, line 3 (Dr. Emanuel); page 121, line 24 to page 125, line 10 (Dr. Parker); and page 189, line 18 to page 190, line 6 (Dr. Lanier).

Notwithstanding these unwarranted constraints, a number of panelists expressly disagreed with or expressed concern about the Agency's stated position on the monograph and the appropriateness of allergic rhinitis as an OTC indication. *See, e.g.*, TR, at page 253, line 9 to page 254, line 5; page 256, lines 2-11; page 311, lines 15-18; and page 315, lines 7-16 (Dr. Blewitt); page 318, lines 16-23 (Dr. Sachs); page 272, line 2 to page 273, line 6; and page 311, line 19 to page 314, line 1 (Dr. Baraniuk); and

page 293, line 11 to page 294, line 17 (Dr. Dykewicz). As Dr. Dykewicz explained “[B]ut I am really almost to the point of grave concern about the simplicity of the monograph . . . So I think the monograph, frankly, for all the antihistamines, needs to be vastly improved . . .” TR, at page 293, lines 11-19; page 294, lines 10-11. Dr. Baraniuk agreed, adding that “Somebody has to pick up the ball [the monograph] and reevaluate how these drugs work given our present knowledge of allergic rhinitis.” TR, at page 312, lines 16-18.

Because the FDA sought very limited advice on one narrow issue – the safety of each molecule – the Committee was precluded from considering a host of critical issues raised by the Citizen’s Petition, and presented or discussed by participants at the meeting. Among these were:

- Whether, in light of the complexity of proper diagnosis and treatment of seasonal allergic rhinitis, as well as associated co-morbid conditions, the disease is appropriate for self-diagnosis, self-treatment, and self-management, *see, e.g.*, TR, at page 86, line 8 to page 88, line 22 (Dr. Spiegel); page 121, line 24 to page 125, line 10 (Dr. Parker); and page 198, line 15 to page 200, line 19 (Ms. Sander);
- Whether, in light of new patient management techniques and new data associating allergic rhinitis with asthma, reliance on a 20-year old monograph to determine the legal status of a new class of drugs is appropriate, *see, e.g.*, TR, at page 90, line 15 to page 93, line 12 (Dr. Spiegel); page 106, line 23 to page 108, line 22 (Dr. Emanuel); and page 128, line 7 to page 129, line 9 (Dr. Quel);
- Differences in use patterns and patient populations associated with first generation and second generation antihistamines, and the related question whether an OTC actual use study is needed, *see, e.g.*, TR, at page 88, line 24 to page 90, line 13; page 93, line 14 to page 94, line 9; page 96, lines 13 to 22; and page 97, line 12 to page 98, line 7 (Dr. Spiegel); page 174, line 16 to page 175, line 11 (Dr. D’Agostino); and page 122, line 9 to page 123, line 22 (Dr. Parker);
- The question whether there is a need for an OTC label comprehension study to evaluate the potential for inappropriate use and to quantify potential risks, *see, e.g.*, TR, at page 83, line 19 to page 84, line 25 (Dr. Spiegel); and page 257, line 23 to page 258, line 14 (Dr. Johnson);
- The impact of forced OTC switches on drug development, *see, e.g.*, TR, at page 193, line 17 to page 197, line 10 (Dr. Kaliner); and page 224, line 17 to page 225, line 11 (Mr. Spilker); and
- The potential shift from use of non-sedating antihistamines to sedating antihistamines due to price differences among those alternatives, and the likely public health impact of such a shift, *see, e.g.*, TR, at page 74, lines 12 to 18 (Dr. Nader); page 94, line 11 to page 95, line 22 (Dr. Spiegel); page 206, line 8 to page 209, line 15 (Dr. Luce); and page 212, line 6 to page 214, line 2 (Dr. Hay).

For instance, the Committee was told it did not need to factor into its analysis co-morbid conditions such as asthma simply because it has been shown that certain of the antihistamines in question do not exacerbate asthma. TR, at page 317, lines 19-24. That simplistic position ignores the potential impact upon patients of the failure to timely diagnose asthma or other co-morbidities. As Dr. Leslie Clapp cogently explained to the Agency, “It is not because treatment of allergic rhinitis will decrease

asthma, but it is that, perhaps, a delay in treatment of allergic rhinitis in an appropriate way, or the misdiagnosis by patients, creates a cascade of events that leads to more complicated medical problems.” TR, at page 321, line 8 to page 322, line 8.

Dr. Sachs also shared her concerns, noting that based on her experience, parents frequently misdiagnose their children as having allergies when in fact those children suffer from asthma. TR, at page 318, lines 16-23. Dr. Meyer, FDA’s Director of the Division of Pulmonary and Allergy Drug Products, foreclosed further discussion by summarily dismissing such concerns, stating – without offering any evidence – that in his opinion they could be handled through labeling. TR, at page 318, line 24 to page 319, line 2.

With respect to actual use studies, several Committee members indicated the need for data on actual use in the OTC setting. *See, e.g.*, TR, at page 256, lines 2-11 and page 315, lines 7-16 (Dr. Blewitt). Dr. Ganley, Director, Division of OTC Drug Products, advised the Committee that the Agency had already concluded that actual use and label comprehension studies are not necessary in light of the monograph, but offered no support for that conclusion. TR, at page 258, line 15 to page 259, line 12. Other FDA representatives reiterated and emphasized this point, again without support. TR, at page 254, line 6 to page 255, line 3 (Dr. Meyer) and page 255, line 4 to page 256, line 1 (Dr. Jenkins). Nevertheless, eight Committee members sought data from actual use studies. *See* TR, at page 321, line 8 to page 322, line 8 (Dr. Clapp); page 316, line 16 to page 317, line 8 (Dr. Vollmer); page 311, lines 19-24 (Dr. Baraniuk); page 174, line 16 to page 176, line 14 (Dr. D’Agostino); page 257, line 23 to page 258, line 14 (Dr. Johnson); page 319, line 4 to page 320, line 2 (Dr. Kelly); page 54, lines 5-17 (Dr. Neill); and page 315, lines 7-16 and page 253, line 9 to page 254, line 5 (Dr. Blewitt). Three of the Committee members also commented upon the lack of label comprehension data. TR, at page 174, line 16 to page 176, line 14 (Dr. D’Agostino); page 257, line 23 to page 258, line 14 (Dr. Johnson); page 253, line 9 to page 254, line 5 and page 256, lines 2-11 (Dr. Blewitt).

Although some panelists challenged the Agency’s assumptions, it is clear that the Committee felt compelled to accept FDA’s constraints for purposes of their votes. *See, e.g.*, TR, at page 231, lines 10 to 14 (Dr. Neill); and page 316, line 16 to page 317, line 8; page 318, lines 3 to 13 (Dr. Vollmer). Accordingly, there can be no question that the resulting vote was tainted. As established by the evidence cited above, had the Committee been permitted to exercise independent judgment on the numerous critical issues, consideration of which was foreclosed by the Agency, the vote tally would have likely differed. Under these circumstances, the final vote neither supports the pending Citizen’s Petition, nor endorses FDA’s suggestion that it may act on that petition in the absence of additional supportive data.

B. Committee Members Also Expressed Reservations and Concerns About the Lack of Data

Putting aside the issue of whether actual use and label comprehension studies are needed, ten of the Committee members raised questions about whether the quantity and quality of other types of data and information presented to the Committee, many indicating that additional data or evidence was necessary. *See* TR, at page 327, lines 17-22 (Dr. Fink); page 52, line 19 to page 53, line 14 and page 310, lines 5-16, page 328, lines 11-13 (Dr. Krenzelok); page 245, line 24 to page 247, line 10; page 249, line 25 to page 250, line 17 and page 309, lines 13-15, 21-24 (Dr. Sachs); page 262, lines 7-18 (Dr. Vollmer); page 62, line 9 to page 63, line 12 (Dr. Baraniuk); page 176, lines 17-23 (Dr. Dykewicz); page 320, line 15 to page 321, line 6 (Dr. Ford); page 323, line 23 to page 324, line 10 (Dr. Johnson); page 235, line 11

to page 236, line 25 and page 319, line 4 to page 320, line 2 (Dr. Kelly); and page 179, line 1 to page 183, line 13 and page 306, lines 4-23 (Dr. Roden). In fact, Dr. Krenzelok went so far as to voice his opinion and concern that the Agency had used data “rather selectively.” TR, at page 310, lines 5-10.

Explaining that her yes vote was “a cautious yes vote,” Dr. Johnson indicated that the data presented by the Agency was “okay” but not of the quantity to which the NDAC is accustomed. TR, at page 323, lines 23 to page 324, line 10. Dr. Kelly was concerned about the fact that all of the professional organizations were opposed to the proposed OTC switch. He also believed that the Agency’s assumptions about OTC use were based upon opinion rather than data. TR, at page 319, line 4 to page 320, line 2. Dr. Krenzelok felt that there was not enough evidence “to draw any conclusions.” TR, at page 328, lines 11-13.¹

By foreclosing consideration of these and other key issues, the Agency effectively prevented the Committee from evaluating the overarching issue presented by the Citizen’s Petition, namely, whether the three antihistamines in question should be sold over-the-counter instead of by prescription. Nor did the Committee address the associated policy issues raised by the Agency’s potential departure from its well-established prior practice of allowing manufacturers, rather than the Agency, to initiate OTC switches. Instead, the Committee was advised that the Agency was actually interested only in the very limited issue of the safety of the molecule itself.

In sum, as reflected by the evidence cited above, there is no question that the Committee felt that its deliberations had been unduly circumscribed. While 18 Committee members responded affirmatively to the Agency’s narrow safety-related question as it related to Allegra®, several members voiced serious misgivings about the proposed switch, effectively qualifying or reversing their votes. As a result, the Committee’s “recommendation” is far weaker than a simple tally of the votes might suggest, and is, at best, inconclusive.

C. The Vote Provides No Guidance on Significant Issues that Must be Resolved Before Any Switch

Even if the final vote reflected the panelists’ independent judgment on the critical issues outlined above, that vote provided no direction on several basic issues that must be resolved in connection with any switch of Allegra® to OTC status. Typically, an advisory committee convened to provide a recommendation on a proposed OTC switch is provided with a detailed application submitted by the sponsor. Materials in such an application specify the formulation(s) to be switched, the proposed indication(s), and the relevant age groups and also provide draft labeling text for the committee’s consideration. Contrary to common practice, in this instance, panelists had no concrete proposal to consider, and instead were tasked with responding to the Agency’s narrow but general questions.

¹ Although Dr. Vollmer voted “no” to a switch of Allegra®, he voted “yes” with respect to Claritin®. He qualified this “yes” vote, stating that he so voted only to comply with the Agency’s instructions to the Panel, but that the vote made him “uncomfortable” because the Panel had been prevented from considering the numerous relevant issues raised during the hearing. TR, at p. 316, line 16 to page 317, line 8; page 318, lines 3-13.

While panelists raised some of these important issues during the Hearing,² there was no comprehensive discussion regarding the switch of specific indications or formulations for certain populations. Similarly, although several panelists offered general suggestions on labeling,³ there was no discussion of specific language, and certainly no assessment that any particular language can adequately convey important risk information to consumers.

There can be no serious contention that the Committee's vote resolved, or even addressed, these important issues. The Committee was expressly instructed to ignore potentially significant distinctions among formulations, indications, populations, and labeling. Specifically, panelists were to vote "yes" if any product containing fexofenadine at any marketed dose in any patient population with any conceivable labeling may be used safely without a prescription. TR, at page 287, line 6 to page 288, line 2. Moreover, FDA officials acknowledged that these issues had not been fully addressed. For example, Dr. Meyer admitted that the Agency's review of safety data focused solely upon single ingredient compounds and did not address the combination formulations. TR, at page 145, line 11 to page 146, line 1. Similarly, Dr. Ganley indicated that the hearing had raised several issues that FDA "may have to look into a little bit further." TR, at page 296, line 14 to page 297, line 4. Given that the Agency neither solicited nor received advice on specific formulations, indications, age groups, or label language, significant further review and analysis is necessary before the Agency even reaches a tentative conclusion on the propriety of a switch.

II. The Committee's Vote Fails To Address Critical Legal Issues that Must be Considered Before Any FDA Attempt To Force An OTC Switch

The Committee's vote is wholly irrelevant to the legal issues that the FDA would necessarily have to resolve in order to *even attempt* a forced switch of Allegra® from prescription to OTC status. As noted in other comments sent to the Docket, there are serious due process and constitutional "taking" issues raised by a forced switch. *See, e.g.*, Comments Submitted on Behalf of Pfizer Inc. (May 11, 2001); Response to Citizen Petition submitted by Washington Legal Foundation (May 11, 2001); *see also* Comments submitted by the Pharmaceutical Research and Manufacturers of America to Docket No. 00N-1256 (Aug. 25, 2000). Aventis reserves its right to revisit these and other legal issues should FDA proceed further in this matter.

III. The Committee Hearing Is No Substitute for the Formal Evidentiary Hearing Required, Should FDA Attempt to Force A Switch

² For example, Dr. Clapp questioned whether urticaria is an appropriate OTC indication. TR, at page 56, line 24 to page 57, line 22. Dr. Vollmer recognized that the Committee's recommendation may depend upon the specific formula at issue. TR, at page 261, lines 11 to 24. Similarly, Drs. Barainuk and Roden sought information on the specific indication(s) at issue. TR, at page 289, lines 9 to 14; page 291, line 15 to page 292, line 4. Other panelists highlighted the lack of available safety data for use with elderly and pediatric patients. *See, e.g.*, TR, at page 301, line 10 to page 302, line 1 (Dr. Bass); TR, at page 309, lines 21 to 24 (Dr. Sachs); and TR, at page 327, lines 17 to 22 (Dr. Fink).

³ *See, e.g.*, TR, at page 320, lines 4 to 13 (Dr. Fink); page 317, lines 10 to 18 (Dr. Sachs); page 314, line 20 to page 315, line 4 (Dr. Apter); page 329, line 16 to page 330, line 13 (Dr. Joad); and page 323, lines 16 to 21 (Dr. Neill).

Even if the Committee vote had reflected a thorough evaluation of all relevant issues, the May 11th hearing could not take the place of the formal evidentiary hearing to which Aventis would be entitled, should FDA attempt to switch Allegra® to OTC status. *See* 21 U.S.C. § 355(e); 21 C.F.R. §§ 314.150, 10.50(c)(16). This view was also expressed by Thomas Scarlet, Chief Counsel of the FDA from 1981 to 1989, in his letter to FDA's Docket Management Branch, dated May 24, 2001. Such a hearing must be conducted in accordance with detailed procedures set forth in 21 C.F.R. Part 12. The May 11th Advisory Committee Hearing was conducted in accordance with 21 C.F.R. Part 14, not Part 12, and Aventis was not afforded the various procedural rights guaranteed in a Part 12 hearing, such as the right to cross-examine witnesses. Indeed, as noted in Aventis' letter of May 8, 2001, because each manufacturer was limited to a 15 minute statement, the meeting failed to provide even the most minimal procedural due process protections. In short, putting aside the obvious deficiencies due to the narrow scope of the Committee's deliberations, the May 11th hearing is no substitute for the formal evidentiary hearing required under Section 505(e) of the Act.

IV. The Meeting Minutes of the May 11, 2001 Hearing Are Inaccurate

Aventis has reviewed the Agency's "Final Minutes" of the May 11, 2001 Advisory Committee Hearing, and notes for the record that those minutes do not accurately reflect the discussion that occurred at the Hearing, and instead are biased in favor of the position advocated by Blue Cross of California in its Citizen's Petition. For example, the minutes report that, "A sponsor asserted that [the] allergy landscape has changed and that it is different now than when [the] monograph was written. When asked how the landscape had changed there was no response." Aventis assumes that this entry refers to the exchange between Dr. Roden and Dr. Spiegel, Chief Medical Officer and Senior Vice President of Medical Affairs for Schering Plough. TR, at page 244, line 18 to page 245, line 22. Dr. Roden's question focused upon whether or not Schering's studies on Claritin took into account the various changes in the "allergy landscape" since finalization of the monograph. Dr. Spiegel fully responded to this question. More importantly, contrary to the implication raised by this entry in the minutes, the transcript is replete with information concerning the numerous developments in the diagnosis and treatment of allergic rhinitis and co-morbid conditions since finalization of the monograph. *See, e.g.*, TR, at page 90, line 15 to page 94, line 9.

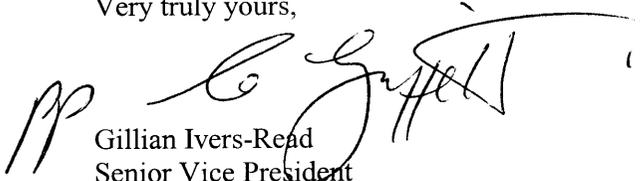
In light of this and other inaccuracies in the Agency's Final Minutes, all interested parties should rely exclusively upon the official transcript for a record of the May 11, 2001 hearing.

V. Conclusion

The May 11, 2001 hearing addressed only one of the numerous important scientific and legal issues raised by the potential switch of Allegra® to OTC status, and in light of the significant reservations expressed by the Committee Members, their vote on this one narrow issue is, at best, inconclusive. Even if the hearing and subsequent vote had broadly addressed all of the relevant issues, it could not serve as the formal evidentiary hearing to which Aventis would be entitled, should the Agency attempt to force a switch. Given the limited scope of the Committee's deliberations and vote, Aventis respectfully submits that the May 11, 2001 hearing failed to address the merits of the pending Citizen's Petition, failed to evaluate the propriety of any future Agency action forcing the sale of Allegra® OTC, and accordingly is wholly irrelevant to any future Agency action on that Citizen's Petition.

Ms. Sandy Titus
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Very truly yours,

A handwritten signature in black ink, appearing to read "Gillian Ivers-Read". The signature is written in a cursive style with a large, sweeping flourish at the end. To the left of the signature, there are two vertical lines, possibly initials or a mark.

Gillian Ivers-Read
Senior Vice President
Global Drug Regulatory Approvals

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