

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203324Orig1s000

OTHER ACTION LETTERS



NDA 203324

COMPLETE RESPONSE

Avedro, Inc.
Attention: Ms. Pamela Nelson
Vice President, Regulatory Affairs
230 Third Avenue
Waltham, MA 02451

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16, 2013, received September 16, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the combination product, Photrexa Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution), 0.146%, Photrexa (riboflavin 5'-phosphate ophthalmic solution), 0.146%, and the KXL-System to deliver UV-A light.

Your application is proposed for the use of the drug and device combination in the collagen corneal cross-linking procedure for the proposed treatment of patients with progressive keratoconus and patients with corneal ectasia following refractive surgery.

The September 29, 2014, submission constituted a complete response to our March 14, 2014, action letter.

We acknowledge receipt of your amendments dated:

June 30, 2014	February 26, 2015
July 14, 2014	March 2, 2015
September 29, 2014	March 12, 2015
October 24, 2014	March 17, 2015
November 14, 2014	March 18, 2015
February 12, 2015	March 27, 2015

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. As discussed during the February 24, 2015, Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and Ophthalmic Device Panel of the Medical Devices Advisory Committee, the application does not include clinical studies that were conducted with the to-be-marketed KXL-System (the device constituent part). Clinical

studies UVX-001, UVX-002 and UVX-003 were conducted with the IROC UV-X device, as stated in the Avedro briefing document and the application. We find that the information submitted to establish similarity of the two device constituent parts is not sufficient. Therefore, the application is deficient under 21 CFR 314.126 in that it does not include adequate and well-controlled studies of the drug/device combination using the to-be-marketed device.¹

To address this deficiency, you should conduct a clinical study (or studies) showing that Photrexa Viscous and Photrexa with the KXL-System when used in the corneal collagen cross-linking procedure is safe and effective in the treatment of patients with progressive keratoconus and patients with corneal ectasia following refractive surgery. The design of this new clinical study (or studies) should be discussed with the Agency before the study is (or studies are) initiated. We recommend a meeting with the Agency be scheduled to discuss the design of the study (or studies)..

Alternatively, if you believe that it is possible to provide sufficient clinical information to bridge the combination product device constituent, KXL System, to the IROC UV-X device used in the above-named clinical studies (e.g., by providing literature or Avedro data), then you may propose such an alternative.

If you propose such an alternative, you need to provide the following information:

2. In the March 14, 2014, Complete Response letter, we requested clarification regarding your list of device differences between the IROC UV-X and the KXL System. In your September 29, 2014, resubmission, you indicate that the original list was not comprehensive, and therefore, you provided new information. However, the additional information you provided in your response does not support your rationale for equivalence between the two systems. Moreover, in light of your presentation at the February 24, 2015, Advisory Committee meeting, and your correspondence received March 16, 2015, there appears to be additional differences, which you did not include in your resubmission; e.g., the focusing differences between the two device constituents. Without a complete description and assessment of the

¹ Specifically 21 CFR 314.126(d) states that, For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation. Your application is for a combination product, consisting of a drug constituent and a device constituent. We agree that the drug constituent is consistent with this section of the regulations. However, as noted above, because the information submitted to establish similarity of the two devices is not sufficient, the device constituent is not compliant with this section of the regulations. Therefore, we are requesting a clinical study (or studies) with the to-be-marketed device constituent, the KXL-System.

differences, e.g., spatial distribution of effective ultraviolet (UV) exposure to the cornea, we cannot determine if these differences could result in increased radiation to the sub-corneal ocular structures or even within the cornea. Further, without a complete assessment of the differences between the two systems it cannot be determined if additional clinical or preclinical data may be needed beyond what is described in this letter. So that we have a more complete picture of the differences between these systems, please provide the following additional information:

- a. To address potential UV irradiance concerns to sub-corneal structures as well as being able to assess how well the energy is distributed across the cornea itself in the X, Y and Z directions, provide a complete and detailed description and explanation of the optical systems of both devices. For example, describe all important components such as light sources, lenses, mirrors, filters, shutters, limiting apertures, beam homogenizers, etc. Include dimensions, distances, angles of divergence (or convergence) at the cornea, and accurate ray trace diagrams. Include explanations of any features intended to modify the beam energy distribution, compensate for corneal curvature, or limit scattered radiation beyond the nominal beam diameter.
- b. To demonstrate the effect of beam propagation differences between the two devices and the potential of how that beam differs on the cornea, provide beam irradiance maps at the corneal plane for both devices. These maps should be accurate out to the full extent of the beam, and the spatial resolution of the measurements should be specified. These maps should show the effect of the beam propagation differences and how the beam differs on the cornea. Also, please explain any differences between the KXL map in the September 2013 submission and the KXL map in the September 29, 2014 resubmission that you provided (b) (4)
- c. For both device constituents, provide a detailed description of all features and procedures used in the clinical trial to limit patient eye movements during the cross-linking procedure, and those for use with the KXL System. For example, describe what fixation targets, instructions to patient and physician, eye position monitoring procedures, and fail-safe provisions in case of excessive movement were employed during the studies and how does that differ from what is provided for the KXL System. In addition, for both device constituents, please provide all available evidence regarding actual sequences of eye movements during the procedure; e.g., a description of any methods used for quantitative eye movement measurements, analyses of across-patient variations, changes in fixation accuracy over time, and the effects of eye movements on the effective beam size and exposure pattern.

- d. Provide measurements or best estimates of the location of the focal plane relative to the cornea for both devices. Also provide data regarding the accuracy and precision of the actual vs. the intended focal depth.
- e. Provide a comparative analysis of the 3-D distribution of UV energy in the corneal stroma for the two devices, taking into account any differences in beam homogeneity, eye movement effects, focal planes, beam divergence angles, maps of percent reflectance from the curved front corneal surface.

3. Electromechanical Compatibility (EMC)

- a. In your September 29, 2014, resubmission in response to Deficiency #9, of our March 14, 2014, Complete Response letter, the EMC test reports identified modifications that were made to the KXL System in order to pass the IEC 60601-1-2 tests. You confirmed that all modifications listed in the test report will be implemented in the marketed version of the device. However, an additional change (b) (4) was made after the original EMC test was completed and found acceptable. The change involved (b) (4).
Because of this significant modification, EMC testing was to be repeated to ensure the KXL System (b) (4) meets the IEC 60601-1-2 standard. You have not provided the new test report for review. Please provide the new test report once EMC testing of the KXL System (b) (4) is completed. This information is needed so that we can assess conformity of the “to be marketed” Photrexa/ KXL UV irradiation system with IEC 60601-1-2:2007.
- b. In our March 14, 2014, Complete Response letter Deficiency #10, we said that in order to demonstrate conformity with the IEC 60601-1-2: 2007 standard, not only evidence of meeting the testing requirements, but evidence of meeting the labeling requirements should be provided. As requested, in your September 29, 2014, resubmission you have modified the system technical description in the Operator’s Manual to include four tables of EMC guidance, based on compliance of the device with the individual EMC test standards. However, we had not noticed previously that the correct “ U_T ” was completely missing from the Compliance level column. The current specifications in the Compliance level column are not properly labeled. To comply with IEC 60601-1-2: 2007, please change, in the Voltage dips row, (b) (4) to “0% U_T for 0.5 cycles”, (b) (4) to “40% U_T for 5 cycles”, (b) (4) to “70% U_T for

25/30 cycles”, and (b) (4) to “0% U_T for 250/300 cycles”.

ADDITIONAL COMMENTS

In addition, we have the following comments, which are not deficiencies, for your consideration as you work to address the above deficiencies. These may provide additional information that helps inform the design or analysis of the new clinical study and or existing literature and Avedro data.

1. During the Advisory Committee meeting, there was discussion about the choice of the appropriate primary endpoint to demonstrate treatment benefit in the progressive keratoconus and corneal ectasia patient populations. Please review and summarize available published information on the correlation of Kmax with patient benefit in a clinically meaningful endpoint (e.g., visual function) and/or include in the next clinical study plans to collect prospectively information on Kmax along with visual function or other clinically relevant endpoints to provide evidence that the change in Kmax following corneal collagen cross-linking correlates with a clinical benefit to the patient. The clinical benefit can be a patient reported outcome, caregiver reported outcome, or a clinical observer outcome.
2. The Advisory Committee discussion identified a number of trial design concerns including the disease definition and entry criteria. In your new study (or studies) for the proposed indication(s) we request you consider inclusion and exclusion criteria for progression of disease, types and number of prior refractive procedures (including non-laser based refractive procedures, time between prior refractive treatment and enrollment in the clinical trial (if known) for these eyes, exclusion for previous corneal collagen crosslinking.
3. We recommend you consider evaluating the existing study data to explore the following:
 - a. Outcomes for eyes which had a pachymetry <400 microns versus > 400 microns, and results for patients who received Photrexa Viscous only, or who received both Photrexa Viscous and Photrexa.
 - b. Outcomes based on the original corneal thickness versus corneal thickness after treatment was <400 microns or > 400 microns.

4. Use of published literature: If you intend to provide clinical literature to support the use of the to-be-marketed combination product with the KXL System, the literature should be based on a comprehensive literature search stratified by key parameters of interest.²

In addition to results, please provide detail regarding how this literature review was performed. Using the PRISMA guidelines, indicate the database(s) searched, search terms, reasons for excluding articles and including them. For this process please give the number of articles screened, assessed for eligibility and included in the review with reasons for exclusion at each stage ideally with a flow diagram. Also indicate which publications represent trials, which were case series, etc. This is requested so that we can determine the adequacy of the review and any potential sources of bias. Please provide PDFs of these complete articles.

- a. Identify the search criteria and methodology to identify the strengths and weaknesses of the articles.
 - b. The publications should identify specific drug/device combination product and the procedure method that was studied
 - c. The publications, where possible, are recommended to describe the specific drug/device combination product you are requesting to market. We note that at the Advisory Committee meeting that you noted that there may not be any literature using the combination product as submitted to the NDA. If you wish to rely on other clinical literature, a strong justification should be provided. Please include in your discussion if any of this literature addresses the concern that differences between the UV-X and KXL systems may affect safety and effectiveness outcomes.
 - d. Please submit any existing publications or manuscripts presenting any data collected in the pivotal trials from this NDA
5. Corneal haze is reported in your pivotal trial results. We recommend that you consider grading corneal haze at all visits in any future trial (s) and provide a discussion of any impact of the haze on visual function.
 6. We recommend that you utilize observed data only (no LOCF) in the primary analysis of corneal endothelial cell count (ECC) in any future trials. We recommend that you include procedures to identify non-physiologic ECC values at the study visits.

² Please refer to the FDA Guidance for - Industry Applications Covered by Section 505(b)(2), <http://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf>
FDA may request additional information on the clinical protocols used, line listing, and inspection of the clinical site.

7. We recommend that for any new clinical trial, the protocol should comprehensively describe all investigator training and details of procedures. The protocol study methodology, e.g. epithelial debridement procedure, should contain adequate detail to ensure that study procedures are standard across all study sites.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. 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>.

In the EMC guidance tables mentioned above, a comma (,) was used as the decimal separator as required by the IEC standard. However, while using the comma for the decimal separator is the convention in Europe, it is not the convention in the US. To assure the usability of the Operators Manual in the US, please use the period (.) where needed in the EMC guidance tables for US version of the Operators Manuals.

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.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

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 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 combination product, including the drug constituent product and the device constituent product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager, at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
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
03/29/2015



NDA 203324

COMPLETE RESPONSE

Avedro, Inc.
Attention: Ms. Pamela Nelson
Vice President, Regulatory Affairs
230 Third Avenue
Waltham, MA 02451

Dear Ms. Nelson:

Please refer to your New Drug Application (NDA) dated September 16, 2013, received September 16, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for riboflavin phosphates ophthalmic solution 1.46 mg/g 20% dextran and riboflavin phosphates ophthalmic solution 1.46 mg/g with the KXL™ System.

We acknowledge receipt of your amendments dated:

October 1, 2013	December 20, 2013	February 19, 2014 (3)
October 10, 2013	January 15, 2014	February 21, 2014
October 17, 2013	January 21, 2014	February 25, 2014 (3)
November 27, 2013	January 24, 2014	February 26, 2014
December 6, 2013	February 14, 2014	

The September 16, 2013, submission constituted a complete response to our May 4, 2012, 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.

DRUG CONSTITUENT PART

1. The validation of the HPLC method is inadequate. Please submit the Method Validation report for the drug product HPLC method.
2. The specifications for the proposed drug products are inadequate. The specifications should be based on the specifications submitted in the amendment submitted November 27, 2013. The description of your two products should be as noted in your amendment submitted February 14, 2014. The degradants should be specified and have acceptance criteria that are based on data from the methods validation report and the stability data provided in the amendment submitted February 14, 2014 as well as any more recent stability data. Include

tests for specified, unspecified, and total degradants in your response. In general the recommendations of Q3B should be followed.

3. The stability data for your two products cannot be evaluated without appropriate drug product specifications as noted above. Please revise your batch analyses and stability data in accordance with the modified specifications.

DRUG FACILITY INSPECTIONS

4. A recent inspection of the (b) (4) manufacturing facility noted deviations from current Good Manufacturing Procedures (cGMP) 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.

DEVICE CONSTITUENT PART

5. You have submitted information regarding the differences between the specifications of the device used in the clinical studies (UV-X Illumination System) and the device proposed for approval (the KXL system). This information was to evaluate the impact that differences may have had on study safety and effectiveness results and their applicability to expected post-market device performance. Your submission on February 21, 2014 raised the following concerns:
 - a. You were asked to clarify whether the differences listed in Table 8 include all differences between the device used in each of your three clinical studies and the device proposed for marketing approval (including, but not limited to, device description, laser settings and/or parameters, software, and instructions for use). If not, you were asked to provide this information. In your response, you describe the differences in Table 8 and state that (b) (4). However, this response is inadequate because you have not clarified whether the list of differences in Table 8 encompasses all differences between the device studied and the device you intend to market. Therefore, please clearly state whether the differences listed in Table 8 include all differences between the device used in each of your three clinical studies and the device proposed for marketing approval (including, but not limited to, device description, laser settings and/or parameters, software, and instructions for use.) If not, please provide a description of all additional differences and discuss whether any of these differences could impact the safety or effectiveness of the device.

Optical Radiation Hazard

6. You have indicated that you intend to use a Radio Frequency Identification (RFID) activation card to determine the lower and upper limits of user-selectable power density levels and the maximum allowable energy dosage. We previously expressed concern regarding the

adequacy of this method to control for safety (i.e., excessive power delivery to the eye). In addition to RFID security issues, there are also electromagnetic compatibility (EMC) concerns regarding the use of RFID integration in the device. Therefore, for adequate control of the energy output of your device, please modify the software of your device to implement a software lock-out of irradiated power above 3 mW/cm².

7. You indicate that the [REDACTED] (b) (4)
[REDACTED]
validation activities for the Homogeneity Measurement Master Validation plan (VAL-0005) are ongoing. Please provide the results of your validation activities.

Electro Magnetic Compatibility

The following deficiencies refer to a Request #6 - #8 and #10 - #12, respectively, in the agency Information Request (IR) letter dated February 11, 2014.

8. In your table of “recognized standards” with which the KXL System is claimed to comply, for many of the standards listed, there was no edition or date information. Requirements of standards can differ considerably from one edition to the next. Therefore, edition or date of publication information is needed. Please note that FDA does not recognize EN standards, and there were several on the list. Conformity with IEC 60601-1-2 was claimed. However, the EMC test report cited EN 60601-1-2. While the two standards are essentially identical, we asked you to be consistent in the claims of conformity. Finally, we asked you to submit an FDA Form 3654 for each standard to which conformity was claimed.

You submitted a revised Table 6: List of Recognized Consensus Standards and an FDA Form 3654 for each standard to which conformity is claimed. This is partially acceptable because the table and forms have the errors listed below. Please correct them.

- a. In Table 6, ISO 14971:2007/(R)2010 is listed, with recognition number 5-70. ISO does not reaffirm standards. The (R) designation and the recognition number are for the AAMI ANSI ISO version of the standard. The corresponding FDA Form 3654 lists the standard correctly.
- b. In Table 6, the recognition number for IEC 60601-1:2005 (Edition 3) is incorrect. The number shown (5-77) is for Edition 3.1. The number shown on the corresponding FDA Form 3654 (5-78) is the correct recognition number for IEC 60601-1:2005 (Edition 3.0).
- c. While Table 6 and the corresponding FDA Form 3654 claim conformance to IEC 60601-1-2:2007, according to the EMC test report, the device is actually in conformance with EN 60601-1-2:2007. Because the IEC and EN versions are identical, this response is acceptable. However, while the FDA Form 3654 correctly cites recognition number 5-53, the number listed in Table 6, 5-54, is incorrect. Recognition number 5-54 is the AAMI ANSI IEC version of the standard.

- d. Table 6 cites conformity with IEC 60601-1-6:2010, Edition 2.0, recognition number 5-85. This is partially incorrect. The correct Edition number is Edition 3.0.
- e. The FDA Form 3654 for IEC 60601-1-6 cites Edition 2 (2006) and recognition number 5-85. Edition 2 is no longer recognized by FDA, and recognition number 5-85 is recognition of Edition 3 (2010).
- f. Table 6 cites conformity with IEC 62471:2008 ED 1.0 and recognition number 12-249. Edition 1.0 was published in 2006.
- g. The following standards are listed in Table 6 and for each one there is also an FDA Form 3654 in the submission:
 - CISPR 11
 - IEC 61000-4-2
 - IEC 61000-4-3
 - IEC 61000-4-4
 - IEC 61000-4-5
 - IEC 61000-4-6
 - IEC 61000-4-8
 - IEC 61000-4-11

These are all normative references of IEC 60601-1-2 and therefore do not need to be listed separately. Also, IEC 60601-1-2 specifies some modifications and additions to these standards, so assuming that the modifications and additions were used, a declaration of conformity to these standards would need to list or describe those modifications and additions. The EMC basic immunity standards are primarily test methods. They have menus of test levels and menus of pass/fail criteria, so a declaration of conformity would need to specify the test level and pass/fail criteria that were used.

If you decide to keep these declarations, [FDA Forms 3654 specify the version and date of publication], please add this information to Table 6 of the application.

9. The immunity pass/fail criteria specified in the EMC test report did not conform to IEC 60601-1-2:2007. The standard lists degradations that are not allowed if associated with Basic Safety or Essential Performance. However, you had not specified the performance that was determined to be the Essential Performance of the KXL System. It is possible that this could be derived from the specification of Criterion A; however, we asked you to specify the Essential Performance explicitly. We recommended that any future EMC testing to IEC 60601-1-2 that you submitted should include immunity pass/fail criteria that conform to the requirements of the standard. Also, as mentioned below, IEC 60601-1-2 requires that the Essential Performance statement be included in the technical description.

You responded with the following Essential Performance Statement: The KXL system delivers to the cornea UV-A radiation of nominally 365 nm wavelength at an irradiance of 3 mW/cm² over an exposure period of up to 30 minutes to deliver a total energy density of up to 5.4 J/cm².

You committed that future EMC testing would include testing to IEC 60601-1-2:2007, including immunity pass/fail criteria that conform to the requirements of the standard. In addition, you committed to updating the operators manual to include the Essential Performance statement.

The Essential Performance statement is acceptable. Your promise to conform to the immunity pass/fail requirements of IEC 60601-1-2 is also acceptable. We note that you intend to include the Essential Performance statement in the operator's manual. Please submit the revised operator's manual and confirmation of inclusion of the Essential Performance statement.

10. Three immunity tests for which IEC 60601-1-2:2007 specifies the following:

For ME EQUIPMENT and ME SYSTEMS that have, for power input, multiple voltage settings or autoranging voltage capability, the test is performed at the minimum and maximum RATED input voltages.

The three tests to which this applies are IEC 61000-4-4 (Transient bursts), IEC 61000-4-5 (Surge), and IEC 61000-4-11 (Voltage dips and interruptions). For these three tests, the EMC test report showed that the testing was performed only at (b) (4) VAC / (b) (4) Hz. We noted that the AC input specifications of the KXL System are 100-240 VAC. Please perform these tests as specified by IEC 60601-1-2, i.e. repeat them at 100 VAC and submit the results of the testing.

11. IEC 60601-1-2:2007 specifies requirements for testing and for labeling. In order to demonstrate conformity with the standard (which you claim), in addition to evidence of meeting the testing requirements of the standard, you need to submit evidence of meeting the labeling requirements. This includes the items listed below. We were not able to find any of these items in the Operator's Manual:

- a. We asked you to modify the system technical description to include the following items:
 - i. A statement of the performance that was determined to be Essential Performance;
 - ii. A warning that the equipment should not be used adjacent to or stacked with other equipment and that if adjacent or stacked use is necessary, the equipment should be observed to verify normal operation in the configuration in which it will be used.

- iii. Four tables of EMC guidance based on compliance of the device with the individual EMC test standards.
 - iv. For devices that incorporate RF transmitters: each frequency or frequency band of transmission, the type and frequency characteristics of the modulation and the EFFECTIVE RADIATED POWER.
 - v. For devices that incorporate RF receivers: each frequency or frequency band of reception; the preferred frequency or frequency band, if applicable, and the bandwidth of the receiving section of the ME EQUIPMENT or ME SYSTEM in those bands; and a warning that the ME EQUIPMENT or ME SYSTEM may be interfered with by other equipment, even if that other equipment complies with CISPR EMISSION requirements.
- b. We asked you to modify the system Instructions for Use to include the following items:
- i. A statement that medical electrical equipment needs special precautions regarding electromagnetic compatibility (EMC) and needs to be installed and put into service according to the EMC information provided in the Instruction Manual.
 - ii. A statement that portable and mobile RF communications equipment can affect medical electrical equipment.

You have committed to updating the operators manual to include all the items above. Please submit complete versions of the operators manual, which include the above statements.

The KXL System incorporates a wireless remote control and radio frequency identification (RFID) capabilities. As noted above, we now request that you provide a software lockout of powers in excess of $3\text{mW}/\text{cm}^2$. Thus, RFID concerns will no longer be applicable in the absence of a RFID mechanism. However, we do still have remaining concerns regarding the effective radiated power of the wireless device. You have indicated that the KXL system minimizes coexistence problems by only enabling the remote receiver at specific portions of the treatment. Specifically, the remote receiver is enabled for 15 seconds at the Preparing System screen. If the physician chooses to continue without a remote, the power to the remote receiver is disabled. Likewise, the power to the receiver is removed when a treatment is complete. Therefore, coexistence testing is not needed.

The information available on the FCC website for FCC ID SXJ87027-T shows that the wireless technology used is the (b) (4) transmitter and receiver. According to www.thetechnologyreview.com, the wireless standard used is Bluetooth. Bluetooth is known to interfere with wireless LAN services such as Wi-Fi. Furthermore, while you discussed the low duty cycle of the receiver, you did not mention a duty cycle for the transmitter, so the assumption is that it is on continuously. Please submit wireless coexistence test results for this service or a valid rationale for not performing wireless coexistence testing.

12. We were not able to find any MRI warnings in the Operator's Manual. We noted that while it is not likely that the device would be taken into the controlled access area of an MRI system, proper precaution is advised for inclusion in your labeling. Thus, an MRI warning should be included in the Operator's Manual and a warning symbol should be included on the device label. These should conform to ASTM F2503, Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment. We asked you to include the "MR Unsafe" symbol on the device label, use the terminology specified by ASTM F2503 (MR Unsafe) in a warning in the Operator's Manual, and show and explain the symbol in the manual. It might be necessary to explain or elaborate on "MR Unsafe", such as "MR Unsafe – keep away from magnetic resonance imaging (MRI) equipment".

You said that you commit to updating the operators manual and device label to include these items. Please submit the revised operator's manual and a reproduction of the device label and review of these items.

CLINICAL/STATISTICAL DEFICIENCIES

13. There is insufficient data from adequate and well controlled trials to establish the efficacy of riboflavin ophthalmic solution and KXL System for the proposed indications.
- a. In your February 2014 submission, you state that seventeen subjects were treated with the large aperture (or illumination diameter) setting based on investigator discretion while the remaining subjects were treated with the medium aperture setting. You state that ten of the 17 subjects treated with the larger aperture were enrolled in the UVX-002 study and the remaining seven were in the UVX-003 study. While the efficacy analyses you provide are consistent with this response, the safety analyses tables (Tables 14.3.1.11) include data from ten subjects each in studies UVX-002 and UVX-003 (implying that the total number of subjects receiving the larger diameter could be twenty). Please clarify this discrepancy and provide corrected analyses.
 - b. With regard to the variable illumination diameter in the device studied, you state that "investigators were instructed to select the medium aperture setting prior to irradiation based upon ease of alignment over the clear cornea and centration to the limbus diameter". However, you do not mention specific instruction regarding protection of limbal stem cells. Please clarify whether investigators were instructed to maintain a pre-specified margin from the corneal limbus. Please describe any other risk mitigation measures in place to protect limbal stem cells (such as use of a metal shield). Please also discuss any risk mitigation measures (to prevent or minimize damage to limbal stem cells) which are planned for the device to be marketed.
 - c. Please provide the location in the application, or provide new analyses of safety data by study visit at month 3, month 6, month 9 and month 12 for each study and each treatment arm to see what adverse events resolved, which continued to be reported and any which may have appeared later in the study

- d. Given that corneal collagen cross-linking is intended to stabilize the cornea and improve visual function, please discuss whether the loss of 15 letters or more in visual acuity represents a lack of efficacy or an adverse reaction/complication of the procedure.

14. Regarding studies UVX-001 and UVX-002, treatment of keratoconus:

- a. The clinical studies do not meet the protocol-specified primary endpoints at 3 months.
- b. We acknowledge that you included an analysis of data at month 12 according to your statistical analysis plan, however, this analysis is not a direct comparison between the CXL arm and the control arm at month 12.
- c. The datasets provided for UVX-01 and UVX-002 contain errors. For example, Kmax cannot be negative or equal to zero as presented in Tables 14.2.1.1.2 and 14.2.1.1.3.
- d. The datasets provided for UVX-01 and UVX-002 for the Endothelial Cell Count data appear to contain errors because they include increases beyond that which might physiologically be expected. Please verify the data sets.

To resolve the above deficiencies, submit clinical data from adequate and well-controlled studies in the treatment of keratoconus and in which the datasets have been verified and the results meet their protocol-specified primary endpoint.

BIORESEARCH MONITORING PROGRAM INSPECTION

During the recent inspection of your study monitoring practices conducted from February 3 -12, 2014, FDA field investigators observed inadequate documentation of study monitoring practices; specifically, for the period from June –September 2010, as specified in the Form FDA 483, initial and interim Monitoring Visit Reports, Data Entry Reports, and documentation of review of those reports is missing. To address gaps in study data monitoring for UVX-002 and UVX-003, we request an independent third party assessment of data entry and monitoring practices at the top five enrolling sites for each of these two studies. We also request a similar independent reassessment for the conduct of Study UVX-001 at Dr. Stulting’s site. We recommend that this reassessment take place at Emory University, the repository of the original source documentation for this study, unless it can be determined that the copies residing at Dr. Stulting’s current site are certified true copies of the original documentation.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

15. The orphan designation for this combination product is for “keratoconus,” but the studies provided enrolled subjects with “progressive keratoconus.” Please discuss the

similarities/differences between these two diagnoses, as they may have impact labeling and the orphan indication.

16. In your NDA, you have provided the reference by Peter S. Hersh, MD, Steven A. Greenstein, Kristen L. Fry, OD, MS, titled, “Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results,” published in *Cataract Refractive Surgery - Volume 37*, January 2011. In the publication, it is stated that the article was submitted for publication on March 2, 2010, the final revision was submitted on July 30, 2010, and the article was accepted for publication on July 30, 2010. In the footnote there is the statement that Dr. Hersh is a paid medical consultant for Avedro, Inc. and further that this study was supported in part by Peschke Meditrade GmbH, Zurich, Switzerland. Under “Patients and Methods” it is stated that, “Patients were enrolled as part of multicenter prospective randomized controlled clinical trials performed under guidelines of the U.S. Food and Drug Administration and approved and monitored by an investigational review board.” Please clarify under which IND(s) these patients were studied and in which clinical trials these patients were enrolled, for example were any of these patients included in studies UVX-001, UVX-002 and/or UVX-003.
17. You market similar products containing riboflavin ophthalmic solution, e.g. VibeX, in Europe which are used with a device for CXL. Please submit any postmarketing data on the VibeX product(s) which could be relevant for the safety profile of your proposed riboflavin ophthalmic solution products and to the device.

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.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
 7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 8. Provide English translations of current approved foreign labeling not previously submitted.

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 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 Jacquelyn Smith, MA, Senior Regulatory Project Manager, at 301-796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
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
03/14/2014