CENTER FOR DRUG EVALUATION AND RESEARCH

75-412

APPLICATION NUMBER:

CORRESPONDENCE

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

August 03, 2000

Ms. Elaine Hu, Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Hu:

Re: MINOR AMENDMENT
Timolol Maleate Ophthalmic Solution USP 0.5%, ANDA No. 75-412

Further to your Minor Amendment letter dated July 10, 2000, we are pleased to provide you with our response in triplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2. A signed Field Copy Certification has been included in Attachment No. 3.

The DMF deficient. The DMF holder has been notified. Please do not respond to this amendment until you have been notified by the DMF holder that the DMF deficiencies have been addressed.

Response: Our supplier has informed us that the DMF holder, , has submitted their response to the DMF deficiencies.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Manager, Regulatory Affairs

DC/cl

Encl.

2 1

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

April 14, 2000

75-412

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

ORIG AMEN

N/AF

LABELING AMENDMENT

RE: ANDA 75-411 and ANDA 75-412
Timolol Maleate Ophthalmic Solution USP,
0.25% and 0.5%

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma of Ontario, Canada, is hereby forwarding a response to the telephone call on April 06, 2000 between Marcy Macdonald of Apotex Corp. and Lily Golson, OGD FDA. An original and a duplicate are being submitted.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:
75-412 (0.5% base)

Date of Submission:
March 31, 2000 (Amendment)

Applicant's Name: Novex Pharma

Established Name: Timolol Maleate Ophthalmic Solution, USP

Labeling Deficiencies:

CONTAINER (10 mL and 15 mL)

In order to assure that the requirements of section 502(c) and 21 CFR 201.15 are met, final printed labeling must be of actual size, color, and clarity. The submitted container labels fail to meet these requirements.

Please revise your labels, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor following web site for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed labeling with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x		
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			

Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Labeling review based on the reference listed drug, (Timoptic™ - Merck & Co., Inc.; approved March 18,1998).

2. Packaging
The RLD packages its product in white, opaque, plastic hthalmic dispensers with controlled drop tips in 2.5 mL, 5 mL, 10 mL, and 15 mL. The 0.25% product has blue caps. The 0.5% product has yellow caps.

The applicant proposes to package its products in 10 mL and 15 mL white, , opaque bottles with white, opaque ophthalmic caps with sealing tape. The opacity of the bottles should adequately protect the product from light.

3. Labeling
Firm has been asked to re-submit container labels because they do not appear clear.

4. **Inactive Ingredients**
There does not appear to be a discrepancy in the listing of inactives between the DESCRIPTION section of the insert labeling and the Components and Composition Statements.

5. **USP Issues**
USP - Preserve in tight, light-resistant containers.
RLD - Store at RT, 15-30°C (59-86°F). Protect from freezing. Protect from light.
ANDA - same as RLD.

6. **Bioequivalence Issues - Waiver granted 10/19/98.**

7. **Microbiology Issues - pending**

8. **Patent/Exclusivity Issues - None pending**

9. **Firm will be telephoned with comments.**

Date of Review:
April 6, 2000

Date of Submission:
March 31, 2000 (Amendment)

Primary Reviewer:
[signature]

Date:
4/6/00

Team Leader:
[signature]

Date:
4/7/2000

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cc:

75411na4.l and 75412na4.l

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

March 31, 2000

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

AF
ANDA AMENDMENT

LABELING AMENDMENT

RE: ANDA 75-411 and ANDA 75-412
Timolol Maleate Ophthalmic Solution USP 0.25% and 0.5%

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma of Ontario, Canada, is hereby forwarding a response to the telephone call on March 28, 2000. An original and a duplicate are being submitted.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
APR 0 3 2000
OGD

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-411 (0.25% base)
75-412 (0.5% base)

Date of Submission:
March 6, 2000 (Amendment)
10

Applicant's Name: Novex Pharma

Established Name: Timolol Maleate Ophthalmic Solution, USP

Labeling Deficiencies:

CONTAINER (10 mL and 15 mL)

Revise to submit only the label depicting the "true size". Delete the 200% representation.

Please revise your labels, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor following web site for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed labeling with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		x	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	x		
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x

Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	x		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. Labeling review based on the reference listed drug, (Timoptic™ - Merck & Co., Inc.; approved March 18,1998).

2. Packaging
The RLD packages its product in white, opaque, plastic ophthalmic dispensers with controlled drop tips in 2.5 mL, 5 mL, 10 mL, and 15 mL. The 0.25% product has blue caps. The 0.5% product has yellow caps.

The applicant proposes to package its products in 10 mL and 15 mL white , opaque bottles with white, opaque ophthalmic caps with sealing tape. The opacity of the bottles should adequately protect the product from light.

3. Labeling
Firm has been asked to re-submit because included a 200% depiction on the same page as the printer's proof which is not FOlable.

4. **Inactive Ingredients**
There does not appear to be a discrepancy in the listing of inactives between the DESCRIPTION section of the insert labeling and the Components and Composition Statements.

5. **USP Issues**
USP - Preserve in tight, light-resistant containers.
RLD - Store at RT, 15-30°C (59-86°F). Protect from freezing. Protect from light.
ANDA - same as RLD.

6. **Bioequivalence Issues - Waiver granted 10/19/98.**

7. **Microbiology Issues - pending**

8. **Patent/Exclusivity Issues - None pending**

9. **Firm will be telephoned with comments.**

Date of Review:
March 27, 2000

Date of Submission:
March 16, 2000 (Amendment)

Primary Reviewer:

Date:
3/27/00

Team Leader:

Date:

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cc:

ɔ cc)
REV\75411na3.l and 75412na3.l

APOTEX CORP.

50 LAKEVIEW PARKWAY • SUITE 127 • VERNON HILLS • ILLINOIS 60061 • TEL: (847) 573-9999 • FAX: (847) 573-1001

March 16, 2000

NDA ORIG AMENDMENT
N/AM

Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
7500 Standish Place
Rockville, MD 20855

MINOR AMENDMENT AND
RESPONSE TO MICROBIOLOGY DEFICIENCIES

RE: ANDA 75-412
Timolol Maleate Ophthalmic Solution USP 0.5%

To Whom It May Concern:

Apotex Corp., as the U.S. agent for Novex Pharma of Ontario, Canada, is hereby forwarding a response to the deficiency letter dated February 10, 2000. An original, a duplicate and a field copy are being submitted.

If you have any further questions, please do not hesitate to contact me.

Sincerely,

Marcy Macdonald

Marcy Macdonald
Associate Director
Regulatory Affairs
Ext. 223

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 20 2000
OGD

NDA 75-412

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

March 15, 2000

Ms. Elaine Hu, Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Ms. Hu:

Re: MINOR AMENDMENT and
RESPONSE TO MICROBIOLOGY DEFICIENCIES
Timolol Maleate Ophthalmic Solution USP 0.5%, ANDA No. 75-412

Further to your Minor Amendment and Microbiology Deficiencies letters dated February 10, 2000, we are pleased to provide you with our responses in triplicate (Archival, Review and Field copies). For ease of review, we have enclosed a copy of your letters as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2. A signed Field Copy Certification has been included in Attachment No. 3.

Please note, the twelve (12) sets of printer's proofs for the final printed labels and labeling required for this amendment have been included in the Archival copy. For ease of review, one (1) additional set of proofs has been provided in each of the Review and Field copies.

CHEMISTRY

A. Deficiencies:

1) Please revise your drug substance specifications to include limits and specifications for organic volatile impurities according to USP 24.

Response: As requested, we have revised our raw material specifications regarding the organic volatile impurities In addition, the limit for has been revised as per the ICH guideline for residual solvents.

Please note that we have also revised the Specific and adopted the specifications as per USP.

The revised raw material specifications have been enclosed in Attachment No. 4.

2) *DMF is deficient. The DMF holder has been notified. Please do not respond to this amendment until you have been notified by the DMF holder that the DMF deficiencies have been addressed.*

Response: On February 22, 2000, Novex Pharma was notified by the supplier that the DMF deficiencies have been addressed by the DMF holder.

MICROBIOLOGY DEFICIENCIES:

1) *A specification for , bioburden must be set.*

Response: Based on the historic data, the limit has been set at In fact, the limit has been recently changed from .

The solution bioburden is tested and monitored by using in accordance with our Microbiology A copy of Exhibit A from this method has been enclosed in Attachment No. 5.

LABELING DEFICIENCIES:

1) *CONTAINER (10 mL and 15 mL)*
Increase the prominence/conspicuousness of the established name on labels. Refer to 21 CFR 201.15 and section 502(c) of the Act for guidance.

2) *CARTON (10 mL and 15 mL)*
See CONTAINER comment.

3) *INSERT*
   a) *PRECAUTIONS (Drug Interactions - Quinidine)*
   Revise to "CYP2D6" rather than "CYP206".
   b) *OVERDOSAGE*
   The following should appear as the third paragraph:
   Significant lethality was observed in female rats and female mice after a single dose of 900 and 1190 mg/kg (5310 and 3570 mg/m^2) of timolol, respectively.

Please revise your labels and labeling, as instructed above, and submit in final print.

Response: As requested, our labels and labeling have been revised as instructed above and 12 sets of printer's proofs for the final printed labels and labeling have been included in Attachment No. 7. We trust that this will be acceptable for final review of our labeling for this product and hereby confirm that the printer's proofs provided are a true

.../cont'd

representation of the final printed labels and labeling. In the event that there are any changes to the proofs prior to approval, Novex Pharma will notify the Agency, as necessary.

Please note that the third paragraph in the OVERDOSAGE section was not added to our insert, as indicated above. As discussed in a telephone conversation between Marcy Macdonald, Associate Director of Regulatory Affairs at Apotex Corp., and Lily Golson, the labeling reviewer for Timolol Maleate Ophthalmic Solution USP, the above comment was an oversight. Ms. Golson had not referred to the NDA labeling approval letter for Timoptic® (dated March 18, 1998) which recommended the deletion of the third paragraph. A copy of this letter was provided in the OGD Major Amendment letter issued to Novex Pharma on December 30, 1998.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following web site for any approved changes -

http:/www.fda.gov/cder/ogd/rld/labeling_review_branch.html

Response: Novex Pharma acknowledges that, prior to approval, it may be necessary to further revise our labeling subsequent to approved changes for the reference listed drug.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the enclosed labeling with all differences annotated and explained.

Response: As requested, and in accordance with 21 CFR 314.94 (a)(8)(iv), a side-by-side comparison of our proposed labeling from our last submission with the enclosed labeling, with all differences annotated and explained, has been enclosed in Attachment No. 6.

However, please note that only the 10 mL package size has been highlighted in the side-by-side comparisons of the bottles and cartons since identical changes were made to the 15 mL size.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 508-2562, or FAX your requests to (905) 884-0357.

Yours sincerely,

for Dawn Culp, B.Sc.
Manager, Regulatory Affairs

DC/cl

Encl.

DEC 30 1998

38. Chemistry Comments to be provided to the Applicant:

ANDA: 75-412 APPLICANT: Novex Pharma

DRUG PRODUCT: Timolol Maleate Ophthalmic Solution USP, 0.5%

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please explain what you mean by "report (for information only)" for assay and for Timolol assay specification on p. 699.

2. Please revise your specifications for the drug product to include test, procedure and acceptance limits for impurities and degradation products.

3. Please provide acceptance limits for the total unknown impurities for the drug substance.

4. Please provide the specific results on the USP reference standard using the British Pharmacopeial method.

5. Please provide in-process acceptance limits for density of the drug product.

6. Please revise your specifications for finished drug product to include quantitative color test (e.g., AphA).

7. Please revise your stability specifications to include a quantitative color test, and osmolality.

8. Please provide stability test and acceptance limits for seal integrity.

9. Please provide limits for total unknown and known degradation products for the stability specifications.

10. Please provide a description for the cycling stability study conditions.

11. Please include specification and results for individual impurity in your accelerated stability report for the mL size.

12. DMF is deficient. The DMF holder has been notified.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your application regarding the manufacturing and testing the drug should be in compliance with CGMPs at the time of the approval.

2. USP methods are the regulatory methods and will prevail in the event of dispute.

3. Your microbiological section is under review.

Sincerely yours,

Patel

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 75-412 APPLICANT: Apotex Corp., for Novex Pharma
DRUG PRODUCT: Timolol Maleate Ophthalmic Solution, USP
0.50%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These Comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

D/ P. Schwartz

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 75-412 APPLICANT: Apotex Corp., for Novex Pharma
DRUG PRODUCT: Timolol Maleate Ophthalmic Solution, USP 0.50%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These Comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOVEX PHARMA

380 Elgin Mills Road East
Richmond Hill, Ontario
L4C 5H2

Telephone 905 884-2050
Facsimile 905 884-9876

July 22, 1999

Mr. Joseph Buccine
Project Manager
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Buccine:

Re: Solicited and Unsolicited Information Submission for Timolol Maleate Ophthalmic Solution USP 0.5 %, Major Amendment, ANDA #75-412

Further to your Major Amendment letter dated December 30, 1998, we are pleased to provide you with our responses in duplicate. For ease of review, we have enclosed a copy of your letter as Attachment No. 1 of this amendment and prepared our responses in a question-and-answer format. An Application Form FDA 356h for this response has been prepared and is enclosed as Attachment No. 2. A signed Field Copy Certification has been included in Attachment No. 3.

CHEMISTRY

Page(s) 3

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

7/22/99

2) *USP methods are the regulatory methods and will prevail in the event of dispute.*

Response: Novex Pharma acknowledges that the USP methods are the regulatory methods and that they will prevail in the event of a dispute.

3) *Your microbiological section is under review.*

Response: Novex Pharma acknowledges that our microbiological section is under review.

LABELING DEFICIENCIES:

1) *CONTAINER (10 mL and 15 mL)*

   a) *We encourage the use of boxing, contrasting colors, or other means to differentiate the strengths of this product.*

   b) *We encourage you to place the "Rx only" statement prominently on the principal display panel.*

   c) *Reverse the order of your storage temperature range so that Celsius precedes Fahrenheit.*

2) *CARTON (10 mL and 15 mL)*

   a) *See CONTAINER comments (a) and (c).*

   b) *Revise the listing of inactive ingredients to identify benzalkonium chloride as a preservative. Refer to the innovator labeling for guidance.*

3) *INSERT*

   a) *GENERAL COMMENT*

   The insert labeling you submitted is based on 1995 labeling for the reference listed drug. However, please revise your labeling to be in accord with the most currently approved labeling for the reference listed drug (Timoptic® Sterile Ophthalmic Solution - Merck & Co., Inc.; approved March 18, 1998), that is mocked-up and enclosed for your convenience.

   Additionally,

   b) *Revise to delete use of the terminal zero (e.g., "5 mg" rather than "5.0 mg").*

   c) *See CONTAINER comment (c).*

.../cont'd

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Response: As requested, our labels and labeling have been revised as instructed above, as well as updated to our current standard format. They are submitted in final print (12 samples) in Attachment No. 10.

However, please note that for the carton labeling only the 10 mL package size has been submitted in final print. Since the text (except for the information that is pertinent to package size), color and dimensions for the 15 mL size is identical to that of the 10 mL, colored copies of the final artwork have been provided for this carton label. Novex Pharma hereby confirms that this artwork is a true representation of the final printed carton labeling for the 15 mL package size and, therefore, we respectfully request that our approval will be granted based on the artwork. In the event that there are changes to the artwork prior to approval, Novex Pharma will notify the Agency of the changes, as necessary.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Response: Novex Pharma acknowledges that the Agency reserves the right to request further changes in our labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a) (8) (iv), please provide a side-by-side comparison of your proposed labeling with the enclosed labeling with all differences annotated and explained.

Response: As requested, and in accordance with 21 CFR 314.94 (a)(8)(iv), a side-by-side comparison of our proposed labeling with our last submission (bottle labels and carton labeling) and the enclosed labeling (inserts), with all differences annotated and explained, is enclosed in Attachment No. 11.

Should you require any further information, or have any questions or comments regarding the enclosed, please do not hesitate to contact me directly at (905) 884-2050, or FAX your requests to (905) 884-0357.

Yours sincerely,

Dawn Culp

Dawn Culp, B.Sc.
Manager, Regulatory Affairs

DC/cv
Encl.