

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-756**

**ADMINISTRATIVE DOCUMENTS AND  
CORRESPONDENCE**

EXCLUSIVITY SUMMARY FOR NDA # 21-756

Trade Name Macugen

Generic Name pegaptanib sodium injection, 0.3 mg

Applicant Name Eyetech Pharmaceuticals, Inc.

HFD # 550

Approval Date If Known December 17, 2004

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES / X / NO / \_\_\_ /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505 (b) 1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / X / NO / \_ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_  
\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_  
\_\_\_\_\_

d) Did the applicant request exclusivity?

YES / X / NO / \_\_\_ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / \_\_\_ / NO / X /

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES / \_\_\_ / NO / X /

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce

an already approved active moiety.

YES /\_\_\_/ NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical

investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_\_/ NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_\_\_/ NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /\_\_\_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO /\_\_\_/

If yes, explain:

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/      NO /\_\_\_/

If yes, explain:

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(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

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Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1                      YES /\_\_\_/      NO /\_\_\_/



3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
!  
!  
Investigation #2 !  
IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
!  
\_\_\_\_\_  
\_\_\_\_\_  
Investigation #2 !  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
!  
\_\_\_\_\_  
\_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

Prepared By: Michael Puglisi  
Project Manager

Concurrence By: Jennifer Harris, M.D.  
Medical Officer

Wiley A. Chambers, M.D.  
Deputy Division Director

Form OGD-011347 Revised 05/10/2004

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Wiley Chambers  
12/22/04 08:52:30 AM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 21-756

Original Stamp Date: June 17, 2004 Action Date: December 17, 2004

HFD-550 Trade and generic names/dosage form: Macugen (pegaptanib sodium injection) 0.3 mg

Applicant: Eyetech Pharmaceuticals, Inc. Therapeutic Class: 1

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1:

**Treatment of neovascular (wet) age-related macular degeneration**

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.**
- No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children**
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval

NDA 21-756

Page 2

Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-756  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 12-22-03)

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

<b>NDA 21-756</b>		
<b>Drug: Macugen (pegaptanib sodium injection) 0.3 mg</b>		<b>Applicant: Eyetech Pharmaceuticals, Inc.</b>
<b>RPM: Michael Puglisi</b>		<b>HFD-550</b>
		<b>Phone # 301-827-2119</b>
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) ( ) 505(b)(2)          (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p><i>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</i></p> <p>( ) Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p>	
<b>❖ Application Classifications:</b>		
<ul style="list-style-type: none"> <li>• Review priority</li> </ul>		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<ul style="list-style-type: none"> <li>• Chem class (NDAs only)</li> </ul>		<b>Type 1</b>
<ul style="list-style-type: none"> <li>• Other (e.g., orphan, OTC)</li> </ul>		N/A
<b>❖ User Fee Goal Dates</b>		
		<b>December 17, 2004</b>
<b>❖ Special programs (indicate all that apply)</b>		
		<input type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> <b>Fast Track</b> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> <b>CMA Pilot 1</b> <input type="checkbox"/> CMA Pilot 2
<b>❖ User Fee Information</b>		
<ul style="list-style-type: none"> <li>• User Fee</li> </ul>		<input checked="" type="checkbox"/> Paid <b>UF ID number - 4736</b>
<ul style="list-style-type: none"> <li>• User Fee waiver</li> </ul>		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<ul style="list-style-type: none"> <li>• User Fee exception</li> </ul>		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
<b>✓ Application Integrity Policy (AIP)</b>		
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ( ) Yes ( ) No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "No," continue with question (5).*

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

*If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>• Exclusivity summary</li> <li>• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<b>Exclusivity Summary Complete</b>
<ul style="list-style-type: none"> <li>• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	( ) Yes, Application # _____ (X) No

Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	none
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	In Package - submitted 12/10/04
• Original applicant-proposed labeling	In Package - submitted 3/17/04
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC- 7/20/04 DMETS- 10/15/01, 11/12/04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	In Package – submitted 3/17/04
• Reviews	DDMAC- 7/20/04 DMETS- 10/15/01, 11/12/04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Reminder in Letter
• Documentation of discussions and/or agreements relating to post-marketing commitments	9/17/04 Discipline Review Letter 12/8/04 Email
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	In Package
❖ Memoranda and Telecons	In Package
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	April 26, 2001
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	November 17, 2004
• Other	Pharmacology/Toxicology Guidance Statistical Guidance Electronic Archiving Guidance Clinical Guidance CMC Guidance Advisory Committee Meeting
	January 25, 2001 February 24, 2003 September 5, 2003 October 30, 2003 February 13, 2004 August 27, 2004
❖ Advisory Committee Meeting	Held on August 27, 2004
Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
❖ Postmarketing Safety Review	N/A

❖ Office Director's Memo	12/17/04
Deputy Division Director's Memo	12/16/04
❖ Clinical Team Leader's Memo	N/A
<b>Summary Reviews</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	
<b>Clinical Review</b>	
❖ Clinical review(s) (indicate date for each review)	9/17/04, 12/7/04, 12/16/04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	In 12/7/04 Clinical Review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Completed
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	8/11/04
❖ Biopharmaceutical review(s) (indicate date for each review)	9/17/04, 11/23/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	9/17/04
• Bioequivalence studies	N/A
<b>CMC Review</b>	
❖ CMC review(s) (indicate date for each review)	12/15/04 (two), 12/17/04
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	In 12/15/04 CMC Review
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	12/3/04
❖ Facilities inspection (provide EER report)	Date completed: 12/13/04 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
<b>Medical/Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	9/9/04, 9/10/04, 11/5/04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

Office Director Memorandum  
NDA 21-756

Proposed Tradename: Macugen  
Drug Name: pegaptanib sodium injection  
Pharmacologic Class: Vascular Endothelial Growth Factor (VEGF)  
Inhibitor

Applicant: Eyetech Pharmaceuticals

Date of Submission: March 18, 2004  
PDUFA Goal Date: December 17, 2004

Related IND: 56,503

Dosage form and Route of administration: pre-filled syringe for intravitreal injection dosed every 6 weeks

NDA Drug Classification: 1P

Proposed Indication: The treatment of the neovascular form of age-related macular degeneration.

Dosage Form and Route of Administration Intravitreal

Clinical Safety and Efficacy/Risk to Benefit

This application was the first accepted into a new program under PDUFA III, the continuous marketing application (CMA). Two well controlled trials were submitted as well as a Phase II trial. The one year clinical data was reviewed at an advisory committee in August 2004. The advisors found the data at one year to be persuasive evidence of safety and efficacy and that adequate risk to benefit had been demonstrated in the trials. The advisory committee also recommended that the labeling take into account patient protections to assess for endophthalmitis including guidelines for post injection follow up and for patient education materials.

The longer term data submitted for review at the 2 year timepoint is draft and does not provide full study reports and case report forms for discontinuations. The data submitted appears to demonstrate a leveling out of effect over time. There were also significantly more discontinuations in the active treatment arms compared to the data in the one year database. It is impossible to fully assess this concern due to the lack of full study reports.

The clinical discipline review letter sent to the applicant September 17, 2004 identified three areas of concern. The first was in regard to analyses to examine

renal clearance which has been adequately resolved. Safety data was requested to assess for potential effects on the neurosensory retina given that VEG F is neuroprotective and for data on potential effects on the corneal endothelium. These concerns have not been adequately addressed by the applicant in this submission and are proposed for phase IV studies.

#### Clinical Pharmacology

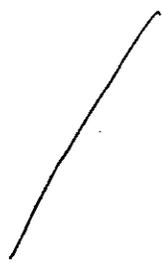
Pharmacokinetic data are informative. Following intravitreal administration, pegaptanib is systemically available, and displays non-linear pharmacokinetics at or doses above 1 mg. Of note is that at 2 mg/eye and 3 mg/eye dose treatment groups, plasma pegaptanib concentrations increased disproportionately with dose. The mean terminal elimination half-life of pegaptanib is 10 days with individual values ranging from 2 to 19 days. Important in light of the proposed dosing regimen, during repeated dosing when administered every 4 or 6 weeks, pegaptanib accumulation is minimal/negligible, if any. Pegaptanib metabolism is not fully characterized, however, it is expected to be metabolized by nucleases to shorter chains of nucleotides. Because of its molecular structure, typical P450 drug-drug interactions are not expected. It is known that renal impairment (<70 mL/min CrCL) results in significant decrease in pegaptanib clearance

Drug interaction studies of potential importance in this population to characterize pharmacodynamic interactions, eg, in patients taking anti-hypertensive or IOP lowering agents, have not been studied.

#### Chemistry and Manufacturing Controls: Adequacy of methods used in manufacturing the drug substance and product

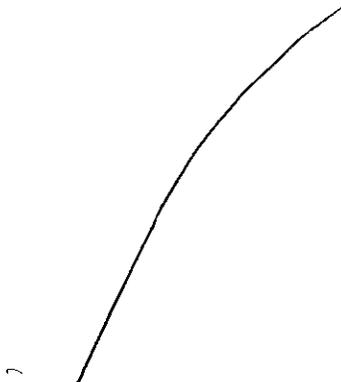
The CMC review for the *drug substance* concluded that adequate information on had been provided for the manufacturing process and quality of the final drug substance.

The *product quality microbiology* review recommended approval. However, the reviewer noted that the manufacturer's proposal (Amendment submitted November 10, 2004). of



Conclusions

The applicant has demonstrated adequate evidence of efficacy in the clinical trials submitted. The draft 2 year data review is preliminary and needs review of the full study reports in order to better characterize long term safety.



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/s/

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Jonca Bull  
12/17/04 06:48:42 PM  
MEDICAL OFFICER

**Division Director Summary of NDA**

**Review completed:** December 16, 2004

**Proposed Name:** Macugen (pegaptanib sodium injection)

**Applicant:** Eyetech Pharmaceuticals, Inc.  
Three Times Square  
12<sup>th</sup> Floor  
New York, NY 10036

**I. Recommendations**

**A. Recommendation on Approvability**

NDA 21-756, Macugen (pegaptanib sodium injection) is recommended for approval with the labeling submitted on December 10, 2004, for the treatment of the neovascular form age-related macular degeneration.

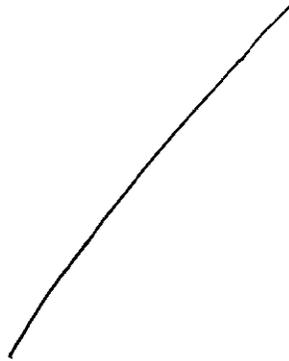
**B. Recommendation on Phase 4 Studies and/or Risk Management Steps**

The following post-approval commitments are recommended. The applicant has agreed to complete these commitments according to the timelines listed below:

1. *Clinical information to support that there are no degenerative effects on the neurosensory retina following the intravitreal administration of Macugen.*
2. *Clinical information to support that there are no adverse effects on the corneal endothelium following the intravitreal administration of Macugen.*
3. *Safety and efficacy data from a 2-year (minimum) clinical study of at least 2 additional doses below 0.3 mg.*

The applicant has agreed to submit a proposed protocol by summer 2005 (the development, manufacturing, and stability of lower doses of pegaptanib is rate limiting). Allowing for 18 months recruitment, the study will be enrolled by January 2007 with database closure in 1<sup>st</sup> Quarter 2009. The potential adverse effects on the cornea (1 year) will be submitted in mid 2008. Draft results for the AMD and ERG studies will be submitted to the Agency by mid 2009.

4. *A commitment to*



## II. Summary of Clinical Findings

### A. Brief Overview of Clinical Program

AMD is a leading cause of blindness in developed countries. AMD is characterized as a progressive degenerative disease of the macula. There are two forms of AMD: neovascular and non-neovascular. The non-neovascular form of AMD is more common and leads to a slow deterioration of the macula with a gradual loss of vision over a period of years. The neovascular form of the disease is responsible for the majority of cases of severe vision loss and is due to proliferation of abnormal blood vessels behind the retina. These blood vessels leak blood and fluid into the retina, which results in visual abnormalities. The development of these abnormal blood vessels is due in part to the activity of VEGF (vascular endothelial growth factor) and its inhibition is expected to impact on the onset and/or severity of vision loss associated with the proliferation of abnormal blood vessels.

Macugen (pegaptanib sodium injection) has been developed by Eyetech, Pharmaceuticals for the treatment of the neovascular form of age-related macular degeneration (AMD). In vitro studies have suggested that pegaptanib binds to VEGF and inhibits its binding to cellular receptors. Macugen is administered as an intravitreal injection which is dosed every six (6) weeks. It has been studied in approximately 1200 patients during the clinical development program. During the two phase 3 trials approximately 300 patients/group received either sham treatment or the 0.3 mg, 1mg or 3mg dose.

**B. Efficacy**

The two phase 3 studies show replicative results in the ability of pegaptanib sodium to reduce the risk of vision loss in patients with neovascular AMD by approximately 15% when the 0.3mg dose was administered every six weeks compared to sham. During the second year of treatment, the drug effect was less than the drug effect during the first year.

**Primary Efficacy Results – All Randomized Patients LOCF – Study 1003**

Number of Patients (%)		0.3 mg N= 153	1 mg N= 158	3 mg N= 155	Sham N= 156
Responders <sup>1</sup>	Baseline				
	Month 3	134 (87.6%)	146 (92.4%)	136 (87.7%)	130 (83.3%)
	Month 6	127 (83%)	137 (86.7%)	128 (82.6%)	112 (71.8%)
	Month 9	117 (76.5%)	126 (79.8%)	125 (80.7%)	105 (67.3%)
	Month 12	112 (73.2%) p=0.01	119 (75.3%) p=0.002	108 (69.7%) p=0.06	93 (59.6%)

<sup>1</sup> Patients who lost < 15 letters of vision.

**Primary Efficacy Results – PP population observed cases only– Study 1003**

Number of Patients (%)		0.3 mg N=133	1 mg N=139	3 mg N=135	Sham N=140
Responders <sup>1</sup>	Month 3	122 (87.8%) N=139	131 (92.9%) N= 141	122 (86.5%) N= 141	120 (82.8%) N= 145
	Month 6	110 (85.3%) N= 129	125 (86.8%) N= 144	116 (82.3%) N= 141	101 (69.7%) N= 145
	Month 9	103 (78.3%) N= 131	115 (79.9%) N= 144	110 (79.1%) N= 139	93 (66%) N= 141
	Month 12	98 (73.7%) p=0.01	105 (75.5%) p=0.005	90 (66.7%)	82 (58.6%)

**Primary Efficacy Results – All Randomized Patients LOCF – Study 1004**

Number of Patients (%)		0.3 mg N= 144	1 mg N= 147	3 mg N= 147	Sham N= 148
Responders <sup>1</sup>	Month 3	125 (86.8%)	118 (80.3%)	121 (82.3%)	115 (77.7%)
	Month 6	118 (81.9%)	106 (72.1%)	102 (69.4%)	85 (57.4%)
	Month 9	106 (73.6%)	108 (73.5%)	103 (70.1%)	78 (52.7%)
	Month 12	97 (67.4%) p=0.016	98 (66.7%) p=0.03	91 (61.9%) p=0.13	79 (53.4%)

**Primary Efficacy Results – PP population observed cases only– Study 1004**

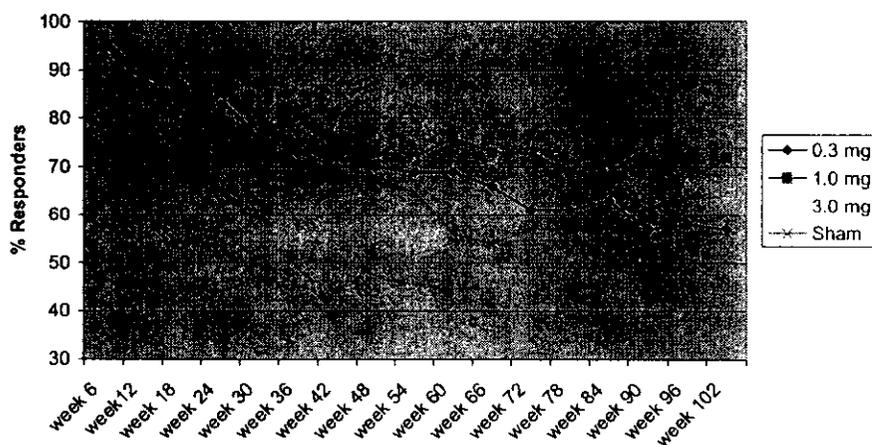
Number of Patients (%)		0.3 mg N=131	1 mg N=127	3 mg N=122	Sham N=128
Responders <sup>1</sup>	Month 3	122 (87.4%) N=140	114 (81.4%) N=140	110 (81.5%) N=135	104 (77%) N=135
	Month 6	112 (82.4%) N=136	96 (72.2%) N=133	91 (67.4%) N=135	77 (58.8%) N=131
	Month 9	94 (74.6%) N=126	94 (75.2%) N= 125	90 (70.9%) N=127	70 (53.4%) N=131
	Month 12	89 (67.9%) p=0.008	85 (66.9%) p=0.06	70 (57.4%) p=0.59	69 (53.9%)

## Division Director Summary of NDA

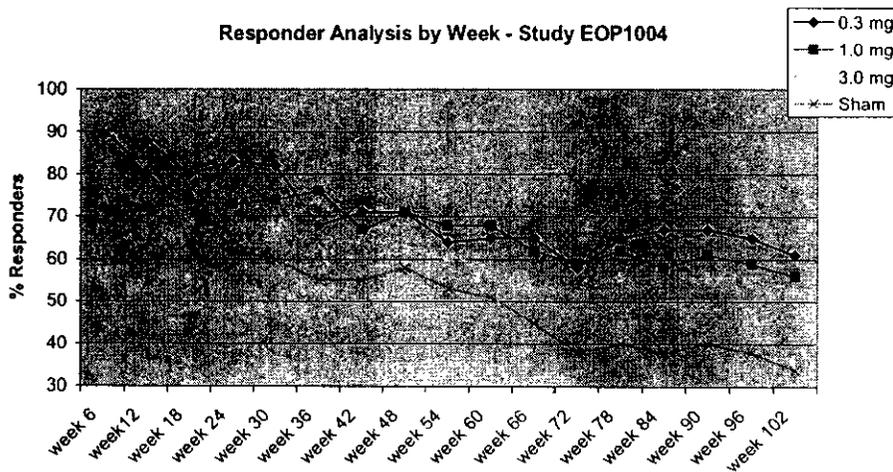
The clinical studies suggest that the lowest dose studied, 0.3 mg, is the most effective. The failure to establish the most effective dose is problematic because it means that a more effective dose might be available but has just not been studied. Additional studies with lower doses of pegaptanib sodium injection have been recommended, and the applicant has agreed to conduct these studies.

The final reports of the second year data have not been completed by the applicant to date. The datasets have been locked. Safety and efficacy tables for each year of the two year studies have been submitted and reviewed. Due to the average age of the patients involved in these studies (75 years), one year has been considered to be a significant portion of their remaining lifespan, and thus efficacy in the first year has been considered sufficiently important upon which to base an benefit/risk decision. In spite of the incomplete final results, the apparent decreased efficacy during the second year compared to the first year is considered relevant information to be conveyed in the labeling.

Responder Analysis by Week - Study EOP1003



Responder Analysis by Week - Study EOP1004

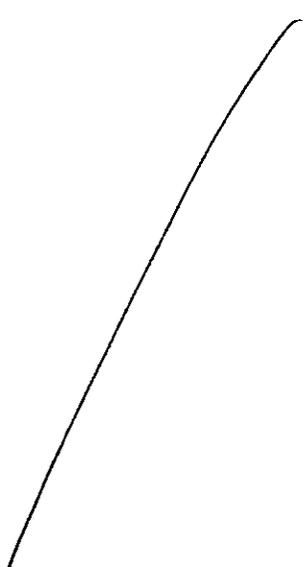


**C. Safety**

The majority of safety concerns raised in the review of this application have been attributed to the intravitreal procedure required to administer pegaptanib sodium. There is concern raised in this database over the rate of endophthalmitis. This event is most likely due to contamination with the patients lids during the injection procedure itself and not to the drug product since cultures of the drug product did not reveal the micro-organism and the organisms cultured were common lid flora organisms. The labeling includes language to reflect the risk of endophthalmitis and the importance of the use of sterile technique. This will allow for physicians and patients to be adequately informed about this risk and steps to take to minimize its occurrence. Ocular neurotoxicity and corneal endothelial toxicity have not been noted but have not been evaluated with the most sensitive measures available (ERG and endothelial cell counts, respectively). Studies using this type of instrumentation have been recommended, and the applicant has committed to conducting these studies.

**D. Chemistry/Manufacturing Review**

The drug substance review recommends approval of the application. The drug product quality microbiology review recommends approval of the application because the application has \_\_\_\_\_ in place. The drug product review identifies the following deficiency in the application:



**E. Pharmacology/Toxicology Review**

The Pharmacology/Toxicology review concludes that adequate nonclinical testing has been conducted, although the animals could have tolerated higher doses in the embryofetal studies. Considering that the dose tested was at least 600 times the human dose based on a dose per body surface area (higher if based on mg/kg) and the drug product will be labeled for an indication which would not include pregnant women, the testing is considered adequate.

**F. Pediatrics**

The indication proposed for the drug product is not applicable for pediatric patients.

**G. Trademark**

DDMAC and DMETS were consulted with respect to the trademark, Macugen. DMETS has not objection to the trademark. DDMAC —

Wiley A. Chambers, MD  
Deputy Division Director, HFD-550

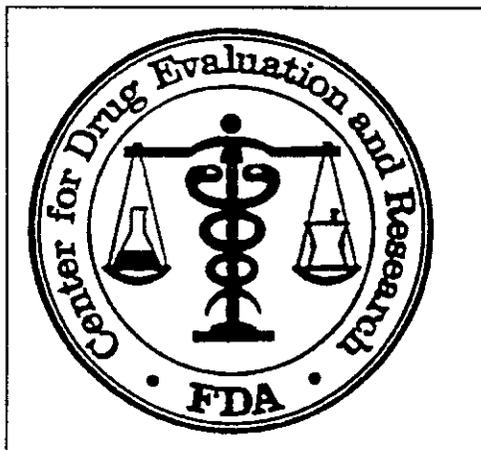
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MEDICAL OFFICER

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12/16/04 05:07:30 PM  
MEDICAL OFFICER

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From: Libaniel Rodriguez, Ph.D.  
Review Chemist

Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products  
HFD-550

Phone 301-827-2069  
Fax 301-827-2531

Date: November 17, 2004

To: Name: Meg Cassais  
Company: EYETECH Pharmaceuticals  
City: New York State: NY  
Phone #: 973 775 4523

FAX #: 973 539 9661

Number of Pages (INCLUDING COVER PAGE): 2

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Should you have any questions about this information request please call me.

Libaniel Rodriguez

November 17, 2004

**NDA 21-756 Macugen (pegaptanib sodium injection)**

**CMC COMMENTS**

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

1. Re-evaluate the acceptance criterion for \_\_\_\_\_
2. Provide an update as to whether the proposed \_\_\_\_\_  
has any effect on the physical properties of the pouch contents.
3. The proposed acceptance criteria for \_\_\_\_\_
4. Please provide a sample of the drug product in pouches A and B. The sample should be addressed to Project Manager Michael Puglisi.

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/s/

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Libaniel Rodriguez  
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CHEMIST

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> October 7, 2004	<b>DESIRED COMPLETION DATE:</b> December 7, 2004	<b>ODS CONSULT #:</b> 01-0200-1
<b>DATE OF DOCUMENT:</b> March 17, 2004	<b>PDUFA DATE:</b> December 17, 2004	

**TO:** Brian Harvey, MD  
Acting Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products  
HFD-550

**THROUGH:** Mike Puglisi  
Project Manager  
HFD-550

<b>PRODUCT NAME:</b> <b>Macugen™</b> (Pegaptanib Sodium Injection) 0.3 mg/90 mcL <b>NDA#:</b> 21-756	<b>NDA SPONSOR:</b> Eyetech Pharmaceuticals, Inc.
--	---

**SAFETY EVALUATOR:** Kimberly Culley, RPh

- RECOMMENDATIONS:**
1. DMETS has no objections to the use of the proprietary name, Macugen. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
  2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
  3. DDMAC has

Carol Holquist, RPh  
Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242, Fax: (301) 443-9664

**Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** August 28, 2004

**NDA#** 21-756

**NAME OF DRUG:** **Macugen**  
(Pegaptanib Sodium Injection)  
0.3 mg/90 mcL

**NDA HOLDER:** Eyetech Pharmaceuticals, Inc.

**\*\*\*NOTE:** This review contains proprietary and confidential information that should not be released to the public.\*\*\*

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550) for re-review of the proprietary name, Macugen, in regard to potential name confusion with other proprietary or established drug names. Container labels and insert labeling were provided for review and comment at this time. This name was previously reviewed in October 2001 (consult # 01-0200) and was found acceptable by both DMETS and DDMAC.

**PRODUCT INFORMATION**

Macugen is the proposed proprietary name for pegaptanib, an intravitreal injection for the neovascular age-related macular degeneration. The recommended dose is 0.3 mg once every six weeks via intravitreal injection. The drug product should be stored under refrigeration and is available as a single-use glass syringe that delivers 0.3 mg in 90 microliters. The drug product is packaged in two pouches; one containing the glass syringe containing the drug product and the second containing the plunger rod and flange.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Macugen to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>4,5</sup>. An expert panel discussion was conducted to review all findings from the searches.

### A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Macugen. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Error Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical skill, professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

#### 1. DDMAC

2. Since our last review, the Expert Panel identified three additional proprietary names that were thought to have the potential for confusion with Macugen. These products with their available dosage forms and usual dosage are listed in table 1 (see page 4).

---

<sup>1</sup> MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://tess2.uspto.gov/bin/gate.exe?f=searchstr&state=m2pu5u.1.1>

Table 1:

## Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel to Macugen

Product Name	Dosage form(s), Established name	Usual adult dose***	Other**
Macugen™	Pegaptanib Sodium Injection, Prefilled syringe with 0.3 mg in 90 mcL.	0.3 mg every 6 weeks by intravitreal injection	
Maxaquin®	Lomefloxacin HCl Tablets, 400 mg	400 mg once daily for 3 to 14 days. Length of administration dependent on diagnosis.	LA/SA
Menogen®	Esterified Estrogens/Methyltestosterone Tablets, 1.25 mg and 2.5 mg	One tablet daily or One tablet daily for three weeks and off for one week	LA/SA
Menopur®*** 04-0018	Menotropins for Injection, USP 75 International Units FSH / 75 International Units LH in each vial	Assisted Reproductive Technology: 225 International Units daily, with subsequent individualized dosing. Not to exceed 450 International Units.	LA

\*Frequently used, not all inclusive.  
\*\* L/A (look-alike), S/A (sound-alike).

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Macugen were captured by the Expert Panel (EPD).

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Macugen, the primary concerns related to look-alike and sound-alike confusion with Maxaquin, Menogen, and Menopur. Upon further review of the names gathered from EPD, the name of Maxaquin was not reviewed further due to a lack of convincing look and sound alike similarities with Macugen and a lack of overlapping product characteristics. The drug products differ in route of administration, available strength, usual dose, frequency of dosing, dispensing amount, and context of use.

1. Menogen may look and sound similar to Macugen when spoken and scripted. Menogen contains esterified estrogens/methyltestosterone in a tablet form for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogens alone. Recommended dosing is cyclical with the lowest dose possible. The patient should take the lowest dose daily for three weeks, and then off for one week. The patient should attempt to discontinue or taper the medication at three to six month intervals. The visual and verbal similarities result from the shared leading "M" and concluding "gen" (see page 5).

\*\*\* Proprietary and confidential information that should not be released to the public.

*Menogen*  
*Macugen*

The visual similarities may be compounded by the possibility for "cu" of Macugen to resemble the "n" of Menogen. In addition, the "a" of Macugen may look similar to the "e" of Menogen. The verbal similarities may be compounded the auditory likeness of "u" and "o" when amidst a word. Despite these similarities, the drug products do not share product characteristics. They differ in route of administration (oral compared with intravitreal), available strength (1.25 mg and 2.5 mg compared with 0.3 mg in 0.9 mL), dispensing amount (number of tablets compared with one injection comprised of two pouches), and context of use (patient use compared with an injection performed by a physician). Although the drug products may share "week" or "weekly" in their dosing regimens; one is given daily for three weeks while the other is given every six weeks. Additionally, Macugen will be administered by specialists. There is a high probability that these practitioners will order and maintain Macugen for office or clinic use; therefore there is no concern with confusion in the outpatient setting (which is typical setting for Menogen). Due to the context of use and differing characteristics, DMETS believes the possibility of name confusion to be minimal.

2. Menopur\*\*\* may look similar to Macugen when scripted. Menopur is a proposed proprietary name currently under review at the Agency. DMETS reviewed Menopur and found the name acceptable. Menopur\*\*\* contains a purified preparation of gonadotropins for the

Each vial of contains 75 International Units (IU) of follicle-stimulating hormone (FSH) activity and 75 IU of luteinizing hormone (LH) activity in a sterile, lyophilized form intended for reconstitution with sterile 0.9% Sodium Chloride Injection, USP. Menopur\*\*\* is administered by subcutaneous (SC) and dosed on a daily basis. The recommended initial dose in ART is 225 IU, with individualized dosing after that, not to exceed 450 International Units and not to be dosed beyond 20 days.

The visual similarities stem from the shared leading "M" and downstrokes of "p" and "g" (see below).

*Menopur*  
*Macugen*

In addition, an "n" and "c" may look similar when scripted, which is also true with "e" and "a." The concluding letters of "ur" and "en" may serve as a differentiating characteristic, but

\*\*\* Proprietary and confidential information that should not be released to the public.

often ending letters have a tendency to taper off thus obscuring their meaning. The drug products share a similar dosage form (injection), but differ in the route of administration (subcutaneous compared with intravitreal), packaging presentation (vial compared with prefilled syringe), strength (75 IU of each product compared with 0.3 mg), dosing frequency (daily compared with every three weeks), and context of use (patient use for fertility compared with a specialist use for macular degeneration). Due to the differing characteristics, DMETS believes the possibility for error to be minimal.

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton and insert labeling of Macugen, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

#### A. GENERAL COMMENTS

1. This may confuse or mislead the practitioner in regard to the strength or total drug content of the syringe.
2. DMETS questions why the syringe is not supplied as one unit? There is concern that addition of the plunger rod to the syringe could result in error; as the practitioner may punch or pull on the plunger out of habit. This will result in improper injection amount or compromised sterility of the drug product.
3. Revise " $\mu\text{L}$ " to read "mL" as " $\mu$ " has been confused for "m."

#### B. POUCH LABEL (Prefilled Syringe)

1. See Comment A3.
2. Please include a listing of the inactive ingredients per 21 CFR 201.100(b)(5).

#### B. POUCH LABEL (Plastic plunger rod and snap-on flange)

- 1.

C. SYRINGE LABEL

/

D. CARTON LABELING

/

E. INSERT LABELING

1. DESCRIPTION

Please consider revising the second sentence to remove reference to the “formulated as 3.47 mg/mL solution” to avoid any later dosing confusion due to the 1mL syringe size. Consider the revision of “

2. ADVERSE EVENTS

- a. To aid in quicker interpretation of the information provided, please consider revising the presentation of “most frequently reported adverse events” to match the latter presentation. For example, the line listing presentation after an ocular or non-ocular identifier.
- b. Please considering replacing the term \_\_\_\_\_, as it is the more standard accepted term.
- c. Please consider moving the statement ‘ \_\_\_\_\_ ’ to just prior to the last sentence of Adverse Events. It is currently incorporated within the adverse event percentage listings; therefore appearing misplaced for the reader. Differing placement will increase the ease of locating this data.

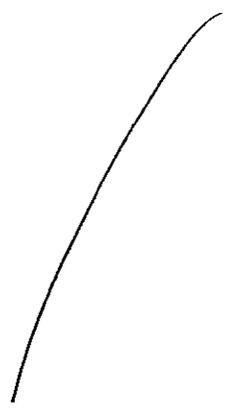
3. DOSAGE AND ADMINISTRATION

/

”

**IV. RECOMMENDATIONS:**

- A. DMETS has no objections to the use of the proprietary name, Macugen. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
- C. DDMAC



DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

---

Kim Culley, RPh  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

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Alina Mahmud, RPh  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

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/s/

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Kimberly Culley  
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DRUG SAFETY OFFICE REVIEWER

Alina Mahmud  
11/12/04 01:09:13 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
11/12/04 03:09:57 PM  
DRUG SAFETY OFFICE REVIEWER



## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** November 3, 2004  
**MEETING TIME:** 3:00 pm  
**LOCATION:** 9201 Corporate Boulevard

**APPLICATION (DRUG):** NDA 21-756  
Macugen (pegaptanib sodium injection)

**SPONSOR:** Eyetech Pharmaceuticals, Inc.

**TYPE OF MEETING:** Guidance

**MEETING CHAIR:** Wiley A. Chambers, MD

**MEETING RECORDER:** Michael Puglisi

### FDA PARTICIPANTS:

Wiley Chambers/ Deputy Division Director  
Jonca Bull/ Director, Office of Drug Evaluation V  
Terri Rumble/ Associate Director for Regulatory Affairs  
William Boyd/ Clinical Team Leader  
Jennifer Harris/ Medical Officer  
Martin Nevitt/ Medical Officer  
Lucious Lim/ Medical Officer  
Mike Puglisi/ Project Manager  
Lori Gorski/ Project Manager  
Alison Rodgers/ Project Manager  
Linda Ng/ Chemistry Team Leader  
Libaniel Rodriguez/ Chemist

### INDUSTRY PARTICIPANTS:

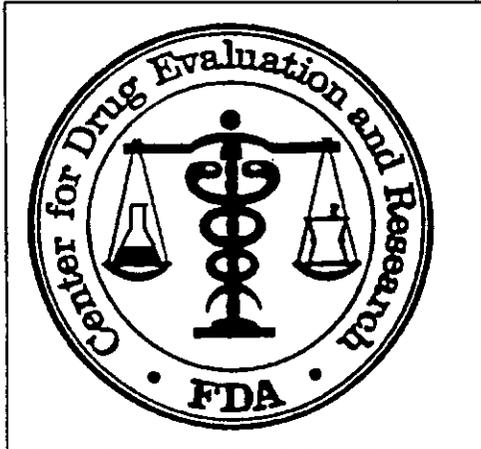
Hamed Abdou/ Senior Vice President, Technical Operations  
David Guyer/ Chief Executive Officer  
Loni da Silva/ Vice President, Regulatory Affairs  
Matt Feinsod/ Clinical  
Sharon Real/ Director, Regulatory CMC  
Kevin Nepvevy/ New Products Manufacturing

### MEETING OBJECTIVE:

To discuss the sponsors proposal for

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From: Libaniel Rodriguez, Ph.D.  
Review Chemist

Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products  
HFD-550

Phone 301-827-2069  
Fax 301-827-2531

Date: October 22, 2004

To: Name: Meg Cassais  
Company: EYETECH Pharmaceuticals  
City: New York State: NY  
Phone #: 973 775 4523

FAX #: 973 539 9661

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Libaniel Rodriguez

October 22, 2004

**NDA 21-756 Macugen (pegaptanib sodium injection)**

**CMC COMMENTS**

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

1. Please explain the lack of controls of critical steps and intermediates in the In Process Controls.
2. With respect to \_\_\_\_\_ month periods. Clarify the number of syringes used per test. State the differences between this test and the test used for the \_\_\_\_\_ month period if any.
3. \_\_\_\_\_ /
4. Please clarify statement about the \_\_\_\_\_
5. Please indicate date of submission and module for locating the Environmental Assessment Or Claim Of Categorical Exclusion section of the application.

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/s/

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Libaniel Rodriguez  
11/5/04 02:40:50 PM  
CHEMIST  
IR #2



**DISCIPLINE REVIEW LETTER**

NDA 21-756

Eyeteq Pharmaceuticals, Inc.  
Attention: Loni da Silva  
Vice President, Global Regulatory Affairs  
Three Times Square  
12<sup>th</sup> Floor  
New York, New York 10036

Dear Ms. da Silva:

Please refer to your New Drug Application (NDA) submission of March 17, 2004, for Macugen (pegaptanib sodium injection). This submission, accepted under the Continuous Marketing Application (CMA)-Pilot 1 program, contained the reviewable units for the Nonclinical Pharmacology and Toxicology, Clinical Pharmacology and Biopharmaceutics, and Clinical portions of your NDA.

We also refer to your submissions dated May 12 and 27, June 7, and July 14 and 28, 2004.

We have completed our review of these reviewable units and have identified the following deficiencies:

1. To better characterize the increases in pegaptanib exposure in patients with renal impairment, the pharmacokinetic data should be reanalyzed by grouping patients according to their creatinine clearance (CL<sub>cr</sub>) values in three groups representing mild renal impairment (CL<sub>cr</sub> = 50-80 mL/min), moderate renal impairment (CL<sub>cr</sub> = 30-50 mL/min) and severe renal impairment (CL<sub>cr</sub> < 30 mL/min). Please refer to CDER's Guidance for Industry "*Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling*", issued in May, 1998, for more information.
2. Please provide clinical information to support that there are no degenerative effects on the neurosensory retina following the intravitreal administration of Macugen.
3. Please provide clinical information to support that there are no adverse effects on the corneal endothelium following the intravitreal administration of Macugen.

Upon receipt and review of your 120-day Safety Update, in coordination with the review of the remainder of the NDA, we will work with you on the proposed labeling for this product.

NDA 21-756

Page 2

We are providing these comments to you before we complete our review of the complete application to give you preliminary notice of issues that we have identified. These comments are being provided to you in conformance with the guidance "Continuous Marketing Applications: Pilot 1 -- Reviewable Units for Fast Track Products under PDUFA" and do not reflect a final decision on the information reviewed. Issues may be added, deleted, expanded upon, or modified as we review the complete application.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

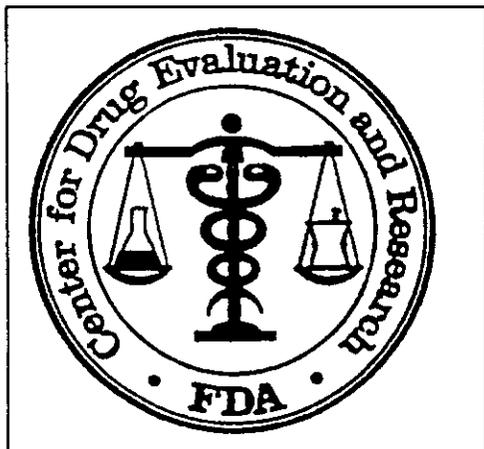
Wiley A. Chambers, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Wiley Chambers  
9/17/04 08:56:34 PM

FACSIMILE TRANSMISSION  
RECORD



From: Libaniel Rodriguez, Ph.D.  
Review Chemist

Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products  
HFD-550

Phone 301-827-2069  
Fax 301-827-2531

Date: September 8, 2004

To: Name: Karen Fleshman  
Company: EYETECH Pharmaceuticals  
City: New York State: NY  
Phone #: 973 775 4523

FAX #: 973 539 9661

Number of Pages (INCLUDING COVER PAGE): 2

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Please telephone (301) 827-2069 IMMEDIATELY if re-transmission is necessary.

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Should you have any questions about this information request please call me.

Libaniel Rodriguez

September 8, 2004

**NDA 21-756 Macugen (pegaptanib sodium injection)**

**CMC COMMENTS**

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

1. The container closure system is composed of two pouches and a carton. The first pouch contains the sterile syringe and rubber plunger stopper. The second pouch contains the syringe plunger and flange adapter
2. Please provide supporting data to assure that the \_\_\_\_\_ used for the syringe and plunger does not contaminate the drug product.
3. Please clarify statement about the \_\_\_\_\_
4. Please clarify statement about the \_\_\_\_\_ prior to packaging the drug product into the foil pouches.
5. Provide updated stability data for the drug product.
6. The proposed acceptance criteria for the drug product should be based on actual data. Please adjust accordingly.

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/s/  
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Libaniel Rodriguez  
9/9/04 07:50:11 AM  
CHEMIST  
IR

Linda Ng  
9/9/04 09:56:22 AM  
CHEMIST  
No activity needed by PM

**This report contains public information that has not been reviewed by the agency or the Dermatologic and Ophthalmic Drugs Advisory Committee. The official summary minutes will be prepared, circulated, and certified as usual. Transcripts will be available and placed on the web in about 3 weeks.**

## **Quick Minutes - DODAC Meeting 27 August 2004**

1. Based on the Inclusion/Exclusion Criteria, are there patients excluded from the studies that you believe need to be studied?
  - **The inclusion/exclusion criteria was appropriate and sufficient data was collected**
  - **There were no obvious exclusions that should have been included**
  - **There is a concern about the lack of long term follow-up (greater than 2 years)**
  
2. Visual acuity measurements were conducted using the ETDRS scale placed at 2 meters from the patient. The validity of the ETDRS scale was established based on readings at 4 meters. Are the visual acuity findings sufficiently robust to overcome the potential bias introduced by visual acuity measurements at 2 meters?
  - **Having a control group and still seeing differences suggests that there is no major issue with the 2 meter measurements**
  - **Data is OK at 2 meters but the committee recommended that data be collected at 4 meters in future trials**
  - **There appears to be good enough robust data to accept the 2 meter visual acuity measurements**
  - **All members of the committee felt that the findings were sufficiently robust to overcome potential bias**
  
3. Has sufficient data been submitted to evaluate the efficacy and safety profile of pegaptanib sodium for the treatment of the neovascular form of AMD? If not, what additional data are needed?
  - **All members of the committee felt sufficient data was available to evaluate the safety and efficacy profile**
  - **The committee recommended that long term data be collected but were unable to state a specific timeframe**
  - **Some members of the committee would like to see post-marketing surveillance data for an extended period of time**
  - **Concern was expressed about the potential for a long length of treatment and when patients and physicians would know to stop - more data needs to be collected**

4. Are additional analyses of the current data needed to understand the efficacy or safety of pegaptanib sodium for the treatment of the neovascular form of AMD?
  - **The committee felt that no additional analyses on the current data was required**
  - **The committee wanted to see some time to treatment failure data (shown at the meeting)**
  - **A progressive disease such as AMD should have continuing analyses**
  
5. (a.) Has the concomitant use of PDT therapy with pegaptanib been explored sufficiently?
  - **The committee felt that the concomitant use of PDT therapy has been explored sufficiently**
  - **There is a desire to see larger number of patients**
  - **The decision to allow PDT therapy was a good idea**

(b) Are there concerns with using this product concomitantly with PDT therapy?

  - **The committee felt the use of PDT therapy concomitantly was appropriate**
  - **Data collection to determine if there is a synergistic effect was recommended**
  
6. Do the route and/or frequency of administration of the drug raise any concerns that are not addressed by the studies?
  - **The majority of the committee felt the route and frequency had been addressed adequately**
  - **Two members deferred to the ophthalmologists on the committee for a response to this question**
  - **The patient population that would use this drug are highly motivated therefore the frequency and route do not appear to be an issue**
  - **The fact that 90% of the participants were retained tempers the concern but multiple injections are a concern**
  - **The company was encouraged to develop other delivery methods (i.e., implantable)**
  - **More data should be collected on the neurotrophic effect of the VEGF**
  
7. Endophthalmitis was observed in approximately 2% of patients in these studies. What is the optimal follow-up needed to minimize the impact of potential endophthalmitis cases?
  - **Include in labeling how frequently the patient should return to be checked for potential endophthalmitis**
  - **If the endophthalmitis is an infrequent recurrence it should be screened more frequently in the early stages**
  - **The 3 day call asking "how do you feel and how is your vision" is one way to catch problems early**

- **Patient education materials should be developed to assist in identifying potential problems early in the process**
  - **Relying solely on the patient to self diagnosis would be a problem**
  - **The current aggressive follow-up resulted in good outcomes and this should be considered as the standard (i.e., call day 3 and visit day 7)**
  - **The FDA and Sponsor should include education in the labeling and incorporate some agreed upon schedule as guidance**
  - **Concern was expressed that not all patients have someone at home to read instructions and that needs to be addressed in the patient education - consider using tape or CD instruction**
  - **An exam on the day after injection should be considered - any lesser amount of follow-up sends the wrong message**
  - **Both patient and physician education and standardized follow-up is important**
8. Are there adverse experiences that are of particular concern for this product?
- **The only one seen is the endophthalmitis**
  - **Retinal detachment is a concern and a precautionary statement should be included in the labeling**
  - **Education up front will help to prohibit inappropriate use**
  - **There is a concern that untrained physicians will treat patients increasing the risk of adverse events - education and appropriate labeling is needed to help control this potential problem**
9. Vascular Endothelial Growth Factor (VEGF) has been shown to be an important component in the development of collateral vessels in ischemic heart disease. Inhibition of VEGF in the systemic circulation could present a theoretical increased risk of symptomatic cardiovascular disease in the target population of elderly patients with AMD.
- a. Has the adverse event profile of the two randomized phase 3 trials raised any concern over the possible systemic effects of this therapy?
- **The committee agreed that there were no concerns raised over the possible systemic effects of this therapy**
- b. Is there additional monitoring that should be in place for patients on pegaptanib sodium therapy?
- **The collection of long term data is important**
  - **Data on the effect of PDT on the Quality of Life issues should be collected**

5 Pages Redacted of  
**Deliberative Process**  
**§ 552(b)(5)**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-756

Eyetechn Pharmaceuticals, Inc.  
Attention: Loni da Silva  
Vice President, Global Regulatory Affairs  
Three Times Square  
12<sup>th</sup> Floor  
New York, New York 10036

Dear Ms. da Silva:

Please refer to your June 17, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macugen (pegaptanib sodium injection).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 16, 2004, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R.Ph.  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Michael Puglisi  
8/30/04 11:30:03 AM  
for Carmen DeBellas



CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. Depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

***Drug Substance:***

*Synthesis/Manufacturing:*

1. For a typical production batch, please provide information regarding exact amount of the \_\_\_\_\_ used. The target amount should be included in the master batch record.
2. Please provide the estimated or calculated yield for the \_\_\_\_\_

*Manufacturing Development:*

3. Please correlate the manufactured batches of the drug substance to the corresponding drug product batches.
4. Please explain what kind of \_\_\_\_\_ is achieved during the manufacturing process development going from \_\_\_\_\_

*Characterization/Proof of structure:*

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/s/

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Michael Puglisi  
8/19/04 02:06:26 PM

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**Deliberative Process**  
**§ 552(b)(5)**

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Loni da Silva **From:** Mike Puglisi, Project Manager

---

**Fax:** 212-824-3238 **Fax:** 301-827-2531

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**Phone:** **Phone:** 301-827-2522

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**Pages:** 2 (including cover page) **Date:** July 9, 2004

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**Re:** Clinical Information Request for NDA 21-756

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**Urgent**    **For Review**    **Please Comment**    **Please Reply**    **Please Recycle**

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● **Comments:**

Loni-

Here's an information request from the Clinical folks concerning NDA 21-756. Please respond in an amendment to your NDA. Please let me know if you have any questions about these comments. Thanks.

-Mike

July 9, 2004

*Please provide the following information for both trials EOP1003 and EOP1004:*

1. *Responder analysis at baseline, month 3, month 6, month 9 and month 12 for the following populations:*
  - a. *True ITT (all randomized patients) with LOCF*
  - b. *Per-protocol Observed Cases Only*
  - c. *True Worst Case Analysis (sham patients without an observation are considered successes, Macugen patients without an observation are considered failures)*
  - d. *All Patients who never received PDT before or during study*
  - e. *All Patients who only received PDT before the study*
  - f. *All Patients who only received PDT during the study*
  - g. *All Patients who received PDT before and during the study*
  
2. *Subset analysis (for each study individually) for the True ITT with LOCF population and the Per-protocol Observed Cases Only Population. Subsets should be based on age, gender, race, eye color, lesion size, and lesion type.*

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/s/

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Michael Puglisi  
7/9/04 02:56:23 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-756

Eyetechn Pharmaceuticals, Inc.  
Attention: Loni da Silva  
Vice President, Global Regulatory Affairs  
Three Times Square  
12<sup>th</sup> Floor  
New York, New York 10036

Dear Ms. da Silva:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Macugen (pegaptanib sodium injection)

Review Priority Classification: Priority (P)

Date of Application: June 17, 2004

Date of Receipt: June 17, 2004

Our Reference Number: NDA 21-756

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 16, 2004, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be December 17, 2004.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

NDA 21-756

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
9201 Corporate Boulevard  
Rockville, Maryland 20850

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R.Ph.  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

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Michael Puglisi  
7/1/04 11:44:37 AM  
for Carmen DeBellas

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Loni da Silva **From:** Mike Puglisi, Project Manager

**Fax:** 212-824-3238 **Fax:** 301-827-2531

**Phone:** **Phone:** 301-827-2522

**Pages:** 1 (including cover page) **Date:** May 27, 2004

**Re:** Statistician's Information Request for NDA 21-756

**Urgent**  **For Review**  **Please Comment**  **Please Reply**  **Please Recycle**

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● **Comments:**

Loni-

Per our earlier conversation, here's that request from our Statistician concerning Macugen (NDA 21-756). Please respond in an amendment to your NDA. Please let me know if you have any questions about this request. Thanks.

-Mike

**Reviewer's Comments:**

*On May 12, 2004, you provided a table with numbers of patients in each country in both studies. Please provide a similar table but break down by each study.*

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/s/

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Michael Puglisi  
5/27/04 01:24:23 PM

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Loni da Silva

**From:** Mike Puglisi, Project Manager

**Fax:** 212-824-3238

**Fax:** 301-827-2531

**Phone:**

**Phone:** 301-827-2522

**Pages:** 2 (including cover page)

**Date:** May 21, 2004

**Re:** Medical Officer's Information Request for NDA 21-756

**Urgent**    **For Review**    **Please Comment**    **Please Reply**    **Please Recycle**

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● **Comments:**

Loni-

Here's a request from our Medical Officer concerning Macugen (NDA 21-756). Please respond in an amendment to your NDA. Please let me know if you have any questions about this request. Thanks.

-Mike

Reviewer's Comments:

There's some confusion concerning the patients that were discontinued in Study EOP1003 for Macugen. In particular, there are many discrepancies in the following tables:

List 5.1 – Subject Evaluation groups (which has a column for “study completed”)

List 3.4 – Patients who discontinued due to adverse events

List 11 – Discontinuation

List 3.3 – Serious adverse events

Here are just a few examples:

1. Patients 130-002, 082-002, 092-023 and 130-016 are on list 3.4 as pts who discontinued due to adverse events however they are not on List 11 (discontinuations) . On List 5.1 they are “study completers”.
2. Patients 064-019, 064-014, 064-019, 065-010, 081-005, 087-014, 092-012, 093-028, 102-009, 123-005, are on List 11 as “discontinuations” however are on List 5.1 as “study completers”.
3. Patients 095-003, 101-010, 122-002 and 154-026 are on List 11 as discontinued due to an adverse event however no adverse event is listed on List 3.4 “patients who discontinued due to adverse events”.
4. List 3.4 shows patient 093-018 as being discontinued on day 355 due to “arthralgia” will List 3.3 shows the patient had a “pulmonary embolism” on day 355.

Also, there are numerous patients on List 11 that were listed as discontinued due to “patient request”. More detail is needed about the exact reason for discontinuation.

Please address these issues in an amendment to the NDA. Corrected tables should be provided. In addition, a comprehensive table which list the patient number, treatment group, exact reason for discontinuation ( i.e. if it was due to an adverse event, the exact event needs to be listed), and day of discontinuation should be provided.

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/s/

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Michael Puglisi  
5/21/04 03:55:15 PM

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Loni da Silva **From:** Mike Puglisi, Project Manager

---

**Fax:** 212-824-3238 **Fax:** 301-827-2531

---

**Phone:** **Phone:** 301-827-2522

---

**Pages:** 2 (including cover page) **Date:** May 19, 2004

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**Re:** Statistician's Information Request for NDA 21-756

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**Urgent**    **For Review**    **Please Comment**    **Please Reply**    **Please Recycle**

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● **Comments:**

Loni-

Here's another request from our Statistician concerning Macugen (NDA 21-756). Please respond in an amendment to your NDA. Please let me know if you have any questions about this request. Thanks.

-Mike

Reviewer's Request

1. Please provide results of subgroup analyses (including at least age, gender and race. Pooled results of Studies EOP1003 and EOP1004 are acceptable. Treatment by subgroup interaction should be evaluated).
2. Please provide detailed rationale (i.e., who made the decision and what result was based on) for not doing interim analysis as originally planned.
3. Please provide more detailed reason, if available, for treatment discontinuation due to 'patient request'.

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/s/

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Michael Puglisi  
5/19/04 04:09:13 PM

# Fax



**Division of Anti-Inflammatory, Analgesic,  
Ophthalmic Drug Products**  
Center for Drug Evaluation and Research, HFD-550  
Parklawn Building  
5600 Fishers Lane, Rockville, MD 20857

**To:** Loni da Silva **From:** Mike Puglisi, Project Manager

---

**Fax:** 212-824-3238 **Fax:** 301-827-2531

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**Phone:** **Phone:** 301-827-2522

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**Pages:** 2 (including cover page) **Date:** April 19, 2004

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**Re:** Statistician's Request for Information for NDA 21-756

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**Urgent**    **For Review**    **Please Comment**    **Please Reply**    **Please Recycle**

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● **Comments:**

Loni,

Here's an information request from the Statistician concerning NDA 21-756. Please respond in an amendment to your NDA. Let me know if you have any questions about this request. Thanks.

-Mike

Reviewer's Comments:

*For Studies 1003 and 1004:*

- 1. The sponsor should specify the exact minimization algorithm used in randomization. A re-randomization procedure should be used to examine the distribution of test statistic for the primary endpoint.*
- 2. Treatment by center interaction should be explored for the primary endpoint.*
- 3. The sponsor should provide patient number for each country.*
- 4. The sponsor should provide a by-patient/visit (one record per patient/visit) dataset (SAS transport) including all randomized patients. Each dataset should include patient number, treatment code, center codes, patient demographics and baseline characteristics, patient disposition (time to withdrawal (study duration) and reason of withdrawal), and efficacy variables.*

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/s/

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Michael Puglisi  
4/19/04 02:51:52 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 56,503

Eyetechn Pharmaceuticals, Inc.  
Attention: Loni da Silva  
Vice President, Regulatory Affairs  
500 Seventh Avenue, 18<sup>th</sup> Floor  
New York, New York 10018

Dear Ms. da Silva:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Macugen (Anti-VEGF Pegylated Aptamer).

We also refer to the meeting between representatives of your firm and the FDA on February 13, 2004. The purpose of the meeting was to discuss CMC issues concerning your product.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Enclosure



**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** February 13, 2004  
**APPROXIMATE START TIME:** 2:00 pm  
**APPROXIMATE END TIME:** 2:45 pm  
**LOCATION:** 9201 Corporate Boulevard

**APPLICATION (DRUG):** Macugen (Anti-VEGF Pegylated Aptamer)

**SPONSOR:** EyeTech Pharmaceuticals, Inc

**TYPE OF MEETING:** Type C - Guidance

**MEETING CHAIR:** Wiley A. Chambers, MD

**MEETING RECORDER:** Michael Puglisi

**FDA PARTICIPANTS:**

Wiley Chambers/ Deputy Division Director  
William Boyd/ Clinical Team Leader  
Jennifer Harris/ Medical Officer  
Carmen DeBellas/ Chief Project Manager  
Mike Puglisi/ Project Manager  
Lori Gorski/ Project Manager  
Nancy Halonen/ Project Manager  
Raphael Rodriguez/ Project Manager  
Linda Ng/ Chemistry Team Leader  
Shawn Hossein Khorshidi/ Chemist

**INDUSTRY PARTICIPANTS:**

David Guyer/ CEO  
Tony Adamis/ Chief Scientific Officer  
Karen Flesham/ Sr. Director, CMC Regulatory  
Loni da Silva/ VP, Global Regulatory  
Paul Chaney/ COO  
Steven Scypinski/ VP, Analytical Development  
Donald Hodgson/ Director, Manufacturing  
Keith Westby/ Sr. Manager, Project Management  
— Consultant  
Sharon Real/ CMC Regulatory  
David Baker/ Analytical  
Jon Beaman/ Analytical

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/s/

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Wiley Chambers  
3/12/04 04:22:10 PM

## MEETING MINUTES

MEETING DATE: 10/30/03      TIME: 10:00 am      LOCATION: CORP. S300

IND # 56,503

Meeting Request Submission Date – 9/5/03

Date Scheduled – 9/11/03

Meeting Packages Submitted – 10/24/03

DRUG: Macugen (pegaptanib sodium)

SPONSOR: EyeTech Pharmaceuticals, Inc.

TYPE OF MEETING: Type C

### FDA PARTICIPANTS:

Wiley A. Chambers/ Deputy Division Director

William Boyd/ Clinical Team Leader

Lucious Lim/ Medical Officer

Jennifer Harris/ Medical Officer

Mike Puglisi/ Project Manager

Lori Gorski/ Project Manager

Raphael Rodriguez/ Project Manager

Nancy Halonen/ Project Manager

### INDUSTRY PARTICIPANTS:

David Guyer/ CEO

Loni da Silva/ VP, Regulatory Affairs

Denis O'Shaughnessy/ Clinical Development

— Statistician Consultant

Susanne Dorn/ Pfizer Regulatory Affairs

Chan Beals/ Clinical Development

Marlene Modi/ Clinical Pharmacologist

Jeffrey Finman/ Biostatistician

Harvey Masonson/ Clinical Development

Manju Patel/ Clinical Development

Emmett Cuningham/ Clinical Development

Naitee Ting/ Biostatistician

### MEETING OBJECTIVES:

To discuss the Sponsor's preliminary study data for the upcoming NDA for Macugen (pegaptanib sodium) for treatment of neovascular AMD.

**Questions for the Agency:**

1. Pfizer/Eyetech is in the process of developing an amendment to EOP 1003/1004 to allow patients to continue to receive drug after they have completed the two year treatment period. Does the Agency agree that the 0.3 mg dose should be used for all patients who wish to continue receiving pegaptanib sodium once they have completed the two year treatment period?

**Agency Response:**

*This determination can not be made until after a review of the NDA. Based on the draft data submitted, it appears that the 0.3mg and 1.0 mg doses have similar efficacy and safety profiles. We recommend that both doses be continued in patients who wish to continue receiving the drug product.*

2. Does the Agency agree that Macugen (pegaptanib sodium) has established a benefit in \_\_\_\_\_

**Agency Response:**

*This can not be determined based on the preliminary draft data that has been submitted. A final conclusion about the efficacy of this drug will be made after review of the NDA. There is no objection to an NDA submission which propose: \_\_\_\_\_*

3. Does the Agency agree that there is sufficient evidence to conclude that Macugen has a treatment benefit independent of PDT?

**Agency Response:**

*This can not be determined based on the preliminary draft data that has been submitted. A final conclusion about the efficacy of this drug may be made after review of the NDA. The absence of arms which utilize multiple concomitant treatments of PDT may make it difficult to conclude that the treatment benefits are completely independent of PDT.*

4. Does the Agency agree with our definition of ITT as described in section 2.2.2.1 of this submission?

**Agency Response:**

*The ITT population is not clearly defined in section 2.2.2.1. The division defines the ITT population as all randomized patients. In the NDA submission, the Division expects to see an ITT analysis with last observation carried forward and a Per-Protocol analysis using only the observed data points. If there is a disparity in these analysis results, an explanation should be provided.*

Prepared by: Michael Puglisi  
Consumer Safety Officer

Concurrence by: William Boyd, M.D.                      Wiley A. Chambers, M.D.  
Clinical Team Leader                      Deputy Division Director

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/s/

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Wiley Chambers  
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## MEETING MINUTES

MEETING DATE: 9/5/03    TIME: 11:30 am    LOCATION: CORP. S400

IND # 56,503

Meeting Request Submission Date – 4/29/03

Date Scheduled – 6/3/03

Meeting Packages Submitted – 4/29/03

DRUG: Macugen (Anti-VEGF Pegylated Aptamer)

SPONSOR: EyeTech Pharmaceuticals, Inc.

TYPE OF MEETING: Type C

### FDA PARTICIPANTS:

Wiley A. Chambers/ Deputy Division Director

Jonca Bull/ Office Director

Terri Rumble/ Office Assoc. Dir., Reg. Affairs

Randy Levin/ Office of Information Mgmt.

Gary Gensinger/ Office of Information Mgmt.

William Boyd/ Medical Officer

Jennifer Harris/ Medical Officer

Matthew Feinsod/ Staff Fellow

Mike Puglisi/ Project Manager

### INDUSTRY PARTICIPANTS:

Loni da Silva/ VP, Regulatory Affairs

Denis O'Shaughnessy/ Clinical Development

Katherine Burke/ Clinical Development

Kathleen Mulligan/ Regulatory Associate

Manju Patel/ Clinical Development

Kristina Knights/ Electronic Submissions

Stephen Mitchell/ Electronic Submissions

### MEETING OBJECTIVES:

To discuss the Sponsor's proposed plan for electronically submitting and archiving the upcoming NDA for Anti-VEGF Pegylated Aptamer (EYE001) for treatment of neovascular AMD.

QUESTIONS FOR DISCUSSION:

1. The FDA in MAPP 7600.6 discourages the submission of electronic information in a format that cannot be archived. Since the Topcon software uses JPEG images (not PDF), what is the best way to submit the digital pictures to the FDA as part of our eNDA submission?

*Agency Response: The Office of Information Management deferred comment until they receive samples of the proposed files.*

2. Will the Agency accept a laptop computer containing the proprietary software, to enable the review of the angiograms?

*Agency Response: The Office of Information Management deferred comment until they receive samples of the proposed files.*

3. Will the Agency accept an electronic submission in the ICH eCTD format as requested by the Division?

*Agency Response: Please refer to the August, 2003, draft guidance document for eCTD submissions.*

Prepared by: Michael Puglisi  
Project Manager  
HFD-550

Concurrence by: William Boyd, M.D.  
Clinical Team Leader  
HFD-550  
  
Wiley A. Chambers, M.D.  
Deputy Division Director  
HFD-550

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/s/

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Wiley Chambers  
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## MEETING MINUTES

MEETING DATE: 2/24/03 TIME: 10:00 am LOCATION: CORP. S300

IND # 56,503

Meeting Request Submission Date – 2/20/03

Date Scheduled – 2/20/03

Meeting Packages Submitted – 2/20/03

DRUG: Anti-VEGF Pegylated Aptamer (EYE001)

SPONSOR: EyeTech Pharmaceuticals, Inc.

TYPE OF MEETING: Type A

### FDA PARTICIPANTS:

Wiley A. Chambers/ Deputy Division Director

William Boyd/ Clinical Team Leader

Lucious Lim/ Medical Officer

Jennifer Harris/ Medical Officer

Matthew Feinsod/ Staff Fellow

Mike Puglisi/ Project Manager

Carmen DeBellis/ Chief Project Manager

Lori Gorski/ Project Manager

Raphael Rodriguez/ Project Manager

Stan Lin, Ph.D./ Statistics Team Leader

Suktae Choi, Ph.D./ Statistician

M. Atiar Rahman/ Statistician

### INDUSTRY PARTICIPANTS:

David Guyer/ CEO

Loni da Silva/ VP, Regulatory Affairs

Denis O'Shaughnessy/ Clinical Development

— Statistician Consultant

Lynn Hill/ Project Management

Susanne Doin/ Pfizer Regulatory Affairs

Leland Loose/ Pfizer Clinical Development

Chan Beals/ Pfizer Clinical Development

Marlene Modi/ Clinical Pharmacologist

Jeffrey Finman/ Pfizer Statistician

### MEETING OBJECTIVES:

To discuss the Sponsor's proposed statistical analysis plan to be used in support of the upcoming NDA for Anti-VEGF Pegylated Aptamer (EYE001) for treatment of neovascular AMD.

**QUESTION TO THE AGENCY:**

- Would the Agency please provide comments on the proposed statistical testing procedure?

**Agency Response:**

*Using the primary efficacy endpoint as the proportion of patients losing < 15 letters of VA at the highest dose, 3mg and then using a step-down analysis method as follows:*

*3mg Responders vs. sham  
3mg gainers vs. sham  
1 mg responders vs. sham  
1 mg gainers vs. sham  
0.3 mg responders vs. sham  
0.3 mg gainers vs. sham*

*will not provide useful information about the efficacy of each dose. This approach would only be of value if, for instance, the 3 mg dose is known to be more efficacious than the lower doses a priori. A situation could arise in which all patients respond to the 1 mg dose but fail at the 3 mg dose. Based on this proposed analysis plan, the study would be considered a failed trial with no resolution as to the optimal dose. Ideally, the Agency expects dose ranging to be completed prior to commencing phase 3 trials to avoid such situations.*

*The primary efficacy endpoint should be analyzed based on the "responders". Using "gainers" as an efficacy endpoint does not provide useful information. If the study succeeds based on the "responders" analyses, "gainers" could then be studied as a secondary endpoint.*

*We would suggest that the results of the first trial be analyzed before breaking the blind on the second trial. This would allow for changes in the analysis plan for the second trial. These studies would still be considered replicative despite the use of different analyses.*

Prepared by: Michael Puglisi  
Project Manager  
HFD-550

Concurrence by: Wiley A. Chambers, M.D.  
Deputy Division Director  
HFD-550

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**Deliberative Process**  
**§ 552(b)(5)**

## MEETING MINUTES

MEETING DATE: 4/26/01 TIME: 11:00 am LOCATION: CORP. S400

IND # 56,503

Meeting Request Submission Date – 3/7/01

Date Sponsor Requested – 4/26/01

Meeting Packages Submitted – 4/1/01

DRUG: Anti-VEGF Pegylated Aptamer (EYE001)

SPONSOR: EyeTech Pharmaceuticals, Inc.

TYPE OF MEETING: Type C

### FDA PARTICIPANTS:

Wiley A. Chambers, M.D./ Deputy Division Director

Lucious Lim, M.D./ Medical Officer

Jennifer Harris, M.D./ Medical Officer

Zhou Chen, Ph.D./ Pharmacologist

Mike Puglisi/ Project Manager

Lori Gorski/ Project Manager

Raphael Rodriguez/ Project Manager

Joanne Holmes/ Clinical Reviewer

Jonca Bull, M.D./ Deputy Office Director-Acting Division Director

Dennis Bashaw, Pharm.D./ Team Leader-Pharmacokinetics

Stan Lin, Ph.D./ Team Leader- Statistics

Suktae Choi, Ph.D./ Statistician

### INDUSTRY PARTICIPANTS:

David Guyer, M.D./ CEO

Loni da Silva/ VP, Regulatory Affairs

— .s  
Denis O'Shaughnessy, M.D./ Senior VP, Clinical

— Toxicology Consultant

— Statistician Consultant

Lynn Hill, Ph.D./ Project Management

— Clinical Consultant

— /Clinical Consultant

Donald Hodgson/ Manufacturing

MEETING OBJECTIVES: To seek the Agency's input re: the acceptability of the proposed Phase 3 clinical studies to support a future NDA submission.

**QUESTION TO THE AGENCY:**

- 1. Does the Agency agree that the proposed pivotal clinical studies are suitable to support the NDA approval of the anti-VEGF pegylated aptamer (EYE001) for the Neovascular Form of Age-Related Macular Degeneration Disease? Specifically with regard to:**
- Study design, including combination therapy with PDT
  - doses
  - control (proposal to use subconjunctival saline injection in view of the fact that all control patients will receive injections for 48 weeks and half of the control patients will receive injections for 96 weeks)
  - Duration of treatment
  - PK parameters
  - Parameters of efficacy
  - Statistical plan
  - Surrogate Marker at 6 months
  - Would VFQ25 (for quality of life) be satisfactory for the AMD protocol

Reviewers Comments:

1. *The agency recommends that two controlled replicative studies for the proposed application be conducted at a minimum to prove efficacy. The diabetic macular edema study would not be adequate to confirm efficacy for AMD.*
2. *Study Design:*
  - a) *Suggest that the sponsor consider replacing the subconjunctival saline injection arm of the trial with an intravitreal injection of vehicle. The agency does not feel that useful information will be gained from a subconjunctival injection in this setting. The trial can be conducted using just the three doses proposed however there is the potential risk of all of the doses having the same dose-response.*
  - b) *The agency suggests that the sponsor re-consider the multiple categories proposed for satisfying patients who have received PDT. We suggest that the patients be stratified by those who received PDT vs. those who have not since the majority of these patients receiving PDT require multiple treatments.*
  - c) *In accordance with the ICH guidelines, we recommend that at least 300 patients be exposed to drug at or above the proposed marketed concentration at the time of NDA filing. The sponsor proposes to have approximately 333 patients (111 patients in each concentration group; 0.3, 1.0, 3.0 mg/eye) which would only meet the recommendation if the 0.3 mg/eye is the final marketed concentration. This recommendation could*

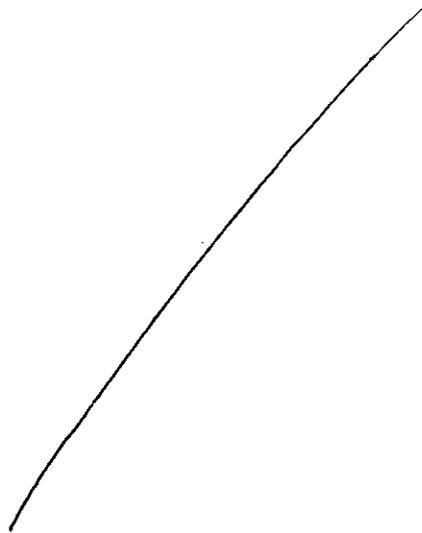
*potentially be met by using the safety data from the diabetic macular edema study but the adequacy of the numbers of patients exposed will again depend on the concentration used.*

- d) The agency accepts the primary efficacy endpoint which is the proportion of patients losing > 3 lines of vision at 54 weeks. The agency recommends that AMD trials be carried out for at least 2 years. We will accept the assessment of efficacy at 1 year with the continuation of the trial for a total of 2 years as proposed.*
- e) The sponsor should reconsider the inclusion criteria of subfoveal choroidal neovascularization ( $\leq 12$  total disc areas in size).*
- f) The agency does not agree with the proposed criteria for reporting adverse events. All adverse events whether mild, moderate or severe should be reported by the ophthalmologist.*

*Additional points:*

*Please clarify if patients found to be eligible for PDT during the course of the study will receive this treatment.*

*Please clarify how the VFQ 25 will be used.*



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Wiley Chambers

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## MEETING MINUTES

MEETING DATE: 1/25/01 TIME: 9:30 am LOCATION: CORP. S300

IND # 56,503

Meeting Request Submission Date – 12/6/2000

Date Sponsor Requested – 1/25/01

Meeting Packages Submitted – 12/22/2000

DRUG: Anti-VEGF Pegylated Aptamer (EYE001)

SPONSOR: EyeTech Pharmaceuticals, Inc.

TYPE OF MEETING: Type C

### FDA PARTICIPANTS:

Wiley A. Chambers, M.D./ Deputy Division Director

Lucious Lim, M.D./ Medical Officer

Jennifer Harris, M.D./ Medical Officer

William Boyd, M.D./ Medical Officer

Zhou Chen, Ph.D./ Pharmacologist

Robert Osterberg, Ph.D./ Pharm/Tox Team Leader

Mike Puglisi/ Project Manager

Lori Gorski/ Project Manager

Raphael Rodriguez/ Project Manager

### INDUSTRY PARTICIPANTS:

David Guyer, M.D./ CEO

Loni da Silva/ VP, Regulatory Affairs

Denise O'Shaughnessy, M.D./ Senior VP, Clinical

..... / Toxicology Consultant

MEETING OBJECTIVES: To seek the Agency's input re: the sponsor's proposed toxicology program in support of a future NDA.

### QUESTION TO THE AGENCY:

Does the Agency agree that the proposed toxicology program is suitable to support the NDA approval of the anti-VEGF pegylated aptamer (EYE001) for the Neovascular Form of Age-Related Macular Degeneration Disease?

MEETING DISCUSSION ITEMS:

**Toxicology Issues**

1. Reproductive toxicity studies are not necessary for the AMD indication. —
2. The planned study is not needed.
3. In the proposed 6-month rabbit study and 9-month dog study, systemic toxicity should be addressed, including histopathological examination.
4. The ICH guideline allows for carcinogenicity studies to be waived for drugs given by the ocular route unless there is cause for concern or unless there is significant exposure. If the sponsor considers the drug eligible for a waiver, they should submit a request for a waiver to the Division based on the ICH guideline. A final decision will be made based on the adequacy of this request.

**Clinical Issues**

1. It is unlikely that 1 trial will be enough to support an NDA approval. Reproducibility of results should be the goal. The average change in visual acuity should be a mean of 3 lines on the ETDRS scale to establish clinical significance. Demonstrating statistical significance alone in trials is not sufficient to support an NDA approval.
2. It is necessary to show reproducibility in your phase 3 studies for a New Drug Application. Once an approval for a drug is achieved, it may be possible to expand the indication with only one additional trial showing efficacy, assuming the results of the original trial are duplicated.
3. Patient numbers – A minimum of 300 patients at planned dose or above, is expected to detect a 1% adverse event profile (provided safety is maintained). Refer to the ICH guidelines.

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Michael Puglisi  
Project Manager

Concurrence: Wiley Chambers, M.D.  
Deputy Division Director

/s/

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Wiley Chambers  
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