CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40257

CORRESPONDENCE

ANDA 40-257

OCT 6 1997

Mallinckrodt Chemical, Inc.
Attention: Marianne Robb
16305 Swingley Ridge Drive
Chesterfield, MO 63017

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Oxycodone and Acetaminophen Capsules USP, 5mg/500mg.

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

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

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,

/S/

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

MALLINCKRODT
Improving Healthcare and Chemistry

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone: 314.654.2000

TELEPHONE AMENDMENT

July 3, 1998

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 40-257: Oxycodone and Acetaminophen Capsules, USP (5 mg/500 mg)

Dear Madame or Sir:

Final Printed Labeling is provided in response to a June 22, 1998 telephone conversation with Chan Park of the Agency. Changes have been made in both the package insert and the immediate container label to comply with the FDA Modernization Act of 1997. In addition, the print size of the package insert has been increased to improve readability.

This amendment consists of one volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. In addition, twelve (12) copies of Final Printed Labeling are provided in a separate folder labeled "Final Printed Labeling".

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 654-6125.

Sincerely,

Marianne Robb
Manager, Regulatory Submissions
Telephone: (314) 654-6258
Telefax: (314) 654-6496

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JUL 1998
CENTER FOR GENERIC DRUGS

MALLINCKRODT
Improving Healthcare and Chemistry

Mallinckrodt Inc.
675 McDonnell Boulevard
PO Box 5840
St. Louis MO 63134
Phone: 314.654.2000

MAJOR AMENDMENT

March 12, 1998

ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

RE: ANDA 40-257: Oxycodone and Acetaminophen Capsules, USP (5 mg/500 mg)

Dear Madame or Sir:

The following information is provided in response to a January 21, 1998 telefax from the Agency. For ease of review, a copy of the January 21 letter is attached and the Agency's comments have been repeated.

This amendment consists of one volume. An archival copy is being filed in a blue folder and a technical review copy is being filed in a red folder. This also certifies that, concurrently with the filing of this Major Amendment, a true copy of the technical sections of the ANDA was sent to the local district office. This "field copy" is contained in a burgundy folder.

Correspondence related to this submission should be addressed to Marianne Robb, Mallinckrodt Inc., 675 McDonnell Blvd., St. Louis, Missouri 63134. If there are any questions concerning this information, please contact myself or Robert Lake, Ph.D. at (314) 654-6125.

Sincerely,

Marianne Robb

Marianne Robb
Manager, Regulatory Submission
Telephone: (314) 654-6258
Telefax: (314) 654-6496

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MAR 13 1998
GENERIC DRUGS

FDA Comments of January 21, 1998 Followed by Mallinckrodt Responses

Comment:

1. *Your components and composition table should be revised to reflect the actual amount of oxycodone hydrochloride equivalent to oxycodone base in your proposed formulation.*

Response

A revised components and composition table which reflects the actual amount of oxycodone hydrochloride equivalent to oxycodone base in the proposed formulation is provided as Attachment 1.

Comment

2. *Your specification and test methods for oxycodone HCl, submitted on page 78, specify the assay value to be in the range of % when calculated on an anhydrous solvent-free basis which is in accordance with the USP. The COA for oxycodone HCl found on page 87 specifies the assay limits as %. Please revise your release COA reporting requirements to comply with the USP specifications.*

Response:

A revised COA for oxycodone HCl lot 8865 T13799 that reflects the revised reporting requirements (specifying the assay value to be in the range of % when calculated on an anhydrous solvent-free basis which are in accordance with current USP specifications for assay) is provided as Attachment 2.

Comment:

3. *The Organic Volatile Impurities analysis should be incorporated into the release tests for Acetaminophen USP. Data obtained for your drug substance lot used to manufacture the demonstration batch should be provided.*

Response:

As allowed by USP 23 <467>, in order to avoid uneccessary testing, the release test for Acetaminophen USP contains a statement that based on the manufacturing process and controlled handing and storage of Acetaminophen, there is no potential for Benzene, Chloroform, 1-4 Dioxane, Ethylene Oxide, Methylene Chloride or Trichloroethylene to be present and the material, if tested, will comply with USP. Annually, Mallinckrodt at the Raleigh manufacturing facility tests three lots of Acetaminophen for OVI to confirm their absence. A copy of the OVI testing data obtained for the drug substance lot used to manufacture the demonstration batch (Mallinckrodt St. Louis Lot 4814T19340, originally Mallinckrodt Raleigh Lot 4814996J032), the original Certificate of Analysis from Mallinckrodt Raleigh, and the Laboratory Analysis from Mallinckrodt St. Louis are provided as Attachment 3. The data are acceptable and no USP OVI were detected in Acetaminophen Lot 4814996J032.

Comment:

In addition, please justify the use of a qualitative analysis for APAP related substances for release purposes.

Response:

Acetaminophen (Code 4814) is not only certified as meeting USP requirements but also as meeting European Pharmacopoeial (Ph Eur) requirements. The qualitative analysis for APAP related substances for release purposes in question is a British Pharmacopoeial (BP) requirement and is performed prior to release of all material. A quantitative chromatographic homogeneity test is noted on pages 461 to 463 of DMF as updated December 1997 and is performed on each lot of Acetaminophen (Code 4814) raw material. A copy of these pages are provided as Attachment 4.

Comment:

4. *FT-IR spectra for the lots of active raw materials used to manufacture the demonstration batch vs. Official USP reference standard lots should be provided.*

Response:

FT-IR spectra for the lots of active raw materials used to manufacture the demonstration batch vs. Official USP reference standard lots are provided as Attachment 5.

Comment:

5. *We noted that the particle size distribution, blend unifomity (for oxycodone hydrochloride which is % w/w of the total formulation) and bulk/tap density analyses were not established as regular in-process controls for the final blend prior to encapsulating. We recommend that these analyses be incorporated as in-process controls to ensure that future production batches will exhibit the potency, uniformity and physical properties as the exhibit batch. Therefore, these analyses should be performed for all post-approval production batches.*

Response:

The following in-process controls for blend uniformity, bulk/tap density, and particle size distribution have been incorporated into the batch record for Oxycodone and Acetaminophen Capsules USP to ensure that future production batches will exhibit the potency, uniformity, and physical properties as the exhibit batch. A copy of the revised batch record for the blend is provided as Attachment 6. A copy of the revised specifications and methods for the blend is provided as Attachment 7.

Blend Uniformity (Assay RSD):	% maximum	
Density:	g/mL	
Particle Size:	US mesh	% maximum
	US mesh	% minimum

Comment:

6. *The proposed in-process control for the capsule weight range is considered to be too broad. Please revise according to the data obtained for the demonstration batch (page 236).*

Response:

The current in-process control for the filled capsule weight range is the result of both weight variations of the empty capsule mg) and the fill-weight range mg). Based on data obtained for the exhibit batch, the revised in-process control for the fill-weight range is mg. A copy of the revised batch record is provided as Attachment 8.

Comment:

7. *It is recommended that a related substances specification be established for drug product release purposes. Also, data showing that reasonable attempts were made to identify the degradants and/or impurities found in your final drug product should be provided.*

Response:

The specifications and methods for Oxycodone and Acetaminophen Capsules, USP (SMM for Code 9127) have been revised to include a release specification for product release purposes of % (by Area) Maximum Each. The only degradant and/or impurity seen in Oxycodone and Acetaminophen Capsules, USP under either accelerated or room temperature storage conditions was free p-aminophenol % (w/w)). A reasonable attempt will be made to identify any degradant and/or impurity seen in Oxycodone and Acetaminophen Capsules, USP under either accelerated or room temperature storage conditions at % (by area) maximum. A revised copy of SMM for Code 9127 is provided as Attachment 9.

Comment:

8. *We noted that the expiration date for the drug product is calculated after encapsulation is complete. State the time frame which you intend to store the final blend before proceeding to encapsulation. It is recommended that the expiry be calculated from the initial time when the first two raw materials are mixed in your proposed formulation.*

Response:

Expiration for the drug product is calculated from the completion of encapsulation. The final blend may be stored without retesting for one month prior to encapsulation. If storage of the final blend exceeds one month, the blend is to be retested prior to encapsulation. Under no circumstances will the final blend be stored prior to encapsulation for a period to exceed two months. If the storage period for the blend exceeds two months, the blend will be destroyed.

In addition, in accordance with 21 CFR §314.94(a)(8)(iv) twelve copies of final printed labeling and a side-by-side comparison of the proposed labeling with that of the last submission with all differences annotated and explained are provided as Attachment 10.