LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.
700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D. C. 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329
www.hpm.com

JAMES R. PHELPS
PAUL M. HYMAN
ROBERT A. DORMER
STEPHEN H. MCNAMARA
ROGER C. THIES
THOMAS SCARLETT
JEFFREY N. GIBBS
BRIAN J. DONATO
FRANK J. SASINOWSKI
DIANE B. MCCOLL
A. WES SIEGNER, JR.
ALAN M. KIRSCHENBAUM
DOUGLAS B. FAROUHAR
JOHN A. GILBERT, JR.
JOHN R. FLEDER
MARC H. SHAPIRO
ROBERT T. ANGAROLA
(1945-1996)

MARY KATE WHALEN
OF COUNSEL

JENNIFER B. DAVIS
FRANCES K. WU
DAVID B. CLISSOLD
CASSANDRA A. SOLTIS
JOSEPHINE M. TORRENTE
MICHELLE L. BUTLER
ANNE MARIE MURPHY
PAUL L. FERRARI
JEFFREY N. WASSERSTEIN
MICHAEL D. BERNSTEIN
LARRY K. HOUCK
DARA S. KATCHER*
KURT R. KARST*
MOLLY E. CHILDS*

*NOT ADMITTED IN DC

DIRECT DIAL
(202) 737-4286

February 10, 2003

BY FACSIMILE/CONFIRMATION COPY BY MAIL

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

Re: Docket No. 02P-0469 – Additional Comments of Bausch & Lomb Incorporated

Dear Sir or Madam:

The following responds to Allergan's January 23, 2003, submission to this docket.

1. Contrary to Allergan's argument on pages 5-6, Congress intended the safety and effectiveness standard under 21 U.S.C. §§ 355(j)(6) and (7)(C) to be the same as under § 355(e). The bill report says:

> Paragraph 6(C) [now 7(C)] of proposed subsection (j) provides that a drug may not be listed as eligible for consideration in an ANDA if the approval of the former or pioneer drug is withdrawn or suspended for safety or effectiveness reasons under section 505(e)(1)-(4) of the Act, 21 U.S.C. § 355(e)(1)-(4), or if approval of the generic drug was withdrawn or suspended under paragraph (j)(5) [now (j)(6)], supra, as authorized by this bill. Also, a drug may not be listed if the FDA determines that it has been voluntarily withdrawn for reasons of safety or effectiveness. In the event

02P-0469

C 3

2603 MAIN STREET
SUITE 760
IRVINE, CALIFORNIA 92614

4819 EMPEROR BOULEVARD
SUITE 400
DURHAM, NORTH CAROLINA 27703
(919) 313-4750
FAX: (919) 313-4761

> such a drug has already been listed, it must be immediately removed from the list.

H. R. Rep. No. 98-857, Part 2, at 16-17. The use of essentially identical language – "reasons of safety and effectiveness" for a voluntary withdrawal, "safety or effectiveness reasons" for a withdrawal under § 355(e) – makes clear that Congress meant the same standard to apply to both situations.

The separate reference to "safety or effectiveness reasons" for voluntary withdrawal in both §§ 355(j)(6) and (j)(7)(C) cannot reasonably support the inference, drawn by Allergan, that Congress meant the standard to be different from that for NDA withdrawal. Most drugs that exhibit problems serious enough to warrant NDA withdrawal are withdrawn voluntarily before formal proceedings can be considered. To distinguish these drugs from those withdrawn solely due to commercial considerations, Congress used the term "safety or effectiveness reasons." There is no evidence that Congress intended to create different standards of safety and effectiveness for voluntary withdrawal from those applicable to NDA withdrawal, referred to earlier in the same sentence, and it is difficult to think either of a logical reason why Congress would have provided for different standards or what those different standards would be.

The NDA and voluntary withdrawal provisions have a simple purpose: to assure that generic drugs are as safe and effective as drugs that meet, and continue to meet, the safety and effectiveness requirements of the Act for NDA approval. A drug does not cease to meet those standards merely because the sponsor identifies some performance attribute that is improved upon by a modified version of the same drug, and then decides to withdraw the original drug from the market. Unless the reasons for Allergan's withdrawal of Alphagan would have justified withdrawal of the NDA, Allergan did not withdraw Alphagan for safety or effectiveness reasons as the term is used in §§ 355(j)(6) and (j)(7)(C).

2. The Alphagan NDA was not a candidate for formal withdrawal proceedings on any of the grounds specified in § 355(e), and Allergan does not assert that it was. Instead, Allergan says that Alphagan was associated with a higher incidence of allergic conjunctivitis than Alphagan P, and therefore it is possible that Alphagan would be less effective due to lower patient compliance.

Even accepting Allergan's characterization of the data at face value, the most that can be said is that Allergan may have identified the basis for a comparative superiority claim that could be made for Alphagan P in relation to Alphagan. Comparative claims are not uncommon. They may legitimately be made in advertising and promotion if supported by data and not misleading. Allergan cites no data that would substantiate improved patient compliance using Alphagan P compared with Alphagan. Even if such

data existed, however, comparative superiority of one drug over a second drug in a particular respect is not grounds for concluding that the second drug no longer meets the safety and effectiveness standard for continued NDA approval.

3. Allergan overstates the performance of Alphagan P by focusing on allergic conjunctivitis, whose incidence was significantly less than Alphagan's in one study and numerically less in the second. Allergic conjunctivitis is only one of the many ocular allergies – among them, eye pruritus, eyelid edema, conjunctival hyperemia, and itching – associated with brimonidine tartrate. Allergan provides no analysis of the 12-month data that would support a claim of overall superiority with respect to ocular allergies. As noted in our December 5, 2002, submission (at p. 8), the FDA characterized the adverse event profiles as "similar" based on the 3-month data. Allergan's 12-month study reports claim "superior safety and tolerability" for Alphagan P over Alphagan. The FDA can make its own judgment about whether the claim is justified. But as noted, comparative superiority is not equivalent to lack of safety and effectiveness of the comparator drug.

Although Allergan discusses the incidences of allergic conjunctivitis in the two studies, it fails to mention that, based on the 12-month data, the overall discontinuation rates were about the same for Alphagan P and Alphagan in both studies, and that discontinuations for lack of efficacy were higher for Alphagan P in both studies, consistent with the FDA reviewer's conclusion based on the 3-month data. The Alphagan P rates of discontinuation for lack of efficacy – 7.6% for both studies – appear to be at least twice as high as those for Alphagan – 3.5% and 3.8% for Studies 007 and 008, respectively. See Study 007 Report § 10.1 at 40; Study 008 Report § 10.1 at 38. Moreover, the "withdrawal" rates cited by Allergan (at p. 8) are misleading because they do not pertain to allergic conjunctivitis, as implied, but to all adverse events, including non-ocular adverse events. See Study 007 Report § 12.2.3.3 at 67 (actual rates of discontinuation were 19.4% for Alphagan P and 25.6% for Alphagan); Study 008 Report § 12.2.3.3 at 66 (actual rates of discontinuation were 24.5% for Alphagan P and 29.3% for Alphagan).

Allergan's larger claim is that Alphagan is less effective than Alphagan P because of lower patient compliance. There are no competent data supporting this claim; the anecdotal information attached to Allergan's January 23 submission proves nothing. In fact, the higher discontinuation rates for lack of efficacy associated with the use of Alphagan P plainly undermine this claim, and strongly justify the continued availability of Alphagan, or therapeutically equivalent 0.2% brimonidine tartrate, since lack of efficacy cannot be overcome by proper, even optimal, compliance. Lack of efficacy may result in a more rapid progression of disease than would poor compliance.

4. The Best Pharmaceuticals for Children Act specifically authorizes the FDA to permit pediatric information to be carved out of ANDA labeling, and to require such labeling to include additional pediatric safety information. Allergan's January 23 submission suggests that there may be fact-specific issues in applying this authority to ANDAs for brimonidine tartrate 0.2% products. However, Allergan provides no reasons why the agency cannot resolve those issues. Allergan erroneously states that B&L suggested that the agency require ANDA labeling to cross-reference the Alphagan P labeling. B&L said only that "health care professionals could simply refer to the Alphagan P pediatric labeling for clarification" of information relating to pediatric use of brimonidine, just as they could refer to exclusivity-protected pediatric information in the labeling of Alphagan, if Allergan continued to market that product.

* * *

For the reasons stated above, and in our December 5 submission. Allergan's petition should be denied.

Sincerely,

Thomas Scarlett
Frances K. Wu
Hyman, Phelps & McNamara, P.C.
Counsel for Bausch & Lomb Incorporated

LAW OFFICES

HYMAN, PHELPS & MCNAMARA, P.C.

JAMES R. PHELPS
PAUL M. HYMAN
ROBERT A. DORMER
STEPHEN H. MCNAMARA
ROGER C. THIES
THOMAS SCARLETT
JEFFREY N. GIBBS
BRIAN J. DONATO
FRANK J. SASINOWSKI
DIANE E. MCCOLL
A. WES SIEGNER, JR.
ALAN M. KIRSCHENBAUM
DOUGLAS B. FARQUHAR
JOHN A. GILBERT, JR.
JOHN R. FLEDER
MARC H. SHAPIRO

ROBERT T. ANGAROLA
(1945-1996)

700 THIRTEENTH STREET N.W.
SUITE 1200
WASHINGTON D. C. 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329

www.hpm.com

MARY KATE WHALEN
OF COUNSEL

JENNIFER B. DAVIS
FRANCES K. WU
DAVID B. GLISSOLD
CASSANDRA A. SOLTIS
JOSEPHINE M. TORRENTE
MICHELLE L. BUTLER
ANNE MARIE MURPHY
PAUL L. FERRARI
JEFFREY N. WASSERSTEIN
MICHAEL D. BERNSTEIN
LARRY K. HOUCK
DARA S. KATCHER*
KURT R. KARST*
MOLLY E. CHILDS*

*NOT ADMITTED IN DC

FACSIMILE TRANSMITTAL SHEET

Tel. No. (202) 737-5600 **Fax No. (202) 737-9329**

FROM:	Thomas Scarlett	DATE:	February 10, 2003
TO:	Dockets Management Branch FDA	FAX NO.:	(301) 827 6870

NO. OF PAGES (including this page): 5

2603 MAIN STREET
SUITE 760
IRVINE, CALIFORNIA 92614
(949) 553-7400
FAX: (949) 553-7433

4819 EMPEROR BOULEVARD
SUITE 400
DURHAM, NORTH CAROLINA 27703
(919) 313-4750
FAX: (919) 313-4751