

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
40277

CORRESPONDENCE

AKORN

February 7, 2000

NEW CORRESP .

NC

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MINOR AMENDMENT TO ANDA 40-277
Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5%
15 mL fill size in 15 cc container

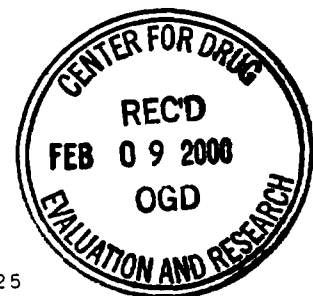
Dear Ladies and Gentlemen:

Akorn, Inc., a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits a Minor Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5%, a prescription ophthalmic drug product indicated for topical anesthesia in ophthalmic practice.

This amendment is in response to an FDA deficiency letter, dated January 27, 2000 (*see Attachment A*), requesting Akorn to provide a response to the deficiency as a *Minor Amendment*. Our response is as follows:

A. Deficiency:

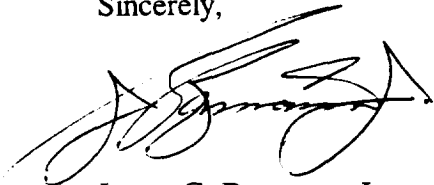
Akorn is filing an archival copy (*original*) of this amendment and a technical review copy (*duplicate*) which is identical to the archival copy. An additional certified copy was sent to the Chicago District Office.



In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Akorn, Inc. certifies that a true copy of this Minor Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5% has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this amendment as **Attachment B**.

Should additional information and/or clarification be required, please contact me at (217) 423-9715, or FAX (217) 423-5206.

Sincerely,

A handwritten signature in black ink, appearing to read 'James G. Baumann, Jr.', written in a cursive style.

James G. Baumann, Jr.
Manager, Regulatory Submissions

cc: Lou Fraser (Akorn, Inc.)



November 19, 1999

NEW CORRESP

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: TELEPHONE AMENDMENT TO ANDA 40-277
RESPONSE TO MICROBIOLOGY DEFICIENCIES
Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%
15 mL fill size in 15 cc container

Dear Ladies and Gentlemen:

Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits a Telephone Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%, a prescription ophthalmic drug product indicated for topical anesthesia in ophthalmic practice.

This amendment is in response to the FDA Deficiency Letter (Facsimile), dated October 8, 1999 (*see Attachment A*), listing microbiology comments regarding ANDA 40-277 and to the FDA teleconference of November 2, 1999, which involved a discussion/clarification of the microbiological deficiency letter of October 8. During the teleconference, Taylor was advised to provide its response to the micro deficiency as a "Telephone Amendment". Accordingly, Taylor is providing the following response to the deficiency item:

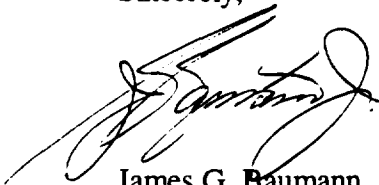
Microbiology Deficiencies:

Taylor is filing an archival copy consisting of one volume (original) of this amendment and a technical review copy (duplicate) which is identical to the archival copy. An additional certified copy was sent to the Chicago District Office.

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Taylor Pharmaceuticals certifies that a true copy of this Telephone Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%, has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this amendment as *Attachment C*.

Should additional information and/or clarification be required, please contact me at (217) 423-9715, or FAX (217) 423-5206.

Sincerely,



James G. Baumann, Jr.
Manager, Regulatory Submissions

cc: Lou Fraser (Taylor Pharmaceuticals)



RECEIVED

June 23, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: AMENDMENT TO ANDA 40-277
Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5%
15 mL fill size in 15 cc container

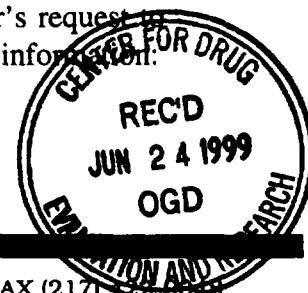
Dear Ladies and Gentlemen:

Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits an Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5%, a prescription ophthalmic drug product indicated for topical anesthesia in ophthalmic practice. The RLD is Ophthaine[®], NDA 08-883, approved on July 1, 1953, and is owned by Apothecon.

This amendment is in response to a telephone conversation held on Wednesday, **June 16, 1999**, between James Baumann (Taylor Pharmaceuticals) and Joe Buccine (FDA), in which Taylor Pharmaceuticals was notified that (an outside contract testing facility) is noncompliant per FDA assessment. Taylor is proposing to *withdraw* as an outside contract testing facility for components and *use an alternate testing facility* was named in the original ANDA as a testing facility for the bottles, tips and caps. The following tests were performed on these components: (a) Elution Cytotoxicity Test, *USP <87>*; (b) Physio-Chemicals Test, *USP <661>*; and (c) Permeation Test, *USP <671>*.

will perform the same USP testing on the components as was performed by

As a result of the telephone conversation with FDA and in support of Taylor's request to use an alternate testing facility for components, we are providing the following information:



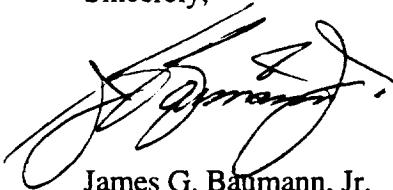
- An authorization letter (*see Attachment A*) from _____ to reference their DMF _____ on behalf of Taylor Pharmaceuticlas;
- A copy of the latest FDA inspection results (August 13 - 26, 1998) and response (*see Attachment B*);
- A copy of the FDA District letter acknowledging _____ compliance (*see Attachment C*).

Taylor is filing an archival copy consisting of one volume (*original*) of this amendment and a technical review copy (*duplicate*) which is identical to the archival copy. An additional certified copy was sent to the Chicago District Office.

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Taylor Pharmaceuticals certifies that a true copy of this Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5% has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this amendment as *Attachment D*.

Should additional information and/or clarification be required, please contact me or Jennifer Fairgrieve at (217) 423-9715, or FAX (217) 423-5206.

Sincerely,



James G. Baumann, Jr.
Manager, Regulatory Submissions



May 20, 1999

~~NEW CORRESP~~
NC to Fax

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: FACSIMILE AMENDMENT TO ANDA 40-277
Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%
15 mL fill size in 15 cc container

Dear Ladies and Gentlemen:

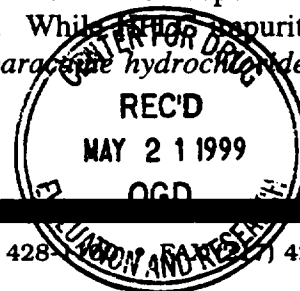
Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits a Facsimile Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%, a prescription ophthalmic drug product indicated for topical anesthesia in ophthalmic practice. The reference listed drug (RLD) is Ophthaine[®], NDA 08-883, approved on July 1, 1953, and is owned by Apothecon.

This amendment is in response to the FDA Deficiency Letter (Facsimile), dated May 10, 1999 (*see Attachment A*), listing deficiencies and/or comments regarding ANDA 40-277 and requesting Taylor to provide a complete response to these deficiencies as a "Facsimile Amendment". Accordingly, Taylor is providing the following responses to the deficiency items listed in the deficiency letter of May 10, 1999:

A. Deficiencies

- 1. Based on the actual data reported in Attachment E, the proposed limit of the individual impurity of not to exceed % is too high. Please tighten the specification of the individual impurity of the Proparacaine Hydrochloride USP drug substance.**

The proposed limit of % for an individual impurity was based on the Related Substances Specifications of the 1993 British Pharmacopoeia and is included in the manufacturers specifications. While impurity data has only been collected on one lot of proparacaine hydrochloride, a



historical review of the manufacturer's certificates of analysis indicates that impurity levels have been consistently low.

The Limit of Quantitation (LOQ) for the _____ impurities method has been determined to be _____ % of Label Claim (Reference Method Validation for Taylor SOP 094, in the original submission.) Therefore, Taylor would like to propose the following **revised specification of _____ %** for an individual impurity. A copy of the revised specification sheet is included as **Attachment B**.

2. **The manufacturing instruction, _____ of the revised master batch record, remains unchanged in the Attachment B. Your answer to the item #11 of the amendment of November 20, 1998 did not match the revised master batch record.**

Taylor has revised the formulation control pages of the master batch record to remove _____. The revised pages are included as **Attachment C**.

3. **You stated that those new stability specifications of the total and individual impurities are consistent with the data obtained from the model product Alcaine®. Please provide analytical data to support the statement.**

Taylor is providing the in-house stability report (*see Attachment D*) for Alcaine® (lot #2VLAE) containing the observed test results for both individual and total impurities at both LTT and RTT conditions. Inspection of these results reveals consistency with those results provided in the previous amendment, dated November 20, 1998 for the proposed drug product Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5%.

4. **The proposed limit NMT _____ % for potential degradants C and D appears to be less than the reported value in Attachment G of the amendment of November 20, 1998. In other words, the observed result is more than the proposed limit for the degradant C of the subject ophthalmic solution. Please explain.**

The value for degradant C for the 18 month long term testing stability point for lot 21196 was reported at % . A review of the raw data indicated that the peak in question had been incorrectly integrated. The data was reprocessed and the degradant value was recalculated to be % . A copy of the initial chromatogram showing the incorrect integration, a copy of the reprocessed chromatogram and revised stability report are include as *Attachment E*. Integration for the other degradation remained unchanged.

5. **Please provide information related to the sample storage orientation, for example, upright, inverted, or horizontal position in the stability report (ref. Attachment G).**

The sample storage orientation *has been added* to the 'Storage Condition' line of the stability reports. Revised copies of the stability reports for lots 21196, 21206, and 21216 at both LTT and RTT conditions are included as *Attachment F*.

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

1. **Since the reference listed drug is Ophthaine® (Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5%), all comparisons (for example, as mentioned above in the deficiency #3) should be made with it.**

Taylor notes and acknowledges that the referenced listed drug is Ophthaine® and that all comparisons *with the exception of stability* were made with Ophthaine. When stability comparisons are made, it is appropriate that formulations are similar. The Ophthaine formulation contains chlorobutanol as well as benzalkonium chloride whereas Taylor's proposed formulation contains only the benzalkonium chloride. Hence, the reason for the stability comparison of the Taylor product with a similar approved drug product (Alcaine®) which does not have chlorobutanol present in its formulation. Justification for the deletion of from the proposed Taylor formulation was previously stated in Section II Basis for ANDA Submission in the original application.

2. **The microbiology review is pending. Comments, if any, will be conveyed at a later date.**

Taylor notes and acknowledges that the microbiology review is pending.

3. **The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval.**

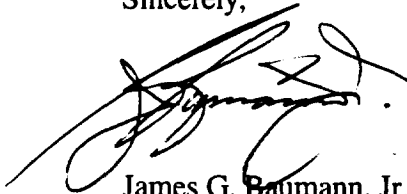
Taylor notes and acknowledges the firms referenced in our ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval.

Taylor is filing an archival copy consisting of one volume (original) of this amendment and a technical review copy (duplicate) which is identical to the archival copy. An additional certified copy was sent to the Chicago District Office.

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Taylor Pharmaceuticals certifies that a true copy of this Facsimile Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%, has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this amendment as *Attachment G*.

Should additional information and/or clarification be required, please contact me at (217) 423-9715, or FAX (217) 423-5206.

Sincerely,



James G. Baumann, Jr.
Manager, Regulatory Submissions

Taylor Pharmaceuticals an Akorn Co.

• generics • injectables • ophthalmics • contract services

November 20, 1998

Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MAJOR AMENDMENT
AC

RE: MAJOR AMENDMENT TO ANDA 40-277
Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%
15 mL fill size in 15 cc container

Dear Ladies and Gentlemen:

In accordance with 21 CFR § 314.96 (a)(3), and by reference § 314.60 (a), Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits a Major Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%, a prescription ophthalmic drug product indicated for topical anesthesia in ophthalmic practice. The reference listed drug (RLD) is Ophthaine[®], NDA 08-883, approved on July 1, 1953, and is owned by Apothecon.

This amendment is in response to the FDA Deficiency Letter (Facsimile), dated September 10, 1998 (*see Attachment A*), listing *major* deficiencies and/or comments regarding ANDA 40-277 and requesting Taylor to provide a complete response to these deficiencies as a "Major Amendment". Accordingly, Taylor is providing the following responses to the deficiency items listed in the deficiency letter of September 10, 1998:

A. Deficiencies

- 1. Please provide the revised master formula cards in addition to the updated finished product specifications with % overage of the proparacaine HCl in the Attachment C, and update the component and composition section.**

Per request, Taylor is providing a revised master batch record (*see Attachment B*), a copy of the updated finished product specifications (*see Attachment C*), and an updated component and composition section from the original application (*see Attachment D*). These revisions reflect the reduction from % overage which is sufficient to insure that the product will be released at near 100% of the labeled amount of proparacaine hydrochloride.

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NOV 25 1998

2. The result of impurity reported in Attachment B as "LT %" is unacceptable. The actual data (quantitative amount of individual impurity) observed should be reported.

The testing data report form has been amended to report the actual data observed and has been provided in *Attachment E*.

3. Your response to comment #6 in the major amendment dated March 16, 1998 is unsatisfactory. On page 373, the title, "Test for particulate matter in small volume injections" and Akorn batch No: was incorrect. The sample is Proparacaine Hydrochloride Ophthalmic Solution 0.5%, not a small volume injection. Please provide the instructions and the correct dosage form to match with the appropriate sample.

4. Your response to comment #8 in the major amendment dated March 16, 1998 is incomplete. Please provide the procedures for the visual determination of color in the Proparacaine Hydrochloride ophthalmic solution in comparison with APHA color standards.

As per request, Taylor is providing a copy (*see Attachment F*) of the procedures (SOP RD126) for the visual determination of color in the Proparacaine Hydrochloride Ophthalmic Solution in comparison with APHA color standards.

5. Stability data show that the Proparacaine HCl Ophthalmic Solution USP, 0.5% (lot 21206.LTT) fails to meet the specification of the appearance of the product for samples stored at 4-8°C for more than six months (p. 000689). Please explain.

The product is expected to have some yellowing but the subjective evaluations of color recorded in the stability data should not be considered a failure as the description of product appearance can vary from person to person. This is the reason for including the comparison to APHA color standards which provides for a color specification which is not ambiguous.

This test was included near the end of the stability program and is included in the stability data reports appearing in *Attachment G*.

6. **The specification for particulate matter of “essentially particle free” is inadequate. Currently, the Agency recommends that the specifications of the particulate matter for ophthalmic solutions be:**

NMT 50 particles / micrometers in diameter per mL
NMT 5 particles / micrometers in diameter per mL
NMT 2 particles / micrometers in diameter per mL

Please specify the analytical techniques to be used for the determination of particulate matter. Please also submit the analytical procedures.

Taylor will comply with the Agency's request and revise the finished product specifications for Proparacaine Hydrochloride Ophthalmic Solution USP, 0.5% to include the recommended particle specifications for ophthalmic solutions (*see Attachment C*). Taylor is also providing a copy (*see Attachment H*) of SOP ML184 entitled, “Microscopic Particulate Count Test” which is referenced on the revised finished product release specifications and will be employed to determine the particulate matter in a given set of filled units.

7. **Your response to comment #9 in the major amendment dated March 16, 1998 is unsatisfactory. The upper limit of benzalkonium chloride is % at the time of release. The upper limit of benzalkonium chloride of the stability specification is %. From a scientific point of view, the concentration of benzalkonium chloride in the ophthalmic solution should not be increased. Please explain why the concentration of benzalkonium chloride in your ophthalmic solution needs to exceed the original % labeled strength.**

The concentration of benzalkonium chloride on stability is not expected to increase significantly, although concentration may occur due to the small amount of expected evaporation of the product through the LDPE container. ✓ Moreover, it is prudent policy to tier the specifications at pre-fill and release in such a manner that allows for the expected variances in test values such that the shelf or regulatory specifications are assured not to be exceeded.

8. **Your response to comment #10 in the major amendment dated March 16, 1998 is unsatisfactory. The question was not for the purpose of the stress challenges. On page 629, the analytical data under thermal challenge shows that the subject ophthalmic solution is thermally stable.**

Yet, the analytical results of the room temperature stability samples (23° - 27°C) indicate that a significant loss of proparacaine HCl content is observed after 12 months storage. Please explain.

9. In Attachment D, the results of degradation products reported as “NMT %” are unacceptable. The amount of degradation products determined using _____ should be quantified and reported.

The stability reports in the above mentioned attachment have been revised to report the actual numerical values of the degradation products. These revised reports are included in *Attachment G*.

10. Please justify the limits of the total degradants (NMT %) and individual impurities (NMT %) for the product shelf life. Individual specifications NMT % for impurity C and D are too high. Full term (24 months) stability data and comparison with innovator’s product at expiry may be used to support your conclusion. We recommend different specifications for each individual impurity based on the actual data.

We have revised the specifications (*see Attachment C*) to reflect individual limits for the impurities expected or observed on stability. The proposed limit for total is %; the limit for 3-amino-4-propoxy benzoic acid is %; the limit for “degradant A” is % for potential degradants C and D. These limits are consistent with the observed stability data for the Taylor produced product and the data obtained from assay of the model product, Alcaine[®] at a stability time point corresponding to the labeled expiration date.

-
11. Your manufacturing instruction on page 243 of the application, says "If necessary, adjust the proparacaine hydrochloride, USP content of the solution." This practice is considered to be not acceptable. The proposed % overage of the active is intended to account for the manufacturing losses.

The manufacturing in question, involving the adjustment of proparacaine hydrochloride, USP content of the solution *has been deleted* and the revised master batch record reflecting this change has been provided in *Attachment B*.

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

1. The sterilization process including sterilization methods and testing procedures, and the preservative effectiveness testing are under microbiological review. After the review is completed, any deficiencies found will be communicated to you under a separate cover.

Taylor acknowledges that any microbiological deficiencies found will be communicated under separate cover at a later date.

Labeling Deficiencies:

Taylor Pharmaceuticals has revised the labeling as instructed in the deficiency letter, dated September 10, 1998 and is submitting representations of final printed copies of the labeling as follows:

1. **CONTAINER:** Twelve (12) representations of final printed container labels (Review Copy) and three (3) representations of final printed container labels (Archival Copy) are provided in *Attachment I*.
2. **CARTON:** Twelve (12) representations of final printed carton labels (Review Copy) and three (3) representations of final printed carton labels (Archival Copy) are provided in *Attachment J*.
3. **INSERT:** Twelve (12) representations of final printed package inserts (Review Copy) and three (3) representations of final printed package inserts (Archival Copy) are provided in *Attachment K*.

Taylor is also providing *in each of the above labeling attachments* a side-by-side comparison of the final printed labeling with the labeling provided in our last

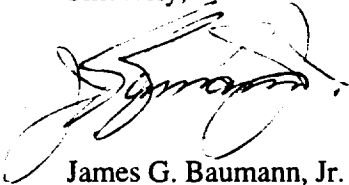
submission, dated September 10, 1998, with all the differences annotated and explained in accordance with 21 CFR § 314.94 (a)(8)(iv).

Taylor is filing an archival copy consisting of one volume (blue folder) of this amendment and a technical review copy (red folder) which is identical to the archival copy. An additional certified copy (maroon folder) was sent to the Chicago District Office.

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Taylor Pharmaceuticals certifies that a true copy of this Major Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%, has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this amendment as *Attachment L*.

Should additional information and/or clarification be required, please contact me at (217) 423-9715, or FAX (217) 423-5206.

Sincerely,

A handwritten signature in black ink, appearing to read "James G. Baumann, Jr.", written in a cursive style.

James G. Baumann, Jr.
Manager, Regulatory Submissions



September 7, 1999

NEW CORRESP
VC 4074

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**RE: FACSIMILE AMENDMENT TO ANDA 40-277
RESPONSE TO MICROBIOLOGY DEFICIENCIES
Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%
15 mL fill size in 15 cc container**

Dear Ladies and Gentlemen:

Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits a Facsimile Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%, a prescription ophthalmic drug product indicated for topical anesthesia in ophthalmic practice. The reference listed drug (RLD) is Ophthaine[®], NDA 08-883, approved on July 1, 1953, and is owned by Apothecon.

This amendment is in response to the FDA Deficiency Letter (Facsimile), dated August 10, 1999 (*see Attachment A*), listing microbiology comments regarding ANDA 40-277 and requesting Taylor to provide a complete response to these deficiencies as a "Facsimile Amendment". Accordingly, Taylor is providing the following response to the deficiency item listed in the deficiency letter of August 10, 1999:

Microbiology Deficiencies:

↓

Taylor agrees with the reviewer's observation that the actual formulation used when performing bacterial retention validation. Our bacterial retention validation procedures will be enhanced to include the preservative in the actual formulation.

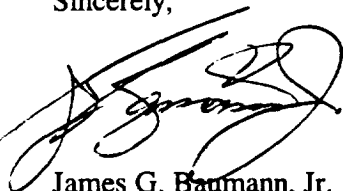


Taylor is filing an archival copy consisting of one volume (original) of this amendment and a technical review copy (duplicate) which is identical to the archival copy. An additional certified copy was sent to the Chicago District Office.

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Taylor Pharmaceuticals certifies that a true copy of this Facsimile Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%, has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this amendment as *Attachment B*.

Should additional information and/or clarification be required, please contact me at (217) 423-9715, or FAX (217) 423-5206.

Sincerely,



James G. Baumann, Jr.
Manager, Regulatory Submissions

cc: Lou Fraser (Taylor Pharmaceuticals)

Taylor Pharmaceuticals an Akorn Co.

• generics • injectables • ophthalmics • contract services

March 16, 1998

ORIG AMENDMENT

Office of Generic Drugs
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/A

RE: **MAJOR AMENDMENT TO ANDA 40-277**
Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%
15 mL fill size in 15 cc container

Dear Ladies and Gentlemen:

In accordance with 21 CFR § 314.96 (a)(3), and by reference § 314.60 (a), Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits a Major Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%, a prescription ophthalmic drug product indicated for topical anesthesia in ophthalmic practice. The reference listed drug (RLD) is Ophthaine[®], NDA 08-883, approved on July 1, 1953, and is owned by Apothecon. The suitability of the ANDA is documented in the submission.

This amendment is in response to the FDA Deficiency Letter (Facsimile), dated January 16, 1998 (*see Attachment A*), listing *major* deficiencies and/or comments regarding ANDA 40-277 and requesting Taylor to provide a complete response to these deficiencies as a "Major Amendment". Accordingly, Taylor is providing the following responses to the deficiency items listed in the deficiency letter of January 16, 1998:

A. **Deficiencies**

MAR 18 1998

Redacted

4

pages of trade

secret and/or

confidential

commercial

information

Labeling Deficiencies:

Taylor Pharmaceuticals has revised the labeling, as instructed in the deficiency letter, and is submitting comments/draft copies of the proposed labeling as follows:

1. **GENERAL COMMENTS:**

We find your proposed proprietary name objectionable. Our review has revealed several names which sound like or look like the proposed proprietary name:.....We believe these names and your proposed name are sufficiently similar to find your proposed name misleading as defined in 21 CFR 201.10 (c)(5).

Taylor has reviewed the FDA comments, together with currently available options regarding the proposed name for the finished drug product. We have decided to *withdraw the proposed proprietary name "AKTAINÉ"* and *replace it with the established name "Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%"*. The draft labeling presented in this section will reflect this name change.

2. **CONTAINER (15 mL):** With regard to comment #2.b., Taylor Pharmaceuticals manufactures all of our products utilizing Water for Injection. This is the only grade of water available in our formulation area, and therefore, all manufacturing records specify Water for Injection. However, all ophthalmic products are labeled to contain Purified Water as that is the grade of water required for ophthalmics. The quality of the Water for Injection exceeds the quality of Purified Water as defined in the USP.

We would prefer to utilize the term "Purified Water" on the labeling (to include the container label, carton, and insert) to remain consistent with our other ophthalmic drug products, as well as other ophthalmic drug products on the market.

In addition, the use of the term "Water for Injection" may be misleading as it could imply that the product could be injected.

Four (4) draft container labels (both Review Copy and Archival Copy) are provided in *Attachment E*.

3. **CARTON: (15 mL):** Four (4) draft carton labels (both Review Copy and Archival Copy) are provided in **Attachment F**.
4. **INSERT:** Four (4) draft package insert labels (both Review Copy and Archival Copy) are provided in **Attachment G**.

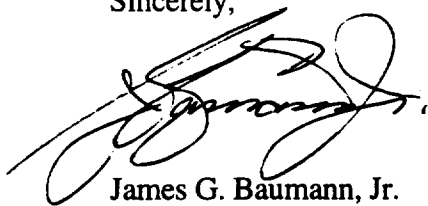
Taylor is also providing *in each of the above labeling attachments* a side-by-side comparison of the final printed labeling with the labeling provided in our last submission, dated September 11, 1997, with all the differences annotated and explained in accordance with 21 CFR § 314.94 (a)(8)(iv).

Taylor is filing an archival copy consisting of one volume (blue folder) of this amendment and a technical review copy (red folder) which is identical to the archival copy. An additional certified copy (maroon folder) was sent to the Chicago District Office.

In accordance with 21 CFR § 314.96 (b), and by reference 314.60 (c), Taylor Pharmaceuticals certifies that a true copy of this Major Amendment to ANDA 40-277 for Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%, has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this amendment as **Attachment H**.

Should additional information and/or clarification be required, please contact Laura Shotton, Regulatory Affairs Specialist, or me at (217) 423-9715, or FAX (217) 428-8514.

Sincerely,



James G. Baumann, Jr.
Manager, Regulatory Submissions

Taylor Pharmaceuticals an Akorn Co.

• generics • injectables • ophthalmics • contract services

September 11, 1997

Office of Generic Drugs, CDER, FDA
Metro Park North II, HFD-600
7500 Standish Place
Rockville, MD 20855-2773

505(j)(ii) a CK
10/14/97
Jugay S. Davis

**RE: ABBREVIATED NEW DRUG APPLICATION
AKTAINE® (Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%)
15 mL fill size in 15 cc container**

Dear Madam or Sir:

In accordance with 21 CFR § 314.92 (a)(1), Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Abbreviated New Drug Application for AKTAINE® (Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%), a prescription ophthalmic drug product indicated for topical anesthesia in ophthalmic practice. The reference listed drug (RLD) is Ophthaine®, NDA 08-883, approved on July 1, 1953, and is owned by Apothecon. The suitability of the ANDA is documented in the submission.

Akorn, Inc. would like to take this opportunity to inform OGD that its manufacturing subsidiary has been renamed Taylor Pharmaceuticals, which was previously known as Akorn Manufacturing, Inc., as of August 21, 1996.

To support the ANDA, which is the subject of this application, one (1) L batch (21206) was compounded and filled into one (1) package size (15 mL/15 cc). This L batch is 10% of the requested largest commercial batch size L) for this product, as suggested by the OGD Policy and Procedure Guide 22-90. The packaging of the exhibit batches was performed in accordance with the OGD Policy and Procedure Guide 41-95 and the directives provided in OGD's Letter to Industry, dated August 4, 1993. All operations during the manufacture of AKTAINE® (Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%) stability batches were performed by production personnel according to established cGMPs and were monitored by Quality Assurance (QA) personnel, using established production equipment. All material used was released by the Quality Control (QC) laboratory according to established specifications and procedures. The stability studies for AKTAINE® (Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%) were performed in their marketed container/closure systems. The stability samples were labeled with draft labels made with the same paper,

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CHECKLIST FOR COMPLETENESS AND ACCEPTABILITY FOR FILING
ABBREVIATED APPLICATIONS

	Section	Yes	No
Regulatory and Administrative Requirements			
Methods Validation package (if non-USP drug product) 3 copies	XVI	✓	
Cover Letter		✓	
Letters of Authorization		✓	
U.S. Agent (If Needed, Countersignature on 356h)	XXI.1	✓	
DMF Referral and Authorizations		✓	
356h Form - Completed/Original Signature	I (original in Archival copy)	✓	
Table of Contents	copy in each volume	✓	
Listed Drug or		✓	
AADA monograph (if appropriate)	N/A		✓
information to show proposed product is the same as the listed product: (i)(a) indications (ii) active ingredient(s) (iii)(a) route (b) dosage form (c) strength (iv) labeling -- side by side comparison of insert labeling and container labels.	IV and V	✓	
Formulation for Ophthalmics/Otics/Externals/Parenteral + Meet requirements per 21 CFR 314.94? + Characterize and explain differences as required Parenterals: Same Size Container (strength/volume)	VII	✓	
Petition Required			✓
Debarment Certification with original signature	XXI.2 (original in Archival copy)	✓	
List of Convictions with signature	XXI.2	✓	
Third Copy Certification with original signature	XXI.3 (original in Archival copy)	✓	
Patent Certification with signature	III	✓	
Use Patent Statement? (if required)	N/A		✓
If so, exclude Use in labeling/indications?			✓
Exclusivity Addressed	III	✓	
Labeling: 4 copies of draft (✓) or 12 copies of FPL()	V	✓	
Environmental Assessment	XX	✓	
Compliance Statement	XX	✓	
Statement re Rx / OTC Status	Cover Letter & V	✓	
Chemistry, Manufacturing and Controls Information			
Components & Composition of the drug product	VII	✓	
Batch Formulation	VII.3	✓	
Manufacturing Procedures (Executed Batch Records for exhibit batch)	XII.2	✓	
Package entire exhibit batch	XII	✓	
Master Production Batch Record for largest batch size intended for production. (No more than 10x pilot batch)	XI.2	✓	
Certification of cGMPs	IX	✓	
Description of Facility (or DMF reference?)		✓	

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GENERIC DRUG

	Section	Yes	No
Address of Manufacturing Site for Exhibit/Production Batches	IX	✓	
If sterile product, information provided for Procedures ✓	XI	✓	
Specifications and Tests for Active Ingredient and Dosage Form	VIII.1 (d) & XVI	✓	
Source of Active Ingredient	VIII.1(a)	✓	
Cert. of Analysis from Manufacturer of Active Ingredient	VIII.1(c)	✓	
Applicant Cert. of Analysis for Active Ingredient	VIII.1(d)	✓	
Cert. of Analysis for finished product	XV.3	✓	
Specifications and Tests for Inactive Ingredients	VIII.2	✓	
Source of Inactive Ingredients	VIII.2	✓	
Cert. of Analysis from Manufacturer of Inactive Ingredient	VIII.2	✓	
Stability Profile Including Stability Data	XVII	✓	
3 months Accelerated Stability Data	XVII	✓	
Batch Numbers listed on Stability Records	XVII	✓	
Samples Statement Plus Data	XIX	✓	
Bioequivalence Information			
Bioavailability/Bioequivalence	VI	✓	
Complete Study(ies) results			✓
In Vivo Study/Waiver Request	VI	✓	
Comparative Dissolution Data	N/A		✓

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GENERIC DRUG

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adhesive, and ink as the proposed commercial labels. The storage areas used for stability testing are calibrated and monitored by the Quality Assurance Department.

With the exception of the inactive ingredient, _____, the formulation ingredients, both active and inactive are the same for AKTAINE® (Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%) and the reference listed drug (RLD), Ophthaine®. Justification for the deletion of the inactive ingredient, _____ from the proposed Taylor dosage form is provided in **Section II Basis for ANDA Submission** found elsewhere in this application. Since both AKTAINE and Ophthaine are ophthalmic solutions, AKTAINE meets the criteria for waiver of evidence of in vivo bioavailability or bioequivalence as per 21 CFR § 320.22 (b)(1)(i). In addition, the inactive ingredient concentrations for AKTAINE® (Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%) were optimized during development to be the same ($\pm 5\%$) as those for the RLD, in order to qualify the subject product for the ANDA and bioequivalence waiver per the Interim Inactive Ingredient policy issued by Doug Sporn, OGD, in a memo dated November 17, 1994.

This ANDA is contained in two (2) volumes and is organized in the manner recommended by the Office of Generic Drugs in its Policy and Procedure Guide 30-91 and the "Guidance for Industry" document on the organization of an ANDA and AADA issued by OGD in April, 1997. **At this time, Taylor requests approval for AKTAINE® (Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%) manufactured according to the attached documentation, using proparacaine hydrochloride manufactured by _____ and packaging components manufactured by _____. An expiration dating period of twenty four months is requested, based on three months acceptable stability data from stability batches stored at accelerated stability conditions.**

This submission contains sterility assurance data. Taylor Pharmaceuticals is providing sterility assurance information, including documentation for the sterilization process validation for proparacaine hydrochloride ophthalmic solution in this application. The sterility assurance information is organized according to the directives presented in the "Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" (November, 1994).

In support of this application, Taylor Pharmaceuticals references our application for AKTOB™ (Tobramycin Ophthalmic Solution, 0.3%), AADA 64-096, approved on January 31, 1996 and AADA 64-096/S-001, approved on March 19, 1997. This approved application for tobramycin ophthalmic solution, including the supplement, contains the most recently reviewed and approved aseptic validation information regarding the processing of ophthalmics at Taylor Pharmaceuticals.

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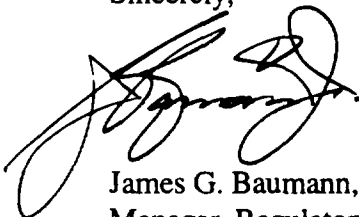
The sterility assurance information provided herein is **in addition to** the information previously approved, and is not intended to stand alone for the purposes of the Validation Package.

Taylor is filing an archival copy (in blue folders) of the ANDA, a technical review copy (in red folders), and a field copy (in maroon folders) sent to the Chicago district office. The technical review and field copies are identical to the archival copy and a certification attesting to this is provided with the field copy.

In accordance with 21 CFR § 314.94 (d)(5), and by reference 314.50 (k)(3), Taylor Pharmaceuticals certifies that a true copy of this Abbreviated New Drug Application for AKTAINÉ® (Proparacaine Hydrochloride Ophthalmic Solution, USP, 0.5%) has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this application.

Should additional information be required, please contact Laura Shotton, Regulatory Affairs Specialist, or me at (217) 423-9715 or FAX (217) 428-8514.

Sincerely,



James G. Baumann, Jr.
Manager, Regulatory Submissions

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