CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-756

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 21-756

Macugen®

(pegatanib sodium) 0.3 mg/90 µl injection

Eyetech Pharmaceuticals

Hossein S. Khorshidi
Division of Anti-Inflammatory/Analgesics & Ophthalmic Drug Products
HFD-550

Table of Contents

Chemistry Review Data Sheet

1. NDA # **21-756**

2. REVIEW # 1

3. REVIEW DATE: 12/14/04

4. REVIEWER: Hossein S. Khorshidi

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED (Drug Substance Section Only):

Submission(s) Reviewed	Document Date
Original	6/17/04
Amendment	9/13/04
Amendment	9/22/04
Amendment	9/23/04
Amendment	9/30/04

7. NAME & ADDRESS OF APPLICANT:

Name: Eyetech Pharmaceuticals

Address: 140 east Hanover Avenue, cedar Knolls, New Jersey 07927

Representative: Karen Fleshman, Director, Regulatory affairs

Telephone: (973)-775-4506

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Macugan®
b) Non-Proprietary Name (USAN): Pagatanib Sodium
c) Code Name #: N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: Rolling NDA, P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: VEGF inhibitor

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.3 mg/90 µl injection

13. ROUTE OF ADMINISTRATION: Intravitreous Injection

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name:

IUPAC: (2-deoxy-2-fluorocytidylyl-(3'→ 5' *O,O*-phosphoryl)-2'-methoxyguanosylyl-(3'→ 5' *O,O*-phosphoryl)-2'-methoxyguanosylyl-(3'→ 5' *O,O*-phosphoryl)-riboadenosylyl-(3'→ 5' *O,O*-phosphoryl)-riboadenosylyl-(3'→ 5' *O,O*-phosphoryl)-2'-deoxy-2'-fluorouridylyl-(3'→ 5' *O,O*-phosphoryl)-2'-deoxy-2'-fluorocytidylyl-(3'→ 5' *O,O*-phosphoryl)-2'-methoxyadenosylyl-(3'→ 5' *O,O*-phosphoryl)-2'-methoxyguanosylyl-(3'→ 5' *O,O*-phosphoryl)-2'-deoxy-2'-fluorouridylyl-(3'→ 5' *O,O*-phosphoryl)-2'-methoxyguanosylyl-(3'→ 5' *O,O*-phosphoryl)-2'-methoxyadenosylyl-(3'→ 5' *O,O*-phosphoryl)-2'-methoxyadenosylyl-(3'→ 5' *O,O*-phosphoryl)-2'-deoxy-2'-fluorouridylyl- (3'→ 5' *O,O*-phosphoryl)-2'methoxyguanosylyl-(3'→ 5' *O,O*phosphoryl)-2'-deoxy-2'-fluorocytidylyl-(3'→ 5' *O,O*-phosphoryl)-2'-deoxy-2'-fluorouridylyl-(3'→ 5' *O,O*-phosphoryl)-2'-deoxy-2'-fluorouridylyl-(3'→ 5' *O,O*-phosphoryl)-2'-methoxyadenosylyl-(3'→ 5' *O,O*-phosphoryl)-2'-deoxy-2'-fluorouridylyl-(3'→ 5' *O,O*-phosphoryl)-2'-methoxyadenosylyl-(3'→ 5' *O,O*-phosphoryl)-2'-deoxy-2'-fluorocytidylyl-(3'→ 5' *O,O*-phosphoryl)-2'-methoxyadenosylyl-(3'→ 5' *O,O*-phosphoryl)-2'-deoxy-2'-fluorouridylyl-(3'→ 5' *O,O*-phosphoryl)-2'-deoxy-2'-fluorocytidylyl-(3'→ 5' *O,O*-phosphoryl)-2'-deoxy-2'-fluorocytidylyl-(3'→ 5' *O,O*-phosphoryl)-2'-methoxyguanosylyl-(3'→ 5' *O,O*phosphoryl)-2'-deoxythymidylyl), 5'-ester with α, α-(4,12-dioxo-6-(((5-(phosphonooxy)pentyl)amino)carbonyl)-3,13-dioxa-5,11-diaza-1,15-pentadecanediyl)bis(ï-methoxypoly(oxy-1,2-ethanediyl)), sodium salt

or

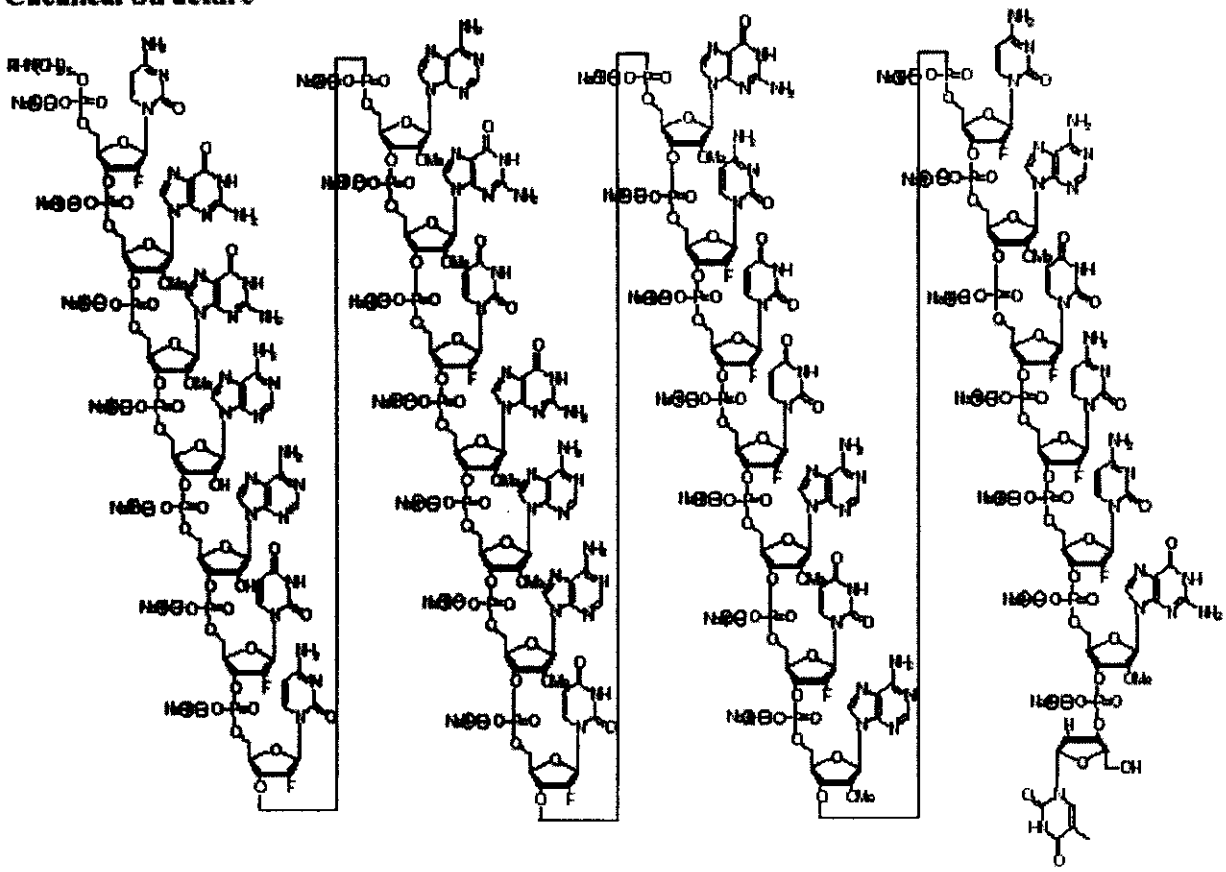
RNA, ((2'-deoxy-2'-fluoro)C-Gm-Gm-A-A-(2'-dedoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-Am-Gm-(2'-deoxy-2'-fluoro)U-Gm-Am-Am-(2'-deoxy-2'-fluoro)U-Gm-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-fluoro)U-Am-(2'-deoxy-2'-fluoro)U-Am-(2'-deoxy-2'-fluoro)C-Am-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-Gm-(3'→ 3')-dT, 5'-ester with α-α'[4,12-dioxo-6-[[5-(phosphoonoxy)pentyl]amino]carbonyl]-3,13-dioxa-5,11-diaza-1,15-pentadecananediyl]bis[ω-methoxypoly{oxy-1,2-ethanediyl)], sodium salt

or

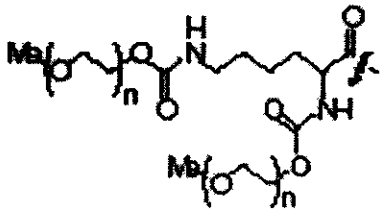
5'-ester of (2'-deoxy-2'-fluoro)C-Gm-Gm-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-Am-Gm-(2'-deoxy-2'-fluoro)U-Gm-Am-Am-(2'-deoxy-2'-fluoro)U-Gm-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-Am-(2'-deoxy-2'-fluoro)U-Am-(2'-deoxy-2'-fluoro)CAm-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'fluoro)C-(2'-deoxy-2'-fluoro)C-Gm-(3'→ 3')dT with α-α'-[[(1*S*)-1-[[5-(phosphooxy)pentyl]carbamoyl]pentane-1,5diyl]bis(iminocarbonyl)] bis[ω -methoxypoly(oxyethane-1,2-diyl)] sodium salt.

Chemistry Review Data Sheet

Chemical Structure



Where R is



and n is approximately 450.

Molecular Weight: Oligonucleaotide moiety: — (free acid) — (sodium salt)
: PEG-conjugated oligo: — (free acid), 50.0 Kilodalton (sodium salt)
Molecular Formula: $C_{284}H_{326}N_{105}O_{183}P_{28}F_{13}Na_{28}$ (salt form of oligo-moiety)
$C_{10}H_{17}N_2O_5(C_2H_4O)_n$ (polyethylene glycol portion, i.e. R above)
CAS # 222716-86-1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs (for the drug substance only):

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III	/		4	Adequate		
—	III	/		1	Adequate	12/13/04	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	56,503	Pegatanib Sodium, 0.3 mg Injection

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	12/13/04	Dr. Hossein Khorshidi
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Acceptable	12/13/04	James F. Brower
OPDRA			
EA			
Microbiology	Acceptable	12/3/04	Dr. Brian S. Riley

APPEARS THIS WAY
ON ORIGINAL

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From CMC standpoint, the drug substance section of this NDA application is recommended for Approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

NDA 21-756 was accepted as a Continuous Marketing Application (CMA), pilot 1-reviewable units for fast track products under PDUFA. Eyetech Pharmaceuticals has requested a priority review for this application.

A. Description of the Drug Substance(s)

Pegaptanib sodium is a pegylated modified ribonucleic acid (RNA) oligonucleotide (28-mer) developed for the treatment of age-related macular degeneration (AMD). The chemically modified sugars confer stability against nuclease degradation and the covalently attached PEG moiety increases the residence time of the molecule in the vitreous. The drug substance binds specifically to vascular endothelial growth factor ($VEGF_{165}$), inducing the inhibition of angiogenesis. Pegaptanib sodium is

The drug substance

Characterization and proof of structure has been accomplish using several

and methods, including:

. The impurity profile consists of

impurities. A is used for manufacturing of this drug substance. The manufacturing process consists of ; substance is in form of . Several in-process tests and controls are included. The critical in-process controls are identified as:

. The drug substance specification include the following test attributes:

— .. Based on CMC recommendation, the proposed acceptance criteria for the following test attributes were revised: — Pegaptabib sodium is stored in — — . The status of all referenced DMFs are adequate. The stability program and testing have been performed according to ICH guidelines. The primary stability batches (— , were studied through — , at –20°C (± 5°C), recommended storage conditions, and 5 °C (± 3 °C), accelerated storage conditions. In addition, up to — s of stability data on — batches stored at recommended and accelerated storage conditions are also submitted. The submitted stability data support the proposed — of retest period for this drug substance when stored at -20 °C (± 5 °C) and —.

B. Description of How the Drug Product is Intended to Be Used

Refer to the Drug Product review section by Dr. Libaniel Rodriguez, HFD-550.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission has provided adequate information on the chemistry, manufacturing and controls for the manufacturing of the drug substance, Pegaptanib Sodium. The characterization and proof of structure have been established. Adequate in-process controls are placed through the manufacturing process. The drug substance specification and proposed acceptance criteria are acceptable and adequately control the quality of the final drug substance.

III. Adminstrative

A. Reviewer's Signature

Hossein S. Khorshidi, Ph.D. (signed electronically in DFS).

B. Endorsement Block

Linda Ng, Ph.D./Chemistry Team Leader (singed electronically in DFS).

56 Page(s) Withheld

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/s/

Hossein Khorshidih
12/14/04 03:07:25 PM
CHEMIST

Linda Ng
12/15/04 09:55:56 AM
CHEMIST
This is the drug substance review of the NDA

NDA 21-756

Macugen (pegaptanib sodium injection) 0.3 mg/90 (market product) and 1.0 mg/90 μL (currently not intended for marketing)

Chemistry Review 2

EYETECH Pharmaceuticals

Libaniel Rodriguez, Ph.D.
Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

HFD-550

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-756

2. REVIEW #: 2

3. REVIEW DATE: 17-DEC-2004

4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	17-JUN-2004
BC	10-SEP-2004
BC	20-SEP-2004
BC	05-OCT-2004
BZ	07-OCT-2004
BZ	15-OCT-2004
BC	29-OCT-2004
C	10-NOV-2004
BC	12-NOV-2004
BC	19-NOV-2004
BC	23-NOV-2004
BC	01-DEC-2004
C	06-DEC-2004
BL	08-DEC-2004
BL	10-DEC-2004
BC	10-DEC-2004
BZ	10-DEC-2004
BC	13-DEC-2004
BC	14-DEC-2004

6. SUBMISSION(S) BEING REVIEWED: (Drug Product Sections Only)

Submission(s) Reviewed	Document Date
Subject of this review	
BL	16-DEC-2004

7. NAME & ADDRESS OF APPLICANT:

Name: EYETECH Pharmaceuticals

Address: 3 Times Square, 12th Floor, New York, NY 10036

Representative: Loni da Silva
Vice-President Global Regulatory Affairs

Telephone: 212 824 3166

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: MACUGEN
b) Non-Proprietary Name (USAN): pegaptanib sodium
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: VEGF Inhibitor

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.3 mg – mg based on oligonucleotide weight per 90 µL

13. ROUTE OF ADMINISTRATION: Intravitreal injection. One injection every six weeks for at least one year

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

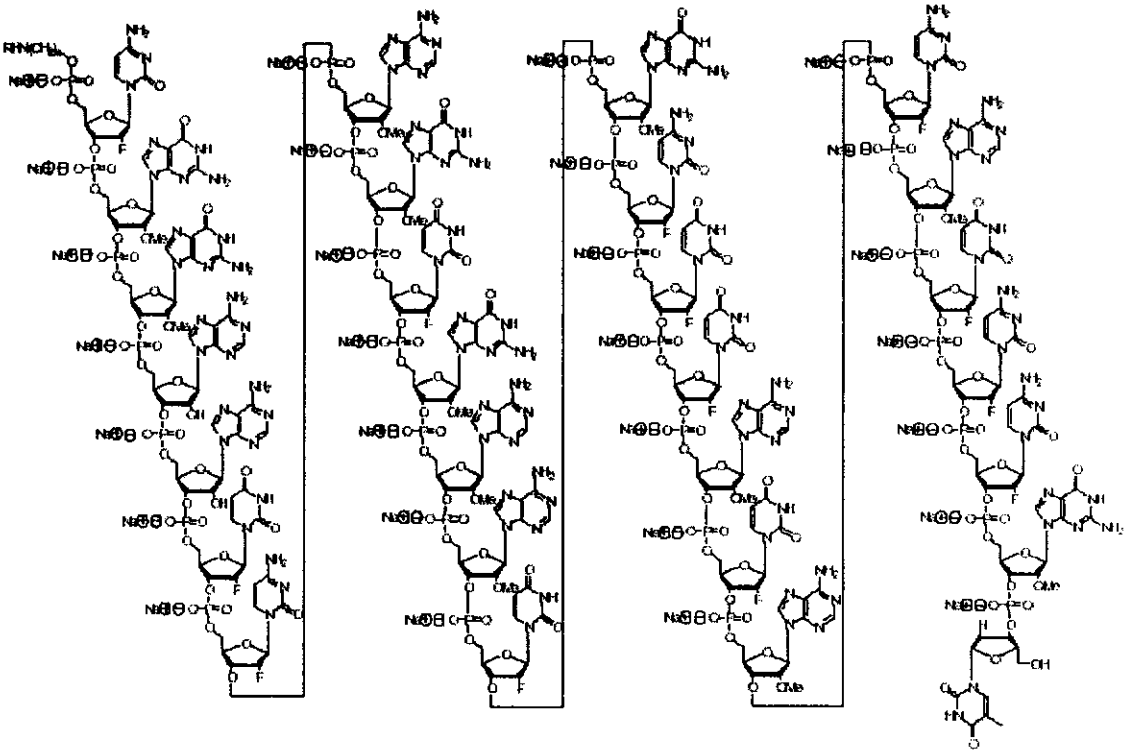
___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

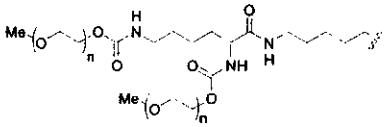
RNA, ((2'-deoxy-2'-fluoro)C-Gm-Gm-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-Am-

Gm-(2'-deoxy-2'-fluoro)U-Gm-Am-Am-(2'-deoxy-2'-fluoro)U-Gm-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-fluoro)U-Am-(2'-deoxy-2'-fluoro)U-Am-(2'-deoxy-2'-fluoro)C-Am-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-Gm-(3'→3')-dT, 5'-ester with α,α'-[4,12-dioxo-6-[[5-(phosphoonoxy)pentyl]amino]carbonyl]-3,13-dioxa-5,11-diaza-1,15-pentadecanediyl]bis[ϖ-methoxypoly{oxy-1,2-ethanediyl), sodium salt.

Chemical Structure



Where R is



and n is approximately 450.

The molecular formula for pegaptanib sodium is $C_{294}H_{342}F_{13}N_{107}Na_{28}O_{188}P_{28}[C_2H_4O]_n$ (where n is approximately 900) and the molecular weight is approximately 50 kilodaltons.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	7			Sufficient information in related DMFs below
[redacted]	III	[redacted]	[redacted]	7			Sufficient information in related DMFs below
[redacted]	III	[redacted]	[redacted]	1		24-SEP-2004	acceptable
[redacted]	III	[redacted]	[redacted]	1		18-OCT-2004	Acceptable

1 Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	56,503	

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	13-DEC-2004	O.C.
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Acceptable	13-DEC-2004	James F. Brower
OPDRA			
EA			
Microbiology	approval	03-DEC-2004	Bryan S. Riley

The Chemistry Review for NDA 21-756

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product section of this application is recommended for an **Approvable** Action.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

In the amendments of November10 and December 9, 2004, EyeTech made a commitment to provide [redacted] drug product prior to marketing. However, at this time there is no sterility data or a proposal to validate the sterilization process to verify that the [redacted]

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Macugen drug product is a sterile aqueous solution containing pegaptanib sodium for intravitreous injection. The product is supplied in single-dose pre-filled 1 mL capacityglass syringes sealed with a [redacted] rubber plunger [redacted] The syringe has a fixed 27 gauge needle with a gray rubber needle shield and a [redacted] rigid outer shield. The syringe is packed in a foil pouch. Another sealed foil pouch holds a polystyrene plunger and a white [redacted] flange. Both pouches are packaged in a carton.

Macugen is formulated as a 3.47 mg/mL solution to deliver 0.3 mg of the oligonucleotide pegaptanib free acid [redacted] [redacted] The volume for delivering [redacted] is 90 µL.

[redacted] the 0.3 mg/90µL will be commercially marketed when approved.

Description of the Drug Substance(s)

Pegaptanib sodium is a pegylated modified ribonucleic acid (RNA) oligonucleotide (28-mer) developed for the treatment of age-related macular degeneration (AMD). The

chemically modified sugars confer stability against nuclease degradation and the covalently attached PEG moiety increases the residence time of the molecule in the vitreous. The drug substance binds specifically to vascular endothelial growth factor ($VEGF_{165}$), inducing the inhibition of angiogenesis. Pegaptanib sodium is — — . The drug substance — Characterization and proof of structure has been accomplish using several — and — methods, including: —

. The impurity profile consists of — impurities. A — is used for manufacturing of this drug substance. The manufacturing process consists of and the final drug substance is in form of — . Several in-process tests and controls are included. The critical in-process controls are identified as: —

The drug substance specification include the following test attributes: —

. Based on CMC recommendation, the proposed acceptance criteria for the following test attributes were revised:

Pegaptabib sodium is stored in —

The status of all referenced DMFs are adequate. The stability program and testing have been performed according to ICH guidelines. The primary stability batches — were studied through — at -20°C (± 5°C), recommended storage conditions, and 5 °C (± 3 °C), accelerated storage conditions. In addition, up to — of stability data on 3 supportive batches stored at recommended and accelerated storage conditions are also submitted. The submitted stability data support the proposed — of retest period for this drug substance when stored at -20 °C (± 5 °C) and —

B. Description of How the Drug Product is Intended to be Used

The Macugen pre-filled syringes contain 90 — of the drug product. The intention is to deliver a minimum volume of 90 µL intravitreally in an aseptic environment. The plunger must be carefully screwed into the rubber stopper prior to injection. The 0.3 mg marketed dosage form is to be injected in patients with exudative age related macular degeneration every 6 weeks for a period of 54 weeks.

The expiration period of the 0.3 mg/90µL Macugen drug product is 15 months when stored at 2°C to 8°C.

C. Basis for Approvability or Not-Approval Recommendation

No data or validated sterilization process are available to verify the . Details are described in pages 41 and 42 of the chemistry review 1B dated December 8, 2004.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Libaniel Rodriguez, Ph.D. HFD-550/830/17-DEC-2004
ChemistryTeamLeader: Linda Ng, Ph.D. HFD-550/830/17-DEC-2004
ProjectManager: Puglisi Mike HFD-550/17-DEC-2004

C. CC Block

NDA 21756
Wiley Chambers, MD. HFD-550/17-DEC-2004
Lin David. Ph.D. HFD-830/17-DEC-2004

1 Page(s) Withheld

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/s/

Libaniel Rodriguez
12/17/04 01:10:23 PM
CHEMIST
Review #2 drug product section, labeling

Linda Ng
12/17/04 01:51:39 PM
CHEMIST

NDA 21-756

Macugen (pegaptanib sodium injection) 0.3 [illegible] g/90 µL

Chemistry Review 1B

EYETECH Pharmaceuticals

Libaniel Rodriguez, Ph.D.
Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

HFD-550

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-756

2. REVIEW #: 1B

3. REVIEW DATE: 08-DEC-2004

4. REVIEWER: Libaniel Rodriguez

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
	17-MAR-2004
IC	06-APR-2004

6. SUBMISSION(S) BEING REVIEWED: (Drug Product Sections Only)

Submission(s) Reviewed	Document Date
Original NDA	17-JUN-2004
BC	10-SEP-2004
BC	20-SEP-2004
BC	05-OCT-2004
BZ	07-OCT-2004
BZ	15-OCT-2004
BC	29-OCT-2004
C	10-NOV-2004
BC	12-NOV-2004
BC	19-NOV-2004
BC	23-NOV-2004
BC	01-DEC-2004
C	06-DEC-2004
BL	08-DEC-2004
BL	10-DEC-2004
BC	10-DEC-2004
BZ	10-DEC-2004
BC	13-DEC-2004
BC	14-DEC-2004

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: EYETECH Pharmaceuticals

Address: 3 Times Square, 12th Floor, New York, NY 10036

Representative: Loni da Silva
Vice-President Global Regulatory Affairs

Telephone: 212 824 3166

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: MACUGEN
b) Non-Proprietary Name (USAN): pegaptanib sodium
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: VEGF Inhibitor

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 0.3 mg – based on oligonucleotide weight per 90 µL

13. ROUTE OF ADMINISTRATION: Intravitreal injection. One injection every six weeks for at least one year

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
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16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-Gm-(3'→3')-dT, 5'-ester with α,α'-[4,12-dioxo-6-[[5-(phosphoonoxy)pentyl]amino]carbonyl]-3,13-dioxa-5,11-diaza-1,15-pentadecanediyl]bis[ϖ-methoxypoly{oxy-1,2-ethanediyl), sodium salt.

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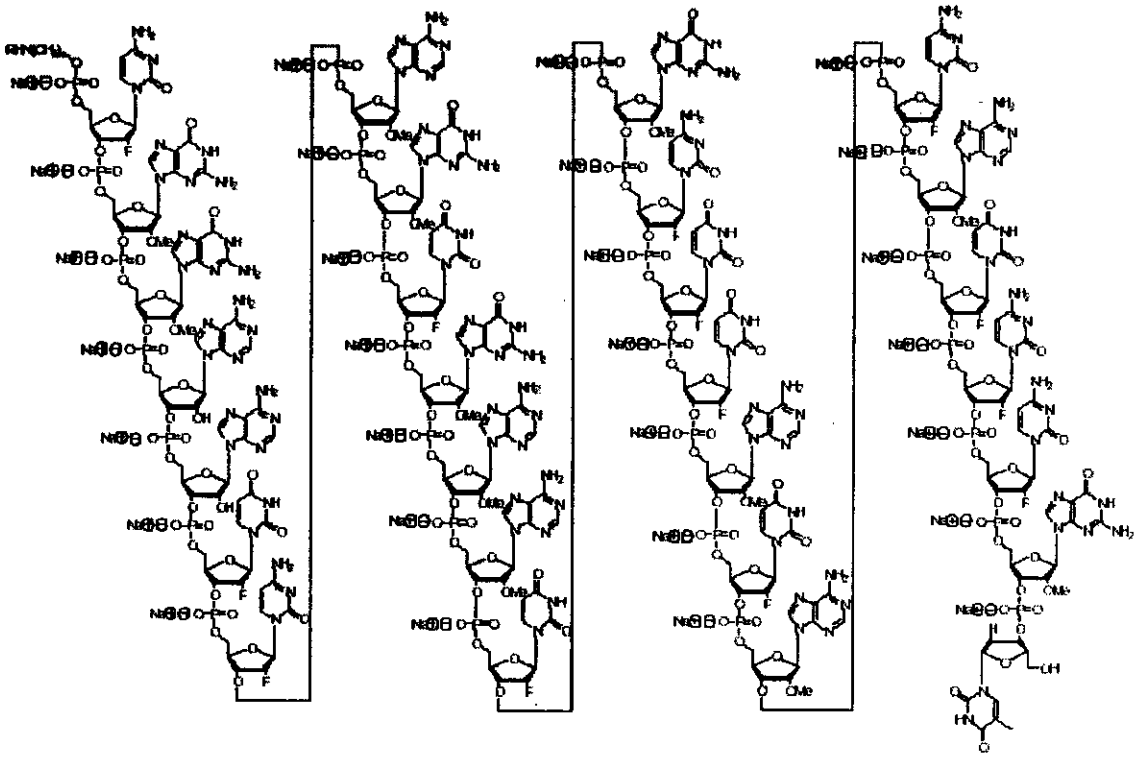

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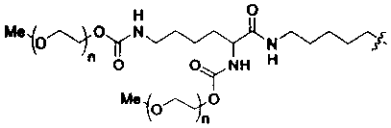

and n is approximately 450.

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	II			7			Sufficient information in related DMFs below
	III			7			Sufficient information in related DMFs below
	III			1		24-SEP-2004	acceptable
	III			1		18-OCT-2004	Acceptable

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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	56,503	

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	13-DEC-2004	O.C.
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Acceptable	13-DEC-2004	James F. Brower
OPDRA			
EA			
Microbiology	approval	03-DEC-2004	Bryan S. Riley

Chemistry Assessment Section

The Chemistry Review for NDA 21-756

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product section of this application is recommended for an **Approvable** Action.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

In the amendments of November10 and December 9, 2004, EyeTech made a commitment to provide a — drug product prior to marketing. However, at this time there is no — . or a proposal to —

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

See chemistry review 1A for the drug substance section.

Macugen drug product is a sterile aqueous solution containing pegaptanib sodium for intravitreous injection. The product is supplied in single-dose pre-filled 1 mL capacityglass syringes sealed with a — rubber plunger — The syringe has a fixed 27 gauge needle with a gray rubber needle shield and a — rigid outer shield. The syringe is packed in a foil pouch. Another sealed foil pouch holds a polystyrene plunger and a white — flange. Both pouches are packaged in a carton.

Macugen is formulated as a 3.47 mg/mL solution to deliver 0.3 mg of the oligonucleotide pegaptanib free acid —
— . The volume for delivering — is 90 µL.

— the 0.3 mg/90µL will be commercially marketed when approved.

B. Description of How the Drug Product is Intended to be Used

The Macugen pre-filled syringes contain 90 — µL of the drug product. The intention is to deliver a minimum volume of 90 µL intravitreally in an aseptic environment. The plunger must be carefully screwed into the rubber stopper prior to injection. The 0.3 mg marketed dosage form is to be injected in patients with exudative age related macular degeneration every 6 weeks for a period of 54 weeks.

The expiration period of the 0.3 mg/90µL Macugen drug product is 15 months when stored at 2°C to 8°C.

C. Basis for Approvability or Not-Approval Recommendation

No data or validated sterilization process are available to verify the — — . Details are described in pages 41 and 42 of this review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist: Libaniel Rodriguez, Ph.D. HFD-550/830/14-DEC-2004
ChemistryTeamLeader: Linda Ng, Ph.D. HFD-550/830/14-DEC-2004
ProjectManager: Puglisi Mike HFD-550/14-DEC-2004

C. CC Block

NDA 21756
Wiley Chambers, MD. HFD-550/14-DEC-2004
Lin David. Ph.D. HFD-830/14-DEC-2004

46 Page(s) Withheld

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

/s/

Libaniel Rodriguez
12/15/04 09:37:12 AM
CHEMIST
Macugen drug product NDA section review, approvable

Linda Ng
12/15/04 10:06:22 AM
CHEMIST
This is the drug product review of the NDA