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BY FACSIMILE/CONFIRMATION COPY BY MAIL

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

**RE: Docket No. 02P-0469 – Comments of Bausch & Lomb Incorporated
in Opposition to Allergan, Inc., Citizen Petition on Brimonidine
Tartrate Ophthalmic Solution 0.2%**

Dear Sir or Madam:

On October 25, 2002, Allergan, Inc. (Allergan), by its counsel, filed the above-referenced citizen petition requesting that the Food and Drug Administration (FDA) "refuse or suspend approval" of any abbreviated new drug application (ANDA) for brimonidine tartrate ophthalmic solution, 0.2%. Allergan markets this product under the trade name Alphagan. Bausch & Lomb Incorporated (B&L) has an ANDA pending before the agency for the product. For the reasons set forth below, Allergan's citizen petition should be denied.

I. Background

Allergan obtained approval of Alphagan, a 0.2% brimonidine tartrate ophthalmic solution, on September 6, 1996 for lowering intraocular pressure in patients with open-angle glaucoma. NDA 20-613. Alphagan qualified for 5-year exclusivity, which received a pediatric extension to March 6, 2002. Allergan obtained a pediatric indication for Alphagan in December 2001. The exclusivity for the pediatric indication expires in June 2005.

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Allergan has aggressively promoted Alphagan as a highly safe and effective alternative to other glaucoma treatments. With the imminent expiration of NCE exclusivity, however, Allergan was confronted with the possibility of generic competition and reduced profits. Accordingly, Allergan undertook steps to protect its Alphagan franchise.

In 2001, Allergan submitted information to FDA on two patents – U.S. Patent Nos. 6,194,415 and 6,248,741. These patents claim the use of brimonidine for its neuroprotective properties. The neuroprotectant use of brimonidine is not approved in the Alphagan NDA. These patents therefore did not qualify for Orange Book listing. See 67 Fed. Reg. 65448, 65452 (Oct. 24, 2002). However, FDA does not screen proposed patent listings. Accordingly, the two patents were listed.

In October 2001, B&L and Alcon Research, Ltd. (Alcon) submitted ANDAs referencing Alphagan. Although neither ANDA sought approval of brimonidine for the patented method of use, FDA's policy is to permit statements under 21 U.S.C. § 355(j)(2)(A)(viii) only if the patented method of use is also an approved use. For this reason, B&L and Alcon were required to submit Paragraph IV certifications with respect to the two Allergan patents.

B&L and Alcon provided notice to Allergan of the Paragraph IV certifications, and Allergan sued each company for patent infringement within the 45-day window, thereby triggering a 30-month stay of approval of the ANDAs. Allergan, Inc. et al. v. Alcon Laboratories, Inc., et al., No. SACV 02-40 DOC (AN) (C.D. Cal) (Attachment 1). On May 8 and June 4, 2002, the district court granted both Alcon's and B&L's motions for summary judgment of noninfringement of both patents. Allergan filed a notice of appeal on June 13 in the Federal Circuit. The appeal is currently pending.

Recently, Allergan has listed a third patent, U.S. Patent No. 6,465,464. This patent is essentially identical to the previously issued patents. B&L has submitted a paragraph IV certification to this patent, and presumably Allergan will file a patent infringement lawsuit to obtain an additional 30-month stay of approval of B&L's ANDA.

Not content with obstructing approval of generic versions of Alphagan by inappropriate Orange Book patent listings, Allergan is now attempting to argue that it withdrew Alphagan from the market for "safety" and "effectiveness" reasons, so as to preclude the use of Alphagan as a reference listed drug. Specifically, in or around July 2002, Allergan announced that it was voluntarily withdrawing Alphagan, and "replacing" it with Alphagan-P. Approved on March 16, 2001, NDA 21-262, Alphagan-P, like Alphagan,

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is indicated for lowering intraocular pressure in patients with open-angle glaucoma. However, Alphagan-P contains 0.15% rather than 0.2% brimonidine, and the preservative Purite® (sodium chlorite) instead of the benzalkonium chloride used in Alphagan.

In light of the Alphagan withdrawal, on August 27, 2002, Alcon filed a citizen petition, pursuant to 21 C.F.R. § 314.161, requesting that FDA determine that the withdrawal was for reasons other than safety or effectiveness. Alcon Citizen Petition, Dkt. No. 02P-0404. Ivax Pharmaceuticals, Inc. (Ivax) filed a similar petition on August 30, 2002. Ivax Citizen Petition, Dkt. No. 02P-0391.

In response to these petitions, Allergan filed a citizen petition requesting FDA to refuse to approve, or to suspend approval of, any ANDAs referencing Alphagan. Allergan stated that the withdrawal of Alphagan was for "safety and effectiveness" reasons. According to Allergan, Alphagan causes more allergic reactions than Alphagan-P. This higher rate of allergenicity allegedly results in decreased effectiveness of Alphagan due to discontinuation of use by patients. Therefore, Allergan contends, under 21 C.F.R. §§ 314.127(a)(11) and 314.161, FDA may not approve the ANDAs that rely on Alphagan as the reference listed drug. Allergan also contends that denial or suspension of approval of a generic version of Alphagan is warranted because its pediatric labeling exclusivity for Alphagan and the withdrawal of the Alphagan labeling render the agency unable to ensure the safety and effectiveness of a generic version of Alphagan for use in the pediatric population.

Allergan's citizen petition should be denied. Allergan withdrew Alphagan from the market for commercial reasons, not for reasons of safety or effectiveness. Allergan's action is an obvious ploy to prevent ANDAs from using Alphagan as a reference listed drug. In fact, Alphagan-P is not safer or more effective than Alphagan. FDA has explicitly stated that Alphagan-P and Alphagan have "similar" safety profiles, and one FDA reviewer even noted the inferiority of Alphagan-P to Alphagan in terms of effectiveness. Allergan's make-weight argument based on the recent pediatric labeling supplement is contrary to the Best Pharmaceuticals for Children Act and factually wrong.

II. Legal Framework

A. Withdrawal for Safety and Effectiveness Reasons

Under FDA's regulations, when the holder of a new drug application (NDA) voluntarily withdraws a drug from sale "for reasons of safety or effectiveness," and there is a pending ANDA at the agency that relies on the withdrawn drug, FDA is required to make

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an independent determination as to the reason for the withdrawal prior to approving the ANDA. 21 C.F.R. § 314.161(a)(1). The regulations also provide that a party may petition the agency to make such a determination, *id.* § 314.161(b), as has been done in this case by Alcon and Ivax. If the final determination of the agency is that the drug was not withdrawn for reasons of safety or effectiveness, FDA may approve the pending ANDAs.¹

1. "Safety or effectiveness reasons"

The purported safety and effectiveness issues raised by Allergan must be put into the context of the statutory provisions governing withdrawal of NDA approval. Section 505(j)(6) of the Federal Food, Drug, and Cosmetic Act (FDC Act) provides that the approval of an ANDA must be withdrawn or suspended if the NDA for the reference listed drug on which the ANDA relies is withdrawn for any of the reasons set forth in the first sentence of section 505(e) of the Act, or if the reference listed drug is voluntarily withdrawn "for safety or effectiveness reasons," as determined by the agency. 21 U.S.C. § 355(j)(6).² Similarly, an ANDA may not be approved if it relies on a reference listed drug whose NDA has been withdrawn or that is voluntarily withdrawn from the market for safety or effectiveness reasons. *Id.* § 355(j)(7)(C).

The grounds for withdrawing NDA approval for safety or effectiveness reasons under section 505(e) are:

¹ Even if FDA determines that the withdrawal was for safety or effectiveness reasons, an ANDA relying on the withdrawn drug may still be approved if the ANDA applicant can demonstrate that the reasons for withdrawal of the listed drug are not relevant to the safety or effectiveness of the drug that is the subject of the ANDA. *Id.* § 314.153(b)(6).

² Section 505(j)(6) also lists a third basis for withdrawal or suspension of an ANDA, i.e., the circumstance in which the ANDA relies on a drug that is the subject of a previously approved ANDA, and the previous ANDA in turn relied on an NDA that has been withdrawn, or determined to be withdrawn, for safety or effectiveness reasons. As a practical matter, this basis will rarely be applicable because sequential reliance for ANDAs occurs infrequently.

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(1) clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved;

(2) new evidence of clinical experience ... evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; and

(3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, ... there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Id. § 355(e)(1)-(3) (emphasis added).

The section 505(e) criteria govern the withdrawal of a drug application by the agency; they do not directly apply to a decision by a manufacturer to withdraw a drug voluntarily for "safety or effectiveness reasons." Nonetheless, the types of "safety or effectiveness reasons" substantial enough to bar approval of generic versions of a drug voluntarily withdrawn by its manufacturer must be the same. This is so because it would be anomalous for one of the bases for withdrawal or denial of ANDA approval in sections 505(j)(6) and (7)(C) to impose a different standard than the others. That would be the result if the phrase "for safety or effectiveness reasons" in sections 505(j)(6) and (7)(C), and in FDA's implementing regulation, 21 C.F.R. § 314.161, were interpreted to mean any aspect of the listed drug that has some conceivable relationship to safety or effectiveness, no matter how minor. Taken to its logical conclusion, such an interpretation would mean that an NDA that could not be withdrawn by FDA under section 505(e) could nonetheless be regarded as voluntarily withdrawn "for safety or effectiveness reasons." Thus, for example, two companies could market the same drug under NDAs. Company A could voluntarily withdraw its drug from the market "for safety or effectiveness reasons" that would be insufficient to warrant withdrawal of Company A's NDA. In that circumstance, FDA could not compel Company B to withdraw the very same drug, even if the reasons underlying Company A's withdrawal also applied to Company B's drug. Under this interpretation, approval of a generic version of Company A's drug would be barred, even

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though the generic was the same as Company B's drug, which was permitted to remain on the market.³

Such an outcome would be both logically indefensible and inconsistent with the purpose of the Hatch-Waxman Amendments to permit the entry of safe and effective generic drugs onto the market. Therefore, to preclude the approval of ANDAs for a discontinued reference listed drug, the "safety or effectiveness" reasons underlying a voluntary drug withdrawal must be the same as those set forth in § 505(e) governing FDA's withdrawal of NDA approval. Examples of voluntary drug withdrawals in recent years demonstrate that the safety or effectiveness issues that lead to such action are of an order of significance that would justify mandatory withdrawal under section 505(e). These examples include: Omniflox (temafloxacin hydrochloride), for risk of hypoglycemia, hemolytic anemia, and kidney failure; Pondimin (fenfluramine hydrochloride) and Redux (dexfenfluramine hydrochloride), for risk of valvular heart disease; Seldane (terfenadine), Hismanal (astemizole), Raxar (grepafloxacin hydrochloride), and Propulsid (cisapride), for risk of Torsades de Pointes, a potentially fatal irregular heartbeat; Duract (bromfenac sodium), for risk of liver failure; and Baycol (cerivastatin sodium) for risk of severe damage to skeletal muscle. These drugs involved serious risks that outweighed their

³ The situation is analogous to the one in which the innovator obtains a new indication or other aspect of its drug labeling, and chooses to discontinue the old labeling on which an ANDA applicant may have relied. See Guidance for Industry: Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications (Oct. 2000): "In theory, the innovator could delay generic competition indefinitely by continuing to make minor – but protectable – changes to the drug, and removing unprotected labeling. If this approach were effective, the Agency also could expect to review many more labeling supplements, possibly for changes that, although sufficiently innovative to warrant patent or exclusivity protection, do not necessarily represent significant improvements in the currently marketed drug." Alphagan-P can not be characterized as an improvement over Alphagan in terms of safety and effectiveness, much less a significant one. If its petition is granted, Allergan could perpetuate a pattern of continually "improving" its current drug and withdrawing the old one from the market, thereby establishing a virtual monopoly for the brimonidine market for treatment of glaucoma. The preclusion of generic drugs from the market in this way is completely at odds with the intent of the statute, as FDA has recognized.

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benefits. This is the threshold level of "safety" and "effectiveness" implicit in a voluntary withdrawal "for safety or effectiveness reasons" under 21 C.F.R. § 314.161.

2. Stated reasons for withdrawal versus manufacturer's actual intent

In evaluating the reasons underlying a voluntary withdrawal, the agency looks beyond the manufacturer's stated reasons in order to determine the manufacturer's actual intent. See 54 Fed. Reg. 28872, 28907 (July 10, 1989) (proposed rule):

The agency may determine whether a listed drug was withdrawn from sale for safety and effectiveness reasons, as required by section 505(j)(5) of the act, by attempting to focus on the intent of its manufacturer.... The legislative history of this provision does make clear ... Congress' intent that the agency examine whether the manufacturer had safety or effectiveness concerns about the withdrawn drug independent of the reasons given by the manufacturer for the withdrawal. Congress, therefore, must have expected the agency to rely upon circumstantial evidence and logical inference to determine the actual intent of those who decided to withdraw the product from the market.

Id. (citation omitted).

One piece of circumstantial evidence that a withdrawal was for safety or effectiveness reasons is that "a pharmaceutical manufacturer would not cease distribution of a profitable drug if safety or effectiveness concerns had not arisen." Id. However, this presumption is overcome by "convincing evidence to the contrary." Id.

B. Pediatric Labeling

Allergan obtained a pediatric indication for the Alphagan product in December 2001, and obtained exclusivity for the indication that extends to August 2005. Under FDA's regulations, a protected labeling condition may be carved out of ANDA labeling, 21 C.F.R. § 314.94(a)(8)(iv), if doing so does not render the proposed drug less safe or effective for the remaining conditions. Id. § 314.127(a)(7). Under the Best Pharmaceuticals for Children Act (BPCA), ANDA labeling can carve out pediatric conditions of use, and FDA can require such labeling to contain a statement of appropriate

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contraindications, warnings, or precautions necessary to the safe use of the drug in children.
21 U.S.C. § 355a(o).

III. Allergan's Petition Should Be Denied

A. Allergan Did Not Withdraw Alphagan for Reasons of Safety or Effectiveness

Allergan's claim that the withdrawal of Alphagan was for reasons of safety and effectiveness is refuted by "convincing evidence to the contrary." The evidence demonstrates that Allergan's action was motivated by business concerns. The safety and effectiveness issues asserted by Allergan do not rise to the threshold level of significance that would lead a company to withdraw a drug for "reasons of safety or effectiveness." Further, Allergan is marketing a replacement product, Alphagan-P, that presents similar safety and effectiveness concerns while assuring continued revenue to Allergan. This revenue will be protected from generic competition for many years if Allergan persuades FDA that Alphagan cannot be used as a reference listed drug for ANDA approvals. Taken as a whole, the evidence makes clear that the withdrawal of Alphagan was not for reasons of safety and effectiveness, but is the latest in a series of tactics intended to delay generic competition.

1. The purported Alphagan "safety issue" does not rise to the threshold implicit in §§ 355(j)(6) and (7)(C)

Allergan claims that the 0.15% product "has a much lower incidence of allergy – greater than 40% lower – than the 0.2% formulation." Allergan Petition at 3. This claim is misleading. Although publicly available information reveals that there may be a difference in the incidence of allergic conjunctivitis between the two drugs, the actual difference is trivial – approximately 7% lower in Alphagan-P. NDA 21-262, Medical Review, 120-Day Safety Data (Attachment 2); Katz, L.J., M.D., Twelve-Month Evaluation of Brimonidine-Purite Versus Brimonidine in Patients With Glaucoma or Ocular Hypertension, J. Glaucoma 11:119-126 (2002) (Attachment 3). The 7% figure may be even smaller when one accounts for various other adverse events that may be classified as an ocular allergy, albeit not allergic conjunctivitis per se – e.g., eye pruritus, conjunctival hyperemia, eyelid edema. See Attachment 2. In any case, the study on which Allergan bases its claim states that there is no statistical difference among the groups regarding adverse events that led to discontinuation of the medication, and FDA itself concluded in its approval of Alphagan-P that "Brimonidine-Purite 0.15%, 0.2% and Alphagan have similar adverse event profiles." NDA 21-262, Medical Review at 56 (Attachment 4).

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Allergan further states that "clinical practice" after one year of marketing has "confirmed" the improved safety of Alphagan-P over Alphagan. Id. at 2. However, the scientific basis for this "confirmation" is entirely unclear. Allergan has furnished no data that would permit one to assess the validity of the claim. What type of study or studies substantiates the claim? What were the endpoints? The p-value?

There are a number of other factors, the absence or presence of which are indicative that there is no true safety issue with Alphagan: There is nothing in the postmarketing adverse event reports for Alphagan that would suggest a serious problem with the product. Allergan does not appear to have conducted, or attempted to conduct, any type of recall of Alphagan, not even a class III recall, which is reserved for products posing the lowest level of health risk. See 21 C.F.R. § 7.3(m)(3) ("Class III is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences"). Alphagan, by all indications, apparently continues to be marketed abroad in a number of countries. As recently as December 2001, FDA granted approval of a pediatric indication for Alphagan. FDA would not have done so if it believed that Alphagan posed a safety concern.

Finally, it bears noting that the safety concern at issue is allergenicity. Of course, any adverse event should be taken into consideration in decisions about whether to prescribe a drug to a patient, but an allergic reaction is generally one that is acceptable on a risk-benefit basis. Moreover, Alphagan-P, Alphagan's "replacement," causes the same adverse event. As discussed above, the safety issues associated with voluntary drug withdrawals that were, in fact, for safety reasons – e.g., liver failure, valvular heart disease, Torsades de Pointes – are of a substantially serious nature and represent a sharp qualitative contrast to the allergenicity associated with Alphagan. All determinations of drug safety necessarily involve some assessment of the risk-to-benefit ratio. It is when the risks of a drug outweigh its benefits that the drug is generally considered to be unsafe. This is the section 505(e) standard under which FDA may withdraw an NDA. The withdrawal of Alphagan clearly does not meet this standard. Moreover, even assuming for the sake of argument that the standard on which a voluntary drug withdrawal "for safety or effectiveness reasons" were based could be lower than the section 505(e) standard, it is clear that slight differences between Alphagan and Alphagan-P in the incidence of allergic reactions fall far short of any conceivable lesser standard. Alphagan simply does not present the type and degree of safety concern that would justify a conclusion that its withdrawal was for "reasons of safety or effectiveness."

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2. Lack of evidence that Alphagan is less effective

Allergan cites "improved patient compliance" as the primary advantage of Alphagan-P over Alphagan in terms of effectiveness. Allergan Petition at 3. Specifically, Allergan asserts that the lower incidence of allergic reactions associated with use of the Alphagan-P product results in less disruption of administration of the drug, and hence improved compliance. "[A] higher incidence of allergy to ophthalmic solutions in glaucoma patients equates to decreased safety and results in overall decreased efficacy because allergic patients are not able to maintain continuous treatment." Id.

However, a proper compliance study requires a sophisticated methodology with, among other things, measures taken to maintain masking of the patient and to avoid any compensating by the patient. An example is the use of a dropper bottle with a "chip" in the dropper device that records how many actual drops were dispensed and on which day and at which time. It is simply not reliable to ask the patient whether he or she missed any of the drops or to employ other methods in which the reliability of the ultimate outcome depends heavily on patient cooperation. Such methods are vulnerable to human error, forgetfulness, and deceit, among other things. There is nothing to demonstrate that Allergan has conducted a proper compliance study to support its claim of "improved patient compliance."

Even more significant, Allergan entirely neglects to discuss what appears to be a critical measure of effectiveness that surfaced in the comparative studies of Alphagan and Alphagan-P. The studies demonstrated a higher rate of withdrawal for lack of efficacy from the Alphagan-P regimen than from the Alphagan regimen. In the first three months of one study (Protocol 190342-007), eight Alphagan-P patients dropped out of the study for lack of efficacy, compared to only three drop-outs among the Alphagan patients. In the first three months of another study (Protocol 190342-008), seven Alphagan-P patients dropped out for lack of efficacy, compared to one Alphagan patient. The significantly higher percentage of Alphagan-P patients who dropped out for lack of efficacy directly undermines Allergan's claim of "improved patient compliance" associated with use of Alphagan-P:

Both Studies 7 and 8 had more patients discontinued treatment due to lack of efficacy in BPOS 0.15% treatment groups compared with that in Alphagan treatment group. Such differences were approaching statistical significant [sic] at level 0.05 in the two studies. Combining the two studies, the

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withdrawal rate due to lack of efficacy was 3.9% in BPOS 0.15% and 1.0% in Alphagan. The p-value for the comparison of BPOS 0.15% to Alphagan was statistically significant at level 0.05 (two sided p-value was 0.011). This analysis suggested that BPOS 0.15% was slightly inferior to Alphagan in lowering IOP.

NDA 21-262, Statistical Review at 10 (Attachment 5).

Allergan's portrayal of Alphagan-P as more effective is thus seriously misleading. There is no evidence of greater discontinuation of Alphagan due to allergenicity, whereas there is evidence of greater discontinuation of Alphagan-P due to lack of effectiveness in controlling intraocular pressure. Although the lowest effective dose of a medication is generally preferred, the 0.15% formulation was apparently ineffective for a significant portion of the patient population in Allergan's comparative trials, and thus does not appear to represent the "lowest effective dose." Rather, based on the available data, the 0.2% formulation is the lowest effective dose.

Furthermore, even assuming there were a slightly higher incidence of allergies associated with the 0.2% formulation, any "improved patient compliance" with the 0.15% formulation would be merely theoretical. As a practical matter, a patient who demonstrates an allergy to a particular drug is likely to be switched to a different drug altogether, i.e., a drug with a different, rather than the same, active ingredient.

3. Market-related factors demonstrate that Alphagan was withdrawn for business reasons

Allergan's decision to withdraw Alphagan was clearly based on marketing and business considerations.

First, as to the "significant sales" presumption employed by FDA to assist in discerning the actual reasons underlying a drug's withdrawal, one need not even bother to calculate the sales for Alphagan, since Allergan's intent is that its new drug, Alphagan-P, replace Alphagan in the market. The Allergan press release cites a study purportedly demonstrating that "a vast majority of ophthalmologists and optometrists surveyed prefer ALPHAGAN® P to the original Alphagan® brand and do not see a medical need for having both products on the market." Allergan Press Release, July 2, 2002 (Attachment 6). Further, Allergan has stated that a determination that "[Allergan] could supply sufficient quantities of ALPHAGAN P to cover ALPHAGAN prescriptions" precipitated the

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withdrawal of Alphagan. Allergan Petition at 4. Because Allergan believes it will not sustain a loss of sales, "significant" or otherwise, this circumstantial evidence that "safety or effectiveness reasons" must have motivated the withdrawal of Alphagan from the market is not present.

On the other hand, Allergan clearly stands to lose an appreciable portion of the brimonidine market when generic versions of Alphagan are approved. By withdrawing the Alphagan product for purported "safety and effectiveness" reasons and simultaneously marketing Alphagan-P, which is subject to additional exclusivity and patents, Allergan is attempting to substantially prolong the sole-source status of its brimonidine. This objective is compelling alternative "circumstantial evidence" that Allergan's real "reasons" for withdrawing Alphagan have nothing to do with "safety or effectiveness," but are the result of commercial considerations.

The timing of the approval of Alphagan-P and withdrawal of Alphagan is also instructive. Alphagan-P was approved in March 2001. Alphagan was withdrawn in July 2002. There was thus a period of overlap of at least one year during which both drugs were on the market. During the period from June 2001 to June 2002, Allergan sold over 4 million units of Alphagan, compared to less than a million units of Alphagan-P. If there were truly a valid safety concern with Alphagan, why were sales of Alphagan during this period over four times as great as those of Alphagan-P? And why was there such a long overlap period? Alphagan could have, indeed, probably should have, been withdrawn from the market as soon as Alphagan-P became available – if, in fact, there were a legitimate safety or effectiveness issue associated with Alphagan.

Allergan's marketing practices are further testament to the company's motives. Since Alphagan first became available in the U.S. in 1996, Allergan appears to have conducted an aggressive marketing campaign for the product, evidenced by a number of promotional pieces that tout the safety of Alphagan, and even claim its superiority to the class of beta-blocker drug products that are also indicated to treat intraocular pressure in glaucoma patients. In fact, Allergan has received at least two FDA warning letters on these materials. See Warning Letters to David Garbe, Director Scientific Information and Medical Compliance, Allergan, Inc., Apr. 15, 1999 and Sept. 22, 2000. Among FDA's criticisms of Allergan's promotional pieces were a lack of fair balance and a misleading presentation. One piece, apparently based on a comparative trial of Alphagan and 0.5% timolol, claimed that "First-line mean peak IOP reduction (26.3%) [was] comparable to timolol (24.4%) at the end of year 1 (N-837)." FDA found this claim to be misleading:

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Your claim is misleading because you omitted material facts. You claim that Alphagan is as effective as timolol at lowering IOP at the end of one year, but fail to present that in this extended study, 44% of the patients treated with Alphagan dropped out of the study (59 patients withdrew because of ocular allergy experienced with brimonidine therapy versus 1 patient with timolol) while only 22% of the timolol patients dropped out.

Sept. 22, 2002 Letter at 3 (Attachment 7). Allergan's misleading claim about Alphagan vs. timolol is strikingly similar to Allergan's treatment in its petition of the comparative trials of Alphagan and Alphagan-P – highlighting the “positives” while omitting any discussion of data that directly undermines the efficacy claims for Alphagan-P, thereby providing a skewed picture of the relative effectiveness of the two products. Allergan's selective portrayal of the data undercuts its claims of improved effectiveness for Alphagan-P and thereby contradicts its contention that its decision to withdraw Alphagan had anything to do with the safety or effectiveness of the product.

B. Pediatric Indication

Allergan also argues that, given its pediatric labeling exclusivity and subsequent withdrawal of the Alphagan labeling, FDA should not approve ANDAs relying on Alphagan because there is no way to label the product for safe use in the pediatric population.

This argument is specious. First, section 11 of the BPCA clearly contemplates that an ANDA applicant may carve out from the labeling of a reference listed drug “a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 505(j)(5)(D).” Section 11, BPCA; 21 U.S.C. § 355A(o)(1). FDA's regulations are in complete accord with section 11 of the BPCA. “[D]ifferences between the applicant's proposed labeling and labeling approved for the reference listed drug may include ... omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) [sic] of the act.”⁴ 21 C.F.R. § 314.94(a)(8)(iv). FDA's regulations further provide that if such an omission is made in a proposed generic

⁴ The reference should be to 505(j)(5)(D) of the Act.

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drug product, FDA must find that the omission “[does] not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use.” Id. § 314.127(a)(7).

Moreover, section 11 of the BPCA specifically addresses the safety issue in the pediatric population in the event of a carve-out of protected pediatric information. It provides that, notwithstanding the pediatric exclusivity on the innovator drug, FDA may require a statement in the labeling of a proposed generic that the drug is not labeled for pediatric use, or other pediatric information FDA deems necessary for safety reasons. Section 11, BPCA; 21 U.S.C. § 355A(o)(2)(A)-(B).

Allergan asserts that this labeling alternative – where an ANDA applicant exercises the carve-out option but FDA nonetheless requires a statement of “appropriate pediatric contraindications, warnings, or precautions” – “logically requires the listed drug to exist on the market” since, “[w]ithout a complete label for reference, a generic BTOS 0.2% formulation is demonstrably unsafe for use in children.” Allergan Petition at 6. This argument fails for two reasons. One, there is nothing inherent in the pediatric carve-out information that would render insufficient any additional pediatric information that FDA may see fit to require, even in the absence of Alphagan on the market. FDA is well-equipped, indeed, is authorized, to devise whatever statements it considers necessary to protect the pediatric population. Two, Alphagan-P is on the market, with complete pediatric labeling information that is identical to the withdrawn, protected pediatric labeling for Alphagan. If indeed there were any confusion or “underestimation” of risks as a result of the inclusion of additional pediatric information in the label of a generic 0.2% formulation, as Allergan has suggested, health care professionals could simply refer to the Alphagan-P pediatric labeling for clarification.

Alternatively, FDA can always, if it deems appropriate, require only the statement that the product is not labeled for pediatric use because of market exclusivity, without further precautionary information concerning pediatric use. Section 11 of the BPCA does not mandate that pediatric information be included in the label of a generic drug that relies on a drug with protected pediatric information. Rather, it states that the agency “may require” such information that it “considers necessary.” Section 11, BPCA. This alternative would dispel the hypothetical risks of the generic drug in the pediatric population that Allergan raises in its petition, since use of the drug by children would be entirely precluded.

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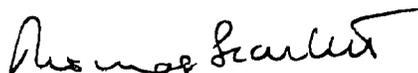
Thus, should there be a legitimate safety issue with respect to use of the 0.2% formulation in the pediatric population, FDA will properly address it by imposing an appropriate labeling requirement. It is this approach Congress created in the BPCA as an alternative to barring approval of generic versions of a drug strictly as a precautionary matter. Allergan's position is thus incompatible with the BPCA.

IV. Conclusion

Allergan's petition represents little more than a transparent effort to retain market share. Indeed, the petition appears to be only one of various aggressive strategies employed by Allergan to maximize its share of the market for glaucoma drugs – beginning with its earlier promotional pieces on Alphagan asserting the superiority of the drug to timolol and other beta-blockers, to the improper listing of patents in the Orange Book, to the paragraph IV litigation on those patents, to the development of an “improved” version of Alphagan covered by new patents, and, now, the withdrawal of Alphagan in a manner that, if FDA were to accept Allergan's stated but fanciful rationale, would prevent generic competition for an extended period of time. These are the very types of anticompetitive tactics that FDA, and, more recently, the Federal Trade Commission, have been working to counteract. Allergan should not be permitted to manipulate the regulatory system in this way.

It is clear that Alphagan was not withdrawn for the types of safety or effectiveness reasons contemplated in § 314.161. It is also clear that the BPCA does not prohibit, but rather expressly permits, the approval of a generic drug that omits pediatric information in the innovator drug's labeling. Contrary to Allergan's contention, any alternative pediatric labeling imposed by FDA under the carve-out provisions of the BPCA will not render the proposed generic drug unsafe. For these reasons, B&L requests that FDA deny the Allergan petition.

Sincerely,



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