CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-300

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA 40-300 **DRUG PRODUCT:** Methylphenidate Hydrochloride

FIRM: Mallinckrodt Inc. **DOSAGE FORM:** Tablets (Oral)

STRENGTH: 5 mg, 10 mg and 20 mg.

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable -
See **ESTABLISHMENT EVALUATION REPORT** in Volume 1.1, found acceptable 3/24/98.

BIO INFORMATION: Satisfactory -
See the Division of Bioequivalence review, dated 6/30/98.

VALIDATION-(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): NA -
Drug substance and drug product are compendia items.

STABILITY: Satisfactory -
Accelerated (40±2°C/75±5% RH) stability data are provided for lot nos. MHSC9719 (5 mg), MHSC9720 (10 mg) and MHSC9721 (20 mg) tested initially, 1, 2 and 3 months in the upright position. The lots were packaged in the 100 and 1000 count HDPE marketed container/closure systems. Controlled room temperature (25°±2°/60%±5% RH/ambient light) stability data tested at the three month test station are also provided. The data are adequate and within the specified limits. The stability protocol is adequate and within FDA guidelines. An expiration dating of 24 month has been granted.

LABELING: Satisfactory -
See Review of Professional Labeling conducted by Chan Park, concurred by Charlie Hoppes, dated 9/4/98.

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?) Satisfactory -
Lot no. MHSC9721 (MALLINCKRODT'S NDS lot no. T19758 used. DMF was found **ADEQUATE**, dated 9/28/98.

SIZE OF STABILITY BATCHES - Satisfactory -
An executed Master Batch record is provided for Master Blend, lot no. MHSC9718 The batches were manufactured using production scale equipment under production conditions. The Master Blend was divided to produce the exhibit batches:

Strength	Lot Number	Blend	Theoretical Yield	Actual Yield
5 mg	MHSC9719			
10 mg	MHSC9720			
20 mg	MHSC9721			

* The actual quantity of blend used to manufacture the 5 mg tablets was

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The Master Blend will be divided to produce commercial batches as follows (p 2332): The manufacturing process is the same as for the lot no. MHSC9718 batch size.

Strength	Master Blend	Tablets
5 mg		
10 mg		
20 mg		

RECOMMENDATION:
APPROVE

Raymond Brown

Raymond Brown

10/19/98
Date

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

ANDA Number: 40-300 Date of Submission: February 27, 1998

Applicant's Name: Mallinckrodt Inc.

Established Name: Methylphenidate Hydrochloride Tablets USP, 5 mg, 10 mg, & 20 mg

Labeling Deficiencies:

1. GENERAL COMMENTS

   Replace the "Caution: Federal law..." statement with "**Rx only**" or "**℞ only**" on labels and labeling. We refer you to the Guidance for Industry, "Implementation of Section 126, Elimination of Certain Labeling Requirements, of the Food and Drug Administration Modernization Act of 1997", at the internet site: **http://www.fda.gov/cder/guidance/index.htm** for guidance.

2. CONTAINER - 100's & 1000's

   a. See general comment.

   b. We encourage you to increase the prominence of the statement "Protect from light".

   c. Revise the storage requirement to read "Store at controlled room temperature 15° - 30°C (59° - 86°F).".

   d. 1000's - You may include the following statement.

      This package is not for household use.

3. INSERT

   a. GENERAL COMMENTS

      You may delete "USP" from the drug product name throughout the text except in the DESCRIPTION and HOW SUPPLIED sections.

b. DESCRIPTION

i. First sentence - Revise to read as follows:

Methylphenidate hydrochloride is a mild... stimulant.

ii. Structural formula

Include "• HCL" in the formula.

iii. Second paragraph

You may delete the last sentence. [redundant]

iv. Last paragraph - Revise to read as follows:

Each tablet, for oral administration, contains 5 mg, 10 mg, or 20 mg of methylphenidate hydrochloride. In addition, each tablet contains...

c. CLINICAL PHARMACOLOGY - First sentence:

Methylphenidate is a mild...

d. CONTRAINDICATIONS - First sentence:

..., to methylphenidate, since ...

e. WARNINGS

i. Replace "methylphenidate hydrochloride" with "methylphenidate" throughout the text.

ii. Second paragraph, second sentence:

... of growth (*i.e.*, weight... [rather than "ie,"]

iii. Second paragraph, third sentence:

Relocate this sentence to begin a new third paragraph.

f. PRECAUTIONS

i. Last paragraph, last sentence:

Relocate this sentence to begin a new last

paragraph.

ii. Carcinogenesis,... Fertility - Last paragraph:

Italicize "in vitro" and "in vivo" throughout the text.

g. ADVERSE REACTIONS

i. First paragraph, last sentence:

... reported in patients taking this drug: instances of abdominal liver function, ranging from transaminase elevation to hepatic coma; isolated...

ii. Include the following statement immediately after the last sentence of the first paragraph.

Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten year old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause.

h. OVERDOSAGE

i. Include the following as the second paragraph:

Consult with a Certified Poison Control Center regarding treatment for up-to-date guidance and advice.

ii. Second paragraph:

A) Revise the third sentence to read as follows:

Gastric contents may be evacuated by gastric lavage.

B) Include the following as the last sentence:

Other measures to detoxify the gut include administration of activated charcoal and a cathartic.

i. DOSAGE AND ADMINISTRATION - Children (6 years and over) - penultimate paragraph:

Methylphenidate hydrochloride tablets should...

j. HOW SUPPLIED

i. See general comment.

ii. See comment (c) under CONTAINER.

iii. Describe your drug products as "unscored".

iv. Delete "a" when describing the debossing of the drug product. [e.g., ...with 5 on one... rather than with a 5 on one...]

v. ... with child-resistant closure. [add a "hyphen"]

vi. Include "Protect from moisture." as appears in the package insert labeling of the reference listed drug.

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

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 the last submitted labeling 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