

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-475

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

DEPARTMENT OF HEALTH AND
HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Clinical Pharmacology & Biopharmaceutics
(HFD 860/870/880)
Tracking/Action Sheet for Formal/Informal Consults

From: Wen-Hwei Chou

To: DOCUMENT ROOM

DATE: 03/17/03

IND No.: NA

NDA No. 21,475

DATE OF DOCUMENT

02/14/2003

NAME OF DRUG

Methylin chewable tablets
(Methylphenidate HCl chewable
tablet)

PRIORITY CONSIDERATION

S

Date of informal/Formal
Consult

03/10/2003

NAME OF THE SPONSOR: [Mallinckrodt Inc.]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

- | | | |
|--|---|--|
| <input type="checkbox"/> PRE-IND | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> IN-VITRO METABOLISM | <input type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> CORRESPONDENCE |
| <input type="checkbox"/> PROTOCOL | <input type="checkbox"/> SUPAC RELATED | <input type="checkbox"/> DRUG ADVERTISING |
| <input type="checkbox"/> PHASE II PROTOCOL | <input type="checkbox"/> CMC RELATED | <input type="checkbox"/> ADVERSE REACTION REPORT |
| <input type="checkbox"/> PHASE III PROTOCOL | <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> ANNUAL REPORTS |
| <input type="checkbox"/> DOSING REGIMEN CONSULT | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS | <input type="checkbox"/> FAX SUBMISSION |
| <input type="checkbox"/> PK/PD- POPPK ISSUES | <input type="checkbox"/> MEETING PACKAGE (EOP2) | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> PHASE IV RELATED | | [Response to approvable letter
dated 10/18/2002] |

REVIEW ACTION

- | | | |
|---|---|--|
| <input type="checkbox"/> NAI (No action indicated) | <input type="checkbox"/> Oral communication with | Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to: | Name: [] | <input checked="" type="checkbox"/> See comments below |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox | <input type="checkbox"/> Comments communicated in meeting | <input type="checkbox"/> See submission cover letter |
| <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others | | OTHER (SPECIFY BELOW): |
| (Check as appropriate and attach e-mail) | | [] |

REVIEW COMMENT(S)

NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

This is a review of sponsor's response to Agency's approvable letter dated 10/08/2002. The sponsor agrees to adopt all the labeling in Clinical Pharmacology section recommended in the approvable letter. Unfortunately, the approvable letter did not accurately incorporate the labeling comments from the Office of Clinical Pharmacology & Biopharmaceutics review dated 8/28/2002. The labeling comments in the Clinical Pharmacology section in the AE letter specifically drug product name (Methylin CT versus Methylin) and some quantitative values were incorrect. [Note: OCPB did not have any opportunity to comment on this letter.] See attachments for details: OCPB labeling comments (attachment 1), labeling comments in approvable letter (attachment 2), and sponsor's revised label (attachment 3).

Recommendation:

Please send the edited version of labeling comments from the Office of Clinical Pharmacology and Biopharmaceutics (described below) to the sponsor. ✓ fixed on 3/20/03

Note: Unless specified, the revised labeling is acceptable. Only the sections that need changes are incorporated here. Strikethrough indicates deletion, underline indicates addition.

Absorption

Methylin chewable tablets are readily absorbed. Following oral administration of Methylin chewable tablets, peak plasma methylphenidate concentrations are achieved at about 1 to 2 hours. Methylin chewable tablets have been shown to be bioequivalent to Ritalin® tablet. The mean Cmax following a 20mg dose is approximately - 10 ng/ml.

Food Effect

In a study in adult volunteers to investigate the effects of a high-fat meal on the bioavailability of Methylin chewable tablets at a dose of 20mg, the presence of food delayed the peak by approximately 1 hour (- 1.5 hours, fasted and - 2.4 hours, fed). Overall, a high fat meal increased the - AUC of Methylin chewable tablets by about - 20 %, on average. Through a cross-study comparison, the magnitude of food effect - is found to be comparable between the Methylin chewable tablets and Ritalin, the immediate release tablet.

Under Metabolism and excretion section:

The pharmacokinetics of the Methylin chewable tablets have been studied in healthy adult volunteers. The mean terminal half-life ($t_{1/2}$) of methylphenidate following administration of 20mg Methylin chewable tablets ($t_{1/2}$ = 3 hours) is comparable to the mean terminal $t_{1/2}$ following administration of Ritalin (methylphenidate hydrochloride immediate-release tablets) ($t_{1/2}$ = 2.8 hours) in healthy adult volunteers.

SIGNATURE OF REVIEWER: _____
Wen-Hwei Chou, Pharm.D., Ph.D.

Date _____

SIGNATURE OF TEAM LEADER: _____
Ramana Uppoor, Ph.D.

Date _____

CC.: HFD # [120]; TL: [Uppoor]; DD: [Mehta]

Project Manager: Anna M Homonnay-Weikel

Attachment 1: OCPB labeling comments in the review dated 8/28/2002

(2) Labeling:

We note that relevant information related to ADME, PK, and intrinsic and extrinsic factors (such as gender, age, race, renal or hepatic impairment, food, drug-drug interactions) that could affect the pharmacokinetics of methylphenidate is lacking in the current label for the reference listed drug Ritalin® as well as your proposed label for Methylin CT. We request you to update the labeling of Methylin CT to incorporate the above information from literature and/or other available resources. Based on available information from current submission including the three studies, literature and class labeling language from other more recent methylphenidate products, we suggest following relevant PK information should be added to the "Clinical Pharmacology" section of the label:

Clinical Pharmacology

(double strikethrough indicates deletion; underline indicates addition; bracket indicates explanation with reference number in the submission, which should not be included in final label)

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-threo enantiomers. The *d*-threo enantiomer is more pharmacologically active than the *l*-threo enantiomer. [Patrick & Markowitz 1997, class labeling text]

Methylphenidate HCl is a central nervous system (CNS) stimulant.

The mode of therapeutic action in ~ humans is not completely understood, but methylphenidate presumably activates the brain stem arousal system and cortex to produce its stimulant effect. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. [#66, Patrick et al 1987]

There is neither specific evidence which clearly establishes the mechanism whereby Methylin® produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Pharmacokinetics:

Absorption

Methylin CT is readily absorbed. Following oral administration of Methylin CT, peak plasma methylphenidate concentrations are achieved at about 1 to 2 hours. Methylin CT has been shown to be bioequivalent to Ritalin® tablet. Mean Cmax following a 20mg dose is approximately 10 ng/ml. [study #610]

Food Effect:

In a study in adult volunteers investigating the effects of a high-fat meal on the bioavailability of Methylin CT at a dose of 20mg, the presence of food delayed the peak concentrations by approximately 1 hour (1.5 hours, fasted and 2.4 hours, fed). Through a cross study comparison, the magnitude of food

effect is found to be comparable between the Methylin CT and Ritalin, the immediate release tablet. [study #721]

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily via deesterification to alpha-phenyl-piperidine acetic acid (PPA, ritalinic acid). The metabolite has little or no pharmacologic activity. [#66, Patrick et al 1987]

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose. [# 67, Faraj et al 1974]

The pharmacokinetics of the Methylin CT have been studied in healthy adult volunteers. The mean terminal half-life ($t_{1/2}$) of methylphenidate following administration of 20 mg Methylin CT ($t_{1/2}$ =3 hours) is comparable to the mean terminal $t_{1/2}$ following administration of Ritalin (methylphenidate hydrochloride immediate-release tablets) ($t_{1/2}$ =2.8h) in healthy adult volunteers. [study #610]

Special Population:

Gender: The effect of gender on the pharmacokinetics of methylphenidate after Methylin CT administration has not been studied.

Race: The influence of race on the pharmacokinetics of methylphenidate after Methylin CT administration has not been studied.

Age: The pharmacokinetics of methylphenidate after Methylin CT administration have not been studied in pediatrics.

Renal Insufficiency

There is no experience with the use of Methylin CT in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of ritalinic acid [# 67, Faraj et al 1974]. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Methylin CT.

Hepatic Insufficiency

There is no experience with the use of Methylin CT in patients with hepatic insufficiency.

Attachment 2: Labeling comments in the approvable letter

Clinical Pharmacology

Methylphenidate is a racemic mixture comprised of the d- and l-threo enantiomers. The d-threo enantiomer is more pharmacologically active than the l-threo enantiomer.

Methylphenidate HCl is a central nervous system (CNS) stimulant.

The mode of therapeutic action in humans is not completely understood, but methylphenidate presumably activates the brain stem arousal system and cortex to produce its stimulant effect. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

There is neither specific evidence which clearly establishes the mechanism whereby Methylin® produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Pharmacokinetics:

Absorption

Methylin is readily absorbed. Following oral administration of Methylin, peak plasma methylphenidate concentrations are achieved at about 1 to 2 hours. Methylin has been shown to be bioequivalent to Ritalin® tablet. The mean C_{max} following a 20mg dose is approximately g/ml.

Food Effect:

In a study in adult volunteers to investigate the effects of a high-fat meal on the bioavailability of Methylin at a dose of 20mg, the presence of food delayed the peak by approximately 1 hour (nours, fasted and nours, fed). Overall, a high fat meal increased the of Methylin AQ by about . Through a cross-study comparison, the magnitude of is found to be comparable between the Methylin.

— and Ritalin, the immediate release tablet.

Metabolism and Excretion:

In humans, methylphenidate is metabolized primarily via deesterification to alpha-phenylpiperidine acetic acid (PPA, ritalinic acid). The metabolite has little or no pharmacologic activity.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose.

The pharmacokinetics of the Methylin AQ oral solution have been studied in healthy adult volunteers. The mean terminal half-life ($t_{1/2}$) of methylphenidate following administration of 20mg Methylin — $t_{1/2}$ = — hours) is comparable to the mean terminal $t_{1/2}$ following administration of Ritalin (methylphenidate hydrochloride immediate-release tablets) ($t_{1/2}$ = 2.8h) in healthy adult volunteers.

Special Populations:

Gender: The effect of gender on the pharmacokinetics of methylphenidate after Methylin — administration has not been studied.

Race: The influence of race on the pharmacokinetics of methylphenidate after Methylin — administration has not been studied.

Age: The pharmacokinetics of methylphenidate after Methylin — administration have not been studied in pediatrics.

Renal Insufficiency:

There is no experience with the use of Methylin — in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of ritalinic acid. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Methylin —

Hepatic Insufficiency:

There is no experience with the use of Methylin — in patients with hepatic insufficiency.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

_____ ¹ Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ ✓ § 552(b)(4) Draft Labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Wen-Hwei Chou
3/19/03 01:39:37 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
3/19/03 01:59:49 PM
BIOPHARMACEUTICS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Clinical Pharmacology & Biopharmaceutics
(HFD 860/870/880)
Tracking/Action Sheet for Formal/Informal Consults

From: Wen-Hwei Chou

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)
Please log-in this consult and review action for the specified IND/NDA submission

DATE: 10/03/2002

IND No.: NA

NDA No. 21,475
Amendment

DATE OF DOCUMENT
09/24/2002

NAME OF DRUG
Methylin CT
(Methylphenidate HCl chewable tablet)

PRIORITY CONSIDERATION
S

Date of informal/Formal Consult 09/25/2002

NAME OF THE SPONSOR: [Janssen Research]

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS RELATED ISSUE

- | | | |
|--|---|--|
| <input type="checkbox"/> PRE-IND | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> IN-VITRO METABOLISM | <input type="checkbox"/> IN-VIVO WAIVER REQUEST | <input type="checkbox"/> CORRESPONDENCE |
| <input type="checkbox"/> PROTOCOL | <input type="checkbox"/> SUPAC RELATED | <input type="checkbox"/> DRUG ADVERTISING |
| <input type="checkbox"/> PHASE II PROTOCOL | <input type="checkbox"/> CMC RELATED | <input type="checkbox"/> ADVERSE REACTION REPORT |
| <input type="checkbox"/> PHASE III PROTOCOL | <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> ANNUAL REPORTS |
| <input type="checkbox"/> DOSING REGIMEN CONSULT | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS | <input type="checkbox"/> FAX SUBMISSION |
| <input type="checkbox"/> PK/PD- POPPK ISSUES | <input type="checkbox"/> MEETING PACKAGE (EOP2) | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> PHASE IV RELATED | | [Amendment-reviewer requested information] |

REVIEW ACTION

- | | | |
|---|---|--|
| <input checked="" type="checkbox"/> NAI (No action indicated) | <input type="checkbox"/> Oral communication with | Formal Review/Memo (attached) |
| <input type="checkbox"/> E-mail comments to: | Name: [] | <input type="checkbox"/> See comments below |
| <input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox <input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others (Check as appropriate and attach e-mail) | <input type="checkbox"/> Comments communicated in meeting | <input type="checkbox"/> See submission cover letter |
| | | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| | | [] |

REVIEW COMMENT(S)

- NEED TO BE COMMUNICATED TO THE SPONSOR HAVE BEEN COMMUNICATED TO THE SPONSOR

Sponsor submitted an amendment to Agency's request to change dissolution specification to Q- in 30 minutes (as an interim specification now and data to be collected as Phase IV). The sponsor has, however, accepted Q- in 30minutes right now as regulatory specification. Therefore, no Phase IV commitment is necessary. Sponsor's amendment is attached. No action is indicated at this point.

SIGNATURE OF REVIEWER: _____
Wen-Hwei Chou, Pharm.D., Ph.D.

Date 10/03/02

SIGNATURE OF TEAM LEADER: _____
Ramana Uppoor, Ph.D.

Date _____

C.: HFD # [860]; TL: [Uppoor]; DD: [Mehta]

Project Manager: Anna M Homonnay-Weikel

Appendix

**AMENDMENT- REVIEWER REQUESTED INFORMATION
RESPONSE TO COMMENTS**

Anna Marie H. Weikel's email comments dated August 29th, 2002:

Dissolution specification:

The selected dissolution method is acceptable. However, we recommend a change in dissolution specification for all three strengths of Methylin CT to Q= — in 30 minutes.

Sponsor proposed specification: Q= — in 45 minutes

Agency recommended specification: Q= — in 30 minutes

We recommend that Q= — in 30 minutes be accepted as interim dissolution specification for all 3 strengths of Methylin CT until additional data (described below) is submitted and reviewed.

Phase IV commitment regarding dissolution specification: Submit dissolution and stability data, for production batches of all three strengths (— per strength) using sponsor proposed and agency recommended dissolution specifications (i.e. 30 and 45 minutes). These batches could be next — production batches or batches currently on stability. These data should be submitted to the agency no later than 1½ years from the date of approval of this product. The sponsor should make a Phase IV commitment to submit this data for finalization of dissolution specification.

** Additional comment from the Chemistry:*

Setting the expiration date at the approval of this application will be based on dissolution data at 45 minutes. But when the Phase IV commitment has been fulfilled which means you have generated sufficient stability data including dissolution at 30 minutes, the expiration date may have to be revised based on the dissolution stability data at 30 minutes.

RESPONSE: Mallinckrodt agrees to incorporate the Agency recommended dissolution specifications, Q= — in 30 minutes. Mallinckrodt is convinced that these drug products can meet these specifications throughout the proposed shelf life and, therefor will implement these specifications as final specifications. No Phase IV commitment need be made to address intermediate specifications.

Analytical methods, drug product release and stability specifications and stability protocols will be changed to reflect the revised dissolution specification for all three strengths of Methylin CT.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Wen-Hwei Chou
10/4/02 12:25:09 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
10/4/02 12:34:04 PM
BIOPHARMACEUTICS

**Office of Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation I**

NDA: 21,475
Relevant NDA: 21,419 (Methylin AQ, oral solution)
Brand Name: Methylin CT (chewable tablet)
Generic Name: Methylphenidate Hydrochloride (MPH HCl)
Dosage form and Strength: Chewable tablet, 2.5mg, 5.0mg, and 10mg
Route of administration: Oral
Indication: Attention Deficit Disorders and narcolepsy
Sponsor: Mallinckrodt Inc.
Type of submission: New NDA [505(b)(2)]
Clinical Division: HFD-120/Neuropharmacological Drug Products
OCPB Division: HFD-860/DPEI
Priority: Standard
Submission date: 12/19/2001;
01/16/2002;
04/10/2002 (Response to FDA request on dissolution issues), 04/18/2002
(electronic submission)
OCPB Consult date: 01/09/2002
Reviewer: Wen-Hwei Chou, Pharm.D., Ph.D.
Team leader: Ramana Uppoor, Ph.D.

Executive summary

This is a 505 (b)(2) NDA submission for Methylphenidate in a new chewable tablet (CT) formulation (2.5mg, 5.0mg, and 10mg). The sponsor submitted three BE studies (one pivotal in fasted condition, one in fed condition, and one comparing Methylin CT chewed versus unchewed) using highest strength tablet against reference listed drug, Ritalin® tablet. The sponsor requested waiver of BE study on two lower strength tablets (2.5mg and 5mg). The acceptability of this NDA from the Office Clinical Pharmacology and Biopharmaceutics perspective is based on the three BE studies submitted. No clinical trials were conducted with Methylin CT. In addition, the sponsor requests the Agency to grant a deferral of the requirement to perform pediatric studies in accordance with 21 CFR 314.55(b). The Sponsor indicated that pediatric studies (preschool age children, under age 6) are presently being conducted by the NIH which will be used to develop class labeling into the labeling proposed herein, once it is available.

Overall, the sponsor has submitted sufficient information to support the approval from the Office of Clinical Pharmacology and Biopharmaceutics perspective. This is based on the bioequivalence of the 10mg tablet and granting of biowaivers for the two lower strength (2.5 and 5 mg) tablets based on the proportional similarity in composition of three tablet strengths and comparable dissolution profile. In addition, based on the submitted supportive information on the bioequivalence of chewed and unchewed Methylin CT tablet and unchewed Ritalin tablet, it is unlikely that this new chewable tablet will behave differently than reference listed product Ritalin tablet in pediatrics. Therefore, from Clinical Pharmacology perspective, granting a deferral of pediatric studies is acceptable, as is done for Methylin AQ.

The proposed label text is essentially the same as the reference listed drug product Ritalin® tablet except the text that reflects change from reference listed product Ritalin® to a chewable tablet dosage form. However, relevant clinical pharmacology information is lacking in current Ritalin® label. In the forty-five days filing meeting, we have requested the sponsor to update label from available sources. Unfortunately, the sponsor did not propose additional labeling changes. From the Office of Clinical Pharmacology and Biopharmaceutics perspective, it is important to modify and incorporate current knowledge of methylphenidate in the Methylin CT labeling. The sponsor will be requested to update label from literature and/or other available resources. Based on available information from current submission including the three studies, literature and class labeling language from other more recent methylphenidate products (such as Concerta, methylin AQ, Metadate CD), we have suggested some relevant PK information below to be incorporated in the label.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I has reviewed this NDA and finds it acceptable. Please forward "comments to the sponsor" including (1) and (2) to the sponsor. These labeling comments should be adequately addressed by the sponsor.

Comments to the sponsor (including Phase IV commitment & detailed Label Recommendation):

(1) Dissolution specification:

The selected dissolution method is acceptable. However, we recommend a change in dissolution specification for all three strengths of Methylin CT to $Q=$ - in 30 minutes.

Sponsor proposed specification:	$Q=$ - in 45 minutes
Agency recommended specification:	$Q=$ - in 30 minutes

We recommend that $Q=$ - in 30 minutes be accepted as interim dissolution specification for all 3 strengths of Methylin CT until additional data (described below) is submitted and reviewed.

Phase IV commitment regarding dissolution specification: Submit dissolution and stability data, for production batches of all three strengths / — (per strength) using sponsor proposed and agency recommended dissolution specifications (i.e. 30 and 45 minutes). These batches could be next — production batches or batches currently on stability. These data should be submitted to the agency no later than 1½ years from the date of approval of this product. The sponsor should make a Phase IV commitment to submit this data for finalization of dissolution specification.

(2) Labeling:

We note that relevant information related to ADME, PK, and intrinsic and extrinsic factors (such as gender, age, race, renal or hepatic impairment, food, drug-drug interactions) that could affect the pharmacokinetics of methylphenidate is lacking in the current label for the reference listed drug Ritalin® as well as your proposed label for Methylin CT. We request you to update the labeling of Methylin CT to incorporate the above information from literature and/or other available resources. Based on available information from current submission including the three studies, literature and class labeling language from other more recent methylphenidate products, we suggest following relevant PK information should be added to the "Clinical Pharmacology" section of the label:

Clinical Pharmacology

(double strikethrough indicates deletion; underline indicates addition; bracket indicates explanation with reference number in the submission, which should not be included in final label)

Methylphenidate is a racemic mixture comprised of the *d*- and *l*-threo enantiomers. The *d*-threo enantiomer is more pharmacologically active than the *l*-threo enantiomer. [Patrick & Markowitz 1997, class labeling text]

Methylphenidate HCl is a central nervous system (CNS) stimulant.

The mode of therapeutic action in — humans is not completely understood, but methylphenidate presumably activates the brain stem arousal system and cortex to produce its stimulant effect. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space. [#66, Patrick et al 1987]

There is neither specific evidence which clearly establishes the mechanism whereby Methylin® produces its mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

Pharmacokinetics:

Absorption

Methylin CT is readily absorbed. Following oral administration of Methylin CT, peak plasma methylphenidate concentrations are achieved at about 1 to 2 hours. Methylin CT has been shown to be bioequivalent to Ritalin® tablet. Mean Cmax following a 20mg dose is approximately 10 ng/ml. [study #610]

Food Effect:

In a study in adult volunteers investigating the effects of a high-fat meal on the bioavailability of Methylin CT at a dose of 20mg, the presence of food delayed the peak concentrations by approximately 1 hour (1.5 hours, fasted and 2.4 hours, fed). Through a cross study comparison, the magnitude of food

effect is found to be comparable between the Methylin CT and Ritalin, the immediate release tablet. [study #721]

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily via deesterification to alpha-phenyl-piperidine acetic acid (PPA, ritalinic acid). The metabolite has little or no pharmacologic activity. [#66, Patrick et al 1987]

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPA, accounting for approximately 80% of the dose. [# 67, Faraj et al 1974]

The pharmacokinetics of the Methylin CT have been studied in healthy adult volunteers. The mean terminal half-life ($t_{1/2}$) of methylphenidate following administration of 20 mg Methylin CT ($t_{1/2}$ =3 hours) is comparable to the mean terminal $t_{1/2}$ following administration of Ritalin (methylphenidate hydrochloride immediate-release tablets) ($t_{1/2}$ =2.8h) in healthy adult volunteers. [study #610]

Special Population:

Gender: The effect of gender on the pharmacokinetics of methylphenidate after Methylin CT administration has not been studied.

Race: The influence of race on the pharmacokinetics of methylphenidate after Methylin CT administration has not been studied.

Age: The pharmacokinetics of methylphenidate after Methylin CT administration have not been studied in pediatrics.

Renal Insufficiency

There is no experience with the use of Methylin CT in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of ritalinic acid [# 67, Faraj et al 1974]. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of Methylin CT.

Hepatic Insufficiency

There is no experience with the use of Methylin CT in patients with hepatic insufficiency.

Signature

Wen-Hwei Chou, Pharm.D., Ph.D. _____

RD/FT Initialed by Ramana Uppoor, Ph.D. _____

Briefing Date: 08/22/2002.

Briefing Attendees: Marroum, P; Uppoor, R; Venitz, Jurgen; Chou, W

cc: NDA21-475 Methylin CT, HFD-120 (Laughren, Hearst, Homonnay-Weikel), HFD-860 (Mehta, Marroum, Uppoor, Chou), Central Documents Room (Biopharm-CDR)

Table of contents

Executive summary	2
Recommendation	2
Comments to the sponsor (including Phase IV commitment & detailed Label Recommendation--	2-4
Signature	4
Table of Contents	5
Summary of Clinical Pharmacology and Biopharmaceutics findings	6
Question based review	7-11
Appendices	12-51
Individual study review and Reviewer's comments	12-26
MI Protocol 1137-00-610	12-16
An Open-Label, Randomized, Three-Way, Crossover Study to Evaluate the Relative Bioavailability of Two Test Formulations (10 mg Chewable Tablet and 2 mg/ml Liquid) of Methylphenidate Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin® 20 mg Tablet, Ciba-Geigy Corporation) in Normal Human Subjects Under Fasting Conditions	
Reviewer's comments	15-16
Study 1137-00-721	17-21
An Open-Label, Randomized, Three-Way, Food Effect Study to Evaluate the Relative Bioavailability of a Test Formulation of Methylphenidate HCl 10 mg Chewable Tablet (2 x 10 mg) (fed and fasted) Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin®20 mg Tablet, Ciba-Geigy Corporation) (fed) in Normal Human Subjects.	
Reviewer's comments	20-21
Study 1137-99-596	22-26
A Randomized, Two-Period Crossover, Six Sequence, Open-Label Study to Evaluate the Relative Bioavailability of a Test Tablet Formulation of Methylphenidate 10 mg Chewable (2 x 10 mg) (chewed or unchewed) Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin® 20 mg Tablet, Ciba-Geigy Corporation) Under Fasting Conditions.	
Reviewer's comments	25-26
Bioanalytical Method	27
Formulation	28
Dissolution	29-32
Sponsor's proposed label and side-by-side comparison with Ritalin label	33-44
Filing memo	45-51

Summary of clinical pharmacology and biopharmaceutics findings

Methylphenidate is indicated for the treatment of Attention Deficit Disorder and narcolepsy. The daily dose for adults is on average 20 to 30mg daily administered in divided doses 2 or 3 times daily preferably 30 to 45 minutes before meals. Some patients may require 40 to 60 mg daily. In others, 10 to 15mg daily will be adequate. In children 6 years of age and older, treatment should start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dose of above 60mg is not recommended. Adverse reactions include nervousness, insomnia, palpitations, blood pressure and pulse changes, hypersensitivity, anorexia, nausea, dizziness, headache, dyskinesia, tachycardia.

This is a 505 (b) (2) NDA submission for Methylin CT (chewable tablet, 2.5, 5 and 10 mg). The sponsor submitted three BE studies (one pivotal in fasted condition, one in fed condition and one supportive study comparing chewed or unchewed) using highest strength against reference listed drug, Ritalin® tablet. The sponsor requested waiver of BE study on two lower strength (2.5 and 5 mg) tablets. In addition, the sponsor requests the Agency to grant a deferral of the requirement to perform pediatric studies in accordance with 21 CFR 314.55(b). The Sponsor indicated that pediatric studies (preschool age children, under age 6) are presently being conducted by the NIH which will be used to develop class labeling into the labeling proposed herein, once it is available. The approvability of this NDA is based on the three BE studies submitted. In addition, whether pediatric studies are required is briefly discussed from OCPB perspective.

Overall, the sponsor has submitted sufficient information to support the approval. This is based on the bioequivalence of the 10 mg tablet in both fasted and fed states and granting of biowaivers for the two lower strength (2.5 and 5 mg) tablets based on the proportional similarity in composition of three tablet strengths and comparable dissolution profile. In addition, based on the submitted supportive information on the bioequivalence of chewed and unchewed Methylin CT tablet and unchewed Ritalin tablet, it is unlikely that this new chewable tablet will behave differently than reference listed product Ritalin tablet in pediatrics. Therefore, from Clinical Pharmacology perspective, granting a deferral of pediatric studies is acceptable.

The Division of Scientific Investigation (DSI) was requested to audit the clinical study site and analytical site for the pivotal BE study (#610) under NDA 21-419 (Methylin AQ). A form 483 was issued by DSI at the analytical site. All the DSI issues under NDA21-419 were resolved and supportive data submitted were satisfactory. (See CPB review (Chou) of N21-419 for more details).

Question based review

What are the proposed dosage strengths, indication, dosing regimen and age ranges for Methylin CT?
 Methylin CT has three strengths (2.5mg, 5mg and 10mg). Methylin CT is indicated for the treatment of Attention Deficit Disorder and narcolepsy. The daily dose for adults is on average 20 to 30mg daily administered in divided doses 2 or 3 times daily preferably 30 to 45 minutes before meals. Some patients may require 40 to 60 mg daily. In others, 10 to 15mg daily will be adequate. In children 6 years of age and older, treatment should start with 5 mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10 mg weekly. Daily dose of above 60mg is not recommended.

Is the chewable tablet bioequivalent to the reference tablet?

Yes, the test product of Methylin CT (10mgx2) is bioequivalent to the reference product of Ritalin® tablet. Specifically, the sponsor has conducted a fasting BE study on the highest strength of Methylin CT tablet (10mg). The 90% CI of test-to-reference ratio fell within the recommended 0.80-1.25 goal-post for the log transformed PK parameters (Cmax and AUC0-inf) and the elimination half-lives and tmax were comparable for test and reference products. (Fig 1; Table 1, 2)

Table 1

Parameter	Treatment Groups		
	MPH HCl Chewable Tablet (A)	MPH HCl Oral Solution (B)	Ritalin® Tablet Unchewed (C)
N	33	33	34
AUCinf (ng·hr/mL)	49.97 (16.28)	46.70 (15.58)	49.66 (14.80)
AUCt (ng·hr/mL)	48.32 (15.95)	45.10 (15.37)	48.01 (14.35)
Cmax (ng/mL)	9.982 (2.607)	9.075 (2.610)	9.804 (2.723)
Kel (1/hr)	0.2515 (0.0363)	0.2604 (0.0385)	0.2579 (0.0374)
T1/2 (hr)	2.826 (0.516)	2.725 (0.449)	2.756 (0.506)
Tmax (hr)	1.530 (0.413)	1.712 (0.597)	1.868 (0.432)

Reference: Tables 14.2.1-8 through 14.2.1-10 of MI report for Study 610

Fig 1

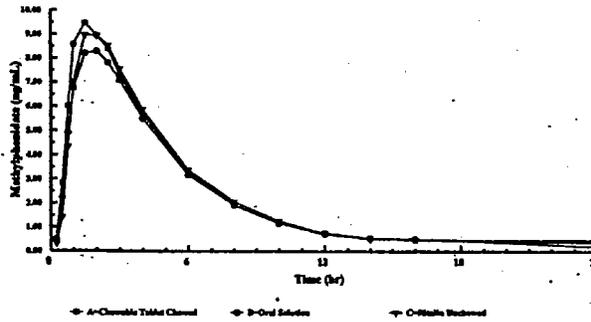


Figure 11.5-1: Mean Plasma Concentration Profile of Methylphenidate Formulations (20 mg)

Table 2

	ln (AUCinf)	ln (AUCt)	ln (Cmax)	Kel	T1/2	Tmax
90% CI (%)	99.69-107.08	99.63-107.15	100.95-111.01	N/A*	N/A*	N/A*
LSM Ratio A/C (%)	103.32	103.32	105.86	98.48	101.68	81.41
CV (%)	8.34	8.48	11.08	7.26	8.68	24.82

*N/A = Not applicable
 Reference: Tables 14.2.1-11 through 14.2.1-15 of MI report for Study 610

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Is there a food effect on bioavailability of the Methylin CT? Is the magnitude of food effect comparable for test (methylin CT) and reference (Ritalin tablet) products ?

Yes, the high fat meal prolonged the tmax and increased the exposure of methylphenidate. The 90% CI of test (fed)-to-reference (fasted) ratio fell slightly outside the 0.80-1.25 goal-post for average BE assessment for the log transformed PK parameters (AUC0-inf & Cmax) and these differences were statistically significant (p<0.0001)(Fig 2; Table 3, 4). Specifically, mean tmax was prolonged with food from 1.4 hours to 2.4 hours. Mean AUC0-inf was increased from 56.37 to 66.96 ng.hr/ml. The mean Cmax and elimination half-lives were comparable.

The magnitude of food effect on the PK parameters of methylphenidate appears to be comparable for the test formulation methylphenidate HCl CT (10 mgx2) and Ritalin® tablet 20 mg. Specifically, based on the bioequivalence results of Methylin CT and Ritalin tablet in fed state, high-fat breakfast appears to have similar effect on the PK parameters of test formulation methylin CT and Ritalin tablet (Table 5).

Table 3

Fig 2

Summary of Untransformed Pharmacokinetic Data [Mean (SD)] - Study 721			
Parameter	Treatment Groups		
	Methylin® CT Tablets Fasting (A)	Methylin® CT Tablets With Food (B)	Ritalin® Tablet With Food (C)
N	23	23	24
AUCinf (ng·hr/mL)	56.37 (25.64)	66.96 (29.65)	66.75 (27.66)
AUCt (ng·hr/mL)	54.23 (24.49)	65.01 (29.13)	65.00 (27.16)
AUCmx (ng·hr/mL)	14.05 (4.93)	12.21 (3.87)	13.43 (6.81)
Cmax (ng/mL)	11.041 (3.970)	11.055 (3.308)	12.979 (4.429)
Kel (1/hr)	0.2438 (0.0540)	0.2520 (0.0394)	0.2510 (0.0388)
T1/2 (hr)	3.047 (1.032)	2.824 (0.500)	2.828 (0.456)
Tmax (hr)	1.489 (0.443)	2.413 (0.718)	2.167 (0.940)

Reference: Tables 14.2.1-3 through 14.2.1-10 of study report for MI Protocol 1137-00-721
AUCmx = AUC_{0-t}

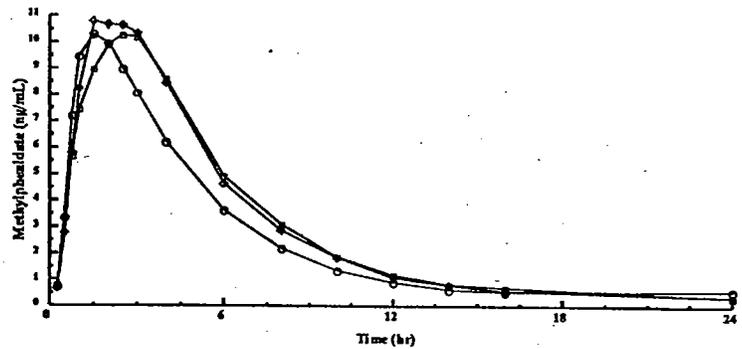


Figure 11.5-1 Mean Plasma Concentration-Time Profile of Methylphenidate Formulations (20 mg)

Table 4

Summary of 90% Confidence Intervals and CV Methylin® CT Tablets with Food (B) versus Methylin® CT Tablets Fasting (A)							
	AUCinf	AUCt	Cmax	AUCmx	Kel	T1/2	Tmax
90% CI (%)	114.48-125.90	115.39-126.94	94.77-109.80	71.55-106.04	N/A*	N/A*	N/A*
LSM Ratio B/A (%)	120.06	121.03	102.01	87.10	103.22	92.96	161.27
CV (%) ^a	9.20	9.22	14.24	38.07	11.28	18.95	29.51
p ^b	0.0001	0.0001	0.6389	0.2259	0.3497	0.1929	0.0001

*N/A = Not applicable ^aIntra-subject coefficient of variation
^bp-value from ANOVA contrast of treatments (B) and (A)
 Reference: Tables 14.2.1-11 through 14.2.1-15 of study report for MI Protocol 1137-00-721

Table 5

Summary of 90% Confidence Intervals and CV Methylin® CT Tablets with Food (B) versus Ritalin® Tablet with Food (C)							
	AUCinf	AUCt	Cmax	AUCmx	Kel	T1/2	Tmax
90% CI (%)	96.10-105.47	95.80-105.16	80.70-93.19	82.18-120.75	N/A*	N/A*	N/A*
LSM Ratio B/C (%)	100.67	100.37	86.72	99.62	100.17	100.12	112.57
CV (%) ^a	9.20	9.22	14.24	38.07	11.28	18.95	29.51
p ^b	0.8057	0.8926	0.0015	0.9730	0.9599	0.9841	0.1302

*N/A = Not applicable ^aIntra-subject coefficient of variation
^bp-value from ANOVA contrast of treatments (B) and (A)
 Reference: Tables 14.2.1-11 through 14.2.1-15 of study report for MI Protocol 1137-00-721

Are PK characteristics similar when CT is swallowed as a whole tablet or chewed?

Yes, the PK parameters (AUC_{0-inf} & C_{max}) are similar when comparing methylin CT (swallowed as a whole) and methylin CT thoroughly chewed before swallowing (Table 6)

Table 6

Summary of 90% Confidence Limits and CV						
Methylin® Tablets CT Chewed (A) versus Methylin® CT Tablets Unchewed (B)						
	AUC _{inf}	AUC _t	C _{max}	K _{el}	T _{1/2}	T _{max}
90% CI (%)	98.38-107.71	98.45-108.15	95.48-109.51	N/A*	N/A*	N/A*
LSM Ratio (A/B) %	102.94	103.19	102.25	102.89	99.07	111.69
CV (%) ^a	8.12	8.42	12.29	10.81	10.41	26.94
p ^b	0.2969	0.2755	0.5932	0.4294	0.7945	0.2397

*N/A = Not applicable ^aIntra-subject coefficient of variation
^bp-value from ANOVA contrast of treatments (B) and (A)
 Reference: Tables 14.2.1-11 through 14.2.1-13 of Study report for MI Study 1137-99-596

Is the bioanalytical assay validated prior to and during the studies?

Overall, the pre- and within-study validity of the bioanalytical assay is satisfactory. The validation of the non-chiral LC/MS/MS analytical method for methylphenidate in EDTA treated human plasma was reviewed under NDA21-419 (Methylin AQ) from the same sponsor and assay was found to be specific, reproducible, sensitive and adequate to characterize the PK of methylphenidate (Table 7, 8)

Table 7

Table 3.4.1 Pre-study Assay Validation Summary for MPH in EDTA Human Plasma		
Parameter	Quality Control Samples	Standard Curve Samples
Concentration (ng/mL)	0.75, 10.0, 20.0, 50.0	0.25, 0.50, 1.00, 2.00, 5.00, 25.0
Intra-Day Precision (% CV)	1.9-21.9	0.29-17.2
Intra-Day Accuracy (% Accuracy)	86.2-90.6	87.0-111.0
Inter-Day Precision (% CV)	1.9-17.6	2.6-11.3
Inter-Day Accuracy (% Accuracy)	90.6-93.8	97.9-102.0
Correlation (Range of R ² values)	N/A	0.9983-0.9995
Linear Range (ng/mL)	N/A	0.25-25.0
Sensitivity/ LLOQ	N/A	0.25
Extraction Recovery of MPH	N/A	102.0-119.0
Extraction Recovery of Internal Standard	N/A	108.0
Stability in Plasma		
1) Bench-Top stability at Room Temp. (hrs.)	6.5	N/A
2) Auto-Sampler Stability of Extract at Room Temp. (hrs.)	24	N/A
3) Freeze-Thaw Stability (N Cycles)	3	N/A
4) Storage Stability (Temp. Duration)	-20° C, 10 Months	N/A
Specificity	Specific to analytes. No significant interference observed from endogenous substances in blank plasma. No interference observed from commonly used OTC drugs.	

Ref: Table 8 in Analytical Data Report for MI Study 721

Table 8

Table 3.4.2 Within-Study Assay Performance for Methylphenidate in EDTA Human Plasma						
Parameter	Study 596		Study 610		Study 721	
	Quality Control Samples	Standard Curve Samples	Quality Control Samples	Standard Curve Samples	Quality Control Samples	Standard Curve Samples
Concentration (ng/mL)	0.75, 10.0, 20.0	0.25, 0.50, 1.00, 2.00, 10.0, 22.0, 25.0	0.75, 10.0, 20.0	0.25, 0.50, 1.00, 2.00, 10.0, 22.0, 25.0	0.75, 10.0, 20.0	0.25, 0.50, 1.00, 2.00, 10.0, 22.0, 25.0
Intra-Day Precision (% CV)	N/A	N/A	N/A	N/A	N/A	N/A
Intra-Day Accuracy (% Accuracy)	N/A	N/A	N/A	N/A	N/A	N/A
Inter-Day Precision Range (% CV)	6.4-13.9	4.0-8.6	3.0-7.3	1.2-8.4	4.1-17.9	2.4-10.0
Inter-Day Accuracy Range (% Accuracy)	94.0-101.6	99-101.4	97.5-98.4	97.5-100.7	101.0-106.0	98.0-104.0
Correlation (Range of r ² values)	N/A	0.9938-0.9999	N/A	0.9995-0.9999	N/A	0.9989-0.9997
Linear Range (ng/mL)	N/A	0.25-25.0	N/A	0.25-25.0	N/A	0.25-25.0
Sensitivity/ LLOQ (ng/mL)	N/A	0.25	N/A	0.25	N/A	0.25

Was the to-be-marketed formulation used in the pivotal BE studies?

Yes, the sponsor used final to-be-marketed formulation in the 2 pivotal BE studies: one fasting BE study (#610) and food-effect study (#721).

Are the proposed dissolution specifications and method appropriate to distinguish sub-optimal batches?

Yes, based on the dissolution profiles in 4 media (pH 1.2, 4.5, 6.8 buffers and H2O), the selected dissolution method is acceptable. However, we recommend the sampling time point should be changed to 30 minutes and the specification should be changed to Q= - in 30 minutes. The sponsor proposed using the same dissolution method and specification for methylphenidate HCl tablet USP given below:

- Apparatus 1: 100rpm
- Medium: water; 900ml
- Not less than —(Q) in 45 minutes

Are in-vitro dissolution profiles similar for all the 3 individual strengths (to-be-marketed formulation)?

Yes, all strengths of to-be-marketed formulation of Methylin CT exhibited rapid release of methylphenidate [average percent dissolved >85% in all pH buffers (pH 1.2, 4.5 and 6.8) and >80% in water] in 15 minutes. This reviewer had plotted the graph and compared the dissolution profiles across 3 strengths (10mg Methylin CT as reference) using an f2 test (fig 5-8, Table 33, page 31). The dissolution profiles across 3 strengths in above 4 media including the proposed medium (water) are similar. However, f2 comparison may not be suitable for this rapidly dissolved product. Specifically, all, but two values in H2O medium, of the average value of % release in dissolution profiles demonstrated more than 85 % release of methylphenidate in 15 minutes.

Based on the method and dissolution profiles from 4 media (pH 1.2, 4.5, 6.8 buffers and water) submitted, this reviewer agrees with the selected medium (H2O) for dissolution testing since only H2O demonstrated some discriminatory capability for all 3 strengths. However, the specification should be set at Q= - in 30 minutes.

Are the formulations proportionally similar for all 3 different strengths?

Yes, all three strengths are considered proportionally similar and they are made from the same master blend (Table 9).

Quantitative Formulation

Table 9.

Official USP/NF Material Name	Brand Name (Grade) and Manufacturer's Name	%	Grams / Kg Master Blend	Strength		
				2.5 mg	5 mg	10 mg
Methylphenidate HCl USP	Code: 1571 (Mallinckrodt, Inc.)			2.5 mg	5 mg	10 mg
Maltose	/					
Microcrystalline Cellulose NF *						
Guar Gum NF *						
Pregelatinized Starch NF						
Aspartame						
Grape Flavor						
Stearic Acid NF		(Mallinckrodt, Inc.)				
TOTAL		100%		150 mg	300 mg	600 mg

Can we waive BE of two lower strength tablets based on the in vitro dissolution profiles?

Yes, the biowaiver for lower strength chewable tablets (2.5 and 5 mg) can be granted based on the following:

- The in-vivo BE study performed on the highest strength (10mg) versus Ritalin tablet met the recommended criteria for BE (0.8-1.25).
- The proportional similarity in composition for the three strengths and they were manufactured from the same master blend.
- Dissolution profiles of the lower strengths are similar to the 10 mg Methylin CT tablet in 4 different media (pH 1.2, 4.5, 6.8 buffers and water).

What are the manufacturing batch sizes for biobatches and commercial batches across 3 strengths?

As per chemists, Drs. Christy John and Xiao-Hong Chen, the scales for bio-batches and commercial batches are summarized in the table below :

	2.5mg	5mg	10mg
Batch scale*	— (Lot# MHSC0041)	— (Lot# MHSC0042)	— (biobatch Lot# MHSC0043)
Commercial batch scale	—	—	—

*Batch for 10 mg tablet used in pivotal BE and food studies and 2.5 mg and 5 mg tablets used in in-vitro dissolution studies.

Is a study in pediatrics required for this new chewable tablet formulation of methylphenidate?

(Dr. Arzu Selen was consulted for this question)

No, based on the submitted supportive information on the bioequivalence of chewed and unchewed Methylin CT tablet and unchewed Ritalin tablet, it is unlikely that this new chewable tablet will behave differently than the reference listed product Ritalin tablet in pediatrics. Therefore, from Clinical Pharmacology perspective, granting a deferral of pediatric studies is acceptable as is done for Methylin AQ.

Specifically, the labeling approved for the reference listed drug, Ritalin, and proposed labeling for this product includes the pediatric population age 6 years and above. The sponsor requested the Agency to grant a deferral of the requirement to perform pediatric studies in accordance with 21 CFR 314.55(b). The Sponsor indicated that pediatric studies (preschool age children, under age 6) are presently being conducted by the NIH which will be used to develop class labeling into the labeling proposed herein, once it is available.

From a Clinical Pharmacology and Biopharmaceutics perspective, a separate study in pediatrics using this new chewable tablet may not be needed based on the finding from supporting study (#596). Briefly, Methylin CT was shown to be bioequivalent when chewed thoroughly before swallowing or swallowed as a whole. Therefore, the ability of pediatric patients to chew the tablet thoroughly before swallowing may not be of concern and one can rely on pediatric data generated on Ritalin tablet.

Appendices

Individual study review

MI Protocol 1137-00-610:

An Open-Label, Randomized, Three-Way, Crossover Study to Evaluate the Relative Bioavailability of Two Test Formulations (10 mg Chewable Tablet and 2 mg/mL Liquid) of Methylphenidate Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin® 20 mg Tablet, Ciba-Geigy Corporation) in Normal Human Subjects Under Fasting Conditions.

(Note: This pivotal fasting BE study #610 was reviewed under NDA21,419 Methylin AQ. Only relevant information regarding Methylin CT will be reviewed here)

INVESTIGATOR: _____

STUDY CENTER: _____

STUDY PERIOD: Period 1 -October 28 through October 30, 2000
 Period 2- November 4 through November 6, 2000
 Period 3 -November 11 through November 13,2000

Analytical testing Laboratory: _____

The objective of this study was to compare the oral bioavailability of two Mallinckrodt test formulations of methylphenidate HCl (chewable tablets and oral solution) to an equivalent oral dose of commercially available methylphenidate HCl product (Ritalin® 20 mg tablet, Ciba-Geigy Corporation) in a group of healthy subjects under fasting conditions.

Study design:

An open-label, randomized, three-period, three-treatment; six-sequence crossover study in which healthy subjects randomly received three separate drug administrations separated by a washout period of at least 7 days. Subjects fasted for 10 hours prior to dosing and an additional 4 hours after dosing. Drug administration consisted of two Mallinckrodt methylphenidate HCl chewable tablets 10 mg formulation (chewed), 10 mL (20 mg) of the Mallinckrodt 2 mg/mL methylphenidate HCl oral solution, or a single 20 mg tablet of Ritalin® swallowed whole. Subjects were excluded if they were chronic users of tranquilizers, sedatives, aspirin, antibiotics; other medications.

NUMBER OF SUBJECTS:

	Age (years)	Gender
Planned (N=36)	18-48	Males/Females
Actual (N=36)	18-46	Males

Treatment group/Dose/Route/Lot number:

- (A) Methylphenidate HCl (2 x 10 mg) chewable tablets (Mallinckrodt Inc., Lot # MHSC0043, batch size _____). Note: (as per chemists, Dr. Christy John and Xiao-Hong Chen) Commercial batch size is _____
- (B) Methylphenidate HCl 10 mL (2 mg/mL) oral solution (Mallinckrodt Inc., Lot #MHSC0044, batch size _____ Note: proposed commercial batch size is _____
- (C) Reference treatment, Ritalin® 20 mg tablet, Ciba-Geigy Corporation, Lot #1T197608, expiration date 01/02.

PK measures:

Blood samples (10 mL) were obtained prior to dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours post-dose following each dose. Blood samples were collected using potassium ethylenediaminetetraacetate (potassium EDTA) as the anticoagulant. Plasma was separated from the collected blood samples. All plasma samples were analyzed for methylphenidate using LC-MS/MS analytical method.

Safety Measures: The safety of methylphenidate oral solution and Ritalin® tablet was monitored by the following parameters: adverse events (AEs), vital signs, medical history, physical examination, and clinical laboratory values.

Data Analysis

Pharmacokinetics: PK parameters were compared between the two methylphenidate HCl test formulations [2 x 10 mg chewable tablets (chewed) and 10 mL oral solution (2 mg/mL)] and the reference formulation -Ritalin® 20 mg tablet swallowed as a whole tablet. In addition, 90% confidence intervals were calculated for the log-transformed AUCt, AUCinf, and Cmax.

PK parameters, such as AUCt, AUC0-inf, Cmax, Tmax, terminal elimination half-life (T1/2), and apparent first-order terminal elimination rate constant (Kel) were calculated using the standard non-compartmental approach.

RESULTS:

Pharmacokinetics: Systemic exposure of methylphenidate HCl was similar for the methylphenidate HCl test formulations, 2 x 10 mg chewable tablets (chewed) and 10 mL oral solution (2 mg/mL), as compared to the reference formulation, Ritalin® 20 mg tablet, swallowed as a whole tablet (Fig 3, Table 10). The 90% CI requirements for average bioequivalence were met for all PK parameters (Cmax, AUC0-inf) (Table 11, 12, 13). BE was demonstrated among all three formulations.

Fig 3

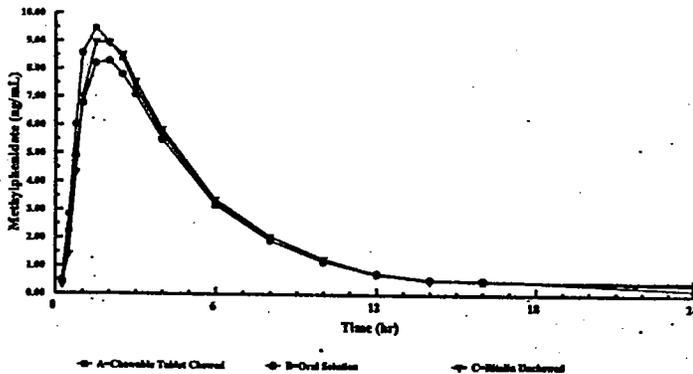


Figure 11.5-1: Mean Plasma Concentration Profile of Methylphenidate Formulations (20 mg)

Table 10

Parameter	Treatment Groups		
	MPH HCl Chewable Tablet (A)	MPH HCl Oral Solution (B)	Ritalin® Tablet Unchewed (C)
N	33	33	34
AUCinf (ng·hr/mL)	49.97 (16.28)	46.70 (15.58)	49.66 (14.80)
AUCt (ng·hr/mL)	48.32 (15.95)	45.10 (15.37)	48.01 (14.35)
Cmax (ng/mL)	9.982 (2.607)	9.075 (2.610)	9.804 (2.723)
Kel (1/hr)	0.2515 (0.0363)	0.2604 (0.0385)	0.2579 (0.0374)
T1/2 (hr)	2.826 (0.516)	2.725 (0.449)	2.756 (0.506)
Tmax (hr)	1.530 (0.413)	1.712 (0.597)	1.868 (0.432)

Reference: Tables 14.2.1-8 through 14.2.1-10 of MI report for Study 610

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Table 11

Table 3.1.3 Summary of 90% Confidence Intervals and CV MPH HCl Chewable Tablet (A) versus MPH HCl Oral Solution (B)						
	ln (AUCinf)	ln (AUCt)	ln (Cmax)	Kel	T1/2	Tmax
90% CI (%)	105.34-113.28	105.64-113.73	106.73-117.53	N/A*	N/A*	N/A*
LSM Ratio A/B (%)	109.24	109.61	112.00	97.01	103.44	89.91
CV (%)	8.34	8.48	11.08	7.26	8.68	24.82
*N/A = Not applicable Reference: Tables 14.2.1-11 through 14.2.1-15 of MI report for Study 610						

Table 12

Table 3.1.4 Summary of 90% Confidence Intervals and CV MPH HCl Chewable Tablet (A) versus Ritalin® Tablet (C)						
	ln (AUCinf)	ln (AUCt)	ln (Cmax)	Kel	T1/2	Tmax
90% CI (%)	99.69-107.08	99.63-107.15	100.95-111.01	N/A*	N/A*	N/A*
LSM Ratio A/C (%)	103.32	103.32	105.86	98.48	101.68	81.41
CV (%)	8.34	8.48	11.08	7.26	8.68	24.82
*N/A = Not applicable Reference: Tables 14.2.1-11 through 14.2.1-15 of MI report for Study 610						

Table 13

Table 3.1.5 Summary of 90% Confidence Intervals and CV MPH HCl Oral Solution (B) versus Ritalin® Tablet (C)						
	ln (AUCinf)	ln (AUCt)	ln (Cmax)	Kel	T1/2	Tmax
90% CI (%)	91.26-98.02	90.90-97.75	90.13-99.11	N/A*	N/A*	N/A*
LSM Ratio B/C (%)	94.58	94.26	94.52	101.51	98.29	90.55
CV (%)	8.34	8.48	11.08	7.26	8.68	24.82
*N/A = Not applicable Reference: Tables 14.2.1-11 through 14.2.1-15 of MI report for Study 610						

Demographic and other baseline characteristics:

- Only male subjects were enrolled. Race distribution was primarily Caucasian (83.3 %, 30/36), with 5 Black subjects (13.9%) and 1 Asian subject (2.8%)(table 14)

Table 14

Table 11.2-1 Summary of Demographics	
Parameter	N = 36
Sex N (%)	36 (100)
Male	
Race N (%)	
Asian	1 (2.8)
Black	5 (13.9)
White	30 (83.3)
Age (years)	
Mean	26.6
Standard Deviation	8.2
Range	18 - 46
Weight (lb)	
Mean	187.8
Standard Deviation	22.2
Range	144 - 232
Height (in)	
Mean	70.3
Standard Deviation	2.3
Range	65 - 76
Reference: Table 14.1	

CONCLUSION: The two Mallinckrodt methylphenidate HCl formulations of chewable tablet (2 x 10 mg) and 10 mL oral solution (2 mg/mL) are well tolerated and bioequivalent to each other and to a commercially available reference formulation of 20 mg methylphenidate tablet (Ritalin®, Ciba-Geigy Corporation).

Reviewer's Comments:

Study design: We consider the design acceptable.

PK measures

- % CV for Cmax and AUC 0-inf were comparable for test products (Methylin AQ and methylphenidate chewable tablet) and reference listed product Ritalin®.
- Terminal t1/2 for test products (Methylin AQ and methylphenidate chewable tablet) were comparable to the reference listed product Ritalin® tablet.

BE:

- We consider the test products of Methylin AQ oral solution and Methylin CT(chewable tablet) bioequivalent to the marketed products of Ritalin®. The 90% CI of test-to-reference ratio fell within the recommended 0.80-1.25 goal-post for average BE assessment for log transformed PK parameters (Cmax and AUC0-inf). The elimination half-lives and tmax were comparable for test and reference products. There was no significant sequence or period effect for AUC0-inf and Cmax.
- This reviewer has confirmed the validity of the statistical analysis (90% CI) using an in-house BE program. Following are the results from this analysis for 2 pivotal PK parameters (AUC0-inf and Cmax):

Methylin CT versus Ritalin tablet

AUC

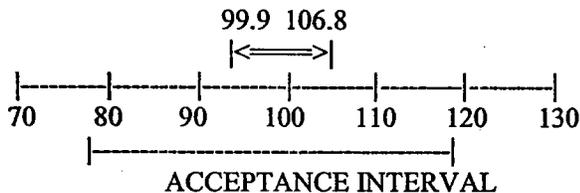
P VALUE ANALYSIS

 ERROR MEAN SQUARE .. .00696
 REFERENCE MEAN (LN) . 3.858474
 TEST MEAN (LN) 3.891128
 NUMBER OF SUBJECTS .. 36
 DEGREES OF FREEDOM .. 34
 DELTA2

 E VALUE: 3.265476E-02
 THETA VALUES: -.2231436 .1823215
 T VALUES: 13.00856 7.611268
 P VALUES: <0.00017 <0.00017

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 99.94054
 UPPER CI (% OF REF MEAN): 106.8125
 CONCLUSION: PASS



C_{max}

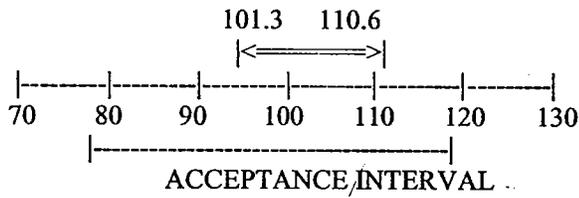
P VALUE ANALYSIS

 ERROR MEAN SQUARE .. 1.227221E-0
 REFERENCE MEAN (LN) . 2.250468
 TEST MEAN (LN) 2.307406
 NUMBER OF SUBJECTS .. 36
 DEGREES OF FREEDOM .. 34
 DELTA 2

 E VALUE: 5.693841E-02
 THETA VALUES: -.2231436 .1823215
 T VALUES: 10.72655 4.801909
 P VALUES: <0.00017 <0.00017

90% CONFIDENCE INTERVAL

 LOWER CI (% OF REF MEAN): 101.2869
 UPPER CI (% OF REF MEAN): 110.6376
 CONCLUSION: PASS



**APPEARS THIS WAY
ON ORIGINAL**

Study 1137-00-721

An Open-Label, Randomized, Three-Way, Food Effect Study to Evaluate the Relative Bioavailability of a Test Formulation of Methylphenidate HCl 10 mg Chewable Tablet (2 x 10 mg) (fed and fasted) Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin@20 mg Tablet, Ciba-Geigy Corporation) (fed) in Normal Human Subjects.

INVESTIGATOR: _____

STUDY CENTER: _____

63301 .

STUDY PERIOD: Period 1 -January 6 through January 8, 2001
 Period 2- January 13 through January 15, 2001
 Period 3- January 20 through January 22, 2001

Analytical testing Laboratory: _____

OBJECTIVE:

To compare the oral bioavailability of methylphenidate HCl chewable tablet (2 x 10mg) to an equivalent oral dose of a commercially available methylphenidate HCl product (Ritalin@ 20 mg tablet, Ciba-Geigy Corporation) in a group of healthy subjects under fasting and fed conditions.

Study Design:

An open-label, randomized, three-period, three-treatment, six-sequence crossover study in which healthy subjects randomly received three separate drug administrations separated by a washout period of at least 7 days. Subjects were excluded if they were chronic users of tranquilizers, sedatives, aspirin, antibiotics, other medications. Drug administration consisted of three treatment groups:

Treatment Group/Dosing/Treatment Conditions/ Lot number

- (A) Mallinckrodt test formulation -Methylphenidate chewable tablet (2 x 10mg) following an overnight fast and orally administered under fasting conditions without high fat breakfast. (Mallinckrodt Inc., Lot MHSC0043).
- (B) Mallinckrodt test formulation-Methylphenidate HCl chewable tablet (2 x 10mg) following an overnight fast and consumption of a standardized high-fat breakfast 15 minutes prior to dosing. (Mallinckrodt Inc., Lot MHSC0043).
- (C) One 20 mg Ritalin@ tablet (Ciba-Geigy Corporation) following an overnight fast and consumption of a high-fat breakfast* 15 minutes prior to dosing. (Ciba-Geigy Corporation, Lot 1T197608, expiration date 01/2002).

*High-fat breakfast consisted of one buttered English muffin, one fried egg, one slice American cheese, one slice Canadian bacon, one serving of hash brown potatoes, 6 fluid ounces of orange juice, and 8 fluid ounces of whole milk.

NUMBER OF SUBJECTS:

	Age (years)	Gender
Planned (N=24)	18 years or older	Males/Females
Actual (N=24, 23 in treatment A &B)	18-41	18Males/6 females

PK measures:

Blood collections (1 x 10 mL) in pre-chilled EDTA tubes were obtained via venipuncture at 0 (pre-dose), 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours post-dose. Plasma was separated

from the collected blood samples. All plasma samples were analyzed for methylphenidate using a non-chiral LC-MS/MS analytical method. PK parameters (AUC_t, AUC_{tmax}^{*}, AUC_{0-inf}, t_{max}, K_{el}, t_{1/2}) were calculated using non-compartmental methods. (*AUC_{tmax}: area under the plasma concentration curve to median t_{max} value of reference treatment, a measure of an early exposure)

Safety Measures: The safety of methylphenidate chewable tablet and oral solution administration was monitored by the following parameters: adverse events (AEs), vital signs, medical history, physical examination, and clinical laboratory values.

Data analysis:

PK: In evaluating the food effect on MPH PK, treatment A (test-fasting) was regarded as the reference treatment. For evaluating the relative bioavailability under the fed condition, treatment C (reference with fed) was used as the reference. Parametric General Linear Model (GLM) methodology was used in the analysis of selected PK parameters. The natural logarithm of AUC_t, AUC_{0-inf}, AUC_{tmax} and C_{max} were used in the analysis of bioequivalence.

Results:

- **Methylin CT, fed (treatment B) versus fasted (treatment A):** The 90% CI of test (fed)-to-reference (fasted) ratio fell slightly outside the 0.80-1.25 goal-post for average BE assessment for the log transformed PK parameters (AUC_{0-inf} & C_{max}) and these differences were statistically significant (p<0.0001). Specifically, the LS mean ratios were approximately 120.9% for AUC_{0-inf} and 102.0% for C_{max}. Mean t_{max} was prolonged from 1.489 hours for 2.413 hours (Fig 4, Table 15, 16). All of these contrasts were statistically significant (p<0.001) except C_{max} (p=0.6389).
- **Methylin CT, fed (treatment B) versus Ritalin tablet fed (treatment C):** The 90% CI of AUC_{0-inf} and C_{max} fell within the 80-125% goal post. Specifically, the LS mean ratios were 100.67% for AUC_{0-inf} and 86.72% for C_{max}. Mean t_{max} was comparable. (Table 15, 17, 18). All of these contrasts were not statistically significant except for C_{max} (p=0.0015).

Fig 4

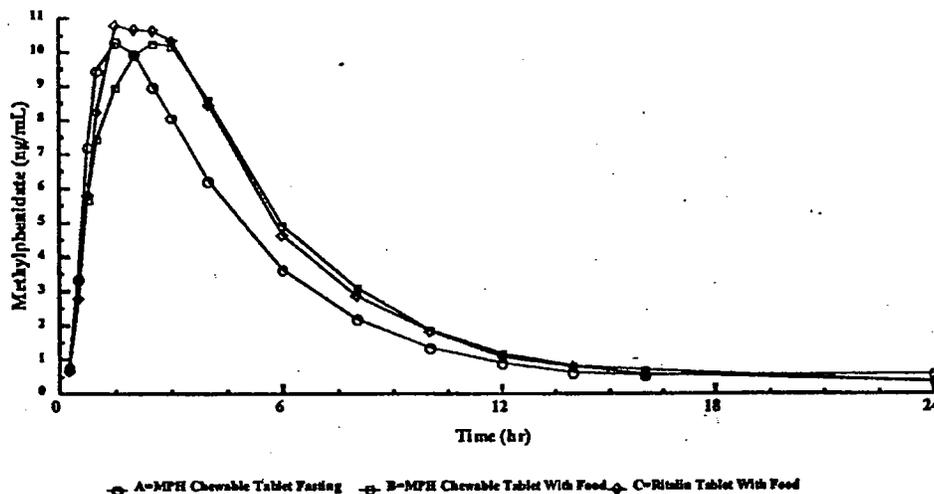


Figure 11.5-1 Mean Plasma Concentration-Time Profile of Methylphenidate Formulations (20 mg)

Table 15

Summary of Untransformed Pharmacokinetic Data [Mean (SD)] - Study 721			
Parameter	Treatment Groups		
	Methylin® CT Tablets Fasting (A)	Methylin® CT Tablets With Food (B)	Ritalin® Tablet With Food (C)
N	23	23	24
AUCinf (ng-hr/mL)	56.37 (25.64)	66.96 (29.65)	66.75 (27.66)
AUCt (ng-hr/mL)	54.23 (24.49)	65.01 (29.13)	65.00 (27.16)
AUCmx (ng-hr/mL)	14.05 (4.93)	12.21 (3.87)	13.43 (6.81)
Cmax (ng/mL)	11.041 (3.970)	11.055 (3.308)	12.979 (4.429)
Kel (1/hr)	0.2438 (0.0540)	0.2520 (0.0394)	0.2510 (0.0388)
T1/2 (hr)	3.047 (1.032)	2.824 (0.500)	2.828 (0.456)
Tmax (hr)	1.489 (0.443)	2.413 (0.718)	2.167 (0.940)

Reference: Tables 14.2.1-8 through 14.2.1-10 of study report for MI Protocol 1137-00-721
AUCmx = AUC_{0-∞}

Table 16

Summary of 90% Confidence Intervals and CV Methylin® CT Tablets with Food (B) versus Methylin® CT Tablets Fasting (A)							
	AUCinf	AUCt	Cmax	AUCmx	Kel	T1/2	Tmax
90% CI (%)	114.48- 125.90	115.39- 126.94	94.77- 109.80	71.55- 106.04	N/A*	N/A*	N/A*
LSM Ratio B/A (%)	120.06	121.03	102.01	87.10	103.22	92.96	161.27
CV (%) ^a	9.20	9.22	14.24	38.07	11.28	18.95	29.51
p ^b	0.0001	0.0001	0.6389	0.2259	0.3497	0.1929	0.0001

*N/A = Not applicable ^aIntra-subject coefficient of variation
^bp-value from ANOVA contrast of treatments (B) and (A)
Reference: Tables 14.2.1-11 through 14.2.1-15 of study report for MI Protocol 1137-00-721

Table 17

Table 3.3.5 Summary of 90% Confidence Intervals and CV Ritalin® Tablet with Food (C) versus Methylin® CT Tablets Fasting (A)							
	AUCinf	AUCt	Cmax	AUCmx	Kel	T1/2	Tmax
90% CI (%)	113.83- 124.93	115.09- 126.33	109.46- 126.40	72.13- 105.99	N/A*	N/A*	N/A*
LSM Ratio C/A (%)	119.25	120.58	117.63	87.44	103.05	92.85	143.27
CV (%) ^a	9.20	9.22	14.24	38.07	11.28	18.95	29.51
p ^b	0.0001	0.0001	0.0004	0.2388	0.3759	0.1864	0.0006

*N/A = Not applicable ^aIntra-subject coefficient of variation
^bp-value from ANOVA contrast of treatments (B) and (A)
Reference: Tables 14.2.1-11 through 14.2.1-15 study report for MI Protocol 1137-00-721

Table 18

Summary of 90% Confidence Intervals and CV Methylin® CT Tablets with Food (B) versus Ritalin® Tablet with Food (C)							
	AUCinf	AUCt	Cmax	AUCmx	Kel	T1/2	Tmax
90% CI (%)	96.10- 105.47	95.80- 105.16	80.70- 93.19	82.18- 120.75	N/A*	N/A*	N/A*
LSM Ratio B/C (%)	100.67	100.37	86.72	99.62	100.17	100.12	112.57
CV (%) ^a	9.20	9.22	14.24	38.07	11.28	18.95	29.51
p ^b	0.8057	0.8926	0.0015	0.9730	0.9599	0.9841	0.1302

*N/A = Not applicable ^aIntra-subject coefficient of variation
^bp-value from ANOVA contrast of treatments (B) and (A)
Reference: Tables 14.2.1-11 through 14.2.1-15 of study report for MI Protocol 1137-00-721

- **Demographics (Table 19):** Both male and female subjects were enrolled. Race distribution was primarily Caucasian (91.7 %, 22/24), with 2 Black subjects (8.3%).

Table 19

Table 11.2-1 Summary of Demographics	
Parameter	N = 24
Sex N (%)	
Male	18 (75)
Female	6 (25)
Race N (%)	
Black	2 (8.3)
White	22 (91.7)
Age (years)	
Mean	28.6
Standard Deviation	12.4
Range	19 - 60
Weight (lb)	
Mean	174.5
Standard Deviation	24.8
Range	128 - 240
Height (in)	
Mean	69.4
Standard Deviation	3.7
Range	61 - 76

Reference: Table 14.1

Conclusion (Based on C_{max}, t_{max} and AUC_{0-inf} only):

- The food (high fat meal) affects the bioavailability of methylphenidate chewable tablet (2 x 10mg). Mean AUC_{0-inf} was increased from 56.37 to 66.96 ng.hr/ml. Mean t_{max} was prolonged by 1 hour from 1.4 hours to 2.4 hours. Mean C_{max} was comparable. No change was noted in elimination kinetics.
- Overall, these results (BE of Methylin CT versus Ritalin in fed state), along with the prior demonstration that these formulations are bioequivalent in the fasted state, indicate that although a statistically significant food effect on methylphenidate PK exists, the magnitude of this effect appears to be comparable for the test formulation methylphenidate HCl chewable tablet (2 x 10mg) and Ritalin® tablet 20 mg.

Reviewer's Comments:

- **Study design:** We consider the design acceptable.

PK measures

- % CV for C_{max} and AUC were comparable for test Methylin chewable tablet (fasted and fed condition) and reference listed product Ritalin® (fed condition).
- Terminal t_{1/2} was comparable for test product Methylin chewable tablet (fasted and fed condition) and reference listed product Ritalin® (fed condition).

Food-Effect:

- The high fat meal prolonged the t_{max} and increased the exposure of methylphenidate. The 90% CI of test (fed)-to-reference (fasted) ratio fell slightly outside the 0.80-1.25 goal-post for average BE assessment for the log transformed PK parameters (AUC_{0-inf} & C_{max}) and these differences were statistically significant (p<0.0001)
- This reviewer has confirmed the validity of statistical analysis (90%CI) using an in-house BE program. Following are the results from this analysis for 2 pivotal PK parameters (AUC_{0-inf} and C_{max}):

Methylin chewable tablet fasted versus fed
AUC

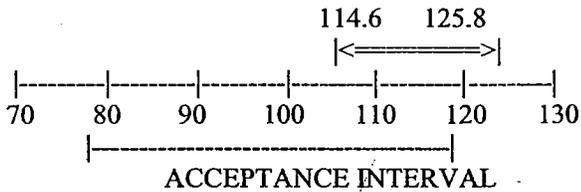
P VALUE ANALYSIS

ERROR MEAN SQUARE .. 8.47309E-03
REFERENCE MEAN (LN) . 3.952088
TEST MEAN (LN) 4.134875
NUMBER OF SUBJECTS .. 23
DEGREES OF FREEDOM .. 21
DELTA2

E VALUE: .1827877
THETA VALUES: -.2231436 .1823215
T VALUES: 14.95479 1.717286E-02
P VALUES: <0.00033 0.49323

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 114.5775
UPPER CI (% OF REF MEAN): 125.7963
CONCLUSION: FAIL



Cmax

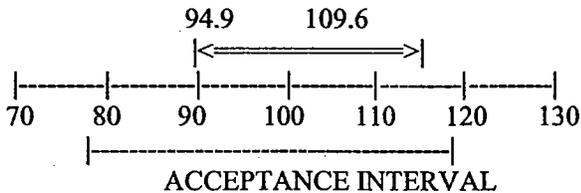
P VALUE ANALYSIS

ERROR MEAN SQUARE .. 2.027712E-0
REFERENCE MEAN (LN) . 2.347057
TEST MEAN (LN) 2.366924
NUMBER OF SUBJECTS .. 23
DEGREES OF FREEDOM .. 21
DELTA2

E VALUE: 1.986742E-02
THETA VALUES: -.2231436 .1823215
T VALUES: 5.787243 3.868802
P VALUES: <0.00033 0.00044

90% CONFIDENCE INTERVAL

LOWER CI (% OF REF MEAN): 94.89623
UPPER CI (% OF REF MEAN): 109.6498
CONCLUSION: PASS



Study 1137-99-596

A Randomized, Two-Period Crossover, Six Sequence, Open-Label Study to Evaluate the Relative Bioavailability of a Test Tablet Formulation of Methylphenidate 10 mg Chewable (2 x 10 mg) (chewed or unchewed) Compared to an Equivalent Dose of a Commercially Available Reference Drug Product (Ritalin 20 mg® Tablet, Ciba-Geigy Corporation) Under Fasting Conditions.

INVESTIGATOR: —

STUDY CENTER: —

STUDY PERIOD: Period 1 -November 19 through November 21, 1999
Period 2- December 3 through December 5, 1999

Analytical testing Laboratory: —

OBJECTIVE:

To compare the oral bioavailability of a test formulation of methylphenidate HCl chewable tablet (either chewed or swallowed as a whole tablet) and an equivalent oral dose of the reference listed drug, Ritalin 20 mg tablet (Ciba-Geigy Corporation), swallowed as a whole tablet, in a group of healthy subjects under fasting conditions.

Study design:

An open-label, randomized, two-period, three-treatment; six-sequence crossover study in which healthy subjects randomly received two separate drug administrations separated by a washout period of 14 days. Subjects fasted for 10 hours prior to dosing and an additional 4 hours after dosing. Drug administration consisted of Mallinckrodt methylphenidate HCl chewable tablets 10 mg formulation either chewed (treatment A), or swallowed whole (treatment B), or a single 20 mg tablet of Ritalin® swallowed whole. Subjects were excluded if they were chronic users of tranquilizers, sedatives, aspirin, antibiotics, other medications.

NUMBER OF SUBJECTS:

	Age (years)	Gender
Planned (N=36)	18-45	Males/Females
Actual (N=36)	18-45	Males

Treatment group/Dose/Route/Lot number:

In first period, each subject received one of the following study drug products. In second period, each subject received an alternate drug treatment. Table 20 summarizes the treatment sequences that subjects received.

- (A) Methylphenidate HCl (2 x 10 mg) chewable tablets (Mallinckrodt Inc., Lot # MHSC9953. Note: This is a preliminary formulation)
- (B) Methylphenidate HCl (2 x 10mg) chewable tablet (Mallinckrodt Inc., Lot #MHSC9953. Note: This is a preliminary formulation) swallowed as a whole.
- (C) Reference treatment, Ritalin® 20 mg tablet, Ciba-Geigy Corporation, Lot #1T197606, expiration date 12/2001.

Table 20

Table 12.1-1 Number of Subjects Receiving a Treatment Sequence	
Treatment Sequence ^a	Number of Subjects
A/B	6
A/C	6
B/A	6
B/C	6
C ^b	1
C/A	5
C/B	6
Total Subjects	36
^a A = Test drug product, chewed. B = Test drug product, swallowed whole. C = Reference drug product, swallowed whole. ^b Subject 596-11-030 withdrew from study after Period 1 dosing. Reference: Table 14.1	

PK measures:

Blood samples (10 mL) were obtained prior to dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, and 24 hours post-dose following each dose. Blood samples were collected using potassium ethylenediaminetetraacetate (potassium EDTA) as the anticoagulant. Plasma was separated from the collected blood samples. All plasma samples were analyzed for methylphenidate using LC-MS/MS analytical method.

Safety Measures: The safety of methylphenidate chewable tablet and Ritalin® tablet was monitored by the following parameters: adverse events (AEs), vital signs, medical history, physical examination, and clinical laboratory values.

Data Analysis

Pharmacokinetics: PK parameters were compared between the two methylphenidate HCl test formulation administrations [2 x 10 mg chewable tablets (chewed or unchewed)] and the reference formulation -Ritalin® 20 mg tablet swallowed as a whole tablet. In addition, 90% confidence intervals were calculated for the log-transformed AUC_t, AUC_{inf}, and C_{max}. PK parameters, such as AUC_t, AUC_{0-inf}, C_{max}, T_{max}, terminal elimination half-life (T_{1/2}), and apparent first-order terminal elimination rate constant (K_{el}) were calculated using the standard non-compartmental approach.

RESULTS:**Pharmacokinetics:**

- Systemic exposure of methylphenidate HCl was similar for the methylphenidate HCl test formulation (2 x 10 mg chewable tablet) either chewed thoroughly before swallowing or swallowed as a whole (Table 21). Similar results were observed when comparing the methylin CT test formulation either chewed or unchewed to reference formulation, Ritalin® 20 mg tablet, swallowed as a whole tablet (Fig 5, Table 22, 23). The 90% CI requirements for average bioequivalence were met for all PK parameters (C_{max}, AUC_{0-inf}) (Table 22).

Fig 5

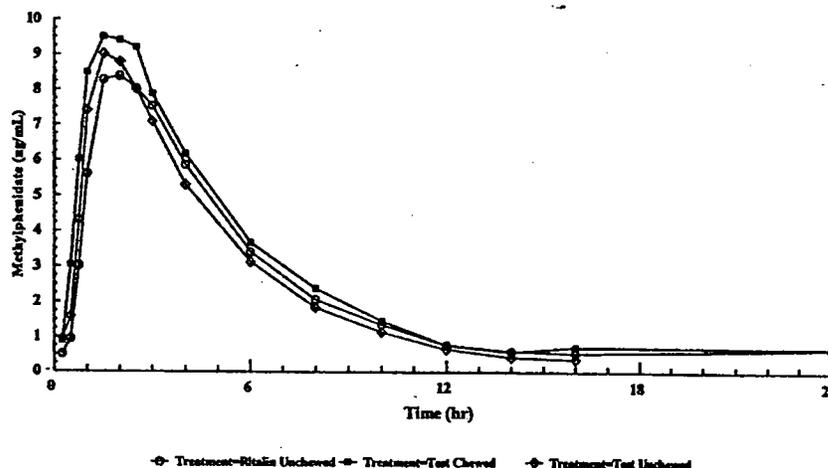


Figure 11.5-1 Mean Plasma Concentration–Time Profile of Methylphenidate Treatments (20 mg)

Table 21

Summary of Untransformed Pharmacokinetic Data [Mean (SD)] Study 596

Parameter	Treatment Groups		
	Methylin® CT Chewed (A)	Methylin® CT Unchewed (B)	Ritalin® Tablet Unchewed (C)
N	23	24	24
AUCinf (ng·hr/mL)	54.49 (29.12)	45.98 (11.36)	48.12 (25.63)
AUCt (ng·hr/mL)	53.08 (28.46)	44.51 (11.31)	46.54 (25.08)
Cmax (ng/mL)	10.541 (3.626)	9.673 (2.570)	9.338 (2.902)
Kel (1/hr)	0.2869 (0.0625)	0.2742 (0.0328)	0.2677 (0.0491)
T1/2 (hr)	2.537 (0.614)	2.563 (0.310)	2.673 (0.505)
Tmax (hr)	1.783 (0.618)	1.604 (0.361)	1.938 (0.517)

Reference: Tables 14.2.1-8 through 14.2.1-10 of Study report for MI Study 1137-99-596

Table 22

Summary of 90% Confidence Limits and CV Methylin® Tablets CT Chewed (A) versus Methylin® CT Tablets Unchewed (B)						
	AUCinf	AUCt	Cmax	Kel	T1/2	Tmax
90% CI (%)	98.38-107.71	98.45-108.15	95.48-109.51	N/A*	N/A*	N/A*
LSM Ratio (A/B) %	102.94	103.19	102.25	102.89	99.07	111.69
CV (%) ^a	8.12	8.42	12.29	10.81	10.41	26.94
p ^b	0.2969	0.2755	0.5932	0.4294	0.7945	0.2397

*N/A = Not applicable. ^aIntra-subject coefficient of variation
^bp-value from ANOVA contrast of treatments (B) and (A)
 Reference: Tables 14.2.1-11 through 14.2.1-13 of Study report for MI Study 1137-99-596

Table 23

Summary of 90% Confidence Limits and CV Methylin® CT Tablets Chewed (A) versus Ritalin® Tablet Unchewed (C)						
	AUCinf	AUCt	Cmax	Kel	T1/2	Tmax
90% CI (%)	101.94-111.61	102.44-112.53	97.70-112.06	N/A*	N/A*	N/A*
LSM Ratio (A/C) %	106.66	107.36	104.63	106.47	95.41	98.29
CV (%) ^a	8.12	8.42	12.29	10.81	10.41	26.94
p ^b	0.0273	0.01906	0.2912	0.1001	0.1967	0.8467

*N/A = Not applicable. ^aIntra-subject coefficient of variation
^bp-value from ANOVA contrast of treatments (A) and (C)
 Reference: Tables 14.2.1-11 through 14.2.1-13 of Study report for MI Study 1137-99-596

Table 24

Summary of 90% Confidence Limits and CV Methylin®CT Tablets Unchewed (B) versus Ritalin® Tablet Unchewed (C)						
	AUCinf	AUCt	Cmax	Kel	T1/2	Tmax
90% CI (%)	99.11-108.34	99.35-108.96	95.66-109.46	N/A*	N/A*	N/A*
LSM Ratio (B/C) %	103.62	104.05	102.33	103.48	96.30	88.00
CV (%)	8.12	8.42	12.29	10.81	10.41	26.94
p ^b	0.2015	0.1704	0.5811	0.3950	0.2860	0.1720

*N/A = Not applicable *Intra-subject coefficient of variation
^bp-value from ANOVA contrast of treatments (B) and (C)
 Reference: Tables 14.2.1-11 through 14.2.1-13 of Study report for MI Study 1137-99-596

Demographic: Only male subjects were enrolled. Race distribution was primarily Caucasian (88.9 %, 32/36), with 2 Black and 2 Asian subjects (5.6%) (table 25).

Table 25

Table 11.2-1 Summary of Demographics	
Parameter	N = 36
Sex N (%)	
Male	36 (100)
Race N (%)	
Asian	2 (5.6)
Black	2 (5.6)
White	32 (88.9)
Age (years)	
Mean	24.5
Standard Deviation	6.4
Range	18 - 41
Weight (lb)	
Mean	180.3
Standard Deviation	27.0
Range	126 - 241
Height (in)	
Mean	70.0
Standard Deviation	3.2
Range	64 - 77

Reference: Table 14.1

Reviewer’s Comments:

Study design:

- This is an incomplete block, two-period, three treatment, six-sequence, cross-over study design. The study consisted of six treatment groups, each of which received two of the three possible treatments. The study design is acceptable.
- The sponsor has taken into consideration the sequence, drug, period, subjects nested within sequences as sources of variation in the data analysis.

PK measures

- % CV for all PK parameters (including Cmax and AUC 0-inf) were consistently smaller if test product (Methylin CT) was swallowed as a whole.

BE:

- We consider the test product Methylin CT is bioequivalent when chewed thoroughly before swallowing or swallowed as a whole. The 90% CI of test-to-reference ratio fell within the recommended 0.80-1.25 goal-post for average BE assessment for log transformed PK parameters (Cmax and AUC0-inf). The elimination half-lives and tmax were comparable for test (Methylin CT swallowed as a whole) and reference (Methylin CT thoroughly chewed before swallowing).

- Similar results were observed when comparing Methylin CT (swallowed as a whole) with Ritalin tablet, or Methylin CT (chewed thoroughly before swallowing) with Ritalin tablet.
- It should be noted that this study used a preliminary formulation which is slightly different from the final formulation (see "Formulation" in appendix for details). However, both this preliminary formulation and final formulation are BE to Ritalin tablet. The dissolution profile of this preliminary formulation (all strengths) in H₂O indicated that dissolution was greater than 95% dissolved in 15 minutes (see "Dissolution" in appendix for details, page 32).

**APPEARS THIS WAY
ON ORIGINAL**

Bioanalytical Assay

- The validation of non-chiral LC-MS/MS bioanalytical method for methylphenidate in EDTA-treated human plasma was previously reviewed under NDA21,419 (Methylin AQ).
- Overall, the assay was found to be specific, reproducible, sensitive and adequate to characterize the PK of methylphenidate.
- DSI issues under the NDA 21,419 regarding pivotal fasting BE study (#610) had been resolved and results were found acceptable.
- Information on the criteria for re-analysis samples for study #721 (a food effect study on Methylin CT) was submitted under NDA21,419.
- Attached below were the pre- and within-study validation directly excerpted from the sponsor's submission (Tables 28 & 29)
- The LLOQ for study #721 (food effect study) should be set at 0.75ng/ml since the inter-day precision for the 0.75ng/ml QC sample were out of the acceptance criteria of ±15%. Specifically, the %CV for inter-day precision of QC sample at the concentration of 0.75ng/ml was 17.9. However, this modification should not affect the significant food effect observed in this study since the quantifiable concentrations in concentration-time curve had captured major portion of the AUC based on the observed concentration-time curve.

Table 28

Parameter	Quality Control Samples	Standard Curve Samples
Concentration (ng/mL)	0.75, 10.0, 20.0, 50.0	0.25, 0.50, 1.00, 2.00, 5.00, 25.0
Intra-Day Precision (% CV)	1.9-21.9	0.29-17.2
Intra-Day Accuracy (% Accuracy)	86.2-90.6	87.0-111.0
Inter-Day Precision (% CV)	1.9-17.6	2.6-11.3
Inter-Day Accuracy (% Accuracy)	90.6-93.8	97.9-102.0
Correlation (Range of R ² values)	N/A	0.9983-0.9995
Linear Range (ng/mL)	N/A	0.25-25.0
Sensitivity/ LLOQ	N/A	0.25
Extraction Recovery of MPH	N/A	102.0-119.0
Extraction Recovery of Internal Standard	N/A	108.0
Stability in Plasma		
1) Bench-Top stability at Room Temp. (hrs.)	6.5	N/A
2) Auto-Sampler Stability of Extract at Room Temp. (hrs.)	24	N/A
3) Freeze-Thaw Stability (N Cycles)	3	N/A
4) Storage Stability (Temp. Duration)	-20° C, 10 Months	N/A
Specificity	Specific to analytes. No significant interference observed from endogenous substances in blank plasma. No interference observed from commonly used OTC drugs.	
Ref: Table 8 in	Analytical Data Report for MI Study 721	

Table 29

Parameter	Study 596		Study 610		Study 721	
	Quality Control Samples	Standard Curve Samples	Quality Control Samples	Standard Curve Samples	Quality Control Samples	Standard Curve Samples
Concentration (ng/mL)	0.75, 10.0, 20.0	0.25, 0.50, 1.00, 2.00, 10.0, 22.0, 25.0	0.75, 10.0, 20.0	0.25, 0.50, 1.00, 2.00, 10.0, 22.0, 25.0	0.75, 10.0, 20.0	0.25, 0.50, 1.00, 2.00, 10.0, 22.0, 25.0
Intra-Day Precision (% CV)	N/A	N/A	N/A	N/A	N/A	N/A
Intra-Day Accuracy (% Accuracy)	N/A	N/A	N/A	N/A	N/A	N/A
Inter-Day Precision Range (% CV)	6.4-13.9	4.0-8.6	3.0-7.3	1.2-8.4	4.1-17.9	2.4-10.0
Inter-Day Accuracy Range (% Accuracy)	94.0-101.6	99-101.4	97.5-98.4	97.5-100.7	101.0-106.0	98.0-104.0
Correlation (Range of r ² values)	N/A	0.9938-0.9999	N/A	0.9995-0.9999	N/A	0.9989-0.9997
Linear Range (ng/mL)	N/A	0.25-25.0	N/A	0.25-25.0	N/A	0.25-25.0
Sensitivity/ LLOQ (ng/mL)	N/A	0.25	N/A	0.25	N/A	0.25

Formulation

- All three strengths are considered proportionally similar and they are made from the same master blend. (Table 25).
- The final formulation (used in pivotal fasting BE and fed study) and preliminary formulation (Methylin CT chewed versus unchewed study) are similar except proportional difference in 2 of the excipients (grape flavor and stearic acid) (Table 25, 26 & 27).
- Pivotal BE study (#610) and food effect study (#721) were conducted using to-be-marketed final formulation. Study #596 (compared Methylin CT chewed versus unchewed) was conducted using preliminary formulation. There is only slightly difference in two formulation. The dissolution profiles in water were similar for the final formulation (used in pivotal fasting BE and fed study) and preliminary formulation (Methylin CT chewed versus unchewed study) (see Fig 9 & 10 under appendix: Dissolution page 32) and both formulations are shown to be BE (in vivo) to Ritalin tablet.
- The batch size for the Methylin CT 10 mg used in the pivotal fasting BE study #610 (Lot # MHSC0043) is _____
- Manufacturing from the same master blend (lot#MHSC0040), the batch size for the final formulation of Methylin CT 2.5mg (lot #MHSC0041), and 5mg (lot#MHSC0042) used in dissolution comparisons is _____, respectively.
- As per chemists, Drs. Christy John and Xiao-Hong Chen, the scales for bio-batches and commercial batches are summarized in the table below :

	2.5mg	5mg	10mg
Batch scale*	_____	_____	_____
	(Lot# MHSC0041)	(Lot# MHSC0042)	(biobatch Lot# MHSC0043)
Commercial batch scale	_____	_____	_____

*Batch for 10 mg tablet used in pivotal BE and food studies and 2.5 mg and 5 mg tablets used in in-vitro dissolution studies.

Quantitative Formulation

Table 25.

Official USP/NF Material Name	Brand Name (Grade) and Manufacturer's Name	%	Grams / Kg Master Blend	Strength		
				2.5 mg	5 mg	10 mg
Methylphenidate HCl USP	Code: 1571 (Mallinckrodt, Inc.)	_____	_____	2.5 mg	5 mg	10 mg
Maltose						
Microcrystalline Cellulose NF *						
Guar Gum NF *						
Pregelatinized Starch NF						
Aspartame						
Grape Flavor						
Stearic Acid NF	(Mallinckrodt, Inc.)					
TOTAL			100%	150 mg	300 mg	600 mg

Table 26

Table 27

Official USP/NF Material Name	%	Batch Composition	Strength		
			2.5 mg	5 mg	10 mg
Methylphenidate HCl USP			2.5 mg	5 mg	10 mg
Maltose					
microcrystalline Cellulose and Guar Gum *					
Pregelatinized starch NF					
Aspartame					
Grape Flavor					
Magnesium Stearate NF					
Total	100.0%		150 mg	300 mg	600 mg

Official USP/NF Material Name	%	Batch Composition	Strength		
			2.5 mg	5 mg	10 mg
Methylphenidate HCl USP			2.5 mg	5 mg	10 mg
Maltose					
microcrystalline Cellulose and Guar Gum *					
Pregelatinized Starch NF					
Aspartame					
Grape Flavor					
Stearic Acid NF					
Total	100.0%		150 mg	300 mg	600 mg

Dissolution

Submission:

- This is a new chewable tablet formulation for methylphenidate HCl. In the original submission, the sponsor proposed using dissolution method and specification for methylphenidate HCl tablet USP and submitted dissolution profiles for all 3 strengths in only one medium (water).
 - Apparatus 1: 100rpm
 - Medium: water; 900ml
 - Not less than $Q=$ in 45 minutes
- At the 45 days filing meeting, the sponsor was requested to provide full report of dissolution method development and dissolution profiles for all 3 strengths in at least three media (pH 1.2, 4.5, and 6.8 buffers).
- Subsequently, the sponsor submitted dissolution profiles for all strengths in additional 3 media (pH 1.2, 4.5, and 6.8 buffers) (Tables 30, 31 & 32)

Results and reviewer's comments:

- All strengths of to-be-marketed of Methylin CT exhibited rapid release of methylphenidate [average percent dissolved >85% in all pH buffers (pH 1.2, 4.5 and 6.8) and >80% in water] in 15 minutes. (Tables 30, 31 & 32).
- Based on the method and dissolution profiles from 4 media (pH .2, 4.5, 6.8 buffers and water) submitted, this reviewer agreed with the selected medium (H₂O) for dissolution testing since only H₂O demonstrated some discriminatory capability for all 3 strengths. However, the specification should be set at $Q=$ in 30 minutes. Note: Chemist Dr. Xiao-Hong Chen was consulted to evaluate the stability data against this recommendation. However, the sponsor did not submit any stability data at 30 minutes. The sponsor will be requested to submit dissolution and stability data for the production batches of all three strengths at the proposed manufacturing site in $Q=$ using recommended specification.
- This reviewer had plotted the graph and compared the dissolution profiles across 3 different strengths (10mg Methylin CT as reference) using an f₂ test (fig 5-8, Table 33; page 32).
 - The dissolution profiles for 3 strengths are similar in all 4 media.
 - However, f₂ comparison may not be suitable for this rapidly dissolved product. Specifically, all but two values (in H₂O medium) of the average value of % release (dissolution profiles) demonstrated more than 85 % release of methylphenidate in 15 minutes.
- The mean t_{max} of Methylin CT is approximately 1.4 hours indicating that dissolution may not be the limiting factor for absorption.
- The dissolution profiles in water were similar for the final formulation (used in pivotal fasting BE and fed study) and preliminary formulation (Methylin CT chewed versus unchewed study) (Fig 9 & 10).

Comments to the sponsor:

Dissolution specification:

The selected dissolution method is acceptable. However, we recommend a change in dissolution specification for all three strengths of Methylin CT to $Q=$ in 30 minutes.

Sponsor proposed specification: $Q=$ in 45 minutes

Agency recommended specification: $Q=$ in 30 minutes

We recommend that $Q=$ in 30 minutes be accepted as interim dissolution specification for all 3 strengths of Methylin CT until additional data (described below) is submitted and reviewed.

Phase IV commitment regarding dissolution specification: Submit dissolution and stability data, for production batches of all three strengths ($Q=$ per strength) using sponsor proposed and

agency recommended dissolution specifications (i.e. 30 and 45 minutes). These batches could be next production batches or batches currently on stability. These data should be submitted to the agency no later than 1½ years from the date of approval of this product. The sponsor should make a Phase IV commitment to submit this data for finalization of dissolution specification.

Table 30

MHSC0041 2.5mg Methylin Chewable Tablets
 Dissolution Profiles
 USP Apparatus 1: 100 RPM, 900mL medium per vessel, 10mL samples taken at 15, 30, 45, and 60 minutes

	pH 6.8 (simulated intestinal fluid without enzymes)				pH 1.2 (simulated gastric fluid without enzymes)				pH 4.5 (mixture of simulated gastric and intestinal fluids without enzymes)				Water			
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
% Dissolved																
average	99.8%	97.9%	96.4%	96.1%	102.3%	102.5%	101.8%	102.4%	102.6%	102.1%	102.6%	101.8%	80.5%	83.6%	86.5%	89.7%
stdev	3.0	3.1	3.0	2.5	3.8	4.3	3.9	3.8	3.3	3.8	3.7	3.9	2.8	4.4	5.0	2.5
%RSD	3.0%	3.1%	3.1%	2.6%	3.7%	4.2%	3.8%	3.8%	3.3%	3.7%	3.6%	3.8%	3.5%	5.3%	5.8%	2.8%
Min																
Max																

Table 31

MHSC0042 5mg Methylin Chewable Tablets
 Dissolution Profiles
 USP Apparatus 1: 100 RPM, 900mL medium per vessel, 10mL samples taken at 15, 30, 45, and 60 minutes

	pH 6.8 (simulated intestinal fluid without enzymes)				pH 1.2 (simulated gastric fluid without enzymes)				pH 4.5 (mixture of simulated gastric and intestinal fluids without enzymes)				Water			
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
% Dissolved																
average	99.5%	98.4%	96.7%	95.8%	103.7%	103.5%	103.0%	103.6%	101.9%	101.8%	101.8%	101.6%	83.6%	85.3%	86.6%	91.7%
stdev	2.7	2.7	2.9	2.6	2.1	2.3	2.1	1.5	2.6	2.4	2.7	2.5	2.6	3.6	3.6	3.2
%RSD	2.7%	2.8%	3.0%	2.7%	2.0%	2.2%	2.1%	1.5%	2.6%	2.3%	2.7%	2.5%	3.1%	4.2%	4.2%	3.4%
Min																
Max																

Table 32

MHSC0043 10mg Methylin Chewable Tablets
 Dissolution Profiles
 USP Apparatus 1: 100 RPM, 900mL medium per vessel, 10mL samples taken at 15, 30, 45, and 60 minutes

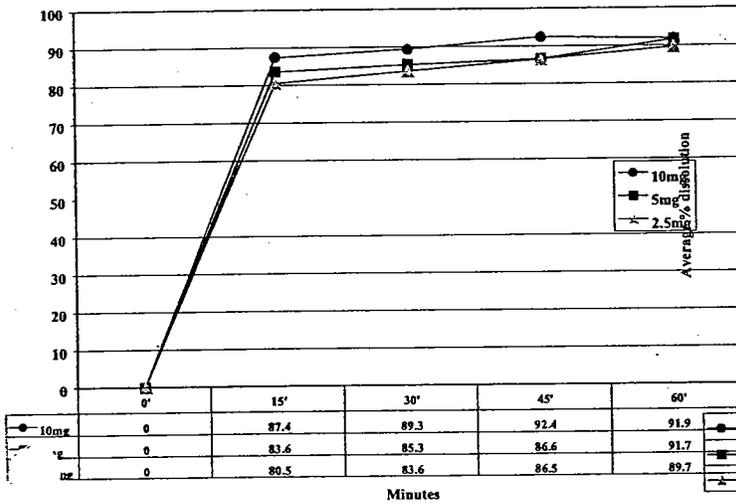
	pH 6.8 (simulated intestinal fluid without enzymes)				pH 1.2 (simulated gastric fluid without enzymes)				pH 4.5 (mixture of simulated gastric and intestinal fluids without enzymes)				Water			
	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min	15 min	30 min	45 min	60 min
% Dissolved																
average	98.7%	97.8%	96.6%	95.6%	102.0%	102.1%	102.2%	102.4%	101.1%	101.4%	101.4%	101.2%	87.4%	89.3%	92.4%	91.9%
stdev	1.7	1.7	1.6	1.6	1.4	1.7	1.2	1.9	1.3	1.2	1.1	1.4	2.9	2.4	2.5	2.8
%RSD	1.7%	1.7%	1.7%	1.7%	1.4%	1.7%	1.2%	1.9%	1.3%	1.2%	1.1%	1.4%	3.3%	2.7%	2.7%	3.0%
Min																
Max																

Table 33. f2 comparison

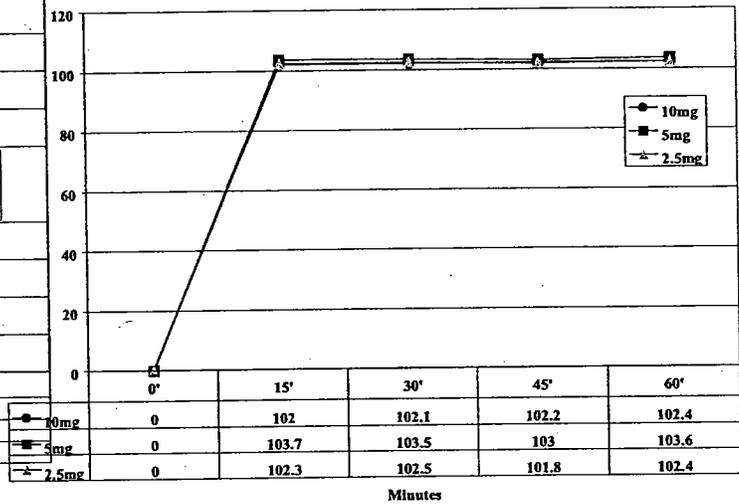
	2.5mg vs 10mg	5.0mg vs 10mg
H2O	68.72	75.35
pH 6.8	97.56	98.25
pH 4.5	93.88	98.14
pH 1.2	99.28	91.66

Fig 5-8 Dissolution profiles of all strengths (2.5m 5.0, 10mg) in 4 media (H2O, pH1.2, 4.5 and 6.8)

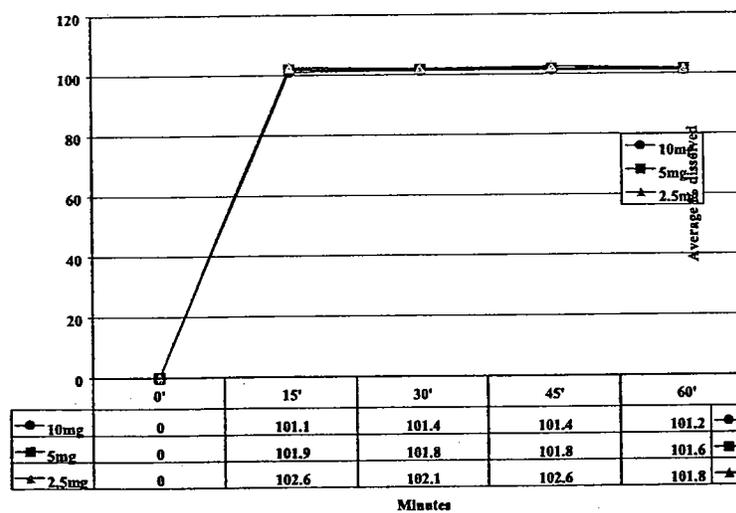
Dissolution profiles in H2O



Dissolution Profiles in pH 1.2



Dissolution profiles in pH 4.5



Dissolution profiles in pH 6.8

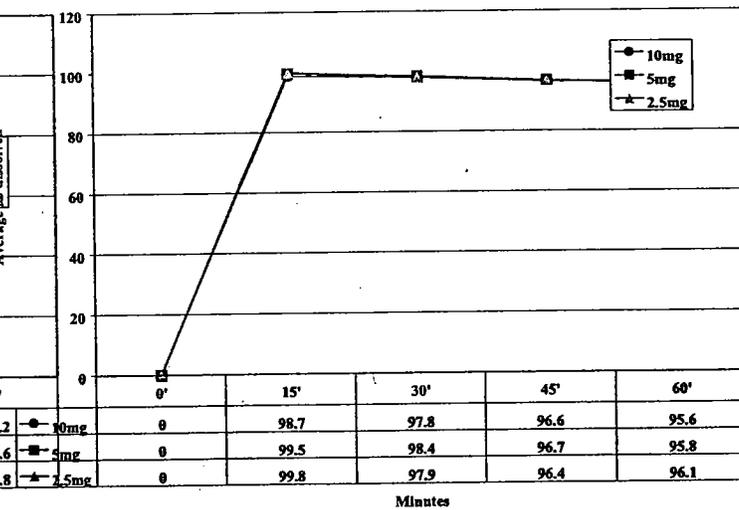


Fig 9 & 10

Figure 3.5-2 Comparative Dissolution Profiles for Ritalin Tablets and Methylin CT tablets - Preliminary Formulation

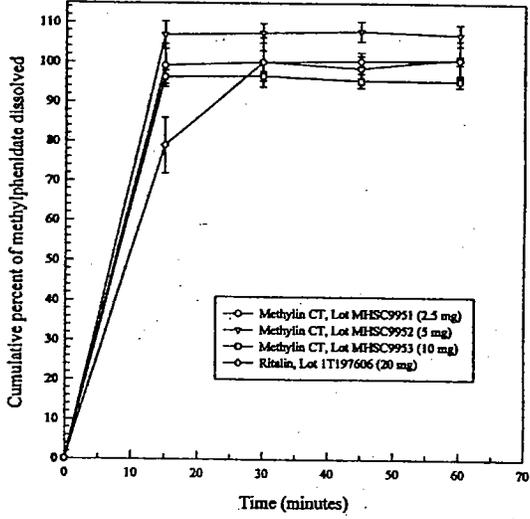
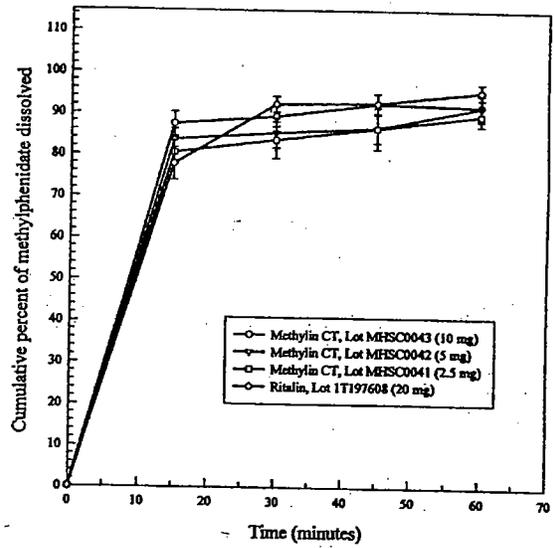


Figure 3.5-1 Comparative Dissolution Profiles for Ritalin Tablets and Methylin CT Tablets - Final Formulation



12 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics				
New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21,475	Brand Name	Methylin CT	
OCPB Division (I, II, III)	I (HFD-860)	Generic Name	Methylphenidate Hydrochloride	
Medical Division	HFD-120	Drug Class		
OCPB Reviewer	Wen-Hwei Chou, Pharm.D., Ph.D.	Indication(s)	Attention Deficit Disorders and Narcolepsy	
OCPB Team Leader	Ramana, Uppoor, Ph.D.	Dosage Form	Chewable Tablets (2.5mg, 5.0mg, and 10mg)	
		Dosing Regimen	Adult: average dosage, 20-30mg daily (10~60mg daily, 2-3 times daily, preferably 30-45 minutes before meals); Children (6 years and older): 2.5mg twice daily (before breakfast and lunch) with gradual increments of 5-10mg weekly.	
Date of Submission	12/19/01	Route of Administration	P.O.	
Estimated Due Date of OCPB Review	5/30/02	Sponsor	Mallinckrodt Inc, 650 McDonnell Boulevard P.O. Box 5840, St. Louis MO63134	
Division Due Date	7/30/02	Priority Classification	S	
PDUFA Due Date	10/18/02			
Clin. Pharm. and Biopharm. Information				
Background				
<ul style="list-style-type: none"> This is 505(b) (2) NDA submission The sponsor submitted 3 BE studies (2 in fasted and 1 in fed condition) using higher strength (10mgx2) against reference listed drug, Ritalin tablet (20mgx1). One BE study (#1137-00-610) was submitted under methylin AQ (NDA 21, 419) The sponsor requests waiver of BE study on lower strengths (2.5 and 5.0mg). The lower strengths are proportionally similar (i.e. they are manufactured from the same — blend) 				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				

Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			<ul style="list-style-type: none"> The proposed text is essentially the same as the reference listed drug. No ADME or PK data is included in the labeling.
Reference Bioanalytical and Analytical Methods	x			The Sponsor had submitted both pre-study assay validation & within-study assay performance
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	2		<ul style="list-style-type: none"> • 1137-99-596: BE study in the fasting state, Methylin CT (chewable tab 10mgx2) either chewed or unchewed, compared to Ritalin 20mg tab (a commercially available product as Reference Listed Drug), [SD, 2-period, 3-treatment, six sequence, crossover in 24 healthy subjects, using preliminary formulation #MHSC9953] • #1137-00-610: Pivotal BE study in the fasting state, comparing Methylin AQ 20mg (10mg/5ml), Methylin CT (chewable tab 10mgx2) and Ritalin 20mg tab (a commercially available product as Reference Listed Drug), [SD, 3-period, 3-treatment, six sequence, crossover in 36 healthy subjects using to-be-marketed product, lot #MHSC0043]
replicate design; single / multi dose:				

Food-drug interaction studies:	x (high-fat meal)			#1137-00-721: food-effect study: 20mg CT (10mgx2, fast or fed) vs Ritalin (20mg tab, fed) SD, 3-period, 3-treatment, six sequence, in 18 healthy subjects using to-be-marketed product, lot #MHSC0043]
Dissolution:	x	x		USP
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				<ul style="list-style-type: none"> • The labeling approved for the reference listed drug, Ritalin, and proposed labeling for this product includes the pediatric population age 6 and above. • The sponsor requests the Agency to grant a deferral of the requirement to perform pediatric studies in accordance with 21 CFR 314.55(b). The Sponsor indicated that pediatric studies (preschool age children, under age 6) are presently being conducted by the NIH which will be used to develop class labeling into the labeling proposed herein, once it is available.
Literature References				
Total Number of Studies	3	3+dissolution +biowaiver		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	x	<ul style="list-style-type: none"> No electronic submission. The Sponsor had included statistical analysis of PK measurements in paper format. New DSI inspection for the pivotal fasting BE study (1137-00-610) is not necessary. DSI consult was requested for the same study under NDA21,419 (MethylinAQ) dated October 4, 2001. [(Clinical Investigator: _____, study center: _____ (Analytical site: _____ Report is expected in May 2002
Comments sent to firm ?	x	<p>The sponsor is requested to:</p> <ul style="list-style-type: none"> provide full report of dissolution method development provide dissolution profiles for all 3 strengths in at least three media (pH 1.2, 4.5, and 6.8 buffers). perform an extensive literature search for methylphenidate in humans and submit all the necessary information along with the reference articles. Information includes ADME (absorption, distribution, metabolism, elimination), special populations (gender, age, race, hepatic and renal impairment), dose proportionality, inhibitory and inductive effect of methylphenidate on the isozymes, activity of metabolites and drug interactions, etc. update label based on the above information. Submit PK data in electronic format for all 3 BE studies 1137-99-596, 1137-00-610 and 1137-00-721). Consult guidance for type of format for electronic submission. Submit annotated proposed labeling in electronic format.

QBR questions (key issues to be considered)	<ul style="list-style-type: none"> • Was the to-be-marketed formulation used in the BE studies? • Is the chewable tablet BE to the reference tablet? • Is there a food effect on bioavailability of the chewable tablet? • Are PK characteristics different when CT is swallowed as a whole tablet or chewed? • Are the dissolution specifications and method used appropriate to distinguish sub-optimal batches? • Are in-vitro dissolution profiles similar for all the 3 individual strengths in to-be-marketed formulation? • Are the formulations proportionally similar for all 3 different strengths? • Can we waive BE of lower strengths based on the in vitro dissolution profiles?
Other comments or information not included above	
Primary reviewer Signature and Date	Wen-Hwei Chou, Pharm.D., Ph.D.
Secondary reviewer Signature and Date	Ramana Uppoor, Ph.D.

CC: NDA 21,475, HFD 860 (Mehta, Sahajwalla, Uppoor, Sekar, Chou), HFD-850(Lee), HFD-120(CSO), CDR

Appendix

Table 3.5.3 Composition Methylin® CT Tablets – Preliminary Formulation (Bio-Batches; Study 596)

Official USP/NF Material Name	%	Batch Composition	Strength		
			2.5 mg	5 mg	10 mg
Methylohexidate HCl USP	/	/	2.5 mg	5 mg	10 mg
Maltose	/	/	/	/	/
microcrystalline Cellulose and Guar Gum *	/	/	/	/	/
pregelatinized Starch NF	/	/	/	/	/
Acetartame	/	/	/	/	/
Grape Flavor	/	/	/	/	/
Magnesium Stearate NF	/	/	/	/	/
Total	100.0%		150 mg	300 mg	600 mg

Table 3.5.2 Composition of Methylin® CT Tablets – Final Formulation (Exhibit Batches; Studies 610 and 721)

Official USP/NF Material Name	%	Batch Composition	Strength		
			2.5 mg	5 mg	10 mg
Methylohexidate HCl USP	/	/	2.5 mg	5 mg	10 mg
altose	/	/	/	/	/
microcrystalline Cellulose and Guar Gum *	/	/	/	/	/
pregelatinized starch NF	/	/	/	/	/
Acetartame	/	/	/	/	/
Grape Flavor	/	/	/	/	/
Stearic Acid NF	/	/	/	/	/
Total	100.0%		150 mg	300 mg	600 mg

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Wen-Hwei Chou
8/28/02 05:37:42 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
8/28/02 05:43:40 PM
BIOPHARMACEUTICS