

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**74-951**

**ADMINISTRATIVE DOCUMENTS**



CDER Establishment Evaluation Report  
for August 28, 1998

Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

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Establishment: \_\_\_\_\_ DMF No: \_\_\_\_\_  
AADA No: \_\_\_\_\_

Profile: **CSN** OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date **06-JAN-1997**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

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Responsibilities: **DRUG SUBSTANCE  
MANUFACTURER**

Establishment: \_\_\_\_\_ DMF No: \_\_\_\_\_  
AADA No: \_\_\_\_\_

**RD**  
**340**

Profile: **CSN** OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date **06-JAN-1997**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

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Responsibilities: **DRUG SUBSTANCE  
MANUFACTURER**

Establishment: \_\_\_\_\_ DMF No: \_\_\_\_\_  
AADA No: \_\_\_\_\_

Profile: **CSN** OAI Status: **NONE**  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date **13-FEB-1997**  
Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

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Responsibilities: **DRUG SUBSTANCE  
MANUFACTURER**



CDER Establishment Evaluation Report  
for August 10, 1998

Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

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Establishment:

MF No:  
ADA No:

Profile: CSN            OAI Status: NONE  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date **06-JAN-1997**  
Decision: **ACCEPTABLE**  
Reason: **BASED ON PROFILE**

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Responsibilities: **DRUG SUBSTANCE  
MANUFACTURER**

Establishment:

DMF No:  
AADA No:

Profile: CSN            OAI Status: NONE  
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Milestone Date **06-JAN-1997**  
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Responsibilities: **DRUG SUBSTANCE  
MANUFACTURER**

Establishment:

DMF No:  
AADA No:

Profile: CSN            OAI Status: NONE  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date **13-FEB-1997**  
Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

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Responsibilities: **DRUG SUBSTANCE  
MANUFACTURER**



## Memorandum

Date . JUN 10 1998  
From Consumer Safety Officer, Investigations &  
Preapproval Compliance Branch/DMPQ (HFD-324)  
Subject Concurrence with District Withhold  
Recommendation, ANDAs 74-988, 74-951 & 63-298  
To Pat Beers-Block, Chief  
Review Support Branch, HFD-617

**Applicant:** Jerome Stevens  
Pharmaceuticals, Inc.  
60 DaVinci Drive  
Bohemia, NY 11716  
CFN 2431950

Division of Manufacturing and Product Quality (HFD-320) has completed review of the Establishment Inspection Report (EIR) of the subject ANDAs. The products for these ANDAs are:

&

ANDA 74-951; Aspirin 325 mg/Butalbital 50 mg/Caffeine  
40 mg/Codeine Phosphate Capsules, 30mg

The EIR covers a physical inspection conducted at the applicant's facility from March 23 - April 6, 1998. The ANDAs identify this site to perform finished product manufacture and testing on the subject ANDAs.

DMPQ concurs with the District's recommendation to withhold approval of these ANDAs. Our concurrence with NYK-DO's withhold recommendation is based on the following significant GMP observations relative to the referenced ANDAs:

- Failure to document when samples were placed onto accelerated and long term stability studies for the following products and lots #'s:

ANDA 74-951; Aspirin 325 mg/Butalbital 50 mg/Caffeine 40mg/Codeine Phosphate 30mg Capsules - lot #'s 015395 and 007196

- Failure to document any investigation of dissolution test failures in accelerated stability study samples in the following product and lot #'s: Aspirin 325 mg/Butalbital 50 mg/Caffeine 40mg/Codeine Phosphate 30mg Capsules - lot #'s 015395 and 007196. Note that a statement did appear in the ANDA on page 219, that states that this drug product "exhibits gelatine capsule pellicle formation during dissolution testing."

- Failure to maintain a system for recording temperature and relative humidity conditions in the accelerated stability chamber to assure that it meets specifications.

- Several discrepancies were observed in raw material inventory records.

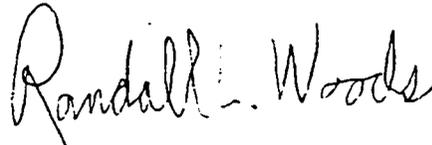
- Failure to perform five replicate injections during system suitability evaluation as required by current USP.

Additionally, numerous minor GMP deficiencies were noted during the inspection.

Finally, in regard to

NYK-DO was contacted on June 10, 1998 and as of this date no response has been received from the applicant.

A copy of the EIR and exhibits are attached for your review. If you have questions, please contact me at (301)-827-0065.

A handwritten signature in cursive script that reads "Randall L. Woods". The signature is written in dark ink and is positioned above the printed name.

Randall L. Woods

Attachments - EIR and Exhibits

ANDA APPROVAL SUMMARY

ANDA: 74-951

DRUG PRODUCT: Butalbital, Aspirin, Caffeine and Codeine Capsules

FIRM: Jerome Stevens Pharmaceuticals, Inc.

DOSAGE FORM: Hard gelatin capsule

STRENGTH: 50 mg Butalbital, 325 mg Aspirin, 40 mg Caffeine,  
30 mg Codeine Phosphate

CGMP STATEMENT: Included - New Correspondence, 10/16/96.

EIR STATUS UPDATE: Acceptable EIR issued 8/3/98.

BIO STUDY: Bio study and dissolution testing found satisfactory  
4/30/97 - H. Nguyen.

VALIDATION: Drug substance and drug product are compendial. The New  
York Regional Laboratory indicated acceptable methods  
verification for compendial tests, 1/6/97.

STABILITY: 3 month accelerated (40°C/75% RH) and 12 month room  
temperature data submitted for drug product packaged in  
the proposed market container/closure systems. Testing  
included appearance, assay, dissolution and free  
salicylic acid. A 24 month expiration date was proposed  
which was supported by the data submitted.

LABELING: Labeling satisfactory for approval, A. Vezza, 8/4/98.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH: The bio study was performed on lot #015395,  
capsules.

SIZE OF STABILITY BATCHES: Stability testing was performed on the  
two test batches, Lot #015395,  
capsules and Lot #007196,  
capsules.

PROPOSED PRODUCTION BATCH: The proposed production batch sizes is  
capsules.

**APPROVAL SUMMARY**  
**REVIEW OF PROFESSIONAL LABELING**  
**DIVISION OF LABELING AND PROGRAM SUPPORT**  
**LABELING REVIEW BRANCH**

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ANDA Number: **74-951**    Dates of Submission: **June 4 and July 27, 1998**

Applicant's Name: **Jerome Stevens Pharmaceuticals Inc.**

Established Name: **Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules USP, 50 mg/325 mg/40 mg/30 mg**

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**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?    Yes

Container Labels:    100s and 500s  
*Satisfactory as of June 4, 1998 submission.*

Professional Package Insert Labeling:  
*Satisfactory as of July 27, 1998 submission.*

Revisions needed post-approval: Container labels - "Total daily dosage ..." rather than "... dose ..." PI - include 2nd sentence in CLIN PHARM section "The role butalbital, aspirin, and caffeine plays in the relief of the complex of symptoms known as tension headache is incompletely understood." Also PI has FDAMA changes in it but has rev date of 8/97 (we did not make an issue of this)

**BASIS OF APPROVAL:**

Was this approval based upon a petition?    No

What is the RLD on the 356(h) form:    Fiorinal with Codeine Capsules

NDA Number:    19-429

NDA Drug Name:    Fiorinal (Butalbital/Aspirin/Caffeine) with Codeine Capsules USP, 50 mg/325 mg/40 mg/30 mg

NDA Firm: Novartis

Date of Approval of NDA Insert and supplement #: 4-29-91 (S-001)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: label on file and side-by-sides submitted

## 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		
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? NO		X	
<b>Packaging</b>			
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	
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	
<b>Labeling</b>			
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	
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	

	Yes	No	N.A.
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.		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? Exceeds NDA but meets USP requirements.		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.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C <sub>max</sub> , T <sub>max</sub> , 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.		X	

**FOR THE RECORD: (portions taken from previous review)**

- Review based on the labeling of the listed drug (Fiorinal with Codeine; Approved April 29, 1991, Revised November 1, 1990). Since recent changes approved for Fiorinal (NDA 17-534) and Fioricet with Codeine (NDA 20-232) should apply to this drug product, PM, Deborah Gunter, has been asked to include this labeling in her analysis. She has responded to an E-mail sent to her concerning this and is in the process of trying to consolidate the insert labeling for all three products.

2. Patent/ Exclusivities:

There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

NDA: Store and dispense below 77°F (25°C) in a tight container.

ANDA: Store and dispense below 77°F (25°C) in a tight, light-resistant container.

USP: Preserve in tight, light-resistant containers.

4. Product Line:

The innovator markets their product in bottles of 100s and unit-dose containers of 25s.

The applicant proposes to market their product in bottles of 100s and 500s.

5. The capsule imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See page 129.

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 55.

7. All manufacturing will be performed by Jerome Stevens Pharmaceuticals. No outside firms are utilized. See pages 118 and 123.

8. Container/Closure:

This product will be packaged in white HDPE containers with a screw cap.

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Date of Review: 7-30-98      Dates of Submission: 6-4 & 7-27-98

Primary Reviewer: Adolph Vezza      Date:

*A. Vezza*

*8/4/98*

Team Leader: Charlie Hoppes      Date:

*Ch Hoppes*

*8/4/98*

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 18, 1998

FROM: Don Shostak, HFD-647 *D. Shostak 5/18/98*

THRU: U. Venkataram, HFD-647 *U.V. Venkataram 5/18/98*

SUBJECT: ANDA 74-951 (Dissolution Testing Waiver)

TO: Timothy Ames

UV, Florence and I discussed Jerome Stevens' dissolution waiver request in their 5/13/98 correspondence. It was decided that we would ask Jerome Stevens to commit to placing the first production batch under accelerated storage conditions (40°C/75% RH) and to perform dissolution testing according to the ANDA procedure followed by the method published in USP 23, Supplement 8 if necessary. We also agreed that if the applicant agrees to this request, we will reclassify the deficiencies to MINOR.

74951.2mem

*74-951 5/18/98*  
*Tim: Done 5/20/98*  
*you can inform the applicant of the above in regard to their dissolution waiver requests they can submit the results when they obtain them*  
*Don S*

Telephone Conversation Memorandum

ANDA: 74-951

DRUG: Butalbital, Aspirin, Caffeine and Codeine Phosphate  
Capsules USP, 50 mg, 325 mg, 40 mg, 30 mg

FIRM: Jerome Stevens Pharmaceuticals, Inc.

PERSONS INVOLVED: Ron Steinlauf, Bill Cardone, Jerome Stevens  
Tim Ames, FDA

PHONE NUMBER: 516-567-1113

DATE: 5/20/98

Called firm to relate decision regarding Item 3 of the May 4, 1998 Major deficiency fax. It was decided by Ffang, Uvenkataram and Dshotak to request the firm to commit to placing the first production batch under accelerated storage conditions (0° C/75% RH) and to perform dissolution testing according to the ANDA procedure followed by the method published in the USP 23, Supplement 8. This request was related to the firm and it was also related that the amendment would now be considered a MINCR amendment and should be designated as such referencing this teleconference.

Timothy W. Ames, R.Ph., M.P.H.  
Project Manager, Div Chem II, Branch 6, OGD



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phone.174

Telephone Conversation Memorandum

ANDA: 74-951

DRUG: Butalbital, Aspirin, Caffeine and Codeine Phosphate  
Capsules USP, 50 mg, 325 mg, 40 mg, 30 mg

FIRM: Jerome Stevens Pharmaceuticals, Inc.

PERSONS INVOLVED: Ron Steinlauf, Bill Cardone, Jerome Stevens  
Tim Ames, FDA

PHONE NUMBER: 516-567-1113

DATE: 5/12/98

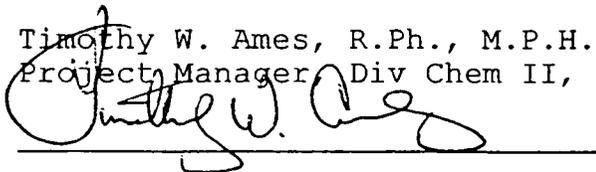
Called firm to relate clarification of Item 3 "Please perform dissolution testing at accelerated conditions using the procedure specified in the 20th IRA to USP 23 published in the Pharmacopeial Forum, Volume 23, # 6, Nov. - Dec. 1997 in the last facsimile deficiency.

I explained that this question was asked as a result of the accelerated stability sample failures at 60 and 90 days. The firm's assertion that this was due to pellicle formation was unsubstantiated and by requesting this testing be performed it would determine if pellicle formation was the actual problem.

The firm countered by indicating that this was unnecessary as their RT data was acceptable and all that was needed to establish an expiry date and all that was necessary for approval. They further claimed that this was a known problem with the RLD and only generic on the market. They explained they felt they were being held to an unnecessarily higher standard since they were a small firm and that this was a disproportionate burden on them. They also claimed that this may effect the classification to a MAJOR AMENDMENT status of this deficiency fax.

I indicated I would discuss their issues with the Chemistry Team Leader and Division Director.

Timothy W. Ames, R.Ph., M.P.H.  
Project Manager, Div Chem II, Branch 6, OGD



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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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THRU: U. Venkataram, HFD-647 *U.V. Venkataram 5/18/98*

SUBJECT: ANDA 74-951 (Dissolution Testing Waiver)

TO: Timothy Ames

UV, Florence and I discussed Jerome Stevens' dissolution waiver request in their 5/13/98 correspondence. It was decided that we would ask Jerome Stevens to commit to placing the first production batch under accelerated storage conditions (40°C/75% RH) and to perform dissolution testing according to the ANDA procedure followed by the method published in USP 23, Supplement 8 if necessary. We also agreed that if the applicant agrees to this request, we will reclassify the deficiencies to MINOR.

74951.2mem

Telephone Conversation Memorandum

ANDA: 74-951

DRUG: Butalbital, Aspirin, Caffeine and Codeine Phosphate  
Capsules USP, 50 mg, 325 mg, 40 mg, 30 mg

FIRM: Jerome Stevens Pharmaceuticals, Inc.

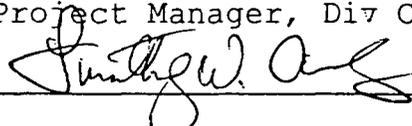
PERSONS INVOLVED: Ron Steinlauf, Bill Cardone, Jerome Stevens  
Tim Ames, FDA

PHONE NUMBER:

DATE: 5/20/98

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Timothy W. Ames, R.Ph., M.P.H.  
Project Manager, Div Chem II, Branch 6, OGD

  
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Telephone Conversation Memorandum

ANDA: 74-951

DRUG: Butalbital, Aspirin, Caffeine and Codeine Phosphate  
Capsules USP, 50 mg, 325 mg, 40 mg, 30 mg

FIRM: Jerome Stevens Pharmaceuticals, Inc.

PERSONS INVOLVED: Ron Steinlauf, Bill Cardone, Jerome Stevens  
Tim Ames, FDA

PHONE NUMBER: 516-567-1113

DATE: 5/12/98

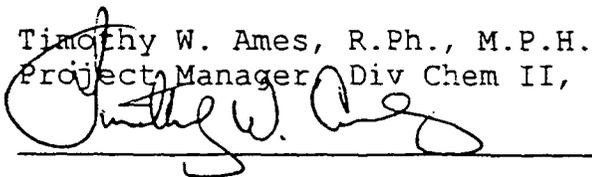
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The firm countered by indicating that this was unnecessary as their RT data was acceptable and all that was needed to establish an expiry date and all that was necessary for approval. They further claimed that this was a known problem with the RLD and only generic on the market. They explained they felt they were being held to an unnecessarily higher standard since they were a small firm and that this was a disproportionate burden on them. They also claimed that this may effect the classification to a MAJOR AMENDMENT status of this deficiency fax.

I indicated I would discuss their issues with the Chemistry Team Leader and Division Director.

Timothy W. Ames, R.Ph., M.P.H.  
Project Manager, Div Chem II, Branch 6, OGD



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

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ANDA Number: **74-951**      Date of Submission: **September 29, 1997**

Applicant's Name: **Jerome Stevens Pharmaceuticals Inc.**

Established Name: **Butalbital, Aspirin, Caffeine, and  
Codeine Phosphate Capsules USP,  
50 mg/325 mg/40 mg/30 mg**

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Labeling Deficiencies:

1. GENERAL COMMENTS:

- a. As a result of the FDA Modernization Act of 1997, the statement "CAUTION: Federal law..." must be replaced with the symbol "Rx only" or "R only" throughout your labels and labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site: <http://www.fda.gov/cder/guidance/index.htm> for guidance.
- b. The FDA Modernization Act of 1997 has deleted the requirement for the presence of the statement "WARNING: May be habit-forming." throughout the labels and labeling of scheduled drugs. You may remove this statement from your labels and labeling.

2. CONTAINER 100s and 500s

- a. See GENERAL COMMENTS above.
- b. Usual Adult Dosage - Revise to read as follows:  
  
1 or 2 capsules every 4 hours. Total daily dose should not exceed 6 capsules. [N.B. not "1-2"]

3. INSERT

a. GENERAL COMMENT

Please improve the print quality, especially of the subscripts, throughout the text of the insert.

b. DESCRIPTION

- i. See GENERAL COMMENTS [under (1)] above.
- ii. Please note you have failed to provide all of the dyes and colorants found in the capsule (omissions include: D&C Red and D&C Red and all the dyes found in the imprinting ink (omissions include: FD&C Blue FD&C Red D&C Blue , and D&C Yellow . Please revise the inactive listing to include these.

c. INDICATIONS AND USAGE

Revise the first sentence of paragraph one to read:

Butalbital, aspirin, caffeine and codeine phosphate capsules are indicated for... (rather than "...is indicated for...")

d. DRUG ABUSE AND DEPENDENCE

Butalbital, aspirin, caffeine and codeine phosphate capsules are controlled... (rather than "This product is controlled...")

e. HOW SUPPLIED

- i. Delete all the terminal zeros in this section (i.e., "greater than 1 g" rather than "greater than 1.0 g" and "lethal dose 0.5 to 1 g" rather than "lethal dose 0.5-1.0 g")
- ii. Replace all the hyphens in this section with the word "to" (e.g., "0.5 to 1 g")
- iii. Each yellow and blue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsule USP, 50 mg/325 mg/40 mg/30 mg is... (delete the

word "capsule" after "30 mg")

Please revise your container labels and package insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve 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.

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 your last submission with all differences annotated and explained.

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

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No  
 If no, list why:

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

**BASIS OF APPROVAL:**

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Fiorinal with Codeine Capsules

NDA Number: 19-429

NDA Drug Name: Fiorinal (Butalbital/Aspirin/Caffeine) with Codeine Capsules USP, 50 mg/325 mg/40 mg/30 mg

NDA Firm: Sandoz Pharmaceuticals Corporation

Date of Approval of NDA Insert and supplement #: 4-29-91 (S-001)

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: label on file and side-by-sides submitted

**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
<b>Error Prevention Analysis</b>			
Has the firm proposed a proprietary name? NO		X	

	Yes	No	N.A.
<b>Packaging</b>			
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	
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	
<b>Labeling</b>			
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	
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.		X	
<b>Inactive Ingredients:</b> (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? See note to chemist.	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

	Yes	No	N.A.
<b>USP Issues:</b> (PTR: 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? Exceeds NDA but meets USP requirements.		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.		X	
<b>Bioequivalence Issues:</b> (Compare bioequivalency values: insert to study. List C <sub>max</sub> , T <sub>max</sub> , 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		
<b>Patent/Exclusivity Issues?:</b> PTR: 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.		X	

\*\*\*\*\*NOTE TO PROJECT MANAGER\*\*\*\*\*

Please ensure the note to the chemist is answered prior to faxing the labeling review. Thanks.

\*\*\*\*\*NOTE/QUESTION TO THE CHEMIST:\*\*\*\*\*

See comment (b) (ii) under INSERT. Do you concur?

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of the listed drug (Fiorinal with Codeine; Approved April 29, 1991, Revised November 1, 1990). Since recent changes approved for Fiorinal (NDA 17-534) and Fioricet with Codeine (NDA 20-232) should apply to this drug product, PM, Deborah Gunter, has been asked to include this labeling in her analysis. She has responded to an E-mail sent to her concerning this and is in the process of trying to consolidate the insert labeling for all three products.
2. Patent/ Exclusivities:  
  
There are no patents or exclusivities that pertain to this drug product.
3. Storage/Dispensing Conditions:  
  
NDA: Store and dispense below 77°F (25°C) in a tight container.

ANDA: Store and dispense below 77°F (25°C) in a tight, light-resistant container.

USP: Preserve in tight, light-resistant containers.

4. Product Line:

The innovator markets their product in bottles of 100s and unit-dose containers of 25s.

The applicant proposes to market their product in bottles of 100s and 500s.

5. The capsule imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See page 129.

6. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **inconsistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 55. See note to chemist and comment (b)(ii) under INSERT.

7. All manufacturing will be performed by Jerome Stevens Pharmaceuticals. No outside firms are utilized. See pages 118 and 123.

8. Container/Closure:

This product will be packaged in white HDPE containers with a screw cap.

9. Review done with red jacket.

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Date of Review: 4-24-98 Date of Submission: 9-29-97

Primary Reviewer: Adolph Vezza

Date:

*A. Vezza*

*5/7/98*

Team Leader: Charlie Hoppes

Date:

*Charlie Hoppes*

*5/7/98*

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cc:

74951NA2.L

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

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ANDA Number: **74-951** Date of Submission: **September 29, 1997**

Applicant's Name: **Jerome Stevens Pharmaceuticals Inc.**

Established Name: **Butalbital, Aspirin, Caffeine, and  
Codeine Phosphate Capsules USP,  
50 mg/325 mg/40 mg/30 mg**

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Labeling Deficiencies:

1. GENERAL COMMENTS:

- a. As a result of the FDA Modernization Act of 1997, the statement "CAUTION: Federal law..." must be replaced with the symbol "Rx only" or "R only" throughout your labels and labeling. We refer you to the Guidance For Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements...", at the internet site: <http://www.fda.gov/cder/guidance/index.htm> for guidance.
- b. The FDA Modernization Act of 1997 has deleted the requirement for the presence of the statement "WARNING: May be habit-forming." throughout the labels and labeling of scheduled drugs. You may remove this statement from your labels and labeling.

2. CONTAINER 100s and 500s

- a. See GENERAL COMMENTS above.
- b. Usual Adult Dosage - Revise to read as follows:  
  
1 or 2 capsules every 4 hours. Total daily dose should not exceed 6 capsules. [N.B. not "1-2"]

3. INSERT

a. GENERAL COMMENT

Please improve the print quality, especially of the subscripts, throughout the text of the insert.

b. DESCRIPTION

- i. See GENERAL COMMENTS [under (1)] above.
- ii. Please note you have failed to provide all of the dyes and colorants found in the capsule

clude

c. INDICATIONS AND USAGE

Revise the first sentence of paragraph one to read:

Butalbital, aspirin, caffeine and codeine phosphate capsules are indicated for... (rather than "...is indicated for...")

d. DRUG ABUSE AND DEPENDENCE

Butalbital, aspirin, caffeine and codeine phosphate capsules are controlled... (rather than "This product is controlled...")

e. HOW SUPPLIED

- i. Delete all the terminal zeros in this section (i.e., "greater than 1 g" rather than "greater than 1.0 g" and "lethal dose 0.5 to 1 g" rather than "lethal dose 0.5-1.0 g")
- ii. Replace all the hyphens in this section with the word "to" (e.g., "0.5 to 1 g")
- iii. Each yellow and blue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsule USP, 50 mg/325 mg/40 mg/30 mg is... (delete the

word "capsule" after "30 mg")

Please revise your container labels and package insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve 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.

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 your last submission with all differences annotated and explained.

A handwritten signature in black ink, appearing to read "Jerry Phillips", is written over a horizontal line. To the right of the signature, there is a large, stylized flourish or mark.

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



CDER Establishment Evaluation Report  
for April 30, 1997

Establishment:

DMF No:

Responsibilities:

**DRUG SUBSTANCE MANUFACTURER**

Profile: CSN

OAI Status: NONE

Last Milestone: OC RECOMMENDATIO 06-JAN-1997

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment:

DMF No:

Responsibilities:

**DRUG SUBSTANCE MANUFACTURER**

Profile: CSN

OAI Status: NONE

Last Milestone: OC RECOMMENDATIO 13-FEB-1997

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
FOOD AND DRUG ADMINISTRATION

**ESTABLISHMENT EVALUATION REQUEST**

REQUEST TYPE (Check One) <input checked="" type="checkbox"/> Original <input type="checkbox"/> FollowUp <input type="checkbox"/> FUR	DATE December 24, 1996	PHONE NO. 594-0305	EER ID #
REQUESTORS NAME: Tim Ames	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-647
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-951			
BRAND NAME:	ESTABLISHED NAME: Aspirin 325 mg/Butalbital 50 mg/Caffeine 40 mg/Codeine Phosphate 30 mg Capsule		
DOSAGE STRENGTH:	STERILE <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
PROFILE CLASS.: CHG	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)		
APPLICANT'S NAME: Jerome Stevens Pharmaceuticals, Inc.			
APPLICANT'S ADDRESS: 60 DaVinci Dr. Bohemia, NY 11716			
COMMENTS :			

**FACILITIES TO BE EVALUATED**

(Name and Complete Address)

RESPONSIBILITY

DMF NUMBER/  
PROFILE CODE

FKEY  
CIRTS ID

HFD-324 USE ONLY

1.		Drug Substance Supplier (Aspirin)	CSN			
2.	F	nisco) Drug Substance Supplier (Butalbital)	CSN			
3.		Drug Substance Supplier (Caffeine)	CSN			
4.		4 Drug substance Supplier (Caffeine)	CSN			
5.	Germany	Drug Product Manufacturer	CHG			

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

OHM FDA 3274 (8/92)

Distribution: Original and Yellow Copy: HFD-324.

c: ANDA 74-951 HFD-647/Div File, HFD-617/JWilson, HFD-617/TAmes, HFD-647/JSimmons HFD-647/GJSmith

*REPLICA REQUEST ?? continue 12/24/96 to 1/2/97 see EER 4/30/97*

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

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ANDA Number: 74-951 Date of Submission: November 26, 1996

Applicant's Name: Jerome Stevens Pharmaceuticals Inc.

Established Name: Butalbital, Aspirin, Caffeine, and  
Codeine Phosphate Capsules USP,  
50 mg/325 mg/40 mg/30 mg

Labeling Deficiencies:

1. GENERAL COMMENTS:

- a. Revise the established name on all labels and labeling to read as follows:

Butalbital, Aspirin, Caffeine and Codeine  
Phosphate Capsules USP

- b. Revise to read "mcg" rather than "µg" throughout the text of the insert.

2. CONTAINER

- a. See GENERAL COMMENTS a above.
- b. Include the product strength on the main panel to appear in conjunction with the established name.
- c. Usual Adult Dosage - Revise to read as follows:  
1 or 2 capsules every 4 hours. Total daily dose should not exceed 6 capsules.
- d. 25°C(77°F)
- e. Place an asterisk after "BUTALBITAL" and after "PHOSPHATE" in the established name.

3. INSERT

- a. TITLE

See GENERAL COMMENTS a.

b. DESCRIPTION

- i. Revise the first sentence to read:  
Each capsule for oral administration contains...
- ii. Revise to read "molecular formula" rather than "empirical formula". [2 places].
- iii. Include the molecular formulas, structural formulas and molecular weights of each active ingredient.
- iv. Inactive Ingredients - Revise to read "pregelatinized starch" rather than "starch" and "colloidal silicon dioxide" rather than "silicon dioxide".

c. CLINICAL PHARMACOLOGY

- i. Pharmacokinetics - Insert the following text to appear as the first paragraph:  
  
Bioavailability: The bioavailability of the components of the fixed combination of butalbital, aspirin, caffeine and codeine is identical to their bioavailability when butalbital, aspirin, caffeine and codeine is administered separately in equivalent molar doses.
- ii. Aspirin - Revise the penultimate sentence of the penultimate paragraph to read as follows:  
  
...component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...
- iii. Butalbital - Revise the first sentence of the penultimate paragraph to read as follows:  
  
...component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...
- iv. Caffeine - Revise the first sentence of the penultimate paragraph to read as follows:  
  
...component for butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...

d. INDICATIONS

- i. Revise this section heading to read:

INDICATIONS AND USAGE

- ii. Revise the first sentence of paragraph one to read:

Butalbital, aspirin, caffeine and codeine phosphate capsules are indicated for...

- iii. Insert the following text to appear as the second paragraph:

Evidence supporting the efficacy of butalbital, aspirin, caffeine and codeine phosphate capsules is derived from 2 multi-clinic trials that compared patients with tension headache randomly assigned to 4 parallel treatments: 1) butalbital, aspirin, caffeine and codeine; 2) codeine; 3) butalbital, aspirin, and caffeine; 4) placebo. Response was assessed over the course of the first 4 hours of each of 2 distinct headaches, separated by at least 24 hours. The combination product of butalbital, aspirin caffeine, and codeine proved statistically significantly superior to each of its components and to placebo on measures of pain relief.

- iv. Revise the last paragraph to read as follows:

...safety of butalbital, aspirin, caffeine, and codeine in the treatment of...

e. CONTRAINDICATIONS

This combination product...

f. PRECAUTIONS

- i. General - Revise the first sentence of paragraph one to read as follows:

Butalbital, aspirin, caffeine, and codeine should be prescribed with caution for...

- ii. Information for Patients

A) Paragraph one - ...that this combination product contains...

- B) Paragraph two - Butalbital, aspirin, caffeine, and codeine may impair...

iii. Drug Interactions

- A) Revise paragraph three to read:

Butalbital, aspirin, caffeine, and codeine may...

- B) Penultimate paragraph - Butalbital, aspirin, caffeine, and codeine may diminish...

iv. Usage in Pregnancy

- A) Revise this subsection heading to read "Pregnancy" rather than "Usage in Pregnancy".

- B) Teratogenic Effects - Revise to read as follows:

...conducted with butalbital, aspirin, caffeine, and codeine. It is...this combination product...

- C) Nonteratogenic Effects - Place a period following the last sentence of the second paragraph.

v. Pediatric Use - Revise to read:

...in pediatric patients below the...

g. ADVERSE REACTIONS

- i. Commonly Observed - Replace "this product" with "butalbital, aspirin, caffeine and codeine".

ii. Incidence in Controlled Clinical Trials

- A) Paragraph one - ...comparing the combination product to placebo...

- B) Paragraph two, last sentence - ...obtained from other clinical...

- iii. Insert the following text to appear as the first paragraph following the table:

**Other Adverse Events Reported During  
Controlled Clinical Trials**

The listing that follows represents the proportion of the 382 patients exposed to butalbital, aspirin, caffeine, and codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving the combination product, the adverse events were not necessarily caused by butalbital, aspirin, caffeine, and codeine.

iv. Miscellaneous, second paragraph - ...patients treated with the combination product, are...

h. DRUG ABUSE AND DEPENDENCE

Butalbital, aspirin, caffeine and codeine phosphate capsules are controlled...

i. OVERDOSAGE

i. Revise paragraph one to read as follows:

...overdosage of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules are attributable...toxicity from this combination product is unlikely.

ii. Treatment

A) Paragraph one, first sentence - ...with this combination product.

B) Paragraph four - ...intravenous administration.

C) Paragraph five, second sentence - ...a dose of 0.4 mg to 2 mg...

iii. Toxic and Lethal Doses - Delete the terminal zeros from "1 g", "2 g" and "5 g".

j. HOW SUPPLIED

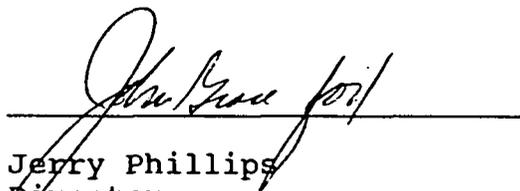
i. Each yellow and blue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsule USP, 50 mg/325 mg/40 mg/30 mg is...

ii. See comment 2(d).

Please revise your container labels and package insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve 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.

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 your last submission with all differences annotated and explained.

A handwritten signature in cursive script, appearing to read "Jerry Phillips", is written over a horizontal line.

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

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

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ANDA Number: **74-951**      Date of Submission: **November 26, 1996**

Applicant's Name: **Jerome Stevens Pharmaceuticals Inc.**

Established Name: **Butalbital, Aspirin, Caffeine, and Codeine  
Phosphate Capsules USP,  
50 mg/325 mg/40 mg/30 mg**

Labeling Deficiencies:

1. GENERAL COMMENTS:
  - a. Revise the established name on all labels and labeling to read as follows:

Butalbital, Aspirin, Caffeine and Codeine  
Phosphate Capsules USP
  - b. Revise to read "mcg" rather than "µg" throughout the text of the insert.
2. CONTAINER
  - a. See GENERAL COMMENTS a above.
  - b. Include the product strength on the main panel to appear in conjunction with the established name.
  - c. Usual Adult Dosage - Revise to read as follows:

1 or 2 capsules every 4 hours. Total daily dose  
should not exceed 6 capsules.
  - d. 25°C(77°F)
  - e. Place an asterisk after "BUTALBITAL" and after "PHOSPHATE" in the established name.
3. INSERT
  - a. TITLE

See GENERAL COMMENTS a.

b. DESCRIPTION

- i. Revise the first sentence to read:

Each capsule for oral administration contains...

- ii. Revise to read "molecular formula" rather than "empirical formula". [2 places].
- iii. Include the molecular formulas, structural formulas and molecular weights of each active ingredient.
- iv. Inactive Ingredients - Revise to read "pregelatinized starch" rather than "starch" and "colloidal silicon dioxide" rather than "silicon dioxide".

c. CLINICAL PHARMACOLOGY

- i. Pharmacokinetics - Insert the following text to appear as the first paragraph:

Bioavailability: The bioavailability of the components of the fixed combination of butalbital, aspirin, caffeine and codeine is identical to their bioavailability when butalbital, aspirin, caffeine and codeine is administered separately in equivalent molar doses.

- ii. Aspirin - Revise the penultimate sentence of the penultimate paragraph to read as follows:

...component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...

- iii. Butalbital - Revise the first sentence of the penultimate paragraph to read as follows:

...component of butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...

- iv. Caffeine - Revise the first sentence of the penultimate paragraph to read as follows:

...component for butalbital, aspirin, caffeine and codeine phosphate capsules is equivalent...

d. INDICATIONS

- i. Revise this section heading to read:

INDICATIONS AND USAGE

- ii. Revise the first sentence of paragraph one to read:

Butalbital, aspirin, caffeine and codeine phosphate capsules are indicated for...

- iii. Insert the following text to appear as the second paragraph:

Evidence supporting the efficacy of butalbital, aspirin, caffeine and codeine phosphate capsules is derived from 2 multi-clinic trials that compared patients with tension headache randomly assigned to 4 parallel treatments: 1) butalbital, aspirin, caffeine and codeine; 2) codeine; 3) butalbital, aspirin, and caffeine; 4) placebo. Response was assessed over the course of the first 4 hours of each of 2 distinct headaches, separated by at least 24 hours. The combination product of butalbital, aspirin caffeine, and codeine proved statistically significantly superior to each of its components and to placebo on measures of pain relief.

- iv. Revise the last paragraph to read as follows:

...safety of butalbital, aspirin, caffeine, and codeine in the treatment of...

e. CONTRAINDICATIONS

This combination product...

f. PRECAUTIONS

- i. General - Revise the first sentence of paragraph one to read as follows:

Butalbital, aspirin, caffeine, and codeine should be prescribed with caution for...

- ii. Information for Patients

A) Paragraph one - ...that this combination product contains...

- B) Paragraph two - Butalbital, aspirin, caffeine, and codeine may impair...

iii. Drug Interactions

- A) Revise paragraph three to read:

Butalbital, aspirin, caffeine, and codeine may...

- B) Penultimate paragraph - Butalbital, aspirin, caffeine, and codeine may diminish...

iv. Usage in Pregnancy

- A) Revise this subsection heading to read "Pregnancy" rather than "Usage in Pregnancy".

- B) Teratogenic Effects - Revise to read as follows:

...conducted with butalbital, aspirin, caffeine, and codeine. It is...this combination product...

- C) Nonteratogenic Effects - Place a period following the last sentence of the second paragraph.

v. Pediatric Use - Revise to read:

...in pediatric patients below the...

g. ADVERSE REACTIONS

- i. Commonly Observed - Replace "this product" with "butalbital, aspirin, caffeine and codeine".

ii. Incidence in Controlled Clinical Trials

- A) Paragraph one - ...comparing the combination product to placebo...

- B) Paragraph two, last sentence - ...obtained from other clinical...

- iii. Insert the following text to appear as the first paragraph following the table:

**Other Adverse Events Reported During  
Controlled Clinical Trials**

The listing that follows represents the proportion of the 382 patients exposed to butalbital, aspirin, caffeine, and codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving the combination product, the adverse events were not necessarily caused by butalbital, aspirin, caffeine, and codeine.

iv. Miscellaneous, second paragraph - ...patients treated with the combination product, are...

h. DRUG ABUSE AND DEPENDENCE

Butalbital, aspirin, caffeine and codeine phosphate capsules are controlled...

i. OVERDOSAGE

i. Revise paragraph one to read as follows:

...overdosage of Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules are attributable...toxicity from this combination product is unlikely.

ii. Treatment

A) Paragraph one, first sentence - ...with this combination product.

B) Paragraph four - ...intravenous administration.

C) Paragraph five, second sentence - ...a dose of 0.4 mg to 2 mg...

iii. Toxic and Lethal Doses - Delete the terminal zeros from "1 g", "2 g" and "5 g".

j. HOW SUPPLIED

i. Each yellow and blue Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsule USP, 50 mg/325 mg/40 mg/30 mg is...

ii. See comment 2(d).

Please revise your container labels and package insert labeling, as instructed above, and submit final printed labels and labeling.

Please note that we reserve 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.

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 your last submission with all differences annotated and explained.

---

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

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling?    Yes    No  
If no, list why:

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

**BASIS OF APPROVAL:**

Was this approval based upon a petition?    Yes    No

What is the RLD on the 356(h) form:

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:  
Has this been verified by the MIS system for the NDA?  
Yes    No

Was this approval based upon an OGD labeling guidance?    No  
Basis of Approval for the Container Labels:  
Basis of Approval for the Carton Labeling:

# 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 Z3	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
<b>Error Prevention Analysis</b>			
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? USAM 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
<b>Packaging</b>			
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	
<b>Labeling</b>			
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.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD? Product is a capsule.			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? See note to chemist.	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? Exceeds NDA but meets USP requirements.		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.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List C <sub>max</sub> , T <sub>max</sub> , 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?: FIR: 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.		X	
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\*\*\*\*\*NOTE TO PROJECT MANAGER\*\*\*\*\*

Please ensure the notes to the chemist are answered prior to faxing the labeling review. Thanks.

\*\*\*\*\*NOTES/QUESTIONS TO THE CHEMIST:\*\*\*\*\*

1. See comment b(iv) under INSERT. Do you concur? *Concur D. Hestak 5/12/9*
2. The firm lists "D&C Yellow #10, FD&C Blue #1 and FD&C Yellow #6" as inactive ingredients. I believe they are the dyes used in the capsule color. I was unable to find the components of the capsule in the raw materials section of the jacket. Can you verify these ingredients? *Applicant to provide this information. See Chem Rev. D. Hestak 5/12/9*

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FOR THE RECORD:

1. Review based on the labeling of the listed drug (Fiorinal with Codeine; Approved April 29, 1991, Revised November 1, 1990).
2. Patent/ Exclusivities:  
  
There are no patents or exclusivities that pertain to this drug product.
3. Storage/Dispensing Conditions:  
  
NDA: Store and dispense below 77°F (25°C) in a tight container.  
  
ANDA: Store and dispense below 77°F (25°C) in a tight, light-resistant container.  
  
USP: Preserve in tight, light-resistant containers.
4. Scoring:  
  
Not applicable. This product is a capsule.
5. Product Line:  
  
The innovator markets their product in bottles of 100s and unit-dose containers of 25s.  
  
The applicant proposes to market their product in bottles of 100s and 500s.
6. The capsule imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products

for Human Use; Final Rule, effective 9/13/95). See page 129.

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be **inconsistent** with the listing of inactive ingredients found in the statement of components and composition appearing on page 55. See note to chemist.

8. All manufacturing will be performed by Jerome Stevens Pharmaceuticals. No outside firms are utilized. See pages 118 and 123.

9. Container/Closure:

This product will be packaged in white containers with a screw cap.

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Date of Review: March 24, 1997 for Jackie White

Date of Submission: November 26, 1996

Primary Reviewer:

Date:

Secondary Reviewer:

Date:

Team Leader:

Date:

---

cc:

L



lallncrodt Chemical Inc.  
.O. Box 5432  
t. Louis, MO 63147

Drug Substance Manufacturer  
(codeine)

4839  
CSN

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DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
FOOD AND DRUG ADMINISTRATION

**ESTABLISHMENT EVALUATION REQUEST**

REQUEST TYPE (Check One) <input checked="" type="checkbox"/> Original <input type="checkbox"/> FollowUp <input type="checkbox"/> FUR	DATE October 9, 1996	PHONE NO.	EER ID #
REQUESTORS NAME: Tim Ames	DIVISION: Office of Generic Drugs		MAIL CODE: HFD-647
APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-951			
BRAND NAME:	ESTABLISHED NAME: Aspirin 325 mg/Butalbital 50 mg/Caffeine 40 mg/Codeine Phosphate 30 mg Capsule		
DOSAGE STRENGTH:			STERILE <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
PROFILE CLASS.: CHG	PRIORITY CLASSIFICATION (See SMG CDER-4820.3)		
APPLICANT'S NAME: Jerome Stevens Pharmaceuticals, Inc.			
APPLICANT'S ADDRESS: 60 DaVinci Dr. Bohemia, NY 11716			
COMMENTS :			

**FACILITIES TO BE EVALUATED**

(Name and Complete Address)

RESPONSIBILITY

DMF NUMBER/  
PROFILE CODE

FKEY  
CIRTS ID

HFD-324 USE ONLY

(Name and Complete Address)	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY
	Drug Substance Supplier (Aspirin)	CSN		
2. (sco)	Drug Substance Supplier (Butalbital)	CSN		
	Drug Substance Supplier (Caffeine)	CSN		
	Drug substance Supplier (Caffeine)	CSN		
3. Applicant	Drug Product Manufacturer	CHG		

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

EROME STEVENS  
0 DAVINCI DR  
OHEMIA

NY 11716

NDA #: N074951

Dear Sir/Madam:

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

## NAME OF DRUG:

MUTALBITAL;ASPIRIN;CAFFEINE;CODEINE PHOSPHATE

Dosage Form: CAP Potency: 50MG/32MG/40MG/30MG

USP: Y

*USP,*

DATE OF APPLICATION: 29-AUG-96

DATE OF RECEIPT: 30-AUG-96

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

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

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

Sincerely yours,

*Simmons*  
*Rendon VII*

HFD-647

Roger L. Williams, M.D.  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION/MEETING

I conveyed to Mr. Steinlauf that the application was lacking a few items before we could accept it for filing. I explained that he should provide this informatin to us within 10 working days. The following items were requested:

- a signed certification of compliance with environmental laws
- a written explanation of the annotated portions of the side-by-side labeling comparisons
- a signed CGMP certification

He promised to fax these items in right away.

DATE

September 30,  
1996

ANDA NUMBER

74-951

IND NUMBER

TELECON

INITIATED BY      MADE  
 \_ APPLICANT/      X BY  
 SPONSOR              TELE.

\_ X FDA              \_ IN  
    PERSON

PRODUCT NAME

Butalbital/  
Aspirin/Caffeine/  
Codeine Capsules

FIRM NAME

Jerome Stevens  
Pharms

NAME AND TITLE OF  
PERSON WITH WHOM  
CONVERSATION WAS HELD

Ronald Steinlauf  
Vice President

TELEPHONE NUMBER

(516) 567-1113

SIGNATURE



RECORD OF TELEPHONE CONVERSATION

Requested that they submit a certification that Jerome Stevens is in compliance with current good manufacturing practices under 21 CFR parts 210 and 211.

DATE

October 16, 1996

APPLICATION NUMBER

74-95

IND NUMBER

TELECON

INITIATED BY      MADE  
\_ APPLICANT/      \_ BY  
SPONSOR              TELE.

X \_ FDA              \_ IN  
                                 PERSON

PRODUCT NAME  
Butalbital, Aspirin,  
Caffeine, and  
Codeine Phosphate

FIRM NAME  
Jerome Stevens

NAME AND TITLE OF  
PERSON WITH WHOM  
CONVERSATION WAS HELD  
  
Ronald Steinlauf

TELEPHONE NUMBER  
  
516-567-1113

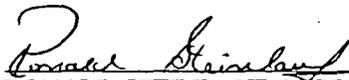
SIGNATURE  
  
Cecelia Parise

SEPTEMBER 30, 1996

FOOD AND DRUG ADMINISTRATION  
MS. ANNA MARIE WEIKEL

PLEASE FIND THE FOLLOWING:

- 2 EACH ... REPLACEMENT FOR PAGE 256
- 2 EACH ... REPLACEMENT FOR PAGE 120
- 2 EACH ... REPLACEMENT FOR PAGE 63
- 2 EACH ... REPLACEMENT FOR PAGE 59
- 2 EACH ... EXPLANATION OF "SIDE BY SIDE LABELING"
- 2 EACH ... COPY OF GRINDSTED NAME CHANGE



RONALD STEINLAUF, VICE PRESIDENT  
JEROME STEVENS PHARMACEUTICALS, INC.

**[314.94(a)(9)] Environmental Impact Analysis Statement**

as per FR Vol.39, No.74 - April 16, 1974

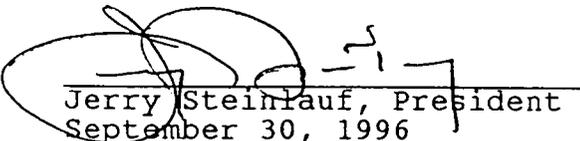
- A. Date: April 6, 1979  
B. Address: Jerome Stevens Pharmaceuticals Inc.  
60 DaVinci Drive  
Bohemia, New York 11716

A Pharmaceutical Manufacturer of compressed and coated tablets and capsules.

1. Described the proposed action.  
No probable impact as no emission to outside atmosphere; and no harmful emission into the water waste.
2. No impact on the environment and no primary or secondary consequences thereby.
  - a) 1. No pollution (air, water, soil)
  2. Complies to ordinance of solid and liquid waste.
  3. No toxic substances are emitted.
  4. No effect on humans, animals or plants.
3. No adverse environmental effect can occur due to the nature of our manufacturing pharmaceuticals in dosage forms as all exhausts are connected to internal closed system dust arrestors.
4. Not applicable
5. Short term and long term actions of production and maintenance does not and cannot result in any adverse emissions to the environment.
6. Not applicable
7. No objections have been received by any other agencies.
8. Not applicable
9. Not applicable

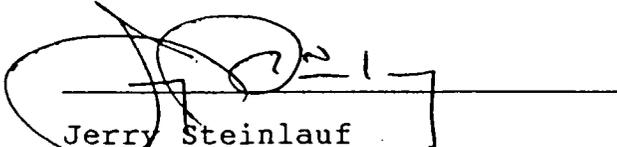
**Certification Statement**

Jerome Stevens Pharmaceuticals certifies that the manufacture of Aspirin 325mg/Butalbital 50mg/Caffeine 40mg/Codeine Phosphate 30mg Capsule is conducted in full accordance with all State and Federal environmental laws.

  
Jerry Steinlauf, President  
September 30, 1996

**CGMP Certification:**

At the time of the filing for this application, Jerome Stevens Pharmaceuticals Inc. believes, to the best of it's knowledge that the firm's faciltiy has CGMP certification from FDA's New York Brooklyn District Office.

A handwritten signature in black ink, appearing to read "Jerry Steinlauf", is written over a horizontal line. The signature is somewhat stylized and includes a large loop on the left side.

Jerry Steinlauf  
President

September 30, 1996

Caffeine USP is manufactured by

located at

4

Reference is made to DMF  
page)

- see authorization letter (next

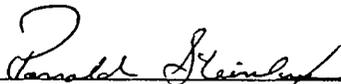
BUTALBITAL USP, MANUFACTURED BY /  
LOCATED AT:

F

K

REFERENCE IS MADE TO DMF

SEE AUTHORIZATION LETTER (NEXT PAGE)

  
\_\_\_\_\_  
RONALD STEINLAUF, VICE PRESIDENT  
JEROME STEVENS PHARMACEUTICALS, INC.  
SEPTEMBER 30, 1996