

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

201923Orig1s000

OTHER ACTION LETTERS



NDA 201923

COMPLETE RESPONSE

Alimera Sciences, Inc.
Attention: Ms. Barbara H. Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your New Drug Application (NDA) dated June 30, 2010, received June 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

We also reference our Complete Response letter dated December 22, 2010, your resubmission dated May 12, 2011 and our second Complete Response letter dated November 10, 2011.

We acknowledge receipt of your amendments dated:

January 23, 2012	July 9, 2012	July 2, 2013
March 8, 2012	August 1, 2012	July 10, 2013
April 12, 2012	March 27, 2013	August 12, 2013
May 21, 2012	April 17, 2013	September 9, 2013
May 29, 2012	April 24, 2013	September 10, 2013
May 30, 2012	June 25, 2013	October 11, 2013

The April 17, 2013, resubmission constituted a complete response to our November 10, 2011, Complete Response letter. We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

Specifically, you have not provided data to support that the product is safe and effective (b) (4)

[Redacted]

- a. You have now proposed to revise your indication (b) (4)

[Redacted]

(b) (4)

- b. The results of the safety analyses of your Phase 3 clinical trials submitted to this NDA¹ have demonstrated elevations of intraocular pressure of such magnitude as to require medical or surgical treatment. In the two trials combined, the percentage of patients in the 0.2 µg/day FA group requiring intraocular pressure (IOP) lowering medications was 38.4% (114/375) and the percentage of patients in the sham group requiring IOP lowering medications was 14.1% (26/185). The difference between the 0.2 µg/day fluocinolone acetonide (FA) group and Sham control was 24.3%. This adds an additional treatment burden to patients who already have to manage their underlying diabetes mellitus and additional risks to these patients from potential adverse drug reactions associated with the use of IOP lowering medications.

The difference between the 0.2µg/day FA and Sham control in the percentage of patients requiring surgical intervention for the reduction of their IOP was 4-5%, therefore a significant percentage of patients with IOP increases required surgical intervention. The surgical risks in these patients and the potential endophthalmitis risks associated with filtering surgery are significant additional risks.

The “Special Optic Nerve Head Assessment of the Fame Fundus Photographs by the (b) (4) - Table 6” demonstrated an imbalance at month 36 in the percentage of patients with a worsening in the vertical cup-to-disc ratio (C/D). Eleven patients out of 219 patients (5%) in the 0.2µg/day FA group had worsening of their vertical C/D, compared to only one patient out of 102 patients (1%) treated with Sham. The reported 95% confidence interval (-7.5%, -0.6%) excluded zero. This finding of glaucomatous progression of the C/D ratio in association with a three-fold increase in the rate of elevated IOP in the FA group in these 3 years trials is a concern about the relative safety of this product.

- c. Results of the safety analyses of your Phase 3 clinical trials showed that there is a significantly higher incidence of cataract formation and cataract surgery in patients treated with Iluvien. At

¹ Two controlled clinical trials: C-01-05-001A (Fluocinolone Acetonide in Diabetic Macular Edema, FAME A) and C-01-05-001B (FAME B)

36 months follow-up, cataract progression occurred in 82% in the 0.2 µg/day FA study eyes versus 50% of the Sham group study eyes, for a difference of approximately 32%. Cataract operation occurred 80% in the 0.2 µg/day FA study eyes versus 27% of the Sham group study eyes, for a difference of approximately 53%. Many of the patients developing cataracts experienced a clinically significant loss in visual acuity, including a loss in vision of 15 letters or more, which was documented at one or more of the scheduled quarterly visits. While many patients had restoration of their visual acuity after a cataract extraction and intraocular lens placement, not all patients had improvement in their visual acuity after the surgical procedure. In addition, a number of patients failed to return for follow-up examinations after cataract removal, therefore their visual acuity after cataract surgery is unknown.

- d. In support of your application you initially submitted an analysis of results based on the primary endpoint of visual acuity at 24 months, Full Analysis Set, and efficacy rates were 26-31% in the FA patients versus 15-18% in the sham control. The interpretation of these results was difficult because of the timing of the development of cataracts and the time needed for post-operative recovery. Therefore, you subsequently provided the results of the trials when 36 months of data were available. The analysis of these results showed that at Month 36, there was no statistically significant difference (benefit) in the patients with DME enrolled in your studies (FAME A and FAME B).

At 36 months, the rates for the number of subjects in the Full Analysis Set who gained ≥ 15 -letters from baseline in best corrected visual acuity (BCVA) in the study eye were 28%-29% in the 0.2 µg/day FA and $\frac{0}{4}$ % in both Sham arms. This difference was not statistically significant. [REDACTED] (b) (4)
[REDACTED] FA was not shown to have a benefit in the treatment of DME, and had a significant risk of serious adverse reactions.

You subsequently stated that you interrogated the data based on the duration of DME and analyzed two separate (complementary) subsets of patients [REDACTED] (b) (4)

[REDACTED] We acknowledge that this analysis is presented in your May 12, 2011, resubmission. We have previously noted that this subset analysis was not included in the protocol(s) for these trials and was not included in the statistical analysis plan (SAP) for these trials, meaning no provision was included for statistically adjusting for additional analyses (multiplicity).

We also note that in your May 21, 2012, briefing package for the June 19, 2012, meeting you explain that this analysis by duration of DME was requested to be added by a study representative prior to unmasking of the study databases at Month 24. We note that the analysis requested in 2009 was for the effect "above and below median for duration of DME," and that your programmer noted that subgroup analyses should be completed for $<$ median and $>$ median. While the median analysis was provided in the May 21, 2012, submission, [REDACTED] (b) (4)

(b) (4) it is not clear how the (b) (4) analyses comply with the analysis requested in 2009.

In the analysis of these two subsets, you reported (b) (4)

In addition, (b) (4) these differences were not statistically significant.

However, we note that for both (b) (4) subgroup of patients, there were comparable degrees of significant adverse reactions of cataracts, cataract surgery and increased IOP as the overall clinical trial population, and in both subgroups, these rates were higher in the FA groups compared to Sham control.

We interpreted these results as showing that the risk of the adverse reactions associated with the use of FA exceeded the benefit, for these subsets. This is particularly evident (b) (4) given (b) (4) the adverse reaction rates are higher in the FA arms.

(b) (4)

- e. In your current resubmission, you provided a summary of the most recent results from the use of the to-be-marketed Iluvien inserter. In this analysis, you describe that 4 patients received the insert via a “noncommercial” inserter and 117 patients received the insert via a “commercial” inserter. In the text you further explain that the first 4 patients received “the first lot,” and after a design improvement a “second lot” was produced and 59 subjects were enrolled. You note that a review of technical complaints for the second lot led to an implementation of a (b) (4) a “third batch” was produced and an additional 58 subjects were enrolled. We have reviewed the data provided in the submission for these additional 58 patients in whom the inserter from the third batch was used, and note that 11/58 or approximately 19% of the observer questionnaires noted that there were observed difficulties with study drug administration. Our review of these results suggests that

either additional training instructions or a re-design of the proposed inserter is needed to reduce the difficulties experienced by investigators in delivering the drug product.

To address the clinical and statistical deficiencies, you will need to provide data from one adequate and well controlled clinical trial that demonstrates that Iluvien, at the dose and formulation proposed for marketing and with the inserter and instructions-for-use proposed to be marketed, is safe and effective for the proposed indication you are seeking (intend to market) and the inserter can be used by practitioners with minimal technical difficulties. It is recommended that the study enroll patients who have failed to respond to a three month or more course of anti-VEGF therapy and are randomized between your drug product and continued anti-VEGF therapy. Results of the new study should be submitted with at least 12 months of follow-up for all enrolled patients. However, given the adverse reaction findings observed in the FAME studies, you should plan to obtain longer follow-up to evaluate safety, including effect on visual acuity. A meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee may be of assistance in addressing the deficiencies identified above and providing advice whether a patient population can be identified in which the benefits of the drug product might outweigh the risks.

2. The methods used in and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product do not comply with the current good manufacturing practice (cGMP) regulations in parts 210 and 211. During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. All facilities and controls will need to comply with the cGMP regulations.

To address this deficiency, please amend the application with facilities that are in compliance with cGMPs or notify us in writing when all currently submitted facilities are in compliance with cGMPs.

3. The study report for Study C-01-11-008 states that a supplementary in-process control during manufacturing of the injector was added, however, information on this change was not included in the current resubmission.

To address this deficiency, submit specific information for this change.

4. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
10/17/2013



NDA 201923

COMPLETE RESPONSE

Alimera Sciences, Inc.
Attention: Ms. Barbara H. Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your New Drug Application (NDA) dated June 30, 2010, received June 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iluvien (fluocinolone acetonide intravitreal insert), 0.19 mg.

We acknowledge receipt of your amendments dated May 12 and 16, June 1, July 1, and October 13, 2011. The May 12, 2011, submission constituted a complete response to our December 22, 2010, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL TRIALS

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

Specifically, based on the results of your controlled clinical trials C-01-05-001A (Fluocinolone Actonide in Diabetic Macular Edema, FAME A) and C-01-05-001B (FAME B), there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. Specifically, you have not provided data to support that the product is safe and effective in the treatment of patients with diabetic macular edema (DME).

- a. Results of your controlled clinical trials C-01-05-001A (Fluocinolone Actonide in Diabetic Macular Edema, FAME A) and C-01-05-001B (FAME B), did not demonstrate statistically and clinically significant benefit for your primary endpoint

of best corrected visual acuity (BCVA) at 36 months. As we have noted previously, efficacy at earlier time points was low (26-^{(b) (4)}% vs. 14-18%), the results were not robust as the difference between groups with respect to mean visual acuity was small and not significant. Although some beneficial effect appeared to occur during the first 6 months, the product then appeared to cause clinically significant decreases in visual acuity at month 24, and was not significantly different from sham treatment by month 36.

- b. Results of the safety analyses of your clinical trials showed that there is a significantly higher incidence of cataract formation and cataract surgery in patients treated with Iluvien. Furthermore, the risk of increased intraocular pressure (IOP) is nearly three times higher in the Iluvien treatment arm than the control arm. The risks of these adverse reactions are significant, and are not offset by the benefits demonstrated by Iluvien in these clinical trials.
- c. The to-be-marketed Iluvien Inserter is different from the inserter used in clinical trials, and clinical data from patients treated for diabetic macular edema with the new inserter are not provided in the application. The application only includes data on 8 patients from Study C-01-08-006 who have been enrolled in this study of macular edema in retinal vein occlusion.

- d. You have proposed to revise your indication ^{(b) (4)}
^{(b) (4)}
^{(b) (4)}
In support of this revision you have submitted a post-hoc analysis of the results based on a retrospectively selected subgroup of patients who are said to have duration of DME ^{(b) (4)}
^{(b) (4)}
^{(b) (4)}
this analysis was not pre-specified in the protocol, was not included in the statistical analysis plan (SAP), was not adjusted for multiplicity. Furthermore, we note that this subgroup of patients shows the same degree of significant adverse reactions of cataracts, cataract surgery and increased IOP as the overall clinical trial population.

To address the clinical and statistical deficiencies, you will need to provide data from two controlled clinical trials that demonstrate that Iluvien, at the dose proposed to be marketed, is safe and effective for the proposed indication you intend to study and seek in labeling. Based on the current trials it appears that neither the 0.2 microgram/day nor 0.5 microgram/day dose is safe and effective, therefore your development program would likely involve new clinical trials, and should include the evaluation of the Iluvien Inserter you propose to market. If these trials are intended to involve patients with diabetic macular edema ^{(b) (4)} duration, you will need to provide specific objective criteria and documentation that subjects had DME ^{(b) (4)} because DME is a

disease that can wax and wane over the course of many years with varying degrees of macular involvement.

PRODUCT QUALITY

2. There is insufficient information to determine the adequacy of the specifications necessary to ensure the identity, strength, quality, purity, and potency of your drug substance and drug product. Specifically,
 - a. The proposed *in-vitro* release rate range (b) (4). Without the release rates of the batches that were tested in the clinical studies, the adequacy of your proposed *in-vitro* release rate cannot be determined. We suggest that the estimation of the range for the release rate be based on mean data and 90% confidence intervals around the mean. Note that the proposed release rate specification range should (b) (4).
In addition, your protocol for the *in vitro* drug release rate test specifies the collection of samples (b) (4). It is not clear from the data submitted in your May 12, 2011 submission, specifically “Table 2: Release Rates of Primary Stability Lots and Scale-up Lots, Manufactured (b) (4)” and “Table 3: Release Rates (b) (4) from Study 10123,” at what time points these samples were collected and how many samples from each batch were tested. These need to be clarified. A detailed raw data sheet (preferably in electronic format) describing all the data used to generate the *in-vitro* release rates in the Tables 2 and 3 needs to be submitted.
 - b. You have not provided the polymorph testing method done at (b) (4) the polymorph testing site proposed in this NDA. The adequacy of the proposed acceptance criterion for the drug substance polymorph testing cannot be evaluated without the appropriate analytical procedure and method validation. Please provide the polymorph testing method in 3.2.S.4.2 of the NDA. The method description should include detailed analytical procedures, e.g., apparatus, settings, sample preparations ((b) (4) method if applicable), operation procedures, and quantitative analysis. Please also provide the method validation for polymorph testing in 3.2.S.4.3 of the NDA. The proposed acceptance criterion for polymorph testing should take into consideration commercial and clinical batch data as well as the effect of polymorphic form on solubility.

In addition, we also remind you that all manufacturing and testing facilities should be ready for inspection at the time of NDA resubmission.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)]

in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-0833.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
11/10/2011



NDA 201923

COMPLETE RESPONSE

Alimera Sciences, Inc.
Attention: Barbara Bauschka
Director, Regulatory Affairs
6120 Windward Parkway, Suite 290
Alpharetta, GA 30005

Dear Ms. Bauschka:

Please refer to your new drug application (NDA) dated June 30, 2010, received June 30, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Iluvien (fluocinolone acetonide intravitreal insert) 0.19 mg.

We acknowledge receipt of your amendments dated July 8, 9, 13, 21, 23 and 28, August 3, 5, 11, 13 and 30, October 13, 22 and 25, and November 11, 2010.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. Specifically,
 - a. The development of cataracts in eyes which were phakic at baseline creates difficulty in interpreting visual acuity during months 12 to 24. Due to the timing of the development of the cataracts and the time needed for postoperative recovery, 36-month clinical trial data will need to be evaluated to assess the potential benefits and risks associated with this drug product. Thirty-six month clinical trial data should be submitted to the application.

In addition to the predetermined analyses in the protocol for the three year data, we recommend that you include the following exploratory analyses:

- i. Risk-benefit analyses at the study eye level. This could be explored using two way tables of major adverse event (such as cataract surgery) versus improvement of BCVA by 15 letters or more.
- ii. Association of decline of BCVA by 15 letters or more to cataract at the study eye level. This could be explored by checking association of cataract surgery to decline in BCVA by 15 letters or more by visit.

- iii. Sensitivity analyses to missing values:
 1. Treating all missing observations as failures in primary endpoint.
 2. Treating all dropouts as failures in primary endpoint, and imputing the other missing values using multiple imputation methods.
 3. Treating all deaths as failures in primary endpoint, imputing other missing values using multiple imputation methods, and imputing observed values for subjects with disallowed medication using multiple imputation methods.
 - b. The risk of increased intraocular pressure (IOP) is nearly three times higher in the drug treatment groups compared to the Sham (control) group. The 36-month data will need to demonstrate that the drug's benefits will be able to overcome this significant risk identified during the first 24 months of the clinical trials. Thirty-six month clinical trial data should be submitted to the application.
 - c. The inserter used in the preclinical and clinical trials was modified; use of the proposed (b) (4) inserter is not supported by clinical data in the application. Clinical data supporting the use of the (b) (4) inserter, including the clinical study report for Study C-01-08-006, should be submitted to the application.
 - d. The safety database for the drug product is incomplete. The 120-day Safety Update and Module 5, Section 5.2, do not include data for all clinical trials utilizing the drug product. This information should be submitted to the application.
 - e. Efficacy rates are low. (26- (b) (4) % vs 14-18%). Results are not robust. Difference between groups with respect to mean visual acuity is minimal. The majority of the beneficial effect appears to occur during first 6 months and the product appears to cause clinically significant decreases in visual acuity at month 24. The need for extended treatment should be justified in the application.
 - f. The product causes steroid class events, it is also likely to impair healing and reduce the eyes ability to recover from infections. This is potentially problematic for a diabetic population. The benefit over these risks needs to be demonstrated.
2. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance and drug product are inadequate to preserve its identity, strength, quality, purity, and stability. Specifically,
 - a. The currently proposed limit (b) (4) is not applicable to the solid dose FA drug product. Without an appropriate descriptor for expressing product endotoxin limit, the acceptability of the proposed limit cannot be evaluated. Please modify the endotoxin limit value so that it is based on a per drug rod or per mg (b) (4)

- b. The testing method presented in attachment MTM-200033 represented only a general SOP for LAL gel clot testing, and did not include procedures and data sets relevant to FA drug product. The stability test results and the proposed post-approval stability protocol are not acceptable without an adequate description of the endotoxin testing procedure and appropriate acceptance criteria. Please provide a description of the endotoxin testing procedure as it applies to FA drug product. The description should include the method by which the drug product rods are prepared for sampling, and the procedures and data sets for interference/enhancement testing.
- c. There is insufficient information for the facilities conducting (b) (4). Please provide information regarding the (b) (4) facility if a site that is different from the drug substance manufacturer facility is conducting (b) (4) of your drug substance.
- d. There is insufficient information for the facilities conducting the polymorph testing. Please provide a method description to be used for the testing of the polymorph content in the fluocinolone acetonide drug substance. Also, provide, once identified, the name, address and contact information for the facility which will be conducting the polymorph testing.
- e. Identification tests have not been included for the inactive components of the drug product. Please include an identification test (e.g., IR) in the specification for each of the inactive components of the drug product, polyvinyl alcohol, (b) (4)%, polyimide tubes, and silicone adhesive.
- f. Report 10066 is incomplete because the full development and validation reports for the *in-vitro* release methodology were not provided. Provide the following information:
- i. Detailed method development and validation report for the *in-vitro* release method (justifying optimization of method parameters, e.g., choice of release medium, medium volume, temperature, agitation speed, maintenance of sink condition etc.) is required in the NDA submission.
 - ii. *In-vitro* release profiles generated for different batches and associated data set (preferably in electronic format) used to generate the *in-vitro* release profiles.
 - iii. Full report of the calculations involved to qualify different formulations, manufacturing sites etc.
 - iv. Time points in generating release profiles should continue either until about (b) (4)% of the labeled dose has been released in (b) (4) has been reached.
 - v. In the formula used to calculate the amount of FA released during a 24-hour period, the injection volume as well as the volume of the medium should be considered unless justified otherwise.

- g. The proposed release rate specifications (b) (4) are (b) (4)
 - h. Excessive bioburden in the fluocinolone acetonide (FA) rods could contaminate the product with microbial toxins, debris, and metabolites. These contaminants would persist after (b) (4) and should be controlled for. The manufacturing process should be modified to include (b) (4) product bioburden testing, and the in-process microbiology quality control parameters should be amended to include product bioburden alert and action levels.
 - i. The proposed hold period is not acceptable. Please provide a description of the bioburden and endotoxin testing procedures performed (b) (4)
(b) (4) Presentation of study results without including the details of how they were performed is not acceptable.
 - j. The description of the (b) (4) procedure is not complete. Please describe the (b) (4) source and the procedure by which shipping boxes containing the product are exposed to the source.
 - k. The (b) (4) studies should be conducted under the conditions to be used (b) (4)
(b) (4) Please provide the procedures, acceptance criteria, and data sets (b) (4)
 - l. The descriptions of the procedures for bioburden determination, sterility testing and bacteriostasis-fungistasis testing are not complete. Please provide the procedures for bioburden determination, sterility testing, and bacteriostasis-fungistasis testing that were carried out in support of (b) (4) verification studies. Though you state that these procedures were presented, respectively, in documents MTM-200030, MTM-200087, and MTM-200042, these documents were not provided.
3. The methods used in and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product do not comply with the current good manufacturing practice (cGMP) regulations in parts 210 and 211. During a recent inspection of the (b) (4) manufacturing facilities for this application, our field investigators conveyed deficiencies to the representative of the facilities. All facilities and controls will need to comply with the cGMP regulations. Please amend the application with facilities that are in compliance with current good manufacturing practice (cGMP) or notify us when all currently submitted facilities are in compliance with cGMPs.

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at (301) 796-1202.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
12/22/2010