

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**40281**

**CORRESPONDENCE**

ANDA 40-280

Endo Pharmaceuticals Inc.  
Attention: Andrew G. Clair, Ph.D.  
500 Endo Blvd.  
Garden City, NY 11530

|||||

NOV 10 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Hydrocodone Bitartrate and Acetaminophen  
Tablets USP, 7.5 mg/500 mg, 7.5 mg/650 mg  
and 10 mg/650 mg

DATE OF APPLICATION: October 17, 1997

DATE OF RECEIPT: October 20, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames  
Project Manager  
(301) 827-5848

Sincerely yours,

JSI

Jerry Phillips  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research



**Endo Pharmaceuticals Inc.**

May 5, 1998

Douglas Sporn  
Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation & Research  
Food and Drug Administration  
Metro Park North II, Room 150  
7500 Standish Place  
Rockville, MD 20855

NDA ORIG AMENDMENT

RECEIVED

Re: **ANDA 40-280; Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 7.5/500mg, 7.5/650mg, and 10/650mg**  
**ANDA 40-281; Hydrocodone Bitartrate and Acetaminophen Tablets, USP, 5/500mg, 7.5/750mg**  
**Amendment**

MAY 06 1998

GENERIC DRUGS

Dear Mr. Sporn:

Reference is made to the 4/17/98 facsimile letters from the Division of Labeling and Program Support regarding labeling comments for the subject files.

We are amending the applications with final printed container labeling which has been revised as per your comments.

Please note that we have combined all five strengths of this product into one package insert, in anticipation of simultaneous approval of the two applications.

In addition, it is our intent to market bottles of 100's and bottles of 500's for each strength upon approval of these applications. Therefore, we have revised the "How Supplied" section of the package insert to reflect the package sizes of 100's and 500's. The 500's will be packaged in the identical container/closure system as that described in the ANDA's. Stability is based on bracketing between the bottle of 100's and bottle of

Included in this submission are the following:

- Responses to each comment in the 4/17/98 FDA facsimile letters
- 12 copies of Final Printed Container Labels
- 12 copies of the revised Package Insert
- A side-by-side comparison of the revised labeling with that previously submitted

This amendment completes all outstanding issues on these applications. It is our understanding that there are no other chemistry, manufacturing and control issues.

If there are any questions regarding this amendment, please contact me at (516) 522-3306.

Sincerely,

A handwritten signature in black ink, appearing to read "Andrew J. Stelter". The signature is fluid and cursive, with a large initial "A" and "S".

For/ Jeanne Stelter  
Regulatory Associate

enclosures



**Endo Pharmaceuticals Inc.**

May 26, 1998

NC

Douglas Sporn  
Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II, Room 150  
7500 Standish Place  
Rockville, MD 20855

**Re: ANDA 40-280; Hydrocodone Bitartrate and Acetaminophen Tablets, USP,  
7.5/500 mg, 7.5/650 mg and 10/650 mg  
ANDA 40-281; Hydrocodone Bitartrate and Acetaminophen Tablets, USP,  
5/500 mg, 7.5/750 mg  
Amendment**

Dear Mr. Sporn:

Reference is made to a telephone conversation today with Julia Johnson.

Per her request, enclosed please find the following:

- Four additional copies of the final printed package insert for ANDA 40-280.
- Seven additional copies of the final printed package insert for ANDA 40-281.

Please note that we have combined all five strengths of this product into one package insert, in anticipation of simultaneous approval of the two applications. Therefore, the inserts are identical for ANDA 40-280 and 40-281.

If there are any questions regarding this amendment, please contact me at (516) 522-3309.

Sincerely,

Andrew G. Clair, Ph.D.  
Director, Regulatory Affairs

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MAY 27 1998

GENERIC DRUGS

Enclosures  
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FDA-1998.doc

ORIGINAL



**Endo Pharmaceuticals Inc.**

June 23, 1998

Douglas Sporn  
Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II, Room 150  
7500 Standish Place  
Rockville, MD 20855

NEW ORIGIN

(N/FA)

RECEIVED  
JUN 24 1998  
GENERIC DRUGS

**Re: ANDA 40-280; Hydrocodone Bitartrate and Acetaminophen Tablets, USP  
7.5/500 mg, 7.5/650 mg and 10/650 mg  
ANDA 40-281; Hydrocodone Bitartrate and Acetaminophen Tablets, USP  
5/500 mg and 7.5/750 mg  
FACSIMILE AMENDMENT**

Dear Mr. Sporn:

Reference is made to your facsimile dated June 22, 1998 for the subject files.

The deficiency provided to us was as follows:

"It is noted that you include two post approval stability protocols, one for the validation batches and one for annual production batches. In the stability protocol for the validation batches, testing is conducted at 0, 3, 6, 9, 12, 18 and 24 months and for the production batches, testing is conducted with reduced testing of 0, 6, 12, 18 and 24 months. Please be advised that a request for reduced stability testing cannot be allowed until you have substantiated your proposed expiration dating on three production batches packaged in the smallest and largest container/closure systems. Post approval, a supplement application should be submitted with sufficient stability data to support a request for reduced stability testing."

In response to your comment, enclosed please find the annual production batch stability protocol which is revised to include testing at 0, 3, 6, 9, 12, 18 and 24 months. These testing intervals now coincide with our validation post approval stability protocol.

Please be advised that our response for ANDA 40-280 and ANDA 40-281 has ✓  
been faxed and mailed directly to your document control room.

If there are any questions, please contact Jeanne Stelter at (516) 522-3306.

Sincerely,

A handwritten signature in black ink, appearing to read "Andrew G. Clair". The signature is fluid and cursive, with a large initial "A" and a distinct "C" at the end.

Andrew G. Clair, Ph.D.  
Director, Regulatory Affairs

Enclosures

AGC:wj  
FDA-1998.doc



**Endo Pharmaceuticals Inc.**

August 28, 1998

Douglas Sporn  
Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation & Research  
Food and Drug Administration  
Metro Park North II, Room 150  
7500 Standish Place  
Rockville, MD 20855

**NDA ORIG AMENDMENT**

*N/FA*

**Re: ANDA 40-280; Hydrocodone Bitartrate and Acetaminophen Tablets, USP  
7.5/500mg, 7.5/650 mg and 10/650mg  
ANDA 40-281; Hydrocodone Bitartrate and Acetaminophen Tablets, USP  
5/500 mg and 7.5/750 mg  
Response to FDA Request for Additional Information**

Dear Mr. Sporn:

Reference is made to the telephone request by Radhika Rajagopalan, Chemistry Reviewer, OGD, this afternoon in connection with the subject files.

Ms. Rajagopalan requested we provide the revised stability specification for p-aminophenol.

Our August 24, 1998 amendment to the referenced files includes the revised Finished Product Monograph, Doc. No. MON9709705 Version 2, which reflects the tightened specification for p-aminophenol of 0.01%. Please be advised that this Finished Product Monograph is the same monograph used in our stability studies. The Post-Approval Stability Protocols for the Validation and the Annual Production Lots references this monograph for the specifications and methods for those tests required on stability.

If there are any questions regarding this amendment, please contact me at (516) 522-3306.

Sincerely,

Jeanne Stelter  
Regulatory Associate

**RECEIVED**

**AUG 31 1998**

attachments

**GENERIC DRUGS**

3-25-98  
2-1



August 24, 1998

**Janssen Pharmaceutica Inc.**

Glenn Sporn  
Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation & Research  
Food and Drug Administration  
Hoffmann-La Roche Building, Room 150  
200 Standish Place  
Rockville, MD 20855

**NDA ORIG AMENDMENT**

N/FA

Re: **ANDA 40-280; Hydrocodone Bitartrate and Acetaminophen Tablets, USP  
7.5/500mg, 7.5/650 mg and 10/650mg**  
**ANDA 40-281; Hydrocodone Bitartrate and Acetaminophen Tablets, USP  
5/500 mg and 7.5/750 mg**  
**TELEPHONE (MINOR) AMENDMENT**

Dear Mr. Sporn:

Reference is made to the telephone request by Brenda Arnwine (FDA) on July 27, 1998 in connection with the subject files.

Ms. Arnwine requested that we tighten the specification for para-aminophenol (4-aminophenol) from our proposed specification of \_\_\_\_\_% in the finished product. In addition, she indicated that the results for 4-aminophenol in the exhibit batches were reported as less than \_\_\_\_\_%, and requested we report the actual values.

As requested, we have tightened the specification for 4-aminophenol from \_\_\_\_\_%. In addition, we are proposing an additional test method to monitor p-aminophenol at this low level.

The \_\_\_\_\_ method for the determination of degradation products in acetaminophen that is proposed in the original application is insufficient to detect p-aminophenol at or below \_\_\_\_\_% on a routine basis. The limit of quantitation (LOQ) for p-aminophenol in the \_\_\_\_\_ method is approximately \_\_\_\_\_%, which is above the new specification limit of \_\_\_\_\_%.

Therefore, we have adapted the USP colorimetric method for the determination of p-aminophenol in Acetaminophen drug substance to detect this impurity in our Hydrocodone Bitartrate and Acetaminophen Tablets. The colorimetric procedure is specific to p-aminophenol with a sensitivity \_\_\_\_\_ down to ppm level. Validation of the colorimetric procedure to detect p-aminophenol in our tablet formulation has been conducted.

**RECEIVED**

**AUG 25 1998**

**GENERIC DRUGS**

Please note that we will continue using the \_\_\_\_\_ method to monitor unknown degradation products of acetaminophen.

Stability samples from the exhibit batches which were stored at controlled room temperature (25 - 30°C) for 12 months were analyzed using \_\_\_\_\_ method. The results are all less than \_\_\_\_\_ %. The individual measurements and calculated values are summarized in the enclosed table.

In support of this amendment we are providing the following documentation:

- Completed FDA Form 3439 and Addendum
- Field Copy Certification
- Revised Finished Product Monograph (Doc. No. MON9709705, Version 2 supersedes Doc. No. 7833, Version 2 previously submitted), which incorporates the USP colorimetric method.
- Summary of 4-aminophenol data for the exhibit batches stability samples (Table I)
- Addendum to the Certificates of Analysis for the exhibit batches
- Validation Report for the Colorimetric Method for Determination of 4-Aminophenol in Endo's Hydrocodone Bitartrate and Acetaminophen Tablets (Doc. No. Endo-1168-01)\*

\* Please note: The validation report references additional strengths of Hydrocodone Bitartrate and Acetaminophen Tablets which are the subject of a separate ANDA.

It is our understanding that this amendment completes all outstanding issues, and we now await the Agency's approval.

If there are any questions regarding this amendment, please contact me at (516) 522-3306.

Sincerely,



Jeanne Stelter  
Regulatory Associate

enclosures