CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
74-974

CORRESPONDENCE

ANDA: 74-974 APPLICANT: Akorn Manufacturing, Inc.

DRUG PRODUCT: Lorazepam Injection USP, 2 mg/mL, (1 mL fill/2.25 mL syringe)

The deficiencies presented below represent MAJOR deficiencies.

A. Chemistry Deficiencies:

Page(s) 2

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

B. Microbiology Deficiencies:

1. The bulk solution bioburden specification found on page 227 of the application was NMT 10 CFU/mL. Yet, it is not apparent whether or not the bioburden testing described on page 234 met the applicant's limit specification. Please explain.

2. You stated on page 739 that the subject drug product should withstand microbial challenge during the holding time of the unfiltered bulk or during filling operations after sterile filtration. Please be reminded that the preservative..."should not be used solely to reduce the viable microbial count as a substitute for good manufacturing practice" [Chapter <51> page 1681 USP 23]. Addition of a preservative is intended to protect the drug product after manufacture.

3. Apparently no syringe media fills have been performed in Room C in the past six (6) years, i.e., since 1990. Commit to perform at least one media fill and submit the results prior to manufacturing product on line C.

C. Labeling Deficiencies:

See the attached labeling comments.

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

1. Removal of the requirement for pre-fill testing for the preservative Benzyl Alcohol, NF, mentioned on page 534, will need to be supported by data, which may be submitted as an amendment to the unapproved ANDA, or as a prior-approval supplement to the approved ANDA.

2. Please acknowledge that the USP methods will be the regulatory methods and will prevail in case of a dispute, and the Akorn methods, when different from the USP methods, will be the alternate methods.

3. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current GMPs at the time of approval. An evaluation by the Division of Manufacturing and Product Quality has been requested.

Sincerely yours,

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

Taylor Pharmaceuticals an Akorn Co.

• generics • injectables • ophthalmics • contract services

FA

July 7, 1998

RECEIVED
JUL
GENERIC DRUGS

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

RE: TELEPHONE AMENDMENT TO ANDA 74-974
Lorazepam Injection, USP, 0.2%
2 mg/mL (1 mL/2.25 mL syringe)

Dear Sir/Madam:

Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Telephone Amendment to our Abbreviated New Drug Application ANDA 74-974 for Lorazepam Injection, USP, 0.2% (1 mL/2.25 mL syringe), an injectable drug intended for use in adult patients as an preanesthetic medication producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery.

This amendment is in response to a teleconference held on July 1, 1998 between FDA personnel (Joseph Buccine, Dr. Rashmikant Patel, Dr. Vilayat Sayeed, and Kathy Woodland) and Taylor Pharmaceuticals personnel (Jim Baumann, Lou Fraser, Rick Taylor, Charles Coates, and Dennis Roberts). FDA had previously requested (teleconference with Dr. Sayeed on June 23, 1998) that Taylor delete the potency adjustment step in the lorazepam batch records (ANDAs 74-974 and 75-025) together with the corresponding potency adjustment (fortification) worksheets.

After a brief discussion of the issue, the following responses are being provided as a follow-up to the teleconference:

1. Taylor will *delete* the manufacturing step that the Lorazepam, USP of the solution, together with the corresponding worksheets from the master batch records as requested by FDA. During the teleconference, Dr. Patel specifically referenced page 000296, step #8, and pages 000299 and 000300 in ***ANDA 74-974 (syringe)*** as the manufacturing step and pages that should be deleted from the batch record. These changes are reflected on the revised master batch record pages (formulation procedure only) for

Lorazepam Injection, USP, 0.2% (syringe) provided as ***Attachment A.*** Both the manufacturing step that would allow for a t, together with the two (2) worksheets, have been deleted.

2. Should a be found necessary on future commercial batches, Taylor will provide a pre-approval supplement regarding as part of the post approval commitments referenced in 21 CFR § 314.70.

3. Per discussion and agreement, Taylor is providing a revised copy ***(see Attachment B)*** of the product specifications for lorazepam to reflect the following changes. *Please note that the revised manufacturing steps provided in **Attachment A** also reflect these changes.*

   - <u>In-Process Specifications:</u> Change lorazepam assay limits ***from*** ' and
   - <u>Finished Product Release Specifications:</u> Change lorazepam assay limits ***from***

Taylor is filing an archival copy consisting of one volume (in blue folder) of this amendment and a technical review copy (in 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 Telephone Amendment to ANDA 74-974 for Lorazepam Injection, USP, 0.2% (1 mL/2 mL syringe) 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 you have additional questions, please feel free to contact me at your convenience 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

ORIG AMENDMENT
N/FA

June 9, 1998

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

RECEIVED
JUN 12 [redacted]
GENERIC DRUGS

RE: TELEPHONE AMENDMENT TO ANDA 74-974
Lorazepam Injection, USP, 0.2%
2 mg/mL (1 mL/2.25 mL syringe)

Dear Sir/Madam:

Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Telephone Amendment to our Abbreviated New Drug Application ANDA 74-974 for Lorazepam Injection, USP, 0.2% (1 mL/2.25 mL syringe), an injectable drug intended for use in adult patients as an preanesthetic medication producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery.

This amendment is in response to a teleconference held on June 2, 1998 between FDA (Joseph Buccine, Project Manager, OGD, and Kathy Woodland, Reviewing Chemist, OGD) and Taylor Pharmaceuticals (Jim Baumann, Mgr., Regulatory Submissions, and Dennis Roberts, Director of Research and Development). FDA indicated that there were some concerns about the limits Taylor had proposed for the degradation products listed in the product specification sheet for lorazepam. During the teleconference, Mr. Buccine indicated that Taylor could provide its response as a "Telephone Amendment".

After a brief discussion of the issues pertaining to the degradant limits, the following responses are provided as a follow-up to the teleconference:

Chemistry discussion

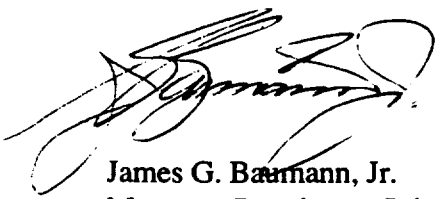
In addition to the above information, Taylor is providing updated stability data (24 month test results) on Taylor's drug product and the RDL, Ativan®, as ***Attachment C.*** During the conversation, Mr. Buccine indicated that Taylor should provide its response as a "Telephone Amendment".

Taylor is filing an archival copy consisting of one volume (in blue folder) of this amendment and a technical review copy (in 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 Facsimile Amendment to ANDA 74-974 for Lorazepam Injection, USP, 0.2% (1 mL/2 mL syringe) 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 you have additional questions, please feel free to contact me at your convenience 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

March 13, 1998

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

RE: TELEPHONE AMENDMENT TO ANDA 74-974
Lorazepam Injection, USP, 0.2%
2 mg/mL (1 mL/2.25 mL syringe)

Dear Sir/Madam:

Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Telephone Amendment *(original and duplicate copy)* to our Abbreviated New Drug Application ANDA 74-974 for Lorazepam Injection, USP, 0.2% (1 mL/2.25 mL syringe), an injectable drug intended for use in adult patients as an preanesthetic medication producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery. The reference listed drug (RLD) is Ativan®, the subject of NDA 18-140, which is held by Wyeth Ayerst and was approved on July 25, 1980.

This amendment is in response to teleconference held with FDA (Andrea High and Dr. James McVey) and Taylor personnel (Jim Baumann, Lou Fraser, Rick Taylor, and Charlie Coates) on Thursday afternoon, March 12, 1998, regarding certain microbiological questions raised by FDA during the review of Taylor's submission of August 15, 1997. Specifically, the following microbiological issues were briefly discussed and responded to:

1. **Was a growth promotion test performed for the media fill provided in the response of August 15, 1997?**

   Growth promotion tests are performed on media fills and the results generally accompany the media fill batch record. We are providing a copy of the growth promotion results for the media fill (**Attachment A**) provided in the response of August 15, 1997. It is important to note that the growth promotion test is performed *at the end of the 14 day incubation period* to demonstrate that the media is "viable" for the entire incubation period.

2. **How does the length of time it takes for the actual production run compare to the length of time for the media fill run?**

   Media fills performed at Taylor are designed to simulate normal production. The line speed of the media fill was slightly less than that of production runs to allow greater exposure of the media to the environment simulating a "worse case" situation. The line speed for the production filling will be approximately syringes per hour. The media was filled at approximately syringes per hour.

   We agree with the Agency's suggestion that the media fill should simulate the actual production time. We have been discussing this issue internally and plan to lengthen the media fill process to more closely simulate actual production time.

3. **How do the number of units filled on an actual production run compare to the number of units filled on the media fill run?**

   The only major difference between media fills and production runs is the number of units filled. The production batch size for Lorazepam will be up to approximately syringes, while the media fill was approximately syringes.

4. **Does the media fill represent "worse case" scenario?**

   As previously indicated, the line speed of the media fill was slightly less than that of production runs to allow greater exposure of the media to the environment simulating a "worse case" situation.

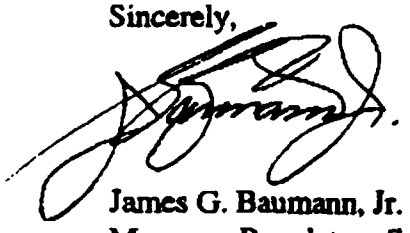
   During a typical production run, there would be a personnel change in the filling room. This is also done approximately half way through a media fill and is indicated in the batch record. This change simulates production and introduces more personnel into the area thus providing for a "worse case" scenario.

Some of the above responses were previously provided in Taylor's original syringe application, dated October 1, 1996, and located in the Aseptic Validation Documentation, Volume 3, pp. 748-751. For your convenience, we have provided these pages for your review in **Attachment B** of this telephone amendment.

Since this telephone amendment to an unapproved application does not affect the chemistry, manufacturing, and controls of the drug product [ref. §§ 314.96 (b) and 314.60 (c)], Taylor will not file a copy of this amendment with the FDA Chicago District Office.

Should you have additional questions, please feel free to contact me at your convenience at (217) 423-9715 or FAX (217) 423-5206.

Sincerely,



James G. Baumann, Jr.
Manager, Regulatory Submissions

Page(s) 7

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

Quality Control Records

Taylor
Pharmaceuticals an Akorn Co.

• generics • injectables • ophthalmics • contract services

NEW CORRESP

March 2, 1998

N L
FAX

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

RE: FACSIMILE AMENDMENT TO ANDA 74-974
Lorazepam Injection, USP, 0.2%
2 mg/mL (1 mL/2.25 mL syringe)

Dear Sir/Madam:

Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Facsimile Amendment to our Abbreviated New Drug Application ANDA 74-974 for Lorazepam Injection, USP, 0.2% (1 mL/2.25 mL syringe), an injectable drug intended for use in adult patients as an preanesthetic medication producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery. The reference listed drug (RLD) is Ativan®, the subject of NDA 18-140, which is held by Wyeth Ayerst and was approved on July 25, 1980.

This amendment is in response to the FDA Deficiency Letter (Facsimile), dated February 11, 1998 *(see Attachment A),* listing *minor* deficiencies and/or comments regarding ANDA 74-974 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 February 11, 1998:

A. Chemistry Deficiencies

1 Please include the impurities 7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-1-hydroxy-2H-1,4-benzodiazepin-2-one and

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

chemistry

Taylor notes and acknowledges that the microbiology portion of its application is currently under review and that comments, *if any,* will be transmitted at a later date.

Labeling Deficiencies:

Taylor Pharmaceuticals has revised the labeling, as instructed in the deficiency letter, and is submitting draft labeling for review as follows:

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

- CARTON: Four (4) revised draft carton labels (both Review Copy and Archival Copy) are provided in ***Attachment F.***

- INSERT: Four (4) revised draft package inserts (both Review Copy and Archival Copy) are provided in ***Attachment G.***

Taylor is also providing *in each of the above attachments* a side-by-side comparison of our proposed labeling with the labeling provided in our last submission, dated August 15, 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 Facsimile Amendment to ANDA 74-974 for Lorazepam Injection, USP, 0.2% (1 mL/2.25 mL syringe) 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 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

August 20, 1997

NDA ORIG AMENDMENT

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

RE: AMENDMENT TO ANDA 74-974
Lorazepam Injection, USP, 0.2%
2 mg/mL (1 mL/2.25 mL syringe)

Dear Sir/Madam:

In accordance with 21 CFR § 314.96 (a)(1), and by reference § 314.60 (a), Taylor Pharmaceuticals (an Akorn Company), a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits an Amendment to ANDA 74-974 for Lorazepam Injection, USP, 0.2% (1 mL/2.25 mL syringe) an injectable drug intended for use in adult patients as an preanesthetic medication producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery. The reference listed drug (RLD) is Ativan®, the subject of NDA 18-140, which is held by Wyeth Ayerst and was approved on July 25, 1980.

This amendment revises existing information and provides the following additional information not previously submitted with the original application, dated October 1, 1996:

- A revised copy (**Attachment A**) of the "Stability Protocol and Commitments" for Lorazepam Injection, USP, 0.2% (1 mL/2.25 mL pre-filled syringe). The revised copy reflects: (a) changes in microbiology testing (e.g., sterility and bacterial endotoxins) and (b) the addition of a "Stability Sample Requirements" page.

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 Amendment to ANDA 74-974 for Lorazepam Injection, USP, 0.2%, has been provided to the FDA Chicago District Office.

RECEIVED

150 S. Wyckles Road • P.O. Box 1220 • Decatur, IL 62525-1220 • (217) 428-1100 • FAX (217) 422-9048

GENERIC DRUGS

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 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

August 15, 1997

AMENDMENT N/C - NC 5/22/97

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

RE: MAJOR AMENDMENT TO ANDA 74-974
Lorazepam Injection, USP, 0.2%
2 mg/mL (1 mL/2.25 mL syringe)

Dear Sir/Madam:

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 74-974 for Lorazepam Injection, USP, 0.2% (1 mL/2.25 mL syringe) an injectable drug intended for use in adult patients as an preanesthetic medication producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery. The reference listed drug (RLD) is Ativan®, the subject of NDA 18-140, which is held by Wyeth Ayerst and was approved on July 25, 1980.

Akorn, Inc. would like 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.

This amendment is in response to the FDA Major chemistry, microbiology, and labeling deficiency letter, dated June 12, 1997.

For ease of reference, this amendment is numbered sequentially in the lower right corner so that both the text and attachments bear consecutive numbers. A table of contents is provided for additional convenience of review.

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.

150 S. Wyckles Road • P.O. Box 1220 • Decatur, IL 62525-1220 • (217) 428-1100 • FAX (217) 422-9048

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 74-974 for Lorazepam Injection, USP, 0.2%, 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 N.**

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

ANDA 74-974

Akorn, Inc.
Attention: James G. Baumann, Jr.
P.O. BOX 1220
Decatur IL 62525

FEB 24 1997

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Lorazepam Injection USP, 2 mg/mL.

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Akorn

505(b)(2)(a)(ok)
11/13/96
Anna Marie H. Waitel
11/19/96

October 1, 1996

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

RE: ABBREVIATED NEW DRUG APPLICATION
Lorazepam Injection, USP, 0.2%
2 mg/mL (1 mL/2.25 mL syringe)

Dear Madam or Sir:

In accordance with 21 CFR § 314.92 (a)(1), Akorn, Inc., a manufacturer, marketer, and distributor of ophthalmic and injectable drug products hereby submits this Abbreviated New Drug Application for Lorazepam Injection, USP, 0.2% (1 mL/2.25 mL syringe), an injectable drug intended for use in adult patients as an preanesthetic medication producing sedation, relief of anxiety, and a decreased ability to recall events related to the day of surgery. The reference listed drug (RLD) is Ativan®, the subject of NDA 18-140, which is held by Wyeth Ayerst and was approved on July 25, 1980. The suitability of the ANDA is documented in the submission.

This ANDA is contained in 3 volumes, and is organized in the manner recommended by the Office of Generic Drugs in its Policy & Procedure Guide 30-91. **At this time, Akorn requests approval for Lorazepam Injection, USP, 0.2% (1 mL/2.25 mL syringe) manufactured according to the attached documentation, using Lorazepam, USP manufactured by and components manufactured by An expiration dating period of twenty four months is requested, based on the available three months acceptable stability data from stability batches stored at accelerated stability conditions.**

This submission contains sterility assurance data. Akorn is providing sterility assurance information, including documentation for the sterilization process validation for lorazepam injection, in **Volume 3**. This documentation 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).

Akorn is filing an archival copy (in blue folder) of the ANDA, a technical review copy (in red and orange folders), and a field copy sent to the Chicago district office (in maroon folders). The technical review copy and the field copies are identical to the archival copy

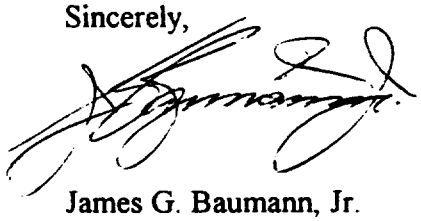
Akorn, Inc.
■
Post Office Box 1220
■
Decatur, Illinois 62525
■
217-423-9715 FAX 217-428-8514

and a certification attesting to this is provided with the field copy. Four copies of the draft labeling are included in all copies of this ANDA.

In accordance with 21 CFR § 314.94 (d)(5), Akorn certifies that a true copy of this Abbreviated New Drug Application for Lorazepam Injection, USP, 0.2% (1 mL/2.25 mL syringe) has been provided to the FDA Chicago District Office. A copy of this certification with an original signature is provided with this application.

Should you have additional questions or if more information is needed, please do not hesitate to contact me at (217) 423-9715, or fax (217) 428-8514.

Sincerely,



James G. Baumann, Jr.
Manager of Regulatory Affairs (Submissions)