

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-278**

**ADMINISTRATIVE DOCUMENTS**

PATENT CERTIFICATION [314.94(a)(12)]

and

EXCLUSIVITY STATEMENT [314.94(a)(3)]

The following information is submitted as called for by 21 CFR 314.53 (c):

- (i) Patent Number and Date Patent Will Expire
  - 1) 5,908,850 Expires on December 4, 2015
  - 2) 5,922,736 Expires on December 4, 2015
- (ii) Type of Patent [*i.e.*, drug, drug product (formulation and composition)], or method of use
  - 1) 5,908,850 Method of Use
  - 2) 5,922,736 Method of Use
- (ii) Name of Patent Owner
  - 1) 5,908,850 Celgene Corporation, Warren, New Jersey
  - 2) 5,922,736 Celgene Corporation, Warren, New Jersey

The undersigned declares that Patent No(s). 5,908,850 and 5,922,736 cover(s) the formulation, composition, and/or method of use of d-*threo*-methylphenidate HCl. This product is the subject of this application for which approval is being sought.



Steve Thomas, Ph.D.  
Vice President, Regulatory Affairs and Project Management

10/18/2000  
DATE



d) Did the applicant request exclusivity?

YES /\_\_\_/ NO /\_X\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO / X/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /\_\_\_/ NO /\_X\_/

If yes, NDA #\_\_\_\_ Drug Name:

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /\_X\_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

### **1. Single active ingredient product.**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_X\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 10-187 \_\_\_\_\_ Ritalin \_\_\_\_\_

NDA# 18-029 \_\_\_\_\_ Ritalin SR \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A                      YES/\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

NDA# \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES // NO /\_\_\_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES // NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO //

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /  / NO /  /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /  / NO /  /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 97-M-02

Investigation #2, Study # 97-M-03

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.





(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/

NO /\_X\_/

If yes, explain: \_\_\_\_\_

\_\_\_\_\_

Signature  
Title:

Date

Signature of Office/  
Division Director

Date

cc: Original NDA    Division File    HFD-93 Mary Ann Holovac

DEBARMENT CERTIFICATION

Celgene Corporation hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Steve Thomas, Ph.D.  
Vice President, Regulatory Affairs and Project Management

10/18/2000  
DATE

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

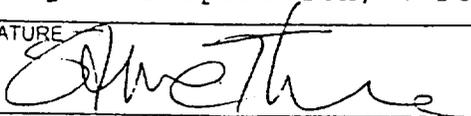
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Please see attached list.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Steve Thomas, Ph.D.	TITLE Vice President, Regulatory Affairs & Project Management
FIRM/ORGANIZATION Celgene Corporation, 7 Powder Horn Drive, Warren, NJ 07059	
SIGNATURE 	DATE 10/20/2000

#### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

## MEMORANDUM OF TELECON

**DATE:** March 14, 2001

**APPLICATION NUMBER:** NDA 21-278 [redacted]

**BETWEEN:**

**Name:** Dr. S. Thomas – Regulatory Affairs Dr. Jaworski  
Dr. P. Diango Dr. Vilanti  
Ms. A. Smith Mr. Zeber  
**Representing:** Celgene Corporation

**AND**

**Name:** Division of Neuropharmacological Drug Products, HFD-120  
Dr. R. Seevers – CMC Team Leader Dr. D. Klein – CMC Reviewer  
Ms. T. Wheelous - Regulatory Management Officer

**SUBJECT:** To discuss the March 8, 2001 submission providing a response to a February 28, 2001 facsimile. The submission regards the decision of [redacted] not to manufacture commercial batches of d-threo-methylphenidate (d-MPH) tablets, and Celgene's subsequent proposal to amend the NDA to include an alternative commercial drug product manufacturer, [redacted]

**DISCUSSION:**

[redacted]

- The FDA compliance staff has not yet been contacted by the division's CMC staff, but FDA compliance will be contacted in the near future to request an inspection of [redacted] site for clinical batch data validity.

**Drug Product Stability Data**

- If the stability lots currently held by [redacted] are transferred to another manufacturing facility and stability testing is continued then the ordinary stability testing requirements will be satisfied.
- The proposed [redacted] pilot scale and validation batches will suffice unless there is a significant change in the scale up procedure. [The Agency does not have a preference in regard to the product strength selected as the validation batch.]

Proposed Stability Data Timeline

- Although Celgene proposes a stability data submission timeline, Celgene was informed of an Agency March 1999 proposal regarding relative potential of site change of result in stability problems.

- The Agency March 1999 proposal recommends that for immediate release products (such as this one), no up front stability data will be required from the new manufacturing site and expiration can be based upon data from the former site. However, the sponsor should commit the first three batches to stability assessment.

**Pre-approval Inspection of [REDACTED]**

- Ordinarily FDA Compliance schedules site inspections upon filing of the NDA. Given that we are already 5-months into the review it is unknown when Compliance will be able to schedule site inspections. The new facility, [REDACTED] must be inspected.
- Celgene and [REDACTED] have a signed contract. Celgene will submit a new drug product manufacturing site amendment containing [REDACTED] as the new manufacturing facility, as well as, all available data, and a request for an expedited review.
- If the proposed amendment, which we will consider a major amendment, is received within the last 3 months of the review cycle then the review clock will be extended by 3 months.

**Gains Lab Status as a Drug Substance Supplier**

- Celgene does not plan to procure material from [REDACTED] at least until all compliance issues have been addressed.
- Celgene should consider withdrawing [REDACTED] as a supplier, from the NDA. Then post-approval [REDACTED] can be reinstated once compliance issues are resolved. This change should be stated in the forthcoming amendment.

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Robert Seevers, Ph.D.  
CMC Team Leader

/s/

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Teresa Wheelous  
3/22/01 09:26:45 AM  
CSO  
Robert H. Seevers  
3/22/01 10:02:23 AM  
CHEMIST

**MEMORANDUM**  
SERVICES

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

RESEARCH

**Date:** January 23, 2001  
**To:** Connie Lewin, GCPB Reviewer/HFD-47  
**From:** Anna Marie Homonnay, Regulatory Health Project Manager, HFD-120  
**Subject:** **Request for Clinical Inspections**  
NDA 21-278  
Celgene Corporation  
 (d-threo-methylphenidate HCl) Tablets

**Protocol/Site Identification:**

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)
attention deficit disorder	97-M-02	
attention deficit disorder	97-M-03	

**Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.**

**Goal Date for Completion:**

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) 7/25/01. We intend to issue an action letter on this application by (action goal date) 8/25/01.

Should you require any additional information, please contact Anna Marie Homonnay.

**MEMORANDUM**

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

**DATE:** April 10, 2001  
**TO:** NDA 21-278  
**FROM:** Teresa Wheelous, Regulatory Project Manager  
**SUBJECT:** Biopharmaceutics Request for Information Read During March 12, 2001 Telecon for NDA 21-278, [REDACTED]

This memorandum is created in order to add the biopharmaceutics information request to the March 14, 2001 telecon file for NDA 21-278.

During a March 14, 2001 CMC telecon with Celgene, Dr. Robert Seevers read a list containing biopharmaceutics information request as a result of Celgene's change in manufacturer.

Since a biopharmaceutics representative was not available to attend this telecon, an information request e-mail from the biopharmaceutics reviewer, Dr. Sunzel, was provided to Dr. Seevers to be relayed to Celgene during the March 14, 2001 telecon.

The specific information request (regarding the change in manufacture) contained within the email is as follows:

1. We agree that no new in vivo bioequivalence studies in man to compare the products from the two manufacturing sites are necessary, and that in vitro dissolution data comparing the previous and new tablets would suffice.
2. However, we would like the sponsor to provide comparative dissolution profiles in three different media [REDACTED] in addition to the proposed comparative dissolution tests [REDACTED]

The reason for the requested, extended dissolution tests is that even though differences may be minor between manufacturing sites, there are multiple changes, e.g. the equipment [REDACTED] are not identical between manufacturers, and the SOPs may also differ slightly between the two manufacturing sites. Further, there is no approved dissolution method for this product yet.

MEMORANDUM

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

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**Date:** June 15, 2001

**To:** Russell Katz, M.D.  
Director, Division of Neuropharmacological Drug Products  
HFD-120

**Through:** Deborah B. Leiderman, M.D.  
Director, Controlled Substance Staff  
HFD-009

**From:** Ann-Kathryn Maust, M.D.  
Silvia Calderon, Ph.D.  
Controlled Substance Staff, HFD-009

**Subject:** Abuse Liability of [redacted] (*d-threo*-methylphenidate hydrochloride tablets, NDA 21-278)  
Sponsor: Celgene Corporation

Recommendations

*D-threo*-methylphenidate hydrochloride should be placed in Class II and changes should be made to the controlled substance portions of the label. It may not be possible to make some of the label changes unless the labels for other methylphenidate products are also changed.

Introduction

The Controlled Substance Staff (CSS) reviewed published literature, the Drug Abuse and Liability Assessment volume submitted by the sponsor, and other parts of the NDA.

Much of the material in the drug abuse volume refers to *d,l*-methylphenidate or the marketed product Ritalin. No human abuse liability studies using *d*-MPH were performed. Celgene requests that *d*-MPH be placed in Schedule II, which is the schedule assigned to *d,l*-MPH.

Presented below are background information, brief summaries of the chemistry and pharmacology of *d*-MPH and *d,l*-MPH and of the information that Celgene submitted to CSS, comments regarding the withdrawal phase of Study 97-M-03, and suggestions for the labeling.

## Background

Celgene Corporation has developed an immediate release formulation of the *d-threo*-methylphenidate hydrochloride isomer. This new product will be known as [redacted] and will be indicated for the treatment of 6 to 17 year old children with Attention Deficit/Hyperactivity Disorder (ADHD). It will be available in three strengths: 2.5 mg, 5 mg and 10 mg. The recommended dose is 5 to 20 mg/day, and the recommended dosing schedule is twice a day.

Assessment of the abuse liability of a drug is based upon evaluation of its chemistry, pharmacology (preclinical and clinical), and pharmacokinetic and pharmacodynamic profiles. It is useful to compare a new drug with a pharmacologically similar comparator drug. The logical pharmacological comparator for *d-threo*-methylphenidate (*d*-MPH) is racemic *d,l-threo*-methylphenidate (*d,l*-MPH). Racemic methylphenidate (Ritalin®, various generic products, and the recently approved sustained formulation [Concerta]) is the most commonly used stimulant in the treatment of ADHD. It has been available since January 1982. Manufacturing and distribution of methylphenidate is regulated under the controls imposed by Schedule II of the Controlled Substances Act. Drugs included in this schedule are considered to have high potential for abuse and their abuse may lead to severe psychological and physical dependence. Methylphenidate is also controlled under Schedule II internationally.

## Chemistry

Methylphenidate has two asymmetric centers and, therefore, four stereoisomers are recognized. Stereoisomers are molecules with identical atomic constitution, but they differ in the spacial arrangement of the atoms. In other words, the three dimensional distribution of the substituents at asymmetric carbons is different. Enantiomers are mirror image stereoisomers with one or more asymmetric centers that have the same physical and chemical properties with the exception of optical rotation. *D,l-threo*-methylphenidate is a mixture of two enantiomers. The *d-threo* isomer possesses a 2*R*, 2'*R* configuration.

## Preclinical Pharmacology

The pharmacological activity of *d,l*-MPH is attributed to the *d*-enantiomer. In a rat study cited by Celgene, doses of 5 mg/kg of *d,l*-MPH and 2.5 mg/kg of *d*-MPH increased the extracellular dopamine level in the striatum by 4.7 and 4.2 times, respectively. In animals the onset of activity for the *d*-enantiomer is rapid, and its action is relatively short-lived. Minimal activity is seen for the *l*-enantiomer and distribution to the CNS is limited and non-specific. (Patrick *et al.* 1986; Eckerman *et al.* 1991). Studies have demonstrated that the main metabolite, ritalinic acid (RA), does not possess significant pharmacological activity.

### Clinical Pharmacology

A four-way, crossover study has been published (Srinivas *et al.*, 1992) comparing the pharmacokinetic and pharmacodynamic profiles of *d,l*-MPH, *d*-MPH, and *l*-MPH in children with ADHD. The pharmacokinetic results illustrate that when *d*-MPH is given in one-half the total *d,l*-MPH dose (*i.e.*, equimolar with respect to the *d*-enantiomer), exposure to *d*-MPH is comparable. *D*-MPH's onset of activity was rapid while no effect was observed for the *l*-enantiomer in computerized tests designed to assess visuospatial memory, trail sequence, and scanning reaction time. The results of this study are consistent with a Celgene study, which showed that when *d*-MPH is administered in one-half the total *d,l*-MPH dose, both forms have the same activity as measured by Connors Rating Scale and a Math Test.

The rapid and selective distribution of *d*-MPH to the striatum of humans has been demonstrated using positron emission tomography (Ding *et al.*, 1997). Pharmacokinetic studies using *dl*-MPH have also shown that after oral administration, the absolute bioavailability of *d*-MPH is 0.23 and that of *l*-MPH is 0.05 (Srinivas *et al.*, 1993). This study suggested that enantiomeric differences in the pharmacokinetics of oral methylphenidate are the result of enantioselectivity in presystemic metabolism.

The sponsor has also conducted three clinical studies analyzing the *in vivo* pharmacokinetics of *d*-MPH. Two of the studies were conducted in children who have ADHD and who were between the ages of 6 and 16 years. The third study examined the effects of food on *d*-MPH pharmacokinetics in healthy adult volunteers. Results are similar to those reported in the published literature for equimolar doses of *d,l*-MPH.

In children with ADHD, *d*-MPH is rapidly absorbed with peak concentrations occurring within 1 to 2 hours. The plasma elimination half-life is approximately 2 to 2½ hours, regardless of dose or duration of administration. Levels of the primary metabolite, *d*-ritalinic acid (*d*-RA), are higher than those of the parent drug.

Following administration of *d*-MPH, *d*-RA is the primary metabolite with no measurable *l*-RA. Following administration of *d,l*-MPH, comparable levels of both *l*-RA and *d*-RA are seen and pharmacokinetic parameter values are virtually identical to those seen following administration of *d*-MPH. Although *l*-MPH comprises 50% of the total administered *d,l*-MPH dose, systemic exposure to *l*-MPH is minimal. Metabolism to *l*-RA is evident in all subjects, with exposure increasing proportionally with dose.

To summarize, since the pharmacological activity of methylphenidate resides in the *d*-enantiomer, administration of 5 mg of *d*-MPH is equivalent to administration of 10 mg of *d,l*-MPH, except that patients who receive pure *d*-MPH will not be exposed to the inactive enantiomer. Thus, *d*-MPH should be considered to have an abuse potential that is similar to that of *d,l*-MPH.

Summary of Drug Abuse and Liability Assessment Submission

Celgene states that *d*-MPH was developed because of the theory that chirally pure pharmaceuticals may have superior profiles of safety and efficacy as compared to racemic mixtures.

Celgene reports that no diversion of *d*-MPH occurred in the clinical trials and that to their knowledge, there are no illegal sources of *d*-MPH and it is not available commercially in any country.

Celgene states that their evaluation of the abuse liability of *d*-MPH consists of a Celgene-sponsored animal study (Evaluation of the Amphetamine-Like Discriminative Stimulus Effects of Methylphenidate Enantiomers in Rats), the DEA's 1995 review of the abuse potential of *d,l*-MPH, and published research papers. Celgene included a summary of their *d*-MPH rat study and copies of the DEA's review and of the cited literature in the CSS submission. The result of the *d*-MPH rat study was that *d*-MPH, *l*-MPH, and *d,l*-MPH completely substituted for amphetamine, differing only in potency. *D*-MPH and *d,l*-MPH were both approximately four times more potent than *l*-MPH. The conclusion of the DEA's review was that "methylphenidate has a high potential for abuse...and that abuse can lead to severe psychological or physical dependence."

Celgene asserts that the risk to the public health from *d*-MPH appears to be not greater than the risk due to *d,l*-MPH and may be less. They argue that in their study *l*-MPH produced amphetamine-like discriminative stimulus effects in rats; thus it may be responsible for some of the properties of *d,l*-MPH that lead to abuse problems. However, *l*-MPH appeared to be four times less potent than *d*-MPH and *d,l*-MPH; the raw data was not provided; and it is not possible to determine human abuse potential from a single rat study.

Celgene concludes that *d*-MPH should be placed in Schedule II for the following reasons: *d*-MPH is pharmacokinetically and pharmacodynamically similar to *d,l*-MPH that is equimolar with respect to the *d*-enantiomer; *d,l*-MPH has a high potential for abuse; *d,l*-MPH has an accepted medical use; abuse of *d,l*-MPH may lead to severe physical or psychological dependence.

CSS Comments Regarding the Withdrawal Phase of Study 97-M-03

This study consisted of three parts. In Part A, which lasted six weeks, all patients received *d*-MPH. During the first four weeks of Part A, the dose of *d*-MPH was titrated to find the optimal dose for each patient. During the last two weeks of Part A, the optimal dose was continued. Seventy-five of the patients who completed Part A participated in Part B, which was the two week, double-blind, randomized, placebo-controlled, withdrawal phase. Thirty-five patients continued their optimal dose of *d*-MPH and 40 patients were given placebo. Part C was an open-label phase during which all patients received *d*-MPH for up to 44 weeks. The primary objective of the study was to determine the efficacy of *d*-MPH relative to placebo in maintaining a reduction of

ADHD symptoms in children who were responding to *d*-MPH. The secondary objectives were to determine the long-term safety of *d*-MPH in children with ADHD and to determine the duration of efficacy of *d*-MPH.

Patients who reported adverse events during the first three days of Part B were examined to assess for a drug rebound or withdrawal effect. Three patients taking *d*-MPH and six patients taking placebo reported adverse events during these three days. None of the events that occurred in the patients taking placebo were judged by the investigator to be related to study drug. It appears from the study report that no formal measures of withdrawal were used.

The events that occurred during the first three days of Part B in the patients taking placebo are as follows:

Patient 12-01-pharyngitis

Patient 12-05-myalgia

Patient 13-24-headache

Patient 14-04-nasal discharge and sneezing

Patient 32-03-"flu syndrome" on the day placebo was dispensed and which resolved two days later. The patient had received *d*-MPH 10 mg b.i.d. during Part A.

Patient 32-05-mild gastrointestinal distress

Withdrawal symptoms have been reported in patients who discontinue therapeutic doses of stimulants. Although Celgene concluded that abrupt discontinuation of *d*-MPH during the transition from Part A to Part B was not associated with a drug-related rebound or withdrawal effect, one of the adverse events suggests otherwise. Patient 32-03 had "flu syndrome," and fatigue is a common flu symptom. (This patient's symptoms were not described in more detail than is noted above.) Fatigue could be consistent with a stimulant withdrawal syndrome.

#### CSS Suggestions Regarding the Proposed Labeling

CSS recognizes that HFD-120 may not be able to make some of the following recommended changes unless HFD-120 decides to make similar changes in the labels for other methylphenidate products.

1. In the Description section, it would be more accurate to describe the drug as a CNS stimulant, rather than as a "mild" CNS stimulant. Whether the drug's effects are "mild" or otherwise varies among individuals.
2. In the first sentence under Pharmacodynamics, make the same change that is noted in number 1.
3. The first sentence in the Drug Abuse and Dependence black box is acceptable. In between the first and the second sentences, add the following sentence: "Physicians should monitor all patients for signs of abuse or dependence and carefully monitor the amount of Attenade which is dispensed."

4. Change the second sentence in the Drug Abuse and Dependence black box to "Chronic, abusive use of racemic methylphenidate can lead to marked tolerance and dependence with varying degrees of abnormal behavior; frank psychotic episodes can occur."
5. Delete the third sentence in the proposed Drug Abuse and Dependence black box.
6. The remainder of the proposed black box is acceptable.
7. The Drug Abuse and Dependence section which appears after the Adverse Events with Other Methylphenidate HCl Products section is acceptable.

Summary

1. Human abuse potential studies using *d*-MPH were not performed.
2. At least one child may have experienced withdrawal symptoms in the withdrawal phase of Study 97-M-03.
3. CSS recommends that some changes should be made to the controlled substance portions of the proposed label. (However, it may not be possible to make some of these changes unless the labels for other methylphenidate products are also changed.)
4. *D*-MPH should be scheduled as Class II because *d*-MPH is the active enantiomer of racemic MPH.

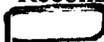
**APPEARS THIS WAY  
ON ORIGINAL**

**MEMORANDUM**

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

**DATE:** August 8, 2001

**FROM:** Thomas P. Laughren, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation for Approvable Action for  
 (d-methylphenidate) Tablets for the Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

**TO:** File NDA 21-278  
[Note: This overview should be filed with the 10-25-00 original submission.]

**1.0 BACKGROUND**

Methylphenidate is a stimulant that has been available for many years in the US as a treatment for ADHD, both in an immediate release form (Ritalin and various generic versions of the IR) and in several sustained release forms (Ritalin SR and various generic versions of the SR; Concerta; and Metadate CD). Concerta and Metadate CD are both modified release forms that can be given qd and are intended to essentially mimic the plasma levels seen when the IR is given in the morning and at lunchtime.

Other immediate release stimulant products approved for ADHD include various amphetamines (d-amphetamine, a mixture of d- and l-amphetamine, and methamphetamine) and pemoline. D-amphetamine is also available in a sustained release formulation.

Methylphenidate is a racemic (50:50) mixture of d- and l-methylphenidate. There are data, both human and animal, to suggest that essentially all of the activity of methylphenidate resides in the d-isomer. Thus, it is reasonable to develop the d-isomer, and to target doses one-half those found to be effective for the racemate, as was done in this development program. Celgene proposes to market 3 strengths of d-MPH, i.e., 2.5, 5.0 and 10.0 mg. The proposed dosing range will be 5 to 20 mg/day (given on a bid schedule, i.e., morning and noon).

IND [redacted] for d-methylphenidate (d-MPH) was originally submitted 12-16-96.

An EOP2 meeting with the sponsor was held on 1-14-98 to discuss preclinical issues and the clinical program. We indicated that, given lack of knowledge of d-MPH, we would like to see two studies, however, we agreed to a typical short-term study along with a randomized discontinuation phase for that study.

A preNDA meeting was held with the sponsor on 1-6-00. We discussed and provided advice on the two key studies (02 and 03).

The original NDA 21-278 for [redacted] (d-MPH) was submitted 10-25-00, and was filed as a 505(b)(2) application on 12-19-00. A safety update was submitted on 5-17-01 and was included in the clinical review.

We decided not to take [redacted] (d-MPH) to the Psychopharmacological Drugs Advisory Committee.

## 2.0 CHEMISTRY

The chemistry review was conducted by Donald Klein, Ph.D. The chemistry group is recommending a non-approvable action, based on the fact that the sponsor was not ready for a site inspection at the time it was originally scheduled. There are also a number of other more minor deficiencies. As an alternative, I recommend that we issue an approvable letter, with the requirement of a satisfactory inspection, as well as correction of the other minor deficiencies, prior to final approval

We are still waiting for OPDRA to make a recommendation on the proposed name, [redacted]

## 3.0 PHARMACOLOGY

The original pharmacology/toxicology review was conducted by Ed Fisher, Ph.D. As of this time, I am not aware of any pharmacology/toxicology issues that would preclude the approvability of [redacted]

## 4.0 BIOPHARMACEUTICS

The biopharmaceutics review was conducted by Maria Sunzel, Ph.D. In summary, the PK of d-MPH appears to be identical to that of d,l-MPH. As of this time, I am not aware of any biopharmaceutics issues that would preclude the approvability of [redacted]

## 5.0 CLINICAL DATA

## 5.1 Efficacy Data

The sponsor has provided efficacy data from two placebo-controlled clinical studies in children and adolescents with ADHD in support of the efficacy claim for d-MPH, i.e., 97-M-02 and 97-M-03. The efficacy data were reviewed by Roberta Glass, M.D. of the clinical group and Kallappa Koti, Ph.D., of the biometrics group.

### 5.1.1 Summary of Studies Pertinent to Efficacy

#### 5.1.1.1 Study 97-M-02

This was a randomized, double-blind, parallel group, 4-week, multicenter (11 US sites) study comparing d-MPH (5-20 mg/day; bid schedule); d,l-MPH (10-40 mg/day; bid schedule); and placebo in n=132 pediatric patients aged 6-17 with ADHD (DSM-IV) who were either already considered responders to methylphenidate (about 25%), or were methylphenidate naive but considered candidates for methylphenidate treatment (about 75%). The sample included patients who were of the combined type, the predominantly hyperactive-impulsive type, or the predominantly inattentive type. The double-blind phase was preceded by a 1 week single-blind placebo run-in to ensure patients were back to their baselines before randomization. The d-MPH dose was initiated at 2.5 mg bid (all doses were given between 7 and 8 am and between 11:30 am and 12:30 pm), and could be doubled at weekly intervals, based on clinical response and tolerability, up to the maximum dose permitted. d,l-MPH was dosed in an identical manner, except at double the dose. The primary outcome was mean change from baseline of the averaged score (an average of two ratings during the week) of the teacher's version of the SNAP-ADHD Rating Scale at week 4. Secondary outcomes included: (1) CGI-I at week 4; (2) parent SNAP-ADHD ratings from the weekend; (3) proportion of responders on the CGI-I; and (4) math test scores. For the primary outcome, ANCOVA of the LOCF data was the protocol specified analysis.

The mean age was about 9, and the sample was mostly male and Caucasian. A subgroup of the sample included adolescents, aged 12-17 (n=39). N=132 patients were available for the analysis in the ITT sample. Overall, 90% of the patients completed to 4 weeks.

During week four, 85% of d-MPH patients had been titrated up to the maximum dose of 10 mg bid, compared to 69% of d,l-MPH patients being titrated to their maximum dose of 20 mg bid.

The mean changes from baseline for the teacher's version of the SNAP-ADHD Rating Scale after 4 weeks of treatment were as follows:

d-MPH	-0.7
d,l-MPH	-0.7
Placebo	-0.2

The d-MPH vs placebo comparison was highly significant ( $p < 0.0001$ , LOCF and  $p < 0.0004$ , OC). The d,l-MPH vs placebo comparison was also highly significant.

Drs. Glass and Koti concluded that this study supported the primary claim for overall efficacy of d-MPH, and I agree.

#### **5.1.1.2 Study 97-M-03**

This 7-center, US study was designed as a relapse prevention trial. There was a 6-week, open label run-in phase during which children and adolescents with ADHD were titrated to an effective dose of d-MPH and then maintained at that dose. 87 patients considered responders during this run-in were randomized to continuation on either the same dose of d-MPH that was considered effective or to placebo, for a 2-week, double-blind phase. The primary outcome was proportion of treatment failures at the end of the 2-week withdrawal phase, where treatment failure was defined as a rating of 6 (much worse) or 7 (very much worse) on the investigators CGI-I. The mean age of patients was approximately 10, and as with study 02, patients were predominantly male and Caucasian. The results were 6/35 (17%) for d-MPH vs 24/39 (62%) for placebo ( $p < 0.001$ ).

I think this study provides independent evidence for the efficacy of d-MPH in ADHD, however, it does not address longer-term efficacy, the usual goal of a relapse prevention trial.

#### **5.1.2 Comment on Other Important Clinical Issues Regarding**

##### Secondary Outcomes

Several of the secondary outcomes were also positive, however, none of these were prespecified as key secondary outcomes, and none adds any critical information, in my view. Thus, we have not added any of these to labeling as proposed by the sponsor. The sponsor also sought to add comparative information regarding duration of effect with d-MPH vs d,l-MPH, however, this comparison was also not appropriately prespecified, nor was this study adequately designed for such a comparison. In fact, examination of baseline scores reveals that the d,l-MPH group had higher scores at baseline compared to the d-MPH group. Thus, we have also not added this information.

##### Evidence Bearing on the Question of Dose/Response for Efficacy

Both studies 02 and 03 involved flexible dosing, and thus, there is no information in these studies pertinent to dose/response for efficacy.

##### Clinical Predictors of Response

There were insufficient non-Caucasian patients to conduct an analysis by race. Dr. Koti did conduct an exploratory analysis for gender, and found no difference in the primary outcome based on this subset.

An exploratory analysis based on subsets of children and adolescents was suggestive that the overall effect was coming from the children, with little effect demonstrated in the adolescents. However, he did not provide the mean changes for the different subgroups. We will ask for more details regarding this analysis from the sponsor in the approvable labeling. In the meantime, we will suggest in labeling that, given the small adolescent subgroup, the data do not provide any meaningful information regarding this age group.

#### Size of Treatment Effect

While it is difficult to assign clinical significance to the observed differences between [redacted] and placebo on the teacher's version of the SNAP-ADHD Rating Scale, these differences are similar to those seen in other studies considered by most experts proof of efficacy of the IR product. Thus, I consider these clinically meaningful results.

#### Duration of Treatment

There were no data presented in this program pertinent to the question of longer term efficacy of [redacted] in ADHD. Study 03, while providing some additional evidence for the efficacy of d-MPH, does not address efficacy beyond the 6 weeks of open label treatment in that study, and clearly, this product will be used for years in patients with this condition.

#### **5.1.3 Conclusions Regarding Efficacy Data**

In summary, I consider studies 02 and 03 positive support for the claim of short-term effectiveness of d-MPH in the treatment of ADHD. In the approval letter, we will need to ask Celgene to commit to conducting, postapproval, a study in children less than 6, under the Pediatric Rule.

#### **5.2 Safety Data**

##### **5.2.1 Clinical Data Sources for Safety Review**

The safety data for [redacted] were reviewed by Dr. Roberta Glass. This original review was based on an integrated database including all subjects in the development program; apparently, all studies in the program were completed at the time of original submission of the NDA.

There was 1 study in normal adults (PK), and 6 clinical studies in children/adolescents with ADHD (ages ranging from 6 to 17). As noted, 2 of the peds studies were focused on efficacy (02 and 03). Two of the peds studies were focused on PK, and the remaining two (04 and 05) were open label safety studies. N=15 adults and n=684 pediatric patients were exposed to [redacted] in this program. Of the 684 pediatric patients exposed to d-MPH, n=426 were exposed for  $\geq 6$  months and n=146 were exposed for  $\geq 1$  year. Patients in phase 2-3 studies were roughly 83% male and predominantly white. The mean age of patients was 10.

## **5.2.2 Adverse Event Profile for [REDACTED]**

### **5.2.2.1 Common Adverse Event Profile**

The adverse event profile for [REDACTED] was similar to that known for other methylphenidate products, including notably insomnia, anorexia, abdominal pain, and nausea.

### **5.2.2.2 Conclusions Regarding Safety Data**

Overall, there were no adverse event findings observed in the clinical trials with [REDACTED] that would preclude an approvable action. The adverse event profile observed is similar to that seen with other methylphenidate formulations and it can be adequately characterized in labeling.

## **5.3 Clinical Sections of Labeling**

We have substantially rewritten the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

## **6.0 WORLD LITERATURE**

There were 6 published papers regarding d-MPH, and none contained unexpected safety findings regarding this drug.

## **7.0 FOREIGN REGULATORY ACTIONS**

To my knowledge, [REDACTED] is not approved anywhere at this time. We will ask for an update on the regulatory status of [REDACTED] in the approvable letter.

## **8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING**

We decided not to take [REDACTED] to the PDAC.

## **9.0 DSI INSPECTIONS**

DSI inspections of random sites from the key studies did not reveal any deficiencies that would render the data unacceptable.

## **10.0 LABELING AND APPROVABLE LETTER**

### **10.1 Final Draft of Labeling Attached to Approvable Package**

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made substantial changes to the sponsor's draft from the 7-6-01 labeling submission.

### **10.2 Approvable Letter**

The approvable letter includes draft labeling and requests for a regulatory status update.

## **11.0 CONCLUSIONS AND RECOMMENDATIONS**

I believe that Celgene has submitted sufficient data to support the conclusion that  is effective and acceptably safe in the treatment of ADHD. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:

Orig NDA 21-278

HFD-120

HFD-120/TLaughren/RKatz/RGlass/TWheelous

## MEMORANDUM

DATE: August 21, 2001

FROM: Division Director  
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-278

SUBJECT: Action Memo for NDA 21-278, for the use of dexamethylphenidate in patients with ADHD

NDA 21-278, for the use of dexamethylphenidate in patients with ADHD, was submitted by Celgene Corporation on 10/25/00. Dexamethylphenidate is the d-threo-enantiomer (and the active moiety) of racemic methylphenidate, which is also available for the treatment of patients with ADHD. There is little to no interconversion of the d- to the l-enantiomer. The application contains the results of 2 randomized controlled trials that establish the effectiveness of the drug, as well as safety experience that establishes the safety of the product. The recommended dose range for this product is exactly half that of the approved racemic methylphenidate, given that the circulating amount of dexamethylphenidate resulting from a given dose of this product is half that resulting from the same dose of the racemic product.

All reviewers recommend that the application be considered approvable, except the chemistry team, which recommends that the application be found not approvable; this is based on a recommendation of the Office of Compliance made because certain manufacturing facilities were not prepared to be, and have not been, inspected. I agree with Dr. Laughren (see his Team Leader memo, 8/8/01) that the application can be considered approvable, pending the results of the inspections.

I agree with the review team that the application is approvable. I would point out that the staff of the Medication Error Prevention Office of the Office of Post-Marketing Drug Risk Assessment has recommended, in a memo dated 7/28/01, that the sponsor's proposed name, [REDACTED] not be permitted. Their concern arises out the similarity of this name to Ritalin, the tradename of the marketed racemate. I agree that the similarity in names may be problematic.

In particular, patients prescribed Ritalin 40 mg/day (the maximum recommended dose), may accidentally receive Ritadex 40 mg/day, which would result in their being exposed to twice the level of dexamethylphenidate than that associated with the highest labeled dose of the enantiomer (or racemate). Conversely, errors in the other direction would result in under-dosing.

For these reasons, I will issue the attached Approvable letter, with appended labeling, referring to the drug as TRADEMARK at this time.

Russell Katz, M.D.

**MEMORANDUM**

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

**DATE:** November 9, 2001

**FROM:** Thomas P. Laughren, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation for Approval Action for  
D-Methylphenidate) for the Treatment of Attention Deficit Hyperactivity Disorder  
(ADHD)

**TO:** File NDA 21-278  
[Note: This overview should be filed with the 9-14-01  
response to our 8-21-01 approvable letter.]

**Background**

In our 8-21-01 approvable letter, we proposed draft labeling, and we asked for a safety update, a regulatory status update, the adoption of our proposed dissolution specifications, and a commitment to conduct a phase 4 preclinical study on the effects of d-methylphenidate on developing systems. Finally, we conveyed a number of CMC questions and comments.

The sponsor responded with a 9-14-01 package that responded to all of these issues.

**Safety Update**

This final safety update included safety data from an additional 38 patients, and thus represented a small amount of new data. Dr. Glass reviewed these data, and concluded that there were no new safety findings that would impact on the approvability or labeling of this product. I agree.

**Regulatory Status Update**

To my knowledge, this product has been submitted to only one other country, i.e., Canada, but is not yet approved anywhere.

### **Dissolution Specifications**

The sponsor did not initially accept our proposed dissolution specifications, however, we have not obtained their agreement.

### **Preclinical Study**

The sponsor now has, due to its financial arrangement with Novartis, access to a juvenile animal study that was conducted with d,l-mph. We have agreed that this study meets the requirement expressed in our approvable letter.

### **CMC Deficiencies**

To my knowledge, all remaining CMC issues have been resolved.

### **Tradename**

As noted in the approvable letter, OPDRA recommended that we not accept the originally proposed name, [redacted]. The sponsor subsequently submitted the names [redacted] and Focalin. OPDRA has also rejected the name [redacted] out of concern for name confusion with Ritalin. Dr. Katz and I conveyed these concerns to the sponsor in a 11-8-01 telcon. As of this time, we are still awaiting a response from OPDRA on this new proposal. Consequently, labeling will simply refer to the product as Tradename.

### **Pediatric Rule**

As with all methylphenidate labeling, the labeling for this product recommends that it not be used in children under 6. We have added to the approval letter the standard language asking the sponsor to submit a development plan for studying this drug in children with ADHD who are less than 6.

### **Labeling**

We reached agreement with the sponsor on final labeling on 11-5-01. There were no significant points of disagreement.

### **Recommendations**

I believe that Celgene has submitted sufficient data to support the conclusion that d-methylphenidate tablets are effective and acceptably safe in the treatment of ADHD. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling that is attached to the approval package.