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0382 '03 JAN 24 09:21

January 23, 2003

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

Re: Docket No. 02P-0469 - Reply to Bausch & Lomb Incorporated Comments in Opposition to Allergan's Citizen Petition on Brimonidine Tartrate Ophthalmic Solution 0.2%

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WASHINGTON, DC

Fish & Richardson P.C. submits this Reply, on behalf of Allergan, Inc., to the comments filed by Bausch & Lomb Inc. (B&L) in opposition to Allergan's Citizen Petition on Brimonidine Tartrate Ophthalmic Solution 0.2% (BTOS 0.2%).

I. INTRODUCTION AND SUMMARY

Allergan's Citizen Petition concerns the voluntary withdrawal of ALPHAGAN® BTOS 0.2%. The petition raises several important issues of first impression that Allergan believes require careful analysis by the Food and Drug Administration (FDA). Rather than treat these issues with the seriousness they deserve, however, B&L's opposing comments attempt to cloud a proper analysis with irrelevant and unsubstantiated allegations of commercial foul play. These charges are wholly without merit. When the issues raised in the Citizen Petition are examined under the correct safety, efficacy, and pediatric exclusivity standards, Allergan is confident FDA will agree that the only legally acceptable means for FDA to meet its mandate under the Federal Food Drug & Cosmetic Act (FFDCA) is to refuse or suspend approval of generic applications for BTOS 0.2%.

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A. B&L's Allegations Regarding the Patent Lawsuit are Irrelevant and Misleading

The lawsuit between Allergan, Alcon, and B&L, raised at the outset of B&L's Opposition, is irrelevant to Allergan's request for FDA to act in accordance with its mission "to promote and protect the public health." That litigation is on-going and relates to the infringement of certain Allergan patents listed in the Orange Book.[1] This case is currently on appeal to the Federal Circuit and a decision in the matter is expected shortly. Regardless of the outcome (or any other patent infringement case brought by Allergan against B&L), Allergan's valid assertion of its patent rights against generic competitors has no relevance or bearing on the legal issues raised by Allergan's decision to withdraw ALPHAGAN® from the market. B&L's misguided effort to merge these distinct matters falls of its own weight.

B. Allergan Developed ALPHAGAN P® in Response to Physicians' Concerns Regarding Allergic Reactions to ALPHAGAN®

As explained in greater detail below, Allergan invested considerable funds in the research, development, testing, and approval of ALPHAGAN P® (BTOS 0.15%) because adverse events, such as allergic reaction, were found to be important efficacy considerations for physicians prescribing ALPHAGAN®. The results of Allergan's longer term clinical studies -- not mentioned in B&L's opposition -- show that ALPHAGAN P®, with its 33% reduced concentration of brimonidine and different preservative, is as effective as ALPHAGAN® in treating open-angle glaucoma while

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[1] Allergan, Inc. v. Alcon Labs., Inc., 200 F.Supp.2d 1219, 1225 (C.D. Cal. 2002). Significantly, the Federal Trade Commission, in a report prepared with the help of the FDA staff and presented to Congress by Commissioner Muris, states that the district court's ripeness decision was wrong and should be overruled. See, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY, Federal Trade Commission, http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf (July 2002).

resulting in a statistically significant decrease in the occurrence of allergic conjunctivitis. Because fewer glaucoma patients experience adverse effects with ALPHAGAN P®, fewer patients are required to discontinue use of brimonidine, a circumstance that would put them at risk of faster visual field degradation. For this reason, ALPHAGAN P® is considered to be a more effective drug than ALPHAGAN® for treating open-angle glaucoma.

B&L's claims that purely "financial" considerations motivated Allergan to withdraw ALPHAGAN® are belied by the facts. Allergan spent over a year (the minimum period needed to evaluate ophthalmic patient allergenicity) gathering relevant feedback, prior to withdrawal, to ensure that ALPHAGAN P® had demonstrated superiority over ALPHAGAN®. Moreover, Allergan withdrew ALPHAGAN® from the market at a time when its sales were four times higher than ALPHAGAN P®, underscoring the fact withdrawal was not for "financial" concerns, but rather for the reasons Allergan has already stated – the availability of a safer, more effective formulation of brimonidine tartrate for the treatment of open-angle glaucoma.

C. B&L Applies the Wrong Legal Standard for Voluntary Withdrawal

B&L incorrectly relies on provisions in the FFDCA that govern mandated product withdrawals, as opposed to voluntary product withdrawals, the matter at issue here. The FFDCA differentiates quite clearly between these two types of withdrawals and holds a mandated withdrawal to a much higher standard due to the Constitutional prohibitions against a regulatory "taking." See 35 U.S.C. § 355(e) (requiring a product to be "unsafe for use" for an FDA-mandated withdrawal). By contrast, when a drug product is withdrawn voluntarily, the standard is not as high to be justified on public safety and welfare grounds -- particularly where there are no generic products yet on the market -- because the government is not acting adverse to the drug manufacturer's property rights. Thus, FDA may find a product not "unsafe for use"

but nonetheless properly withdrawn for "safety and/or efficacy" reasons where it is shown that the withdrawn product (in this case, ALPHAGAN®) was less safe and effective than the product currently available (in this case, ALPHAGAN P®).

D. B&L's Labeling Proposals will not Ensure Safety in the Pediatric Population and Run Afoul of Allergan's Labeling Exclusivity Rights

Unable to resolve the pediatric safety issues raised in Allergan's Citizen Petition, B&L makes numerous, extra-legal suggestions in an attempt to deflect attention from the seriousness of this matter. None of these have merit:

- B&L asserts that FDA is authorized to permit generics to list any protected pediatric labeling information necessary to protect pediatric patient populations, however, nothing in the FFDCA or the Best Pharmaceuticals for Children Act (BPCA) sanctions such relief where the protected labeling comprises a body of information required for safe use in children;[2]
- B&L suggests that FDA allow generics to simply cross-reference the labeling of ALPHAGAN P®, a different drug product with a different formulation than ALPHAGAN®, however, such a procedure is fraught with safety implications as well as outside the law; and
- B&L urges FDA to allow generics to label their BTOS 0.2% products with a statement that the "drug is not labeled for pediatric use," despite the fact that Allergan has shown that such statement will not stop the mis-use of BTOS 0.2% in pediatric populations.

In short, none of B&L's suggestions offer a workable solution that protects Allergan's exclusivity rights and is in accordance with the law.

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[2] FDA has recognized the dilemma presented and, on occasion, has allowed the generic drug to cross-reference the reference listed drug labeling. Once a reference listed drug is withdrawn, however, such labeling alternative is foreclosed.

II. ALLERGAN'S REPLY

A. Issues Regarding Voluntary Withdrawal

1. The Objective Statutory Standards for Government-Imposed Product Withdrawals do not Apply to Voluntary Withdrawals by Manufacturers

B&L's assertion that the voluntary withdrawal of a drug product for reasons of safety and efficacy must meet the same statutory standards as a government-imposed withdrawal (per 21 U.S.C. § 355(e)) is unsupported by law. Section 355(j)(7)(C) of Title 21 of the United States Code, codifying the Hatch-Waxman Act, states:

> If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) [§ 355(e)] of this section **or** was withdrawn or suspended under paragraph (6) [§ 355(j)(6)] **or** if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its publication in such list, it shall be immediately removed from such list . . .

(emphasis added). In other words, Congress separated the requirements of § 355(e), which objectively mandates a withdrawal of a drug that is "unsafe for use," from the FDA's subjective determination of whether a voluntary withdrawal was made for reasons of safety and efficacy under the statute. Congress had good reason for drafting the statute in this manner.

For a government-imposed withdrawal of a drug product to be constitutional it cannot amount to a regulatory taking.[3] Any statute or regulation that allows the FDA to take such action must ensure that a high standard of public safety and welfare is met to justify the economic impact on the drug owner.[4] Where withdrawal is initiated by the drug owner, however, the same high standard ("unsafe for use") does not have

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[3] See, e.g., City of Monterey v. Del Monte Dunes, Ltd., 526 U.S. 687 (1999).
[4] Id.

to be met in order for the Secretary to determine that it was for statutory reasons of safety and efficacy.

Moreover, where a drug product has been voluntarily withdrawn by a manufacturer who makes an alternative product with the same active ingredient and indications for use but with a better adverse event profile, the FDA has no reasonable basis for refusing to accept the manufacturer's assertion that withdrawal was made for statutory reasons of safety and effectiveness. As B&L's Opposition (p.13) even notes, FDA has historically regarded ocular allergy to be an important efficacy concern for glaucoma drugs. A drug with higher rate of ocular allergy than another would be expected to result in a higher rate of patient withdrawal from treatment making such drug "less effective" than the other. Accordingly, it must follow that where a drug is voluntarily withdrawn from sale for this reason -- particularly where the safer or more effective drug is provided by the same manufacturer for the same approved indications -- FDA should conclude that the drug was withdrawn for statutory reasons of safety and effectiveness.

2. The Pertinent Evidence Points to the Conclusion that Allergan Withdrew ALPHAGAN® for Reasons of Safety and Effectiveness Under the Relevant Statutory Provisions.

B&L's biased assertion that Allergan withdrew ALPHAGAN® simply to subvert generic competition is wholly unsubstantiated. Presented below are the established facts, all of which completely undermine this claim.

First, Allergan stated that it withdrew ALPHAGAN® because it had a safer and more effective alternative already on the market. Allergan backed these statements with solid evidence based on clinical data and physician's reports that attested to the superior side effects profile of ALPHAGAN P®.

Second, under the current regulatory standards for examining a withdrawer's intent, FDA is required to presume that ALPHAGAN® was withdrawn for reasons of safety and efficacy under the statute. In its original rulemaking on the matter, FDA stated "[i]f a drug manufacturer withdraws a drug from the market which accounted

for significant sales to that manufacturer, and there is no evidence to the contrary, it will be presumed that the withdrawal was for safety or effectiveness reasons." [5] At the time of withdrawal, ALPHAGAN® was Allergan's second highest grossing product.[6]

Lastly, FDA stated that "[t]he agency will also consider other factors in determining whether a market withdrawal was for safety and effectiveness reasons, such as increases in the number of adverse drug reactions reported on the drug and published or unpublished studies of the drug questioning its safety or effectiveness."[7] Here again, these factors weigh in Allergan's favor. ALPHAGAN P® was developed in specific response to concerns about allergic reactions to ALPHAGAN® and, through clinical trials, it was established that ALPHAGAN P® had a superior adverse event profile than ALPHAGAN®. These facts are undisputed; thus, there can be no sound reason to question the veracity of Allergan's statement that it withdrew ALPHAGAN® from sale for reasons of safety and efficacy in accordance with the statute.

B. Clinical Data and Physician Reports Support Allergan's Reasons for Voluntary Withdrawal of ALPHAGAN®

Using snippets of analyses of short-term clinical trial results in small patient populations, B&L erroneously argues that ALPHAGAN P® does not have a better safety and efficacy profile than ALPHAGAN®. On page 11 of its Opposition, for

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[5] Id.
[6] As B&L points out on page 12 of its opposition, in the year prior to its withdrawal, "Allergan sold over 4 million units of Alphagan, compared to less than a million units of Alphagan-P." This evidence clearly establishes the presumption that Allergan's withdrawal was for reasons of safety and efficacy.
[7] 54 Fed. Reg. 2887, 28907 (July 1989).

example, B&L challenges FDA's approval of ALPHAGAN P® in the first place, by stating that "the 0.2% formulation is the lowest effective dose." This unsubstantiated allegation, like much of B&L's Opposition, is taken out of context from an incomplete report at the three month point of two twelve month studies. To be more specific, the three month analysis cited by B&L "suggested that BPOS 0.15% was slightly inferior to Alphagan in lowering IOP" (emphasis added). NDA 21-262, Statistical Review at 10 (B&L Attachment 5). What the B&L comments fail to mention, however, is that at the conclusion of the full twelve months, both studies showed that BTOS 0.15% was every bit as effective as ALPHAGAN® in lowering IOP while having a much lower incidence of adverse effects than ALPHAGAN®. See Attachment 1 (Study Number 190342-007) and Attachment 2 (Study Number 190342-008).

In fact, in Study Number 190342-007, the rate of allergic conjunctivitis with BTOS 0.15% was 59% less than with ALPHAGAN® (7.1% of patients v. 17.1%), and in Study Number 190342-008, the rate of allergic conjunctivitis with BTOS 0.15% was 21% less than with ALPHAGAN® (12.0% of patients v. 15.2%). At the end of Study Number 190342-007, the rate of withdrawal from the study was 25% less for BTOS 0.15% than for ALPHAGAN®, and in Study Number 190342-008, the rate of withdrawal for BTOS 0.15% was 16% less. After launching ALPHAGAN P® (BTOS 0.15%), Allergan gathered information affirming that ALPHAGAN P® was preferred by both physicians and patients, resulting in better patient adherence to glaucoma therapy. See, e.g., Attachment 3. B&L offers no legitimate basis for questioning these trial results.

C. Generic Versions of BTOS 0.2% Cannot Be Safely Approved Without Expressly Relying on Allergan's Protected Pediatric Labeling

In implementing Section 11 of the BPCA, FDA explained that its task "is to ensure that labeling for ANDAs adequately protects pediatric health and is consistent with marketing exclusivity for the innovator."[8] B&L's comments attempt to undermine FDA's task and subvert the law with proposals that skirt both the BPCA and Allergan's rights to labeling exclusivity.

To ensure the safety of listed drugs and their generic counterparts for use in children, FDA requires these products to disclose any special instructions, warnings, contraindications and other relevant information dealing with pediatric use on their labels. 21 C.F.R. § 201.57. In cases where pediatric labeling is protected by exclusivity, however, generics cannot label their products with the protective pediatric information of the listed drug. A limited exception to this exclusivity is provided in Section 11(a) of the BPCA which authorizes the FDA to approve generic labeling with a statement of appropriate "contraindications, warnings, or precautions" taken from the protected pediatric label provided such selective disclosures do not make the generic label false or misleading and do not make the drug unsafe for use in children. 21 C.F.R. § 314.127(a)(7). By its precise wording, this limited authorization permits only selected portions of protected labeling to be used by generics and thus, is a far cry from the wholesale labeling solution being advocated by B&L ("any...information that FDA may see fit to require"). B&L Opposition at 14. Due to the nature of ALPHAGAN®'s protected pediatric labeling, which goes well beyond the labeling statements authorized by the BPCA and includes extensive safety information and adverse reactions in various pediatric populations, the type of

[8] FDA's Jan 24, 2002 Response to Bristol-Myers Squibb Company's Citizen Petition of December 26, 2001, p. 3.

generic copying permitted under the BPCA is simply insufficient to ensure the safe use of generic BTOS 0.2% for children.[9]

This problem is not one of first impression for the FDA. On several recent occasions, FDA addressed this dilemma by allowing the generic to cross-reference the labeling (and associated pediatric information) of the reference listed drug product. What FDA never previously confronted, however, and is a matter of first impression here, is what happens when the reference listed drug has been withdrawn from the market. Because there is no label to cross-reference by generics, no pediatric safety information for these drugs can be communicated to the public.

B&L's suggestion that FDA simply allow generic BTOS 0.2% products to reference the labeling of ALPHAGAN P®, is unprecedented. Nowhere does the FFDCA permit the substitution of a different drug product for a reference listed drug that has been withdrawn from the market, and for good reason. As noted above, ALPHAGAN P® is a different formulation than ALPHAGAN®. It is 33% less concentrated, has a different formulation and contains a different preservative. Although ALPHAGAN P®'s labeling contains similar (but not identical) pediatric information as the ALPHAGAN® label, the labeling is still very new and based solely on initial pediatric studies. As further data and adverse event reports become available, the labeling for ALPHAGAN P® might very well change.[10] Whether such labeling changes would, or should, be applicable to a BTOS 0.2% generic becomes even more problematic once a labeling cross-reference is allowed. Conversely, should BTOS 0.2% products be found to produce new adverse side effects that may be unrelated to ALPHAGAN P®, there would be no mechanism to change the reference drug label relied on by generics now that ALPHAGAN® has been

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[9] FDA's legal authority to authorize generic use of protected pediatric labeling information in the case of ALPHAGAN® is severely circumscribed by the strictures in the BPCA. There is no "warning" section on the ALPHAGAN® label and the "contraindications" and "precautions" sections of the label contain no mention of pediatric use.

[10] See, e.g., Ass'n of Am. Physicians and Surgeons, Inc., v. United States Food and Drug Admin., Civil Action 00-02898, slip op. at *3-4 (D.D.C. October 17, 2002).

withdrawn. In short, B&L's proposal to allow a generic BTOS 0.2% to reference ALPHAGAN P® is ill considered and would undermine FDA's ability to ensure safe use of brimonidine treatment in children.

B&L's final suggestion that FDA should simply require generics to label their BTOS 0.2% products with a statement that "the drug is not labeled for pediatric use," is at odds with reality. As Allergan's reports to FDA have shown, physicians have been prescribing ALPHAGAN® for children ever since it first appeared on the market in 1996 even though its labeling indicated it was not for pediatric use. Before FDA requested Allergan to run pediatric clinical trials to determine safe use of BTOS 0.2% products in the pediatric population, Allergan had already received several spontaneous reports of serious and potentially life-threatening adverse events (e.g., coma) in infants. By the time Allergan withdrew ALPHAGAN® from the market, pediatric prescriptions were growing despite the fact that the side effects profile in pediatric patients was incomplete and not well documented because such labeling was so new. Accordingly, any notion that physicians will not prescribe generic BTOS 0.2% to children because the drug is "not labeled for pediatric use" is a proven fiction. The only way for FDA to ensure safe use of BTOS 0.2% in children is by refusing to approve any generic application that contains less than the full body of protected pediatric labeling information contained on the current ALPHAGAN® label.

III. CONCLUSION

Because Allergan has withdrawn ALPHAGAN® for safety and efficacy reasons, and because safe use of BTOS 0.2% cannot be assured in the pediatric population without the protected labeling approved for ALPHAGAN®, Allergan

respectfully requests the FDA to refuse or suspend approval of any generic application for BTOS 0.2%.

Respectfully Submitted,

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