DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 3 1 2010

Recd 8/31/2010

Alessandra C. Ravetti
Emily Marden
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

Re: Docket No. FDA-2006-P-0072

Dear Ms. Ravetti and Ms. Marden:

This letter responds to your citizen petition received on November 2, 2006 (the Petition), and a supplement dated August 26, 2008 (Supplement).[1] In the Petition, you request that the Food and Drug Administration (FDA or Agency) (1) revoke approval of Allergan, Inc.'s supplemental new drug application (sNDA) 21-275/S-013 for Lumigan (bimatoprost ophthalmic solution) 0.03% for a first-line indication and (2) deny approval of Alcon, Inc.'s sNDA 21-257 for Travatan (travoprost ophthalmic solution) 0.004% for a first-line indication. You state that both sNDAs were filed under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) and reference the sNDA for Pfizer's listed drug Xalatan (latanoprost ophthalmic solution) 0.005%. You also state that your Supplement addresses new information that was not available to Pfizer when you submitted the Petition. You state that the arguments in the Petition apply to all formulations of Lumigan, including Lumigan 0.01%, and you submit additional information based on FDA's review of Allergan's sNDA for Lumigan, which you argue is relevant to and supportive of the Petition. We have carefully considered the Petition and Supplement as well as the comments filed in the docket. For the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Statutory and Regulatory Framework

1. Section 505(b)(2) Applications

Section 505(b) of the Act establishes the approval requirements for NDAs. To be approved, an application submitted under section 505(b) of the FDCA must be supported by full reports of investigations showing the drug product to be safe and effective (21 U.S.C. 355(b)(1)). One pathway under section 505(b) provides for approval of new drug applications (NDAs) that are supported entirely by full investigations of safety and effectiveness either conducted by the applicant or to which the applicant has a right of reference. For purposes of this discussion, we

[1] This citizen petition was originally assigned docket number 2006P-0450/CP1. The number was changed to FDA-2006-P-0072 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

PDN

FDA-2006-P-0072

refer to these applications as *stand-alone* NDAs. Amendments made to the FDCA as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) provided an alternate approval pathway by adding a new subsection, 505(b)(2), to the Act.

Section 505(b)(2) provides for submission of an application under section 505(b)(1):

> For a drug for which the [safety and effectiveness] investigations . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

The Hatch-Waxman Amendments reflect Congress's intention to balance the need to encourage innovation with the desire to speed the availability of lower-cost alternatives to approved drugs.[2] In recent years, FDA has articulated its interpretation of section 505(b)(2) in responses to several citizen petitions, including petitions submitted by Pfizer.[3] Like a stand-alone NDA, a *505(b)(2) application* is submitted under section 505(b)(1) of the Act and approved under section 505(c). As with a stand-alone NDA, a 505(b)(2) application must satisfy the statutory requirements for safety and effectiveness information. An applicant submitting a 505(b)(2) application may support the safety and/or effectiveness of the proposed drug product with published reports of studies and/or by reliance on an Agency finding of safety and effectiveness for a previously approved drug product or listed drug.[4] Reliance on such reports or findings must be scientifically justified. A 505(b)(2) application may describe a drug product with substantial differences from a drug product previously approved by FDA. These differences may include, for example, a new indication or a different active ingredient, dosage form, strength, formulation,

---

[2] *See Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990); and *Bristol-Meyers Squibb Company v. Royce Laboratories, Inc.*, 69 F.3d 1130, 1132, 1133-34 (Fed. Cir. 1995).

[3] Letter from Janet Woodcock, M.D., Director, CDER, FDA, to Katherine M. Sanzo, Esq., Lawrence S. Ganslaw, Esq., Morgan, Lewis & Bockius LLP; Jeffrey B. Chasnow, Esq., Pfizer Inc.; Stephan E. Lawton, Esq., Gillian R. Woollett, Ph.D., Vice President Regulatory Affairs, Biotechnology Industry Organization; William R. Rakoczy, Esq., Lord, Bissell & Brook LLP (Oct. 14, 2003) (originally assigned Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 and changed to Docket Nos. FDA-2001-P-0369, FDA-2002-P-0390, and FDA-2003-P-0274, respectively, as a result of FDA's transition to Regulations.gov) (505(b)(2) Response) and Letter from Steven K. Galson, M.D., M.P.H., Director, CDER, FDA, to Kathleen M. Sanzo, Esq., Morgan, Lewis & Bockius LLP; Stephan E. Lawton, Esq., Biotechnology Industry Organization; Stephen G. Juelsgaard, Esq., Genentech (May 30, 2006) (originally assigned Docket Nos. 2004P-0231/CP1 and SUP1, 2003P-0176/CP1 and EMC1, 2004P-0171/CP1, and 2004N-0355 and changed to Docket Nos. FDA-2004-P-0339, FDA-2003-P-0003, FDA-2004-P-0214, and FDA-2004-N-0059, respectively, as a result of FDA's transition to Regulations.gov) (2006 Citizen Petition Response).

[4] See 21 CFR 314.3 (*listed drug* means a new drug product that has an effective approval under section 505(c) of the act for safety and effectiveness or under section 505(j) of the Act, which has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(5) of the Act, and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness).

or route of administration.[5] A 505(b)(2) application must support any differences with appropriate safety and effectiveness information.[6]

FDA's long-standing interpretation of section 505(b)(2) is intended to permit the pharmaceutical industry to rely to the extent possible on what is already known about a drug. Our approach permits applicants to use the 505(b)(2) drug approval pathway to avoid conducting and submitting studies that are not scientifically necessary to demonstrate the safety and effectiveness of a drug product. The conduct and review of duplicative studies would (1) divert industry resources that could be used to undertake innovative research, (2) increase drug costs, (3) strain FDA review resources, and (4) slow the process for drug approval with no corresponding benefit to the public health. In addition, the conduct of duplicative studies raises ethical concerns because it could subject humans and animals to medically or scientifically unjustified testing. The 505(b)(2) pathway permits applicants and the Agency to determine what studies are necessary to support the approval of a new aspect of a drug. It then allows an applicant to target drug development resources to those studies needed to support the proposed difference from the previously approved drug product on which it seeks to rely (see 21 CFR 314.54(a) ("[A 505(b)(2)] application need contain only that information needed to support the modification(s) of the listed drug")).

The 505(b)(2) approval pathway recognizes marketing exclusivity and patent protections that apply to a listed drug upon which the 505(b)(2) applicant may wish to rely for approval. Only when applicable exclusivity and patent protections have expired or been challenged may the 505(b)(2) application be approved.

2. Three-Year Marketing Exclusivity

As explained in section I.A.1 of this response, the Hatch-Waxman amendments were designed to balance the need to encourage innovation with a desire to increase competition and thus decrease the costs for approved drug products. While abbreviated drug approval pathways created by the Hatch-Waxman amendments, such as the 505(b)(2) application, were designed to speed lower-cost alternatives to the market, Congress also included in that legislation exclusivity provisions to provide incentives for innovation. The FDCA provides different marketing exclusivity periods for drugs approved in NDAs (including drugs approved in 505(b)(2) applications) based on the level of innovation represented by the drug product. While these exclusivity periods are in effect, FDA may not approve (or in some circumstances accept) certain applications that seek approval for the protected innovation (section 505(c)(3)(E)(i)-(v) and (j)(5)(F)(i)-(v) of the Act).

Of particular relevance to this response is section 505(c)(3)(E)(iv) of the Act, which grants 3-year exclusivity to an applicant if an sNDA is approved and contains reports of new clinical investigations (other than bioavailability studies) that are essential to the approval of the sNDA and were conducted or sponsored by the applicant. If 3-year exclusivity is granted, FDA may

[5] See 21 CFR 314.54(a); *See also* draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999). The draft guidance, when finalized, will represent FDA's current thinking on the topic.

[6] See the 505(b)(2) Response for a more extensive discussion on the 505(b)(2) approval pathway.

not approve for 3 years a 505(b)(2) application or an abbreviated new drug application (ANDA) for the same conditions of approval as those approved in the sNDA.[7]

B. Prostaglandin $F_{2\alpha}$ Analogs

Prostaglandin $F_{2\alpha}$ analogs are a class of drugs used to lower intraocular pressure (IOP) in patients with elevated IOP or glaucoma. The following NDAs are currently approved in this class:

- Xalatan (latanoprost ophthalmic solution) 0.005%, held by Pharmacia and Upjohn (NDA 20-597 approved June 5, 1996)[8]
- Rescula (unoprostone isopropyl ophthalmic solution) 0.15%, held by Sucampo Pharmaceuticals, Inc. (NDA 21-214 approved August 3, 2000)[9]
- Lumigan (bimatoprost ophthalmic solution) 0.03%, held by Allergan (NDA 21-275 approved March 16, 2001)
- Travatan & Travatan Z (travoprost ophthalmic solution) 0.004%, held by Alcon (NDA 21-257 approved March 16, 2001 and NDA 21-994 approved September 21, 2006)

Each of these products was initially labeled as indicated "for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension who are intolerant of other IOP lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another IOP lowering medication" (second-line therapy). Consistent with the regulations (then 21 CFR 201.57(g) and now 21 CFR 201.80), the approved labeling included adverse events and warnings regarding certain class effects. Below, we describe the approval history for each of these drug products except Rescula — Rescula was not raised in your citizen petition and has never been approved as first-line therapy.

---

[7] Section 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the Act; see also 21 CFR 314.108. In addition to market exclusivity, the Hatch-Waxman amendments also require NDA (including 505(b)(2) NDA) applicants to list patents that claim a listed drug. A 505(b)(2) application that relies on FDA's findings of safety and effectiveness for a listed drug must include a patent certification or statement as required under section 505(b)(2) of the Act with respect to any listed patents that claim the listed drug and that claim any other drugs on which the investigations relied on by the applicant for approval of the application were conducted, or that claim an approved use for the listed or other drug. Section 505(b)(2)(A) of the Act; see also 21 CFR 314.54(a)(1)(vi). If an applicant certifies under section 505(b)(2)(A)(iv) of the Act that a patent is invalid or will not be infringed (a paragraph IV patent certification), the applicant must provide notice of such filing to the NDA holder and patent owner who then have an opportunity to sue the applicant for patent infringement. Section 505(b)(2)(A) of the Act; see also 21 CFR 314.52(a). With certain exceptions, if suit is brought within 45 days after the date of receipt of the patent certification notice, FDA may not approve the application for 30 months beginning on the date of the receipt of the patent certification notice or until the patent litigation is resolved, whichever is sooner (section 505(c)(3)(C) of the Act).

[8] Pharmacia and Upjohn is owned by Pfizer.

[9] This NDA was initially held by CIBA Vision/Novartis and transferred to Sucampo in April 2009.

1. Xalatan

Xalatan (latanoprost ophthalmic solution) 0.005% was initially approved on June 5, 1996. Efficacy was demonstrated in double-masked clinical trials comparing Xalatan with timolol, a nonselective beta-adrenergic receptor blocking agent that is not a member of the class of prostaglandin $F_{2\alpha}$ analogs. Xalatan was labeled at the time of approval as indicated for second-line therapy for the reduction of elevated IOP. In the pooled 6-month phase 3 clinical trials for Xalatan, increased iris pigmentation (assessed by serial iris photography) was reported in 7.2 percent of subjects receiving Xalatan and no subjects receiving timolol. Other ocular adverse effects that were increased in Xalatan-treated subjects vs. timolol-treated subjects included conjunctival hyperemia, burning and stinging, punctuate epithelial erosions, foreign body sensation, itching, and blurred vision. Growth of eyelashes was not reported in the clinical trials. The Ophthalmology Advisory Subcommittee (the committee) discussed this NDA on December 8, 1995. The adverse effect of increased iris pigmentation was a concern of the Agency in the course of the review of the NDA as well as of the committee. The committee recommended approval of the product with postmarketing studies to continue to evaluate iridial pigmentation. It was recommended by the committee that labeling should reflect the lack of total understanding of the mechanism and consequences of iridial pigmentation. The Agency medical officer review recommended that the applicant should continue its investigations into the effects of iris pigmentation changes caused by Xalatan. The Agency's major safety concern was that increased iris pigmentation related to treatment with Xalatan could be associated with an increased risk for ocular melanoma or pigmentary glaucoma.

On December 20, 2002, FDA approved a Xalatan sNDA (NDA 20-597/SE1-010) to change the indication for Xalatan to the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension (first-line therapy). The stand-alone sNDA submission by Pharmacia and Upjohn included study reports and publications from the scientific literature. The applicant's study report of follow-up of patients who developed increased iris pigmentation during the phase 3 trials of Xalatan included serial iris photography in these patients after withdrawal from Xalatan treatment. This study also included serial external eye photography. The eyelash changes that had developed during Xalatan treatment resolved during follow-up after Xalatan discontinuation.[10] The applicant's study report of the latanoprost pathology study described the findings of a masked pathology examination of human iris and trabecular meshwork specimens from patients with and without Xalatan exposure. Consistent with primate studies, the study reported an increased amount of melanin within iris stromal melanocytes in irides reported to exhibit color change rather than an increase in melanocyte numbers. Examination of trabecular meshwork specimens did not show deposition of pigment granules.[11]

---

[10] Borg G, Holmqvist E. Long-term follow-up of patients who developed increased iris pigmentation during the phase III trials of latanoprost in patients with primary open-angle glaucoma or ocular hypertension after cessation of latanoprost treatment. Pharmacia & Upjohn Study Report c0026636, 22 May 2000. (NDA 20-597).

[11] Statistical Data Analysis Center, Dept. of Biostatistics and Medical Informatics, University of Wisconsin-Madison. Latanoprost Pathology Study, 16 April 2002. (NDA 20-597).

Pharmacia and Upjohn also submitted a study report of a 3-year clinical study with a 2-year extension that examined the safety of Xalatan when administered once daily as adjunctive therapy in patients with primary open-angle glaucoma.[12] This clinical study included serial iris photography and IOP measurement as well as periodic visits to monitor for adverse events. Approximately one-third of subjects overall developed increased iris pigmentation based on examination of serial iris photographs.[13] As reported by the applicant, among those who developed increased iris pigmentation, 93.7 percent developed the condition by month 24 and all by month 36. Once increased iris pigmentation was noted, there was a statistically significant progression of increased iris pigmentation for the first 3 years of the study, but no statistically significant progression in years 4 and 5. Reduction in IOP was similar among those subjects who developed increased iris pigmentation compared to those who did not. Hypertrichosis, including lengthening of the eyelashes, darkening of the eyelashes, and the patients being more aware of their eyelashes, was reported in 14.2 percent of subjects. There were no cases of hypertrichosis classified as severe and no ocular tumors. The incidence of hypertrichosis was similar among those who developed increased iris pigmentation and those who did not. None of the subjects developed melanoma or pigmentary glaucoma.

Pharmacia and Upjohn also submitted to the NDA studies from the published literature that provided evidence for a mechanism for increased iris pigmentation associated with Xalatan exposure. The studies demonstrated increased transcription of tyrosinase, a key enzyme in the biosynthetic pathway of melanin, in iridial melanocytes in monkey and human cell culture after Xalatan treatment.[14]

The Agency medical officer review of this sNDA concluded that "[t]he increase in pigment color of the iris appears to be related to increases in melanin. There does not appear to be an increase in melanocytes, and the atypia seen in the melanocytes appears to be related cellular activity." The medical officer also concluded that, "... all of the effects, with respect to safety and efficacy, appear to be due to the same mechanism of action for all of the prostaglandin-like products and therefore the conclusions related to the long-term safety of Xalatan are relevant to all of the other prostaglandin like products." As a result of the review of this sNDA, findings were made concerning the long-term adverse effects of increased iris pigmentation and eyelash growth observed with Xalatan. Agency findings were articulated in revised labeling for Xalatan approved December 20, 2002. The *Animal Studies* subsection in the CLINICAL PHARMACOLOGY section was revised to include the following statement:

---

[12] NDA 20-597.

[13] The increased iris pigmentation was not reported on physical examination alone for a substantial proportion of the subjects classified as developing increased iris pigmentation by serial iris photography, as fewer than half of these had increased iris pigmentation reported as an adverse event by the examining physician.

[14] Sternschantz J, Ocklind A, Wentzel P et al. Latanoprost-induced increase of tyrosinase transcription in iridial melanocytes. Acta Ophthalmol Scand 2000; 78:618-22; Lindsey JD, Joens HL, Hewitt EG et al. Induction of tyrosinase gene transcription in human iris organ cultures exposed to latanoprost. Arch Ophthalmol 2001; 119:853-60; Dutkiewicz R, Albert DM, Levin LA. Effects of latanoprost on tyrosinase activity and mitotic index of cultured melanoma lines. Exp Eye Res 2000; 70:563-9.

> The mechanism of increased pigmentation seems to be stimulation of melanin production in melanocytes of the iris, with no proliferative changes observed. The change in iris color may be permanent.

The 3-year clinical study with 2-year extension that examined the safety of Xalatan was described in the CLINICAL STUDIES section:

> A 3-year open-label, prospective safety study with a 2-year extension phase was conducted to evaluate the progression of increased iris pigmentation with continuous use of XALATAN once-daily as adjunctive therapy in 519 patients with open-angle glaucoma. The analysis was based on observed-cases population of the 380 patients who continued in the extension phase.
>
> Results showed that the onset of noticeable increased iris pigmentation occurred within the first year of treatment for the majority of the patients who developed noticeable increased iris pigmentation. Patients continued to show signs of increasing iris pigmentation throughout the five years of the study. Observation of increased iris pigmentation did not affect the incidence, nature or severity of adverse events (other than increased iris pigmentation) recorded in the study. IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

The WARNINGS section was modified to include the following statements:

> After discontinuation of XALATAN, pigmentation of the iris is likely to be permanent while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. The effects of increased pigmentation beyond 5 years are not known.

The PRECAUTIONS section was modified to include the following statement:

> The eye color change is due to increased melanin content in the stromal melanocytes of the iris rather than to an increase in the number of melanocytes.

The sNDA contained reports of a new clinical investigation essential to the approval of the sNDA, and FDA granted the applicant 3 years of marketing exclusivity at the time of approval.

2. Lumigan (0.03%)

Lumigan (bimatoprost ophthalmic solution) 0.03% was initially approved on March 16, 2001. The product was labeled at the time of approval as indicated for second-line therapy for the reduction of elevated IOP. As discussed elsewhere in this letter, the Agency had concluded that increased iris pigmentation seen in trials of other prostaglandin analogs was a class effect and labeled all products in the prostaglandin analog class initially as second-line therapy. In the 3-month human phase 3 studies of Lumigan, increased iris pigmentation (assessed by serial iris photography) was reported in two subjects (<1 percent) receiving Lumigan. In the pooled clinical studies

submitted as part of the Lumigan 0.03% NDA, the most frequent ocular adverse events for Lumigan-treated subjects were conjunctival hyperemia (40 percent), growth of eyelashes (22 percent), and eye pruritis (17 percent). Growth of eyelashes was categorized in the Lumigan studies as mild, moderate, or severe. The vast majority of the events reported for development of eyelash growth were categorized as mild. In addition, the Lumigan 0.03% NDA contained studies of cynomolgus monkeys with ocular exposure to various concentrations of bimatoprost (above and below the ultimately marketed concentration) and other prostaglandin analog molecules, including Xalatan. In these studies, changes in iris pigmentation were noted with all prostaglandin molecules. Of note, histologic examinations of affected irides were similar regardless of the prostaglandin analog to which the animals had been exposed. The Agency medical officer review recommended that the applicant propose a postmarketing plan to adequately address concerns raised by the reports of increased iris pigmentation and eyelash changes as well as conduct a study to evaluate pigment deposition in the trabecular meshwork.

In 2003, Allergan submitted a stand-alone sNDA (21-275/S-013) seeking approval for a first-line indication for Lumigan 0.03%, relying upon a 36-month postmarketing study of Lumigan vs. timolol. This study included serial iris photography. Conjunctival hyperemia was the most frequent adverse effect, occurring in 13 percent of the subjects in the Lumigan 0.03% once-daily group. Eyelash growth was reported in 2.2 percent of the Lumigan 0.03% once-daily group completing 36 months and 7 percent of the Lumigan 0.03% once-daily group completing 24 months. None of the subjects developed melanoma or pigmentary glaucoma. On November 12, 2003, FDA issued a not approvable letter for this sNDA. The not approvable letter stated that "[p]otential safety issues related to increasing ocular pigmentation and growth of ocular structures have not been fully evaluated. Data demonstrating a plateau in these ocular changes and data demonstrating safety at the time of the plateau should be provided prior to changing the indication to first line therapy."

Allergan subsequently resubmitted the sNDA, pursuant to section 505(b)(2) of the Act, referencing FDA's findings regarding Xalatan and published literature. According to the Petition, Pfizer received a paragraph IV patent certification notice indicating that Allergan had submitted an sNDA for a first-line indication for Lumigan 0.03% pursuant to section 505(b)(2) of the Act, referencing Xalatan (Petition at 3). Pfizer did not sue Allergan for patent infringement in response to notice of the certification.

At the time it resubmitted the sNDA, Allergan submitted the 48-month report for the Lumigan 0.03% long-term follow-up study described above, iris photographic assessment of subjects enrolled in this study, and a masked histologic evaluation of trabecular meshwork specimens collected from patients who had been treated with Lumigan for at least 2 years. Allergan submitted studies from the published literature to the NDA. Consistent with ordinary review practice, the Agency medical officer also conducted an independent literature search.

On June 22, 2006, FDA approved the Lumigan 0.03% sNDA to change the indication for Lumigan 0.03% to first-line therapy. This approval is further discussed in section II of this letter. Lumigan 0.03% labeling was revised at the time of the approval of this sNDA. The *Clinical Studies* subsection of the CLINICAL PHARMACOLOGY section was revised to include the following:

> Results of dosing for up to five years with products in this drug class showed that the onset of noticeable increased iris pigmentation occurred within the first year of treatment or the majority of the patients who developed noticeable increased iris pigmentation. Patients continued to show signs of increasing iris pigmentation throughout the five years of the study. Observation of increased iris pigmentation did not affect the incidence, nature or severity of adverse events (other than increased iris pigmentation) recorded in the study. IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

The WARNINGS section was modified to include the following statements:

> After discontinuation of LUMIGAN, pigmentation of the iris is likely to be permanent while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. The effects of increased pigmentation beyond 5 years are not known.

The PRECAUTIONS section was modified to include the following statement:

> The eye color change is due to increased melanin content in the stromal melanocytes of the iris rather than to an increase in the number of melanocytes.

Allergan also submitted NDA 22-184 for Lumigan 0.01% on July 2, 2007. The application was submitted as a stand-alone NDA for the use of Lumigan (bimatoprost ophthalmic solution) 0.01% as a first-line treatment for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Today, FDA approved the Lumigan 0.01% NDA.[15]

3. Travatan

Travatan (travoprost ophthalmic solution) 0.004% was initially approved on March 16, 2001. The product was labeled at the time of approval as indicated for second-line therapy for the reduction of elevated IOP. As was the case for Lumigan 0.03%, the Agency had concluded that increased iris pigmentation was a class effect and labeled all products in the prostaglandin analog class initially as second-line therapy. Alcon submitted a 12-month phase 3 human clinical trial with both Travatan and Xalatan treatment arms. Increased iris pigmentation (assessed by serial photography) was noted in 3.0 percent of Travatan-treated subjects, 5.1 percent of Xalatan-treated subjects, and 0 percent of timolol- (comparator) treated subjects. Clinically significant differences in hyperemia were more common in Travatan-treated subjects (49.5 percent)

[15] The Supplement to the Petition refers to "a new formulation Lumigan – Lumigan 0.01%," but does not provide any specific information on this product. Lumigan 0.01% was submitted and approved as a 505(b)(1) stand-alone NDA. Lumigan 0.01% is labeled for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension (first-line therapy). The approval of Lumigan 0.01% for first-line use does not rely upon the Agency's previous findings of safety for Xalatan, studies that were not conducted by or for Allergan, or literature. Accordingly, your 505(b)(2) arguments as they pertain to Lumigan 0.01% are not relevant and they are not addressed in the remainder of this response.

compared with Xalatan-treated subjects (27.6 percent) and timolol (14.0 percent), but very few subjects (6 of 200 in the Travatan arm) discontinued due to this adverse effect. Eyelash change assessed by serial photography (change in color, length, density, or thickness of eyelashes) was more common in Travatan-treated subjects (57.1 percent) compared with Xalatan (25.8 percent) or timolol (3.1 percent). Other clinical data in the NDA included a 6-month clinical trial with increased iris pigmentation observed in 2.1 percent of Travatan-treated subjects (no cases in the timolol comparator arm), a 9-month clinical trial with increased iris pigmentation observed in 3.6 percent of Travatan-treated subjects (no cases in timolol comparator arm), and a 6-month clinical trial in which Travatan was added to timolol and no cases of increased iris pigmentation were observed. In addition, Alcon submitted a 1-year study of ocular toxicity in cynomolgus monkeys. The animals received ocular administration of Travatan, Xalatan, and vehicle to a single eye. Increased palpebral fissures and increased iris pigmentation were noted in similar proportions in animals exposed to Travatan or Xalatan, but these adverse effects were not observed in animals exposed to vehicle. Histologic examination of the eyes was conducted post mortem. The Agency medical officer review recommended that the applicant propose a postmarketing plan to adequately address concerns raised by the reports of increased iris pigmentation and eyelash changes as well as conduct a study to evaluate pigment deposition in the trabecular meshwork.

Alcon submitted an sNDA seeking approval for a first-line indication for Travatan on June 1, 2006. The sNDA was submitted as a 505(b)(2) application. According to the Petition, Pfizer received a paragraph IV patent certification notice indicating that Alcon had submitted an sNDA for a first-line indication for Travatan under section 505(b)(2) of the Act, referencing Xalatan (Petition at 3). Pfizer did not sue Alcon for patent infringement in response to notice of the certification. Subsequently, Alcon submitted an amendment seeking approval of the Travatan supplement as a 505(b)(1) sNDA. Today, FDA approved Alcon's sNDA.[16]

II. DISCUSSION

In the Petition, you assert that approval of the Lumigan 0.03% sNDA is inappropriate and unlawful because (1) FDA does not have authority under section 505(b)(2) to approve the Lumigan 0.03% sNDA based on confidential, non-public information contained in the Xalatan NDA, and any such reliance on the Xalatan NDA information would constitute a "taking" and a violation of the Trade Secrets Act; (2) even if FDA were authorized to rely on the Xalatan NDA,

---

[16] Travatan is now labeled for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension (first-line therapy). You specifically ask FDA to deny approval of the Alcon sNDA if the approval is predicated on data regarding Xalatan that Pfizer submitted confidentially to the Xalatan NDA (Petition at 7). Your understanding is incorrect. Approval of Travatan for first-line use does not rely upon the Agency's previous findings of safety for Xalatan, studies that were not conducted by or for Alcon, or literature. Accordingly, your 505(b)(2) arguments as they pertain to the Travatan sNDA are not relevant and they are not addressed in the remainder of this response.

FDA also approved sNDA 21-994/SE1/001 for Travatan Z. You did not raise Travatan Z in your petition. We note that the supplement for Travatan Z is a 505(b)(1) sNDA. Your arguments in your petition and supplement are not relevant to Travatan Z; therefore, Travatan Z is not discussed in the remainder of this response.

the data and information in the Xalatan NDA do not provide substantial evidence establishing that Lumigan is appropriate for first-line use, as the drugs have distinct structures, concentrations, and safety profiles; and (3) it would be arbitrary and capricious for FDA to approve Lumigan as a first-line therapy in the absence of clinical data substantiating the safety of the product for first-line use, when FDA required Pfizer, in similar circumstances, to submit significant additional data to obtain a first-line indication for Xalatan. We discuss each of these assertions in further detail below.

A. Reliance of 505(b)(2) Applications on Prior FDA Findings

You assert that in prior citizen petitions,[17] you demonstrated that FDA does not have the authority to rely on confidential, unpublished data in an innovator's NDA to approve a third party's 505(b)(2) application and that only publicly available reports of investigations may be used to satisfy the "full investigations" requirements for applications submitted under section 505(b)(2) (Petition at 7). You also assert that, as you have argued before, FDA reliance on prior FDA "findings" is equivalent to reliance on the data contained in the NDA on which the findings were based (Petition at 7). You assert that FDA reliance on data and information in the Xalatan NDA would constitute a "taking" under the Fifth Amendment and "a violation of trade secrets" and again refer to a prior submission in which you presented this argument to the Agency (Petition at 8). As support for these assertions, you refer to the arguments that you made in prior citizen petitions.

As you are aware, FDA already has issued citizen petition responses that addressed and rejected these arguments.[18] As we explained in our responses, we disagree with your assertion that only publicly available reports of investigations may be used to satisfy the "full reports of investigations" requirements for applications submitted pursuant to section 505(b)(2) and that FDA reliance on prior FDA "findings" for the purposes of approving 505(b)(2) applications is equivalent to FDA reliance on specific data contained in the referenced NDA. Section 505(b)(2) of the Act does not limit the studies on which 505(b)(2) applicants may rely only to those that are found in published literature or are otherwise publicly available. Congress could easily have added such a limitation, but did not.[19] Also, as explained in FDA's petition responses, reliance on FDA's finding or conclusion that an approved drug is safe and effective does not involve disclosure to the 505(b)(2) applicant or to the public of the data in the listed drug's NDA.[20] For the reasons previously described in those responses, we disagree with your assertions. We also

---

[17] You refer to the following submissions: (1) Pfizer's citizen petition dated May 13, 2004, requesting that FDA deny approval of the Omnitrope 505(b)(2) application (originally Docket No. 2004P-0231, now Docket No. FDA-2004-P-0339); (2) Pfizer's citizen petition dated October 11, 2002, requesting, inter alia, that FDA deny approval of Dr. Reddy Laboratories' 505(b)(2) application for amlodipine maleate tablets if the NDA relies on any non-public proprietary data in Pfizer's NDA for Norvasc (originally Docket No. 2002P-0447, now Docket No. FDA-2002-P-0390); and (3) Pfizer's citizen petition dated July 27, 2001, requesting, inter alia, that FDA not rely on or otherwise use non-public proprietary information in an innovator's NDA or other non-public findings to approve 505(b)(2) applications (originally Docket No. 2001P-0323, now Docket No. FDA-2001-P-0369).

[18] 505(b)(2) Response and 2006 Citizen Petition Response.

[19] 505(b)(2) Response at p. 21.

[20] 505(b)(2) Response at p. 15 and 2006 Citizen Petition Response at p. 6.

note that studies similar to the Latanoprost Histology Study,[21] part of the evidence that supported the approval of your sNDA, had been published in the scientific literature at the time of the Lumigan 0.03% sNDA review.[22] These published studies showed that there was an increased amount of melanin within iris stromal melanocytes in irides reported to exhibit color change rather than an increase in melanocyte numbers and no deposition of pigment granules in the trabecular meshwork. It was permissible for FDA to rely (in part) on this literature and other product-specific literature for approval of the Lumigan 0.03% sNDA. Reliance on this literature and our findings regarding the long-term effects of increased iris pigmentation for Xalatan in the course of the review of the Lumigan 0.03% sNDA did not entail the disclosure of, or reliance on, trade secret information from the Xalatan sNDA.

In your Supplement, you argue that FDA should investigate whether it relied improperly on Pfizer's confidential NDA data to approve Allergan's sNDA for Lumigan 0.03% (Supplement at 6). You cite statements in FDA reviews of the Lumigan 0.03% sNDA, state that the FDA reviews refer to information in the Xalatan NDA, and suggest that FDA may have relied directly on Pfizer's confidential Xalatan data (Supplement at 7). You also assert that purported FDA reliance on the data and information in the Xalatan NDA constitutes a "taking" under the Fifth Amendment and a violation of the Trade Secrets Act. In light of your allegations, we have examined closely the reviews of the Lumigan 0.03% sNDA approving the product for first-line treatment and conducted an independent review of the literature available at the time of first-line approval in 2006 and the information contained in the Lumigan 0.03% NDA. Although the medical officer review of data for the Lumigan 505(b)(2) application describes the summary conclusions from the Xalatan sNDA review, this reference was unnecessary for us to approve the application. Our findings of safety for Xalatan (as reflected in the Xalatan labeling), data owned by Allergan and submitted to the NDA, and the published scientific literature would have been sufficient to support the Lumigan 0.03% sNDA approval. This conclusion is further discussed in section II.B. of this letter.

Moreover, as described in this section, FDA may rely on its prior finding or conclusion that an approved drug is safe and effective for approving a 505(b)(2) application referencing the listed drug. As explained in FDA's response to the prior citizen petitions that you cite, the reliance by FDA on its prior findings cannot provide the basis for a "taking" claim because, among other things, Pfizer should have been aware that, subject to applicable patent and exclusivity protections, the Agency would permit a 505(b)(2) applicant to rely on the finding of safety and effectiveness for an approved NDA. Indeed, Pfizer received paragraph IV certifications notifying it that Allergan was relying on Xalatan as a listed drug and declined to initiate patent infringement suits. Therefore, any purported expectation that the Agency would not permit a

[21] Statistical Data Analysis Center, Dept. of Biostatistics and Medical Informatics, University of Wisconsin-Madison. Latanoprost Pathology Study, 16 April 2002. (NDA 20-597)

[22] Pfeiffer N, Grierson I, Goldsmith H et al. Histological Effects of the Iris after 3 Months of Latanoprost Therapy. The Mainz 1 Study. Arch Ophthalmol 2001; 119(2):191-196; Grierson I, Pfeiffer N, Cracknell KBP, and P Appleton. Histology and fine structure of the iris and outflow system following latanoprost therapy. Surv Ophthalmol 2002;47 (Suppl 1): S176-84.

505(b)(2) applicant to rely on the finding of safety and effectiveness for an approved NDA is unreasonable.[23]

B. Reliance by the Lumigan 0.03% 505(b)(2) sNDA on FDA Findings of Safety for Xalatan

You assert that even if FDA had legal authority to approve the Allergan sNDA under 505(b)(2) of the Act in reliance on Pfizer's Xalatan sNDA, such reliance is scientifically unjustified (Petition at 9). You assert that in the absence of data specific to Lumigan 0.03%, FDA does not know whether the product is appropriate for use as a first-line treatment (Petition at 9).

1. Lumigan and Xalatan Common Characteristics

We disagree with your assertion that approval of Allergan's Lumigan 0.03% 505(b)(2) sNDA based (in part) on FDA's findings of safety for Xalatan and relevant published literature was not scientifically justified. As we have stated in our petition responses and in the draft guidance, a 505(b)(2) applicant may rely on the Agency's finding of safety and effectiveness for a listed drug to the extent the listed drug and the drug described in the 505(b)(2) application share characteristics in common (e.g., active ingredient, dosage form, strength, route of administration, indication, conditions of use). We have found that Lumigan shares characteristics with Xalatan such that reliance (in part) on FDA's findings of safety for Xalatan to support approval of Lumigan 0.03% is scientifically justified.

Lumigan (bimatoprost ophthalmic solution) shares key characteristics with the listed drug Xalatan (latanoprost ophthalmic solution) with respect to class of active ingredient, approved use, and certain adverse effects, in addition to dosage form and route of administration. The active ingredient, bimatoprost, is a prostaglandin $F_{2\alpha}$ analog, and thus is a member of the same drug class as latanoprost. As such, bimatoprost and latanoprost share similar chemical characteristics that permit them to act on prostaglandin receptors. There is evidence that bimatoprost and latanoprost are pro-drugs that are converted to the free acid form in the ocular tissue. Bimatoprost has in common with latanoprost the same basic primary mechanism of action, stimulation of the prostaglandin $F_{2\alpha}$ receptor, by which they are believed to reduce intraocular pressure by increasing uveoscleral outflow.[24] Xalatan and Lumigan ophthalmic solutions have both been found by FDA to be effective for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

---

[23] 505(b)(2) Response at p. 31.

[24] As described in the Xalatan approved labeling, "Latanoprost is a prostanoid selective FP receptor agonist that is believed to reduce the intraocular pressure (IOP) by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow." As described in the Lumigan approved labeling, "Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes." Both drugs have the same basic primary mechanism of action by which they are believed to achieve their effect. *See also, e.g.*, Maxey KM, Johnson JL, LaBrecque J. The hydrolysis of bimatoprost in corneal tissue generates a potent prostanoid FP receptor agonist. Surv of Ophthalmol 2002;47: S34-S40.

2. *History of FDA's Concern Related to Iris Pigmentation*

At the time of the original Xalatan approval in 1996, the major safety concern of the Ophthalmology Advisory Subcommittee and the Agency was the long-term effects of increased iris pigmentation. There was concern that patients experiencing this adverse effect could develop ocular melanoma or that melanin deposition in the trabecular meshwork could lead to pigmentary glaucoma. Increased iris pigmentation was a known adverse effect of naturally occurring prostaglandins applied to the eye, having been observed a decade prior to the original Xalatan approval.[25] This adverse effect was an area of focus of the Xalatan development program. In the Xalatan NDA, Pharmacia and Upjohn reported that increased iris pigmentation was noted in cynomolgus monkey studies with Xalatan. Pharmacia and Upjohn carried out histology studies in monkeys with this adverse effect and did not find a proliferation of melanocytes. The sponsor hypothesized that increased iris pigmentation was likely due to stimulation of melanin production in the iris melanocytes. The sponsor carried out additional investigations seeking to understand the mechanism of this adverse effect and included these studies as part of its NDA. With respect to the adverse effect of increased iris pigmentation, Pharmacia and Upjohn concluded in its NDA submission for Xalatan, "This seems to be a class effect of prostaglandins of the F and E type."

FDA agreed with Pharmacia and Upjohn that increased iris pigmentation was a class effect and recommended that the sponsors of all other investigational new drugs for prostaglandin analog products, including Allergan (developing Lumigan) and Alcon (developing Travatan), specifically monitor for this adverse effect in their clinical trials. By the time of the Lumigan 0.03% and Travatan approvals, increased iris pigmentation observed following administration to the eyes of humans and primates had been reported with a number of naturally occurring prostaglandins as well as prostaglandin analogs. As increased iris pigmentation first observed with Xalatan was a class effect, Lumigan and Travatan were labeled as second-line therapy because of concerns regarding the potential long-term risks of increased iris pigmentation for this class of drugs, and the labeling included adverse events and warnings regarding certain class effects consistent with then 21 CFR 201.57(g) (and now 21 CFR 201.80(g)). This action was taken regardless of the frequency of increased iris pigmentation in clinical studies with the product being approved.

As described in section I.B.1. of this letter above, approval of the Xalatan sNDA to change the indication for Xalatan to the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension (first-line therapy) was supported by a study, submitted to the NDA, that reported on long-term follow-up of patients who experienced adverse effects from Xalatan and then were withdrawn from Xalatan treatment. This study found that there was no decrease in iris pigmentation after Xalatan withdrawal, but that eyelash changes reversed after Xalatan withdrawal. The latanoprost pathology study, which reported an increased amount of melanin within iris stromal melanocytes in irides reported to exhibit color change rather than an increase in

[25] Bito LZ, Srinivasan BD, Baroody RA, Schubert H. Non-invasive observations on eyes of cats after long-term maintenance of reduced intraocular pressure by topical application of prostaglandin-E2. Investigative Ophthalmology & Visual Science 1983;24:376-80.

melanocyte numbers and no deposition of pigment granules in the trabecular meshwork, was also important in support of the approval.

Also supportive of the Xalatan sNDA approval was the 3-year clinical study with 2-year extension that examined the safety of Xalatan when administered once daily as adjunctive therapy in patients with primary open-angle glaucoma. In this study, 435 subjects completed 36 months of follow-up and 344 subjects completed 60 months of follow-up, and only one-third of subjects were classified as developing increased iris pigmentation. Although no subjects developed ocular malignancy or pigmentary glaucoma (which were the major concerns with this class of agents), due to sample size, there was limited ability to detect these rare adverse effects of interest. If one only considers the one-third of subjects classified as developing increased iris pigmentation, the ability to detect rare adverse events was further limited. The Agency had been reviewing postmarketing reports of adverse drug experiences submitted by the NDA holder. The postmarketing reports also showed no "safety signal" for ocular malignancy or pigmentary glaucoma associated with Xalatan use.

3. Lumigan 0.03% sNDA

At the time of the Lumigan 0.03% sNDA review of the first-line indication in 2006, a body of published scientific literature was available that supported the conclusion (similar to the conclusion stated by Pharmacia and Upjohn in the original Xalatan NDA) that the side effect of increased iris pigmentation was a prostaglandin receptor mediated class effect. All of these products are members of the same drug class, prostaglandin $F_{2\alpha}$ analogs, and they have the same primary mechanism of action, stimulation of the prostaglandin $F_{2\alpha}$ receptor, by which they are believed to reduce IOP by increasing aqueous humor outflow.[26] All of the approved prostaglandin $F_{2\alpha}$ analogs cause the side effect of increased iris pigmentation.[27] The side effect of increased iris pigmentation had been observed in published clinical trials with Xalatan, Lumigan, and Travatan, as well as with ophthalmic exposure to naturally occurring prostaglandins.[28]

Allergan submitted to its NDA a primate study in which cynomolgus monkeys were exposed to Lumigan, Xalatan, and other prostaglandin analogs and the irides were examined histologically.

---

[26] Stjernschantz JW. From $PGF_{2\alpha}$-isopropyl ester to latanoprost: a review of the development of xalatan. Investigative Ophthalmology & Visual Science 2001;42:1134-45; Eisenberg DL, Toris CB, Camras CB. Bimatoprost and travoprost: a review of recent studies of two new glaucoma drugs. Surv Ophthalmol 2002;47(Suppl 1): S105-115.

[27] Eisenberg DL, Toris CB and Camras CB. Bimatoprost and Travoprost: A Review of Recent Studies of Two New Glaucoma Drugs. Surv of Ophthalmol 2002;47(Suppl 1):S105-115; Eisenberg DL. Latanoprost versus Bimatoprost. Ophthalmol 2003; 110(9):1861-2.

[28] Netland PA, LandryT. Sullivan K. Travoprost compared with latanoprost and timolol in patients with open angle glaucoma and ocular hypertension. Am. J Ophthalmol 2001;132:472-84; Parrish RK, Palmberg P, Wang P. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure: a 12 week randomized masked evaluator study. Am J Ophthalmol 2003;135:688-703; Sherwood M and J Brandt. Six month comparison of bimatoprost once-daily and twice daily with timolol twice-daily in patients with elevated intraocular pressure. Surv Ophthalmol 2001; 45 (Suppl 4): S361-8; Stjernschantz JW. From $PGF_{2\alpha}$-isopropyl ester to latanoprost: A review of the development of Xalatan. Investig Ophthalmol & Vis Sci 2001; 42: 1134-1145.

The affected irides were similar regardless of which prostaglandin analog they had been exposed to, with increased melanin synthesis evident in stromal melanocytes, but no melanocyte proliferation. There was no evidence that melanocytes burst and released melanin intraocularly obstructing aqueous humor outflow. In addition, Allergan submitted to its NDA a masked histologic evaluation that found no deposition of pigment in trabecular meshwork in the specimens collected from patients who had been treated with Lumigan for at least 2 years.

By 2006, a body of published scientific literature was also available that was consistent with the data submitted by Allergan and supported the conclusion based on the Allergan data that increased risk for melanoma and pigmentary glaucoma associated with Lumigan 0.03% exposure is unlikely. The likely mechanism of prostaglandin-induced iris pigmentation was extensively reviewed by Stjernschantz et al. in 2002.[29] A study from the published literature carried out by Pharmacia consultants reported increased tyrosinase activity in murine melanoma cell lines and small increases in tyrosinase activity in human uveal and cutaneous melanoma cell lines after exposure to a number of naturally occurring prostaglandins as well as latanoprost, consistent with the conclusion that increased iris pigmentation was a class effect. Exposure did not increase mitotic index in any of the melanoma lines studied regardless of the prostaglandin or prostaglandin analog to which they had been exposed.[30] This and another in vitro study demonstrated that prostaglandins of the F type exert negligible, if any, mitogenic effect on melanocytes.[31] Other studies in the published literature were similar in design to the latanoprost pathology study submitted with the Xalatan sNDA and would allow one to draw the same conclusions.[32] These studies showed that prostaglandins and prostaglandin analogs stimulate melanogenesis in melanocytes, but not melanocyte proliferation. Therefore, an increased risk for malignancy is unlikely. Published studies also showed that trabeculectomy specimens taken from patients treated with Xalatan did not exhibit deposition of melanin in the trabecular meshwork. Therefore, there was no evidence that melanocytes burst and released melanin intraocularly obstructing aqueous humor outflow.

Allergan also submitted to its NDA the 48-month report for the Lumigan 0.03% long-term follow-up study as well as iris photographic assessment of subjects enrolled in the Lumigan long-term follow-up study. In spite of some limitations in the quality of iris photography, the Lumigan 48-month long-term follow-up study was supportive of the Agency's conclusions with respect to the long-term consequences of increased iris pigmentation as no cases of ocular

---

[29] Stjernschantz JW, Albert DM, Dan-Ning H et al. Mechanism and clinical significance of prostaglandin-induced iris pigmentation. Survey of Ophthalmology 2002;47:S162-75.

[30] Dutkiewicz R, Albert DM, Levin LA. Effects of latanoprost on tyrosinase activity and mitotic index of cultured melanoma lines. Exp Eye Res 2000; 70:563-9.

[31] Hu D-N, Stjernschantz J, McCormick SA. Effect of prostaglandins A_2, E_1, $F_{2\alpha}$ and latanoprost on cultured human iridial melanocytes. Exp Eye Res 2000;70:113-20.

[32] Grierson I, Pfeiffer N, Crackell KBP, and P Appleton. Histology and fine structure of the iris and outflow system following latanoprost therapy. Surv Ophthalmol 2002;47 (Suppl 1): S176-84; Pfeiffer N, Grierson I, Goldsmith H et al. Histologic effects in the iris after 3 months of latanoprost therapy: the Mainz 1 study. Arch Ophtholmol 2001; 119:191-6.

malignancy or pigmentary glaucoma were observed after years of Lumigan 0.03% exposure. Like the Xalatan long-term study, the sample size of the Lumigan long-term study was limited, and there was limited ability to detect rare adverse effects. The Agency had been reviewing postmarketing reports of adverse drug experiences submitted by the NDA holder on an ongoing basis. The postmarketing reports also showed no "safety signal" for ocular malignancy or pigmentary glaucoma associated with Lumigan use. This 48-month study and other studies submitted by Allergan reported on the follow-up of subjects experiencing adverse effects. Eyelash changes were reported to be reversible after discontinuation of Lumigan, and increased iris pigmentation appeared to be permanent.

The Lumigan 0.03% application had been submitted pursuant to section 505(b)(2) of the Act referencing Xalatan; therefore, the Agency also relied upon the findings of safety for Xalatan and published scientific literature in addition to data submitted by Allergan to support the approval of the Lumigan 0.03% sNDA. The published literature itself and the data submitted by Allergan justified the applicability of the earlier Xalatan findings regarding the characterization of increased iris pigmentation (as reflected in the approved labeling described in section I.B.1 of this letter) and product specific published literature for Xalatan to the Lumigan 0.03% application.

C. Postmarketing Experience with Prostaglandin Analogs

We also note that considerable postmarketing experience has accrued for these products since the original approvals, and this experience provides important information regarding the risks and benefits of these products, particularly the risks of ocular melanoma or pigmentary glaucoma. In addition to ongoing review of adverse events with these products submitted by application holders, FDA has conducted additional research in our Adverse Event Reporting System (AERS) database, described below, regarding the safety of all prostaglandin $F_{2\alpha}$ analogs. Our conclusions are supported by our understanding of how adverse events associated with these products are monitored and detected.

The FDA AERS database provides a means to detect low-frequency serious adverse events. FDA searched AERS in October 2008 and updated the search in January 2010, for any cases of ocular melanoma or pigmentary glaucoma associated with the use of a prostaglandin analog. The search of the AERS database identified 13 cases of note:

1. One case of pigmentary glaucoma was reported after 3 months of Xalatan treatment. The case report has limited details but describes an iris nevus (present prior to the start of Xalatan treatment) as being a complicating factor.
2. A second case was reported of a patient on Lumigan 0.03% treatment who was switched to Xalatan treatment; after the switch, the patient was noted to have variable episodes of high intraocular pressure that was diagnosed as pigmentary glaucoma. The patient was then returned to treatment with Lumigan 0.03%.
3. One case of choroidal melanoma was diagnosed after 6 weeks of Xalatan treatment.
4. One case of choroidal melanoma was reported after 11 months of use of Xalatan.
5. One case of a suspected choroidal melanoma was reported after 15 months of Xalatan treatment.

6. One case of ciliary body melanoma was suspected after 2 years of use of Xalatan.
7. One case of a patient with a preexisting iris lesion was treated with Xalatan interchanged with Lumigan 0.03% for 2 years, and the iris lesion was then reported to be a melanoma.
8. One case of iritic melanoma was reported after 16 months of use of Lumigan 0.03%.
9. One case of choroidal melanoma diagnosed within 3 months of starting Xalatan treatment.
10. One case of choroidal melanoma diagnosed 17 months after starting Xalatan treatment.
11. One case of uveal melanoma reported after 5 years of Xalatan treatment.
12. One case of ocular melanoma in a patient with unknown duration of prior Xalatan treatment.
13. One case of iris melanoma in a patient with unknown duration of prior Xalatan treatment.

There are two cases of pigmentary glaucoma reported, one associated with Xalatan exposure, one associated with both Lumigan 0.03% and Xalatan exposure, and none associated with Travatan exposure. The annual incidence rate of pigmentary glaucoma has been reported at 14 cases per million population.[33] Therefore, the expected incidence would be approximately 140 cases of pigmentary glaucoma during a 10-year period per million persons. Based on our analysis of marketing sales data, the observed incidence is well below the expected incidence for either Xalatan or Lumigan 0.03%.

There are 11 cases of ocular melanoma reported, 9 associated with Xalatan exposure, 1 associated with Lumigan 0.03% exposure, 1 associated with both Xalatan and Lumigan 0.03% exposure, and none associated with Travatan exposure. All cases of melanoma described above were in patients over the age of 50. The incidence of choroidal melanoma is approximately 20 cases per million per year in patients over the age of 50.[34] Therefore, the expected incidence would be approximately 200 cases of choroidal melanoma during a 10-year period per million persons. Based on our analysis of marketing sales data, the observed incidence is well below the expected incidence for either Xalatan or Lumigan 0.03%.

Although under-reporting is a limitation of AERS and it is not always possible to use postmarketing reports or lack thereof to support the safety of applications, it is appropriate to rely, in part, on the postmarketing reports in this case to reassure ourselves that the hypothesized concerns that led to the initial limitation to second-line therapy were not seen with sufficient frequency to justify this continued limitation. Further, patients treated for ocular hypertension or glaucoma are regularly followed by ophthalmologists using the magnification provided by biomicroscopes. This magnification with biomicroscopes provides a method for routinely evaluating changes to the iris and/or deposition of pigment in the anterior chamber angle. In addition, intraocular pressure is measured at these follow-up visits. This type of exam would be expected to detect ocular tumors or glaucoma due to pigment deposition. Ophthalmologists are aware of the iris pigmentation adverse effect with this class of products because it is described in the approved labeling. Occurrence of primary ocular melanoma would raise concern regarding

[33] Siddiqui Y, Ten Hulzen RD, Cameron D et al. What is the risk of developing pigmentary glaucoma from pigment dispersion syndrome? Am J Ophthalmol. 2003;135:794-99.

[34] Wilkes SR, Robertson DM, Kurland LT, Campbell RJ. Incidence of uveal malignant melanoma in the resident population of Rochester and Olmstead County, Minnesota. Am J Ophthalmol. 1979; 87:639-641.

association with the prostaglandin analog, and it would be reasonable to expect that such adverse events would be reported to AERS or otherwise come to the attention of the Agency. This would also be the case for pigmentary glaucoma which is more common in young adults while most forms of open-angle glaucoma are more common in older adults. Therefore, it is reasonable to conclude that there is not evidence of a safety signal for the use of any of the drugs in the class of prostaglandin analogs and either pigmentary glaucoma or ocular melanoma.

D. Your Other Assertions Do Not Have Merit and Do Not Warrant Revoking the Approval for Lumigan 0.03% as a First-Line Therapy

1. Assertions Regarding Differences Between Xalatan and Lumigan

In the Petition, you also assert that there are certain differences in these drug products that would make a section 505(b)(2) approval for a first-line indication for Lumigan inappropriate. You state that bimatoprost compared to latanoprost has a distinct molecular structure and concentration used to affect IOP lowering and has significant safety/side effect differences in rates of hyperemia, eyelash changes, and eyelid sulcus (Petition at 9).

As described in section I.A.1 of this response, a 505(b)(2) application may describe a drug product with substantial differences from a drug product previously approved by FDA, including changes of active ingredient, dosage form, indication, strength, formulation, or route of administration, as long as those differences are supported with appropriate safety and effectiveness information. As discussed in section II above, Lumigan shares certain characteristics with Xalatan, such that reliance on certain FDA findings for Xalatan or product-specific literature regarding Xalatan to support the approval of Lumigan 0.03% for first-line use was scientifically justified.

a. Incidence of safety/side effects

You assert that significant differences in conjunctival hyperemia incidence and intensity have been observed among prostaglandins (and prostamides) in comparative trials, bimatoprost produced significantly higher rates of hyperemia than latanoprost, and the package insert reflects these higher rates. You conclude that it is unknown whether long-term exposure to sustained hyperemia will result in increased morbidity (Petition at 5). You also assert that significantly higher rates of eyelash changes (including length, thickness, density, and color) are reported with bimatoprost as compared to latanoprost (Petition at 6). You assert that, generally, higher rates of periocular sulci and palpebral fissure (PF) and/or deepening of the lid sulcus were observed with bimatoprost compared to latanoprost in both animal models and humans (Petition at 6).

Your assertions regarding conjunctival hyperemia or deepening of the lid sulcus are not relevant to whether it is appropriate to rely on findings and literature relating to Xalatan for approval of the Lumigan 0.03% sNDA. The incidence of these effects does not appear to be proportional to increased iris pigmentation, and there do not appear to be long-term adverse consequences. This side effect, hyperemia, was not the reason this class of agents was originally approved as second-line therapy, as the safety of subjects in whom conjunctival hyperemia had occurred was evaluated in clinical trials for each product. The incidence of hyperemia is described in labeling

for each product; therefore, healthcare practitioners and patients will be informed of the adverse effect. With respect to reported changes in the eyelid sulcus, there are no safety concerns identified and the phenomenon is not related to increased iris pigmentation. The reference identified in your Petition reports on three patients in whom there is a deepening of the lid sulcus.[35] In all three cases, there were no medically harmful effects. There are no data presented that demonstrate a difference in the incidence or dose of medication associated with changes in the eyelid sulcus based upon a comparison of these agents in the same study. Further, changes in eyelid sulcus was not the reason this class of agents was originally approved as second-line therapy.

Eyelash growth and other eyelash changes were identified as effects of concern based on observations in the Lumigan 0.03% clinical trials. Agency concerns were reflected in the NDA reviews. This adverse effect (of eyelash growth) had also occurred in the Xalatan clinical trials, although it was not specifically reported in the original NDA and not focused on in the review of that NDA. There is evidence based on published literature that this adverse effect, like increased iris pigmentation, is prostaglandin receptor mediated. As the two adverse effects appear to be prostaglandin receptor mediated, one might anticipate that the frequency of increased iris pigmentation and eyelash changes would be similar or at least proportional if they occurred at the same anatomic location. However, eyelash growth and increased iris pigmentation do not occur at the same anatomic location, as the drug products must pass through the cornea after administration to reach the iris, which can alter the molecule that is present in the aqueous humor. In addition, the method of ascertainment in clinical trials for the two adverse effects is often different. Whereas many clinical trials carried out serial iris photography to monitor specifically for increased iris pigmentation, data regarding eyelash changes were often dependent upon spontaneous reporting. Related to differences in ascertainment method, the frequency of eyelash changes varies in clinical trials of Xalatan, Lumigan, and Travatan. In clinical trials that included two or more of these three drugs and use uniform criteria for eyelash changes, the rate of eyelash changes over a period of up to 6 months was similar among the three drugs.[36] In addition, detection of increased iris pigmentation is associated with eye color whereas detection of eyelash growth and eyelash changes is not associated with eye color. Therefore, differences in reported frequency of eyelash changes compared with the frequency of increased iris pigmentation for the products is not an appropriate reason to conclude that information regarding the safety of Xalatan with respect to the adverse effect of increased iris pigmentation would not apply to Lumigan. While the adverse effect of eyelash changes was an initial concern of the Agency for this class of drugs, it was no longer considered a major adverse effect of concern for the class by the time of the Lumigan 0.03% sNDA review in 2006, as the side effects of eyelash growth and other eyelash changes had been observed to be reversible upon discontinuation of prostaglandin analog administration based on data submitted to the respective NDAs.

---

[35] Peplinski LS and K Albiani Smith. Deepening of Lid Sulcus from Topical Bimatoprost Therapy 2004. Optom and Vis Sci, 81: 574-577.

[36] Parrish RK, Palmberg P, Sheu WP and the XLT Study Group. A comparison of latanoprost, bimatoprost, and travoprost in patients with elevated intraocular pressure; a 12 week, randomized, masked-evaluator multicenter study. Am J Ophthalmol 2003;135:688-703; Noecker RS, Dirks MS, Choplin NT, et al. A six-month randomized clinical trial comparing the intraocular pressure lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. Am J Ophthalmol 2003;135:55-63.

The rates of all events and the consequences of these events were taken into account in the decision to approve the Lumigan 0.03% sNDA. The occurrence and frequency of each adverse event has been evaluated individually for Lumigan and has been adequately described in the labeling for the drug product. It was only the consequences of the increased iris pigmentation that led to the second-line indication.

b. Concentration

You assert that bimatoprost is used at significantly higher concentration than latanoprost when taking into consideration pharmacological potency, but you acknowledge the IOP-reducing effect of the drugs are all very similar. You state that there is evidence to suggest that because bimatoprost is a prostamide, it is more difficult for the drug to penetrate the eye due to poor corneal penetration, necessitating a high concentration of bimatoprost in Lumigan (Petition at 5). You conclude that the increased drug concentration of Lumigan relative to Xalatan may contribute to the higher rates of ocular side effects seen with these drugs (Petition 5).

With respect to concentration, Lumigan (0.03%) is approved at a concentration different from that of Xalatan (0.005%). However, IOP reduction appears to be a reasonable index of pharmacologic potency, and the relative efficacy of the drugs in lowering IOP is similar at their respective marketed concentrations.[37] A comparison of the numerical value of the concentrations of the products prior to application in the eye is not necessarily a useful index for comparing these products as this concentration is not necessarily reflective of the concentration at the prostaglandin receptor, where stimulation leads to IOP reduction and to the adverse effect of increased iris pigmentation.[38] In addition, the formulations of the products differ, and this may play a role in the amount of drug that penetrates the eye.

---

[37] Parrish RK et al. A Comparison of Latanoprost, Bimatoprost, and Travoprost in Patients with Elevated Intraocular Pressure: A 12-week, Randomized, Masked-evaluator Multicenter Study. Am J Ophthalmol 2003; 135:688-703; Stewart WC et al. Meta-analysis of 24-Hour Intraocular Pressure Studies Evaluating the Efficacy of Glaucoma Medicines. Ophthalmol 2008; 115:1117-1122; Van der Valk R et al. Intraocular Pressure – Lowering Effects of All Commonly Used Glaucoma Drugs: A Meta-analysis of Randomized Clinical Trials. Ophthalmol 2005; 112:1177-1185.

[38] Two studies in published literature have reported that the concentration of bimatoprost acid within the aqueous humor is similar or lower than latanoprost acid. *See* Cantor LB, Hoop J, Wudunn D et al. Levels of bimatoprost acid in the aqueous humour after bimatoprost treatment of patients with cataract. Br J Ophthal 2007;91:629-32. Camras CB, Toris CB, Sjoquist B et al. Detection of the free acid of bimatoprost in aqueous humor samples from human eyes treated with bimatoprost before cataract surgery. Ophthalmology 2004;111:2193-98. In both of these studies, patients were treated for a period of time with these medications. A sample of aqueous humor was then removed in the course of cataract surgery and drug level assays performed. Cantor et al. compared latanoprost with bimatoprost levels. The mean levels of latanoprost acid within the aqueous humour were 29.1 nM at hour 1 (post installation of the drug), 41.3 nM at hour 3 and 2.5 nM at hour 6. The mean levels of bimatoprost acid were 5.0 nM at hour 1, 6.7 nM at hour 3, and 1.9 nM at hour 6. Comparing the levels of bimatoprost amide with bimatoprost acid, Cantor et al. found the mean concentration of bimatoprost amide to be similar to that of bimatoprost acid. Camras et al. found the concentration of bimatoprost amide to be considerably lower than that of bimatoprost acid.

Even assuming arguendo that the frequency of the adverse events could be due to the difference in concentration, the frequency of adverse events was not the basis for the second-line determination. Rather, approval of the drugs as second-line therapies was based primarily on the unknown long-term safety consequences related to increased iris pigmentation.

Xalatan and Lumigan[39] have been demonstrated in clinical trials to be safe and effective at the marketed concentrations, as evidenced by their initial approvals. The relatively similar efficacy of each of the prostaglandin analogs in the lowering of intraocular pressure suggests that their potency is similar in stimulating the prostaglandin $F_{2\alpha}$ receptor.

c. Molecular structure

With respect to the structures of the molecules, you assert that in the latanoprost molecule, the double bond between carbon 13 and 14 has been saturated, creating a single bond between carbon 13 and 14, but bimatoprost has a double bond between carbons 13 and 14. You assert that in the development of latanoprost, it was found that the saturation of the carbon 13-14 double bond actually increased the therapeutic index and chemical stability, and the saturation of the bond in latanoprost resulted in an improvement in its receptor profile. Further, you assert that there is evidence that the saturated bond tends to reduce the hyperemic effect as compared to an intact double bond. You cite two studies in apparent support of these propositions (Petition at 4).

We acknowledge that you may have used these findings to help decide on the particular compound that you chose to develop, but we do not agree that differences in this bond alone would lead us to conclude that other prostaglandin analogs are not safe and effective. As noted above, the incidence of hyperemia does not appear to be proportional to the incidence of iris pigmentation. The evidence that bimatoprost is safe and effective in reducing intraocular pressure has been established in clinical trials submitted by Allergan in its NDA. Even if there are actual differences in the frequency of patients exhibiting a hyperemic effect while using a prostaglandin analog, as discussed above, the occurrence and incidence of hyperemia has been studied by the respective applicants, is reflected in the approved labeling, and was not the basis for limiting use of prostaglandin analogs as second-line therapies.

The differences in molecular structure discussed in the Petition are not relevant as the critical scientific evidence that exposure to these drugs was unlikely to increase the risk for ocular melanoma or pigmentary glaucoma was found in spite of these differences among drugs in the class. The research demonstrating that prostaglandins and prostaglandin analogs stimulate melanogenesis in melanocytes, but not melanocyte proliferation, was carried out using the Xalatan and Lumigan molecules. The histologic studies of trabecular meshwork specimens demonstrating an absence of pigment deposition were carried out after exposure to the marketed concentrations of Xalatan and Lumigan. Further, extensive postmarketing history with Xalatan and Lumigan 0.03% has not shown a safety signal for ocular melanoma or pigmentary glaucoma.

[39] We note that despite your assertions, bimatoprost does penetrate the cornea and is pharmacologically active as demonstrated in the adequate and well-controlled studies submitted by Allergan to support the initial approval of Lumigan.

Your petition states that Lumigan is a prostamide, implying that the drug is in a different class than Xalatan. Due to the presence of an amide group as part of the molecular structure, Lumigan is sometimes referred to as a prostamide. Related to the prostamide terminology is an alternate hypothesis regarding the receptor-level mechanism of action of Lumigan in the lowering of intraocular pressure. This hypothesis is summarized in a review by Woodward, Liang, and Krauss published in 2008[40] and is based upon reports that Lumigan effects appear independent of prostanoid FP receptor activation. However, this hypothesis implies the existence of a novel prostanoid receptor that has never been characterized. There is much stronger evidence based on both animal and human studies that Xalatan, Lumigan, and Travatan are pro-drugs that are converted to the free acid form in the ocular tissue, and the free acid form of the drugs acts upon prostaglandin receptors (the amide group is absent when the Lumigan molecule acts upon the prostaglandin receptor).[41] Thus, it is scientifically justified to classify Lumigan as a member of the same drug class as Xalatan and Travatan with the same mechanism of action, stimulation of the prostaglandin receptor, that leads to IOP reduction as well as the adverse effect of increased iris pigmentation.

2. Assertions Regarding Purported Class Judgment

You assert that FDA's decision to approve the Lumigan 0.03% sNDA appears to reflect a class judgment that, because one prostaglandin — Xalatan (latanoprost) — has been shown to be safe for use as a first-line agent, all prostaglandins analogs are safe for such use. You assert that FDA has historically avoided such inductive reasoning (Petition at 9). You quote statements from two FDA office directors and cite two examples in apparent support for your position (Petition at 9-10). We disagree that it is never appropriate to apply findings of safety and effectiveness for one drug to other members of the same class of drugs.[42] The decision to approve the 505(b)(1) NDAs for Lumigan 0.03% and Travatan as second-line treatments was, in part, based on the awareness that increased iris pigmentation was a characteristic shared by prostaglandin analogs that could be considered a class effect and that more long-term information to evaluate the consequences of iris pigmentation was warranted before these drugs could be approved as first-line treatments. As discussed above, FDA's subsequent approval of the Lumigan 0.03% 505(b)(2) sNDA to change from second-line to first-line therapy was based on safety information

[40] Woodward DF, Liang Y, and AH-P Krauss. Prostamides (prostaglandin-ethanolamides) and their pharmacology. British Journal of Pharmacology 2008;153:410-19.

[41] Maxey KM, Johnson JL, LaBrecque. The Hydrolysis of Bimatoprost in Corneal Tissue Generates a Potent Prostanoid FP Receptor Agonist, Surv of Ophthalmol 2002;47: S34-S40; Stjernschantz JW. From $PGF_{2\alpha}$-isopropyl ester to latanoprost: a review of the development of xalatan. Investigative Ophthalmology & Visual Science 2001;42:1134-45; Eisenberg DL, Toris CB, Camras CB. Bimatoprost and travoprost: a review of recent studies of two new glaucoma drugs. Surv Ophthalmol 2002;47(Suppl 1): S105-115; Camras CB, Sharif NA, Wax MB, and J Stjernschantz. Bimatoprost, the prodrug of a prostaglandin analogue. Br J Ophthalmol 2008;92:862-3.

[42] FDA has, at least in one instance, made findings across a set of pharmacologically distinct drug classes, as described in the draft guidance for industry *Hypertension Indication: Drug Labeling Cardiovascular Outcome Claims* (March 2008). Because of consistently favorable effects on outcomes across many drug classes, FDA concluded that a qualitative claim of cardiovascular outcome benefits pertains to all classes of antihypertensive drugs.

in Allergan's NDA, FDA's previous findings of safety for Xalatan, and relevant published literature.

In your Supplement, you contend that FDA inappropriately changed its decision about whether to approve Lumigan 0.03% as a first-line therapy based on a class effect. You claim that in 2003, FDA decided that despite suggestions of a class effect in the review of the Xalatan sNDA, there was a need for Allergan to submit safety data specific to Lumigan. You also claim that FDA must have changed its mind regarding class effect when it ultimately approved the Lumigan sNDA in 2006 (Supplement at 5-6). We disagree with these assertions. As explained above, your arguments ignore the change in the Lumigan sNDA between the time of its initial submission and its ultimate approval by FDA. When initially submitted, Allergan's sNDA was a stand-alone NDA and did not rely on any other listed drug or literature. However, after Pfizer's period of exclusivity expired, Allergan amended its sNDA to rely on FDA's finding with respect to the safety of Xalatan and published literature, as permitted under section 505(b)(2) of the Act.

3. Assertions Regarding Alleged Distinct Long-Term Safety and Efficacy Profiles

You assert that in 2002, Xalatan was the only drug in the prostaglandin therapeutic class granted a first-line indication and that this reflects FDA's recognition that there are distinctions among prostaglandins and prostamides that may result in significant qualitative and quantitative differences in long-term safety (Petition at 6). You assert that neither bimatoprost nor travoprost has demonstrated the same long-term safety for patients. You also assert that although reduction of IOP was not a primary endpoint for this Xalatan study, it was clearly demonstrated that IOP was reduced, and this reduction was maintained at 5 years in those patients who were treated with latanoprost. You assert that, to date, bimatoprost cannot claim this same extent of efficacy (5 years) (Petition at 6).

We disagree with your assumption that because Xalatan was the only drug granted a first-line indication in 2002, this reflected our recognition that there are distinctions among prostaglandin analogs that may result in significant differences in long-term safety or effectiveness. In fact, the FDA review of your sNDA at the time reached the opposite conclusion. FDA generally revises the indication for a drug product in response to an sNDA filed by the holder of a drug's NDA. Pfizer filed an sNDA; FDA reviewed and approved it. For 3 years after the Xalatan sNDA was approved, we were prohibited by law from granting approval to any 505(b)(2) sNDA for a first-line indication because Pfizer received 3-year exclusivity for that condition of approval. That exclusivity expired more than 4 years ago, in December 2005. Further, we disagree that the open label studies you submitted demonstrated maintenance for 5 years of IOP reduction due to Xalatan. Based on data and information submitted and reviewed in the stand-alone NDA, we have found bimatoprost to be effective in the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. The efficacy of these drug products was not a factor in determining whether they should be labeled for first-line or second-line use.

E. Xalatan Is Not Similarly Situated to Lumigan

You assert that it would be arbitrary and capricious for FDA to approve Lumigan as a first-line therapy in the absence of clinical data substantiating the safety of the product for first-line use, when FDA required Pfizer, in closely similar circumstances, to submit significant additional data to obtain a first-line indication for Xalatan (Petition at 10). You assert that Xalatan and Lumigan were all initially approved for second-line treatment of high IOP and, in the case of the Lumigan sNDA to the original NDA, the applicant sought a first-line indication (Petition at 11). You conclude that in this sense, the applicants are similarly situated parties with respect to FDA's review process, and you assert that courts have ruled that an agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so (Petition at 10-11). In your Supplement, you argue that Pfizer was required to conduct extensive additional studies to receive a first-line indication and that you are unaware of a similar complement of robust studies or safety data to support a first-line indication for Lumigan. You cite a "not approvable" letter for Lumigan to support the theory that additional safety data are needed (Supplement at 7-8).

We disagree that Xalatan and Lumigan 0.03% are similarly situated. The Xalatan sNDA was approved as a stand-alone sNDA, and the Lumigan 0.03% sNDA was approved as a 505(b)(2) sNDA. The statutory pathway determines the types of information that may be relied upon to support approval of the application and the appropriate intellectual property considerations. Pfizer submitted the Xalatan sNDA as a stand-alone sNDA because it supported the application with full investigations of safety and effectiveness conducted by the applicant or to which it had a right of reference. Allergan submitted the Lumigan 0.03% sNDA as a 505(b)(2) sNDA, which permitted the applicant to rely upon literature and the Agency's prior findings of safety for the listed drug Xalatan to support its sNDA, to the extent reliance on such reports or findings was scientifically justified, subject to the patent and exclusivity protections for the listed drug.[43]

Pfizer submitted additional clinical investigations to support approval of its sNDA. In return, Pfizer received a statutory benefit of 3-year exclusivity for the first-line indication for Xalatan. As a result, Allergan could not receive approval for 3 years for its sNDA submitted as 505(b)(2) sNDA for the first-line indication. During that period, only Pfizer could label its product for first-line use for reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Also, by relying on the safety finding for Xalatan and not conducting its own clinical studies to support the change, Allergan was not eligible for 3-year exclusivity for the labeling change. In addition, Pfizer was permitted to list patents claiming the first-line indication and other patents claiming the approved drug product or an approved method of use. Allergan was required, as a 505(b)(2) applicant, to certify to these patents and notify Pfizer that it was relying on Xalatan as the listed drug for its 505(b)(2) sNDA. Pfizer could have sued Allergan for patent infringement as a result of these notifications. Pfizer did not sue Allergan.

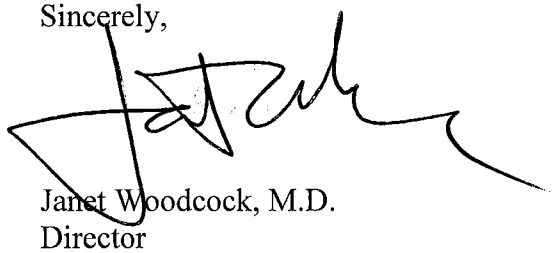
As noted above, the statutory pathway determines the type of information that may be relied upon to support approval of the application. We therefore disagree that it would be arbitrary and capricious for FDA to approve Lumigan as a first-line therapy.

[43] The 2003 "not approvable" letter for Lumigan's sNDA was issued prior to Allergan's decision to use the 505(b)(2) pathway.

III. CONCLUSION

We have concluded that the approvals of the sNDA for Lumigan (0.03%), 505(b)(1) sNDA for Travatan, and 505(b)(1) NDA for Lumigan (0.01%) for a first-line indication are appropriate. We therefore deny your request that FDA revoke approval of the sNDA for Lumigan and your request that FDA deny approvals of the 505(b)(1) sNDA for Travatan and 505(b)(1) NDA for Lumigan (0.01%) for first-line indications.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research